

Association of Admission Plasma D-Dimer Concentration with Diagnosis and Outcome in Horses with Colic

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Background: Coagulopathies detected in horses with gastrointestinal problems seem to be associated with poor outcome. Plasma D-Dimer concentration is a sensitive test for assessing coagulopathies.

Hypothesis: Plasma D-Dimer concentration tested on admission is related to diagnosis and outcome in horses with colic.

Animals: Four hundred and ninety three horses referred for evaluation of abdominal pain.

Methods: Prospective observational clinical study. Horses were grouped according to diagnosis (medical and surgical intestinal obstructions, ischemic disorders with and without intestinal resection, enteritis, peritonitis), outcome (survivors, non-survivors), and number of coagulopathies (normal profile, 1 or 2 coagulopathies, subclinical disseminated intravascular coagulation [DIC]). Blood samples were collected on admission and plasma D-Dimer concentration, clotting times (PT and aPTT), and antithrombin activity were determined. Positive likelihood ratios (LR+) were calculated for evaluation of D-Dimer cut-off values, which were later tested in a logistic regression model.

Results: Horses with enteritis or peritonitis had significantly ($P < .001$) higher plasma D-Dimer concentrations and more severe coagulopathies on admission than horses with other diagnoses. Nonsurvivors also had significantly ($P < .001$) higher plasma D-Dimer concentrations at presentation than did survivors, and those horses with subclinical DIC on presentation had an odds ratio (OR) 8.6 (95% confidence interval [CI], 3.3–22.5, $P < .001$) for nonsurvival. Finally, D-Dimer concentrations $> 4,000$ ng/mL had a LR+ of 5.9 and an OR 8.8 (95% CI, 4.5–17.1, $P < .001$) for nonsurvival.

Conclusion and Clinical Importance: Plasma D-Dimer concentration measured on admission can be used to facilitate diagnosis and outcome prediction in horses with colic. A potential cut-off value for nonsurvival was found at approximately 4,000 ng/mL.

Key words: Coagulopathy; Disseminated intravascular coagulation; Equine; Gastrointestinal disease; Prognosis.

Historically, gastrointestinal (GI) disorders have been the most prevalent cause of coagulation disorders in horses.^{1,2} In horses with acute abdominal pain, coagulation problems are common and usually result in a hypercoagulable state. This can progress to the more severe disseminated intravascular coagulation (DIC), resulting in a subsequent consumption coagulopathy.^{1–4} DIC is rarely clinically evident in horses with colic, although it is possible to diagnose subclinical DIC based on compatible clinicopathologic data.^{2,5}

There is some evidence that the severity of the host inflammatory response to an inciting event may be extremely critical in the development of coagulopathy

Abbreviations:

aPTT	activated partial thromboplastin time
AT	antithrombin activity
CI	confidence interval
DIC	disseminated intravascular coagulation
GI	gastrointestinal
LR+	positive likelihood ratio
OR	odds ratio
PT	prothrombin time

and may play an important role in patient outcome.⁶ Ischemic or inflammatory GI problems and other disorders resulting in endotoxemia and severe systemic inflammatory response syndrome more commonly are associated with marked hypercoagulation and may cause DIC.^{2–4} A high percentage of horses with colitis (up to 36%) and ischemic lesions (up to 70%) have been reported to be in DIC, especially those disorders that have a poor prognosis, such as large colon volvulus.^{5–7} Additionally, approximately 40% of horses with ischemic and inflammatory GI diseases of poor prognosis were found to have massive fibrin deposition in several organs at necropsy consistent with microthrombosis and DIC.⁸ Thus, the severity of coagulopathies in horses with GI disorders appears to be related to the diagnosis.

Furthermore, the severity of coagulopathies in horses with GI problems also seems to be associated with poor outcome.^{3,5,7,9,10} In horses with colitis, the odds of survival in a horse with subclinical DIC were decreased 8-fold relative to horses without subclinical DIC.⁵ A study of hemostatic profiles in horses with large colon volvulus that underwent surgery concluded that there was an

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association between development of coagulopathy and outcome, confirming that horses with 4 of 6 abnormal coagulation tests were more likely to be euthanized, and those with 3 of 6 abnormal tests had a prolonged hospital stay.⁷ Moreover, increases in morbidity and mortality have been associated with alterations in the coagulation and fibrinolysis systems in horses with systemic disease.^{6,11} Other studies have demonstrated that rapid detection and treatment of subclinical coagulopathies in horses and humans decrease morbidity and mortality associated with development of fulminant DIC.^{a,10,12,13}

To make more valid prognostic assessments in colic cases, many authors have evaluated the usefulness of individual variables taken on admission and during hospitalization, including clinical and clinicopathological data.^{3,9-11,14-29} Several of these studies included hemostatic parameters and some have been found to be associated with outcome, although results among studies were variable and sometimes contradictory.^{a,3,9,11,20,21,23,29,30} Common tests to evaluate hemostasis in horses include platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), antithrombin activity (AT), fibrinogen, fibrin(ogen) degradation products, and D-Dimer concentrations.^{b,3,5-7,9-11,21,23,29} Newly available tests, such as mean platelet component (MPC) provided by current CBC analyzers, also have shown to be useful to detect platelet activation.³¹ Other hemostatic parameters typically are not available for evaluation of the clinical patient in a hospital setting.^{4,32}

Plasma D-Dimer concentration is considered the most sensitive test to diagnose thromboembolic disease and DIC in human medicine, and it also has been shown to be a good predictor of mortality.³³ In horses, D-Dimers have been found by our group to be a useful tool for detection of hypercoagulable states in horses with colic and septic foals during hospitalization.^{a,6,34,35} Furthermore, a marked increase in plasma D-Dimer concentration has been found to be associated with ischemic and inflammatory GI disorders, and especially in horses with peritonitis, when determined on presentation.^{a,c,35} Some studies also have advocated the usefulness of plasma D-Dimer concentration as a good prognostic aid in horses with acute GI problems and recommend its determination for routine screening of colic patients upon admission.^{c,21,35}

The objectives of this study were to evaluate (1) the relationship of admission plasma D-Dimer concentration with the likelihood of survival in horses with several types of colic, and (2) the association between admission plasma D-Dimer concentration and other coagulation profile data with diagnosis and outcome in different acute GI disorders.

Materials and Methods

Animals

Horses with colic admitted to the Equine Teaching Hospital of Barcelona between March 2004 and September 2008 were included in this prospective observational clinical study. Foals younger than 21 days, horses with concomitant inflammatory disorders not related to GI disease (eg, pneumonia) or liver disease, horses with 2 or

more GI disorders of similar severity (eg, ischemic and inflammatory disorders), and horses with chronic disorders were excluded from the study.

Horses were grouped according to diagnosis in 6 groups, including medical and surgical intestinal obstructions, GI inflammatory conditions, ischemic intestinal problems with or without intestinal resection, and peritonitis. Horses with ischemic lesions were divided into 2 groups because cases with more severe forms of ischemia and those with prolonged ischemia (> 6 hours) are associated with more severe coagulopathies that contribute to the death of the horse.³⁶

Diagnosis was based on clinical history, complete physical examination, and results of complementary diagnostic tests (CBC, plasma biochemistry, blood gas analysis, abdominal ultrasonography, and peritoneal fluid analysis). Findings of abdominal radiology, exploratory laparotomy, postmortem examination or some combination of these were used for this classification whenever they were performed. The medical obstructive group included all horses with nonstrangulating, noninflammatory disorders of the GI tract (such as impactions and large colon displacements) without signs of intestinal devitalization, which resolved with medical therapy (IV fluids, enteral fluids, laxatives), whereas the surgical obstructive group comprised those that needed surgery (mainly colon displacements). The enteritis group included horses with acute inflammation of small intestine (duodenojejunitis) or large intestine (colitis, typhlocolitis) or both diagnosed by compatible clinical signs (eg, gastric reflux, diarrhea, fever), clinicopathological data (eg, hypoalbuminemia, acid-base, and electrolyte imbalances) as well as results of complementary examinations (abdominal ultrasound, peritoneal fluid analysis). The ischemic group without intestinal resection included horses with strangulating GI lesions, such as intestinal volvulus or torsion, epiploic entrapment, inguinal hernias, and intussusceptions, where the affected intestinal portion was considered viable and subsequently had good recovery. Animals were included in the ischemic group with intestinal resection when any part of the affected bowel needed to be surgically removed. Finally, the peritonitis group included horses with gastric or intestinal ruptures, as well as septic peritonitis (presence of intra- and extracellular bacteria in peritoneal fluid) caused by bowel devitalization but without rupture, intra-abdominal abscesses and other causes.

Horses also were grouped according to outcome: survivors (horses that were discharged from the hospital), nonsurvivors (horses that died during hospitalization because of progressive worsening of disease or that were euthanized based on poor prognosis), and the financial restraint group (horses that did not receive the suitable treatment for financial or personal reasons). Horses that were either euthanized or left the hospital without medical consent because of economic restraints were not considered in outcome analysis.

Finally, a diagnosis of subclinical DIC was made when horses had clinicopathological evidence of DIC (≥ 3 abnormal parameters in the coagulation profile) based on criteria used in the equine literature.^{5,6,37} For the purposes of this study, horses with 1 or 2 abnormal coagulation parameters were considered to have activation of the coagulation system.

Additionally, a group of 30 healthy horses was used as controls, and included horses in regular training from a riding school near the Teaching Hospital, controlled blood donors, and healthy mares (> 1 week postpartum) that had accompanied their hospitalized sick foals.

Blood Sampling and Measured Parameters

On admission, blood samples were obtained by jugular venipuncture into 5 mL tubes containing 3.8% sodium citrate by using a vacutainer system.^d Immediately after, blood samples were centrifuged at $1,000 \times g$ for 15 minutes, and plasma was frozen at -80°C until analysis. Plasma D-Dimer concentration, PT, aPTT, and

AT were measured in duplicate for all samples, as reported in previous studies.^{a,c,6,34–36} Clotting times and AT were determined to complement plasma D-Dimer concentrations and to allow classification of coagulation dysfunction. Coagulation tests were considered abnormal when D-Dimer concentration was >1,000 ng/mL, PT > 15 seconds, aPTT > 65 seconds, and AT < 140%, based on previous studies and reference values in our laboratory.^{a,c,6,35} Other useful hemostatic variables (ie, platelet count, MPC) were not included in this study because after hours sampling prevented insurance of accurate determination in many cases. Also, fibrinogen concentration was not included because of its low sensitivity in assessment of coagulopathies in colic horses.^{5,6,37} Plasma D-Dimer concentration was determined using an immunoturbidimeter^c with commercial reagents and controls⁵; PT and aPTT were determined with a semiautomatic coagulometer^e with commercial reagents and controls^h; and AT was determined with a chromogenic kitⁱ in a semiautomatic analyzer.^j

Statistical Analysis

Results were expressed as frequencies and percentages for qualitative variables and median (interquartile range) for quantitative variables. Univariate inferential analysis was performed by Fisher's exact test for categorical data or the Mann-Whitney *U* test for quantitative variables. D-Dimer concentration was assessed by means of the positive likelihood ratio (LR+) estimation for dying/being euthanized, defined as sensitivity/(1–specificity), to obtain different cut-off values. In general, values of LR+ higher than 5 indicate a moderate increase in the likelihood of the disease, and values higher than 10 indicate a large and often conclusive likelihood. An interval validation of these cut-off values also was performed by means of logistic regression models. Several multivariate models were evaluated by the cut-off values obtained by LR+, adding 1 of the other 3 hemostatic parameters tested (PT, aPTT, or AT) in this statistical study. D-Dimer concentration was included as a fixed factor in all models for different cut-off values (2,000, 3,000, 4,000, 5,000, and 5,500 ng/mL) in order to assess the influence of the 4 hemostatic parameters as covariables. An estimation of the risk of death by number of abnormal coagulation parameters was performed by a univariate logistic regression model. *P* values ≤ 0.05 were considered statistically significant. With the aim of not inflating type I error rate in subtype diagnostic analysis, comparisons with the control group were only performed by global type (obstructions or ischemias) when nonsignificant relations were observed between subtype of diagnosis (medical versus surgical obstructions, and ischemias with versus without intestinal resection). Statistical analysis was performed by the SPSS 15.0 package.^k

Results

Of all horses admitted for colic during the study period, 493 horses met the inclusion criteria and were

included in the study. The sex distribution was 174 females (35.5%), 139 intact males (28.4%), and 177 geldings (36.1%). No sex information was available for 3 horses. The median age (interquartile range) of the population was 8 years (5–12 years). No age information was available for 9 horses. One hundred seventy-four horses (35.6%) were Andalusians, 122 horses (24.9%) were crossbred, 28 (5.7%) Arabians, 26 (5.3%) Warmbloods, 24 (4.9%) ponies, 14 (2.9%) and Draft breeds, and the remaining 97 horses were a mixture of different breeds. No breed information was available for 4 horses.

Diagnoses included 229 horses (46.5%) with medical obstructions, 74 (15%) surgical obstructions, 74 (15%) inflammatory problems, 33 (6.7%) ischemic lesions without intestinal resection, 51 (10.3%) ischemic lesions with intestinal resection, and 32 (6.5%) horses with peritonitis.

Of the 493 horses, 387 (78.5%) survived, 80 (16.2%) died or were euthanized because of poor prognosis, 23 (4.7%) were euthanized because of financial constraints, and 3 horses (0.6%) left the hospital against medical advice. The outcome distribution of horses with different diagnoses is shown in Table 1.

Hemostatic Profile in the Different Diagnostic Groups

Results of coagulation profile data by diagnostic group are presented in Tables 2 and 3. On admission, D-Dimer concentration was markedly and significantly (*P* < .001) higher in inflammatory diseases (enteritis and peritonitis groups) compared with controls. Despite being also increased in the ischemic group that needed resection, concentrations did not reach significant differences. Clotting times were mildly but significantly prolonged in all colic groups, and AT showed mild differences in both obstructive groups when compared with controls. Comparing horses with medical versus surgical obstructive problems, no significant differences were found between them in any of the hemostatic parameters determined.

Despite that fact, when specific cut-off values were compared, only 0.9% of medical obstructive cases had plasma D-Dimer concentrations on admission >5,000 ng/mL, compared with 5.4% in the surgical group (*P* = .04). Comparing horses with ischemic disorders, a tendency toward significance (*P* < .06) was seen for higher plasma D-Dimer concentration on admission in ischemic cases that needed intestinal resection compared with those in which this procedure was not

Table 1. Outcome distribution of horses with different diagnoses.

	Survivors (<i>n</i> = 387)	Nonsurvivors (<i>n</i> = 80)	Financial Restraints (<i>n</i> = 26)
Medical obstructions	211 (54.5%)	2 (2.5%)	16 (61.5%)
Surgical obstructions	67 (17.3%)	7 (8.8%)	0 (0.0%)
Ischemia without intestinal resection	25 (6.5%)	4 (5.0%)	4 (15.4%)
Ischemia with intestinal resection	23 (5.9%)	25 (31.3%)	3 (11.5%)
Enteritis	55 (14.2%)	17 (21.3%)	2 (7.7%)
Peritonitis	6 (1.6%)	25 (31.3%)	1 (3.9%)
	100%	100%	100%

Numbers correspond to absolute number of horses regarding the outcome and percentages to the relative proportion in the same outcome group and within the different diagnostic groups.

Table 2. Coagulation profile results obtained on presentation among the different diagnostic groups.

	Controls (n = 30)	Medical Obstructions (n = 229)	Surgical Obstructions (n = 74)	Ischemic without Resection (n = 33)	Ischemic with Resection (n = 51)	Enteritis (n = 74)	Peritonitis (n = 32)
D-Dimer concentration (ng/mL)	695.0 [586; 742]	308.0* [133; 923]	419.5* [168.5; 919.5]	521.0 [135; 1,212]	1,241.8 [360; 2,687]	1,048.3* [435; 2,711]	4,204.0* [1,652.5; 5,923]
PT (seconds)	11.05 [10.85; 11.4]	12.1* [11.3; 13.8]	12.3* [11.2; 14]	12.7* [11.6; 13.8]	12.9* [11.6; 14.6]	13.6* [12.1; 15.6]	13.9* [13.0; 15.1]
aPTT (seconds)	39.0 [36.9; 41.2]	50.2* [44.7; 59.7]	50.9* [44.8; 60.1]	49.3* [46.0; 58.0]	51.3* [44.2; 61.6]	55.3* [49.5; 64.1]	54.7* [46.0; 61.5]
AT (%)	188.2 [172; 211]	214* [196; 234]	220* [198; 244]	208 [181; 230]	201 [177; 220]	192 [166; 214]	164 [144; 204]

Results are expressed as median [interquartile range: P25th; P75th].
*Statistically significant ($P < .001$) when compared with the control group.

necessary (Table 3). Furthermore, when specific cut-off values were compared, most (90.3%) ischemic cases without intestinal resection had plasma D-Dimer concentrations on admission $\leq 2,000$ ng/mL, compared with 66.7% in the resection group ($P = .017$). Differences in other parameters were not significant.

The distribution of horses by number of altered parameters in the coagulation profile by diagnostic group is shown in Table 4. Horses with enteritis, ischemic lesions that needed intestinal resection, and peritonitis had a higher number of coagulopathies, and clinicopathological DIC already was diagnosed on admission in horses with enteritis and peritonitis (10.8 and 9.4%, respectively).

Hemostatic Profile in the Different Outcome Groups

Results of coagulation profile data by outcome groups are presented in Table 5. Plasma D-Dimer concentration

was marked and significantly ($P < .001$) higher in dead/euthanized horses than in discharged horses. Furthermore, 74.2% of survivors had plasma D-Dimer concentrations within the normal range ($\leq 1,000$ ng/mL) compared with 35% of nonsurvivors (odds ratio [OR], 5.33; 95% confidence interval [CI], 3.19–8.9, $P < .001$). PT also was significantly ($P < .001$) prolonged in nonsurvivors, and the percentage of horses with PT > 15 seconds also was higher in nonsurvivors (OR, 1.9; 95% CI, 1.1–3.5, $P = .03$). Antithrombin activity was significantly ($P < .001$) lower in dead/euthanized horses than in discharged ones, and significantly more animals with poor prognosis had AT $< 140\%$ (OR, 14.7; 95% CI, 5.5–39.1, $P < .001$). Differences were not significant for aPTT.

Regarding the type of coagulopathy, there were significantly ($P = .009$) more horses with clinicopathological DIC (≥ 3 coagulopathies) upon presentation in nonsurvivors (11.3%) than in survivors (3.6%) (Table 6).

Table 3. Distribution of coagulation profile data for different cut-off values (normal or abnormal values) in the main diagnostic groups.

Cut-off Values	Controls (n = 30)	Medical Obstructions (n = 229)	Surgical Obstructions (n = 74)	Ischemic without Resection (n = 33)	Ischemic with Resection (n = 51)	Enteritis (n = 74)	Peritonitis (n = 32)
D-Dimer concentration (ng/mL)							
< 1,000	29 (96.7%)	181 (79%)*	57 (77%)*	23 (69.7%)*	25 (49%)*	38 (51.4%)*	6 (18.7%)*
> 1,000	1 (3.3%)	48 (21%)*	17 (23%)*	10 (30.3%)*	26 (51%)*	36 (48.6%)*	26 (81.3%)*
> 2,000	0 (0%)	22 (10.3%)	10 (13.5%)	3 (9.7%)#	16 (33.3%)*,#	26 (36.1%)*	20 (66.7%)*
> 3,000	0 (0%)	10 (4.7%)	7 (9.5%)	3 (9.7%)	10 (20.8%)*	12 (16.7%)*	17 (56.7%)*
> 4,000	0 (0%)	7 (3.3%)	6 (8.1%)	3 (9.7%)	7 (14.6%)*	7 (9.7%)	16 (53.3%)*
> 5,000	0 (0%)	2 (0.9%)#	4 (5.4%)#	1 (3.2%)	2 (4.2%)	3 (4.2%)	9 (30%)*
PT (seconds)							
< 15	30 (100%)	198 (86.5%)*	63 (85.1%)*	29 (87.9%)	44 (86.3%)*	56 (75.7%)*	24 (75%)*
> 15	0 (0%)	31 (13.5%)*	11 (14.9%)*	4 (12.1%)	7 (13.7%)*	18 (24.3%)*	8 (25%)*
APTT (seconds)							
< 65	30 (100%)	197 (86%)*	64 (86.5%)	29 (87.9%)	41 (80.4%)*	59 (79.7%)*	26 (81.3%)*
> 65	0 (0%)	32 (14%)*	10 (13.5%)	4 (12.1%)	10 (19.6%)*	15 (20.3%)*	6 (18.8%)*
AT (%)							
> 140	30 (100%)	226 (98.7%)	71 (95.9%)	33 (100%)	48 (94.1%)	66 (89.2%)	27 (84.4%)
< 140	0 (0%)	3 (1.3%)	3 (4.1%)	0 (0%)	3 (5.9%)	8 (10.8%)	5 (15.6%)

Results show the number of horses and the percentage in regard to the diagnosis group.
*Statistically significant when compared with controls.
#Statistically significant when compared between diagnostic subgroups (for the obstructive and the ischemic groups).

Table 4. Distribution of horses by number of coagulopathies detected on presentation in the different diagnostic groups.

Number of Abnormal Hemostatic Parameters (out of 4)	Medical	Surgical	Ischemic without	Ischemic with	Enteritis	Peritonitis
	Obstructions (n = 229)	Obstructions (n = 74)	Resection (n = 33)	Resection (n = 51)		
Normal profile	157 (68.3%)	44 (59.5%)	20 (60.6%)	18 (35.3%)	27 (36.5%)	4 (12.5%)
Activated coagulation system (1 or 2 abnormal parameters)	61 (26.6%)	29 (39.2%)	12 (36.4%)	31 (60.8%)	39 (52.7%)	25 (78.1%)
Subclinical DIC (≥ 3 abnormal parameters)	11 (4.8%)	1 (1.4%)	1 (3%)	2 (3.9%)	8 (10.8%)	3 (9.4%)

The numbers correspond to absolute number of horses and percentages to the relative proportion in the diagnostic groups.

Using the univariate logistic regression model, horses with 1 or 2 coagulopathies on presentation were more likely to die (OR, 5.3; 95% CI, 3.0–9.4, $P < .001$). When horses had clinicopathological evidence of DIC (3 or 4 of 4 abnormal parameters) on presentation, the OR value for mortality increased to 8.6 (95% CI, 3.3–22.5, $P < .001$).

Results of the Positive Likelihood Ratios and Logistic Regression Models

D-Dimer concentrations of approximately 4,000 ng/mL showed a LR+ value of 5.9 for dying/being euthanized. No optimal interval of results to suggest potentially useful cut-off values was identified for the remaining parameters (results not shown). The logistic regression model including plasma D-Dimer concentration (crude analysis) resulted in an OR of 8.78 (95% CI, 4.52–17.05, $P < .001$) for nonsurvival when values were approximately 4,000 ng/mL. Adjusted OR for D-Dimer concentration ($> 4,000$ ng/mL) by mean PT (> 15 seconds), aPTT (> 65 seconds), or AT ($< 140\%$) did not show substantial changes from crude OR evaluation of D-Dimer analysis. Only AT values $< 140\%$ maintained a significant effect in the presence of the D-Dimer factor.

Discussion

The most common coagulopathy in horses with colic is a hypercoagulable state that can progress to DIC. The intensity of this coagulopathy will depend on the severity and duration of the GI lesion, with ischemic and inflammatory problems and peritonitis being most frequently affected by coagulopathies.^{6,35} Furthermore, the severity of coagulopathies in horses with GI problems also seems to be associated with poor outcome.^{3,5,7,9} In the present study, plasma D-Dimer concentration was related to diagnosis and prognosis, which could help to differentiate horses with enteritis and peritonitis from other diagnoses, and especially to detect horses with poor outcome. Furthermore, D-Dimer concentration was the most sensitive coagulation parameter for these diagnostic and prognostic purposes of the parameters tested in the present study.

Regarding diagnosis, results of this study indicate that patients with enteritis or peritonitis had significantly higher D-Dimer concentration when tested on presentation, AT was significantly lower and alterations in hemostatic parameters were more severe. These 2 diagnostic groups also included a higher percentage of horses with subclinical DIC on admission. In the literature, inflammatory and ischemic conditions are the diagnoses most often associated with severe coagulopathies,

Table 5. Results of the coagulation profile in the main outcome groups (survivors and nonsurvivors).

	Survivors (n = 387)	Nonsurvivors (n = 80)	Cut-off Values	OR (95% CI)		
				Survivors	Nonsurvivors	
D-Dimer concentration (ng/mL)	383 [143; 1,112]	2,304 [733; 4,489]*	$\leq 1,000$	74.2%	35.0%	5.33 (3.19–8.9)
			$> 1,000$	25.8%	65.0%	$P < .001$
			$\leq 4,000$	94.8%	67.5%	8.78 (4.52–17.05)
			$> 4,000$	5.2%	32.5%	$P < .001$
PT (seconds)	12.3 [11.3; 13.9]	13.8* [12.0; 15.1]	< 15	86%	76.3%	1.9 (1.1–3.5)
			> 15	14%	23.8%	$P = .03$
APTT (seconds)	50.7 [45.3; 60.7]	54.7 [44.4; 61.0]	< 65	85.5%	80%	1.5 (0.8–2.7)
			> 65	14.5%	20%	$P = .21$
AT (%)	212 [190; 234]	192* [144; 212]	> 140	98.4%	81.3%	14.7 (5.5–39.1)
			< 140	1.6%	18.8%	$P < .001$

Results are expressed as median [interquartile range: P25th; P75th]. Distribution (percentage) of these coagulation data for different cut-off values in the main outcome groups is shown, as well as the OR for the corresponding cut-off value.

*Statistically significant ($P < .001$) when compared with survivors for quantitative results.

Table 6. Distribution of horses by number of coagulopathies detected on presentation in the different outcome groups.

Number of Abnormal Hemostatic Parameters on Admission (out of 4)	Survivors (n = 387)	Nonsurvivors (n = 80)	OR (95% CI)	P-Value
Normal profile	240 (62.0%)	18 (22.5%)	Baseline	
Coagulation system activated (1 or 2 abnormal parameters)	133 (34.4%)	53 (66.3%)	5.3 (3.0–9.4)	< .001
Subclinical DIC (≥ 3 abnormal parameters)	14 (3.6%)	9 (11.3%)	8.6 (3.3–22.5)	< .001

The numbers correspond to absolute number of horses and percentages to the relative proportion in the outcome groups.

especially when diagnosed during hospitalization.^{7,8,10,37} In the present study, however, severe coagulopathies were detected upon presentation. In horses with colic and in septic foals, the inflammatory response, and consequently activation of the coagulation system, can be more severe some hours after presentation,^{a,c,7,34,36} which could explain why abnormalities of the coagulation profile detected on admission usually are milder. In addition, in the present study D-Dimer concentration in ischemic disorders taken as a whole was not significantly higher on admission, although a tendency toward significance ($P = .06$) was present when comparing horses with or without resection, with D-Dimer concentration higher in horses that needed enterectomy. Previous studies also suggest that D-Dimer concentrations in ischemic colicky horses tend to increase early after admission.^{a,c} Thus, the lack of significance in the group that needed intestinal resection could be associated with the fact that samples were taken too early in the ischemic process.

Regarding diagnosis, when specific concentrations of D-Dimers were analyzed, one third of ischemic horses with intestinal resection had plasma D-Dimer concentrations on admission of $> 2,000$ ng/mL, compared with just 10% of horses in which intestinal resection was not necessary. This additional information can help the clinician determine prognosis and treatment when confronted with such types of colic. In contrast, in obstructive colics there were significantly more horses with plasma D-Dimer concentrations on admission $> 5,000$ ng/mL in the surgical group compared with the medical group. Most horses in both groups (94.6 and 99.1%, respectively), however, had lower concentrations, which limits the applicability of this information in a clinical setting. Clotting times also showed significant differences when compared with controls, but not between medical and surgical obstructions or ischemic problems with or without resection. Finally, AT did not show significant differences for the cut-off values applied.

Enteritis and peritonitis were the diagnoses with the higher prevalence of subclinical DIC upon admission and, together with ischemic lesions (especially those requiring resection), had the highest number of patients with activation of the coagulation system. These findings are in accordance with previous studies.^{6,7,35} Thus, these severe inflammatory conditions seem to be linked to severe coagulopathies, which are already detected on

admission when using sensitive tests. Other diagnoses (such as ischemic disorders) would need to be retested after presentation or by use of a larger coagulation profile to better assess the associated coagulopathy.

In general, diagnoses corresponding to more severe disorders, most commonly associated with nonsurvival, also had the highest percentage of horses with the highest D-Dimer concentrations.

Several studies have attempted to elucidate the role of coagulation abnormalities with fatality during colic.^{a,c,3,9,11,20,21,23,29} One of the objectives of this study was to evaluate the usefulness of admission results of several hemostatic parameters to predict the likelihood of survival. In this study, plasma D-Dimer concentrations on presentation were significantly higher, PT significantly prolonged and AT significantly lower in nonsurvivors than in survivors. However, while most nonsurvivors had markedly increased D-Dimer concentrations ($> 1,000$ ng/mL), a lower percentage of nonsurvivors had PT and AT results above the reference range (> 15 seconds and $< 140\%$, respectively). Thus, according to these results, D-Dimer concentration seems to be more associated with prognosis than the remaining coagulation variables tested. Other studies in horses with colic also found higher D-Dimer concentrations in nonsurvivors,²¹ as well as prolonged PT and decreased AT, thus confirming these results.^{5,5,7,9,11,29}

Horses with plasma D-Dimer concentrations on admission $> 1,000$ ng/mL and $> 4,000$ ng/mL were found to be 5.33 and 8.78 times more likely to die, respectively. This information can be useful to the clinician to predict outcome in a case of colic. Furthermore, horses with AT results below 140% had 14.7 times more probability of nonsurvival. Nevertheless, results of AT are rarely below this level, even in severe colics, and so this information has little clinical value. In contrast, PT did not show a good predictive value for nonsurvival (OR = 1.9). Thus, following our results, D-Dimer concentration could have better prognostic value than the other coagulation parameters tested.

When the coagulopathies were assessed for outcome, there were significantly more horses with subclinical DIC (≥ 3 altered parameters) in the group of nonsurvivors. Furthermore, horses had 8.6 times more probability to die if they were in subclinical DIC, and 5.3 times more probability if they only had 1 or 2 abnormal coagulation parameters. This finding is not surprising because the

literature reports worse outcomes in horses with GI problems associated with a high number of coagulopathies and DIC.^{3,7,9,10} Postmortem studies also found higher fibrin deposition scores in different organs of horses with colic diagnoses more commonly associated with DIC.^{8,38} Nevertheless, previous results complementary with this study confirm that alterations of the coagulation profile in horses that survived tend to normalize during hospitalization regardless of the diagnosis.^a

Our results have shown that changes in hemostasis are frequent in severe GI disorders of horses. D-Dimer concentration determined on presentation has a clear relationship with outcome. Results of the LR+ in this population of colic horses confirmed that plasma D-Dimer concentration is a sensitive parameter, with concentrations on admission >4,000 ng/mL indicating a moderate to marked increase in the likelihood of dying or being euthanized. This analysis is very similar to ROC curves and area under curve calculations and can be used for equivalent purposes to determine the diagnostic and prognostic utility of a test in different diseases. The LR+ for death used in the present study has the advantage of offering the same optimal cut-off point as does graphical evaluation of the ROC curve, but also considers the goodness of the cut-off point. Furthermore, the logistic regression models combining AT and plasma D-Dimer concentration showed the best LR+ with D-Dimer concentrations to be approximately 4,000 ng/mL. Therefore, based on this study, if a D-Dimer cut-off concentration of 4,000 ng/mL is used on admission, the likelihood ratio of death independently of diagnosis is approximately 6 : 1 (ie, 6 horses with D-Dimer concentration >4,000 ng/mL are likely to die for each horse with D-Dimer concentration >4,000 ng/mL that survives). In contrast, other studies have not found that D-Dimer concentrations provide any additional information in explaining outcome when tested on admission, but they used less accurate methods in a smaller population of horses.^{7,20}

One possible limitation of this study is that the number of hemostatic parameters determined was low, and did not include platelet count or other commonly tested parameters characterized by their low sensitivity. Nevertheless, the parameters determined in this study are those currently used in humans and dogs to evaluate coagulopathies and constitute the basis of DIC scoring systems in these species or are used to increase diagnostic sensitivity.³⁹⁻⁴¹ With such a low number of parameters tested, identification of coagulopathies and diagnosis of DIC could be limited. However, the percentage of coagulopathies and diagnosis of DIC finally detected in the present study was similar to what has been reported in other studies in which more hemostatic parameters were tested.

In conclusion, the present study confirmed that when a simple hemostatic profile that includes D-Dimer concentration was assessed on admission in horses with colic, the most severe coagulopathies were observed in horses with the most severe forms of GI disorders (eg, inflammatory conditions, ischemic intestinal problems that needed intestinal resection, peritonitis) and in nonsurvi-

vors. Furthermore, the diagnoses with higher percentage of nonsurvival also had more horses with high concentrations of D-Dimers. Moreover, this study also supports the usefulness of D-Dimer concentration tested on admission to predict outcome in horses with GI disorders, especially when >4,000 ng/mL. Additional studies are warranted using this cut-off value in a different population of horses to confirm its possible diagnostic and prognostic value.

Footnotes

^a Cesarini C, Monreal L, Armengou L, et al. Hemostatic follow up of horses with medical and surgical colic. *J Vet Intern Med* 2009;23:434 (abstract)

^b Byars TD, Thorpe PE. Prognostic significance of fibrin/fibrinogen degradation products in the surgical equine abdominal crisis. Proceedings of the 1st International Equine Colic Research Symposium, Athens, GA; 1982:28-30 (abstract)

^c Armengou L, Monreal L, Segura D, et al. Plasma D-dimers in horses with colic. Proceedings of the 8th International Equine Colic Research Symposium, Quebec, Canada, 2005:2-5; (abstract)

^d Becton Dickinson Vacutainer Systems, Rutherford, NJ

^e Miniquant-1, Biopool, Trinity Biotech, Wicklow, Ireland

^f Miniquant, Biopool, Trinity Biotech

^g Stago ST4, Stago Diagnostics, Asnières-Sur-Seine, France

^h Boehringer Mannheim, Mannheim, Germany

ⁱ STA Antithrombin III, Stago Diagnostics

^j Cobas-Bio, Roche, Basel, Switzerland

^k SPSS, Chicago, IL

References

- Dallap BL. Coagulopathy in the equine critical care patient. *Vet Clin North Am Equine Pract* 2004;20:231-251.
- Monreal L, Cesarini C. Coagulopathies in horses with colic. *Vet Clin North Am Equine Pract* 2009;25:247-258.
- Prasse KW, Topper MJ, Moore JN, et al. Analysis of hemostasis in horses with colic. *J Am Vet Med Assoc* 1993;203:685-693.
- Dallap BL, Epstein K. Coagulopathy of the critically ill equine patient. *J Vet Emerg Crit Care* 2009;19:53-65.
- Dolente BA, Wilkins PA, Boston RC. Clinicopathologic evidence of disseminated intravascular coagulation in horses with acute colitis. *J Am Vet Med Assoc* 2002;220:1034-1038.
- Dallap BL, Dolente B, Boston R. Coagulation profiles in 27 horses with large colon volvulus. *J Vet Emerg Crit Care* 2003;13:215-225.
- Monreal L, Anglés A, Espada Y, et al. Hypercoagulation and hypofibrinolysis in horses with colic and DIC. *Equine Vet J* 2000;32(Suppl):19-25.
- Cotovio M, Monreal L, Navarro M, et al. Detection of fibrin deposits in tissues from horses with severe gastrointestinal disorders. *J Vet Intern Med* 2007;21:308-313.
- Johnstone IB, Crane S. Haemostatic abnormalities in horses with colic—their prognostic value. *Equine Vet J* 1986;18:271-274.
- Collatos C, Barton MH, Prasse KW, et al. Intravascular and peritoneal coagulation and fibrinolysis in horses with acute gastrointestinal tract diseases. *J Am Vet Med Assoc* 1995;207:465-470.
- Wada H, Wakita Y, Nakase T, et al. Outcome of disseminated intravascular coagulation in relation to the score when treatment was begun. *Thromb Haemost* 1995;74:848-852.

12. Wada H, Sakuragawa N, Mori Y, et al. Haemostatic molecular markers before the onset of disseminated intravascular coagulation. *Am J Hematol* 1999;60:273–278.
13. Orsini JA, Elser AH, Galligan DT, et al. Prognostic index for acute abdominal crisis (colic) in horses. *Am J Vet Res* 1988;49:1969–1971.
14. Furr MO, Lessard P, White NA. Development of a colic severity score for predicting the outcome of equine colic. *Vet Surg* 1995;24:97–101.
15. Parry BW, Anderson GA, Gay CC. Prognosis in equine colic: A study of individual variables used in case assessment. *Equine Vet J* 1983;15:337–344.
16. Puotunen-Reinert A. Study of variables commonly used in examination of equine colic cases to assess prognostic value. *Equine Vet J* 1986;18:275–277.
17. Pascoe PF, Ducharme NG, Ducharme GR, et al. A computer-derived protocol using recursive partitioning to aid in estimating prognosis of horses with abdominal pain in referral hospitals. *Can J Vet Res* 1990;54:373–378.
18. Reeves MJ, Curtis CR, Salman MD, et al. Prognosis in equine colic patients using multivariable analysis. *Can J Vet Res* 1989;53:87–94.
19. Ihler CF, Venger JL, Skjerve E. Evaluation of clinical and laboratory variables as prognostic indicators in hospitalised gastrointestinal colic horses. *Acta Vet Scand* 2004;45:109–118.
20. Sandholm M, Vidovic A, Puotunen-Reinert A, et al. D-dimer improves the prognostic value of combined clinical and laboratory data in equine gastrointestinal colic. *Acta Vet Scand* 1995;36:255–272.
21. Southwood LL, Dolente BA, Lindborg S, et al. Short-term outcome of equine emergency admissions at a university referral hospital. *Equine Vet J* 2009;41:459–464.
22. Darien BJ, Potempa J, Moore JN, et al. Antithrombin III activity in horses with colic: An analysis of 46 cases. *Equine Vet J* 1991;23:211–214.
23. Collatos C, Barton M, Moore J. Fibrinolytic activity in plasma from horses with gastrointestinal disease: Changes associated with diagnosis, surgery, and outcome. *J Vet Intern Med* 1995;9:18–23.
24. Thoenner MB, Ersbøll AK, Hesselholt M. Prognostic indicators in a Danish hospital-based population of colic horses. *Equine Vet J* 2000;32(Suppl):11–18.
25. Dabareiner RM, White NA. Large colon impaction in horses: 147 cases (1985–1991). *J Am Vet Med Assoc* 1995;206:679–685.
26. Phillips TJ, Walmsley JP. Retrospective analysis of the results of 151 exploratory laparotomies in horses with gastrointestinal disease. *Equine Vet J* 1993;25:427–431.
27. Hawkins JF, Bowman KF, Roberts MC, et al. Peritonitis in horses: 67 cases (1985–1990). *J Am Vet Med Assoc* 1993;203:284–288.
28. Henderson IS, Mair TS, Keen JA, et al. Study of the short- and long-term outcomes of 65 horses with peritonitis. *Vet Rec* 2008;163:293–297.
29. Holland M, Kelly A, Snyder J, et al. Antithrombin III activity in horses with large colon torsion. *Am J Vet Res* 1986;47:897–900.
30. Segura D, Monreal L, Armengou L, et al. Mean platelet component as an indicator of platelet activation in foals and adult horses. *J Vet Intern Med* 2007;21:1076–1082.
31. Monreal L. D-dimer as a new test for the diagnosis of DIC and thromboembolic disease. *J Vet Intern Med* 2003;17:757–759.
32. Armengou L, Monreal L, Tarancón I, et al. Plasma D-dimer concentration in sick newborn foals. *J Vet Intern Med* 2008;22:411–417.
33. Delgado MA, Monreal L, Armengou L, et al. Peritoneal D-dimer concentration for assessing peritoneal fibrinolytic activity in horses with colic. *J Vet Intern Med* 2009;23:882–889.
34. Pablo LS, Purohit RC, Teer PA, et al. Disseminated intravascular coagulation in experimental intestinal strangulation obstruction in ponies. *Am J Vet Res* 1983;44:2115–2122.
35. Welch RD, Watkins JP, Taylor TS, et al. Disseminated intravascular coagulation associated with colic in 23 horses (1984–1989). *J Vet Intern Med* 1992;6:29–35.
36. Monreal L, Anglés AM, Monreal M, et al. Changes in haemostasis in endurance horses: Detection by highly sensitive ELISA tests. *Equine Vet J* 1995;18(Suppl):120–123.
37. Cotovio M, Monreal L, Navarro M, et al. Detection of fibrin deposits in horse tissues by immunohistochemistry. *J Vet Intern Med* 2007;21:1083–1089.
38. Wiinberg B, Jensen AL, Johansson PI, et al. Development of a model based scoring system for diagnosis of canine disseminated intravascular coagulation with independent assessment of sensitivity and specificity. *Vet J* 2009;6 (E-pub).
39. Bakhtiari K, Meijers JC, de Jonge E, et al. Prospective validation of the international society of thrombosis and haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med* 2004;32:2416–2421.
40. Toh CH, Downey C. Performance and prognostic importance of a new clinical and laboratory scoring system for identifying non-overt disseminated intravascular coagulation. *Blood Coagul Fibrinol* 2005;16:69–74.
41. Toh CH, Hoots WK. The scoring system of the scientific and standardization committee on disseminated intravascular coagulation of the International Society on Thrombosis and Haemostasis: A 5-year overview. *J Thromb Haemost* 2007;5:604–606.