

Evaluating continuous blood coagulopathy in assessing the severity of acute colitis in Thoroughbred racehorses

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Although severe blood coagulopathy in horses with acute colitis causes multiple organ failure, which may be fatal, few studies have focused on the correlation between the fluctuations of coagulation parameters and severity of colitis. In this study, we evaluated the fluctuations of coagulation parameters in 14 Thoroughbred racehorses with acute colitis for 5 days from the day of hospitalization and compared them between 5 survivors and 9 non-survivors. Noteworthy features in the non-survivors were that antithrombin activity and fibrin degradation products continuously decreased and increased, respectively, for 4 days or more and that thrombin-antithrombin complexes increased in the last 2 days before death. Thus, these parameters should be continuously monitored to observe these fluctuations in assessing the severity of acute colitis.

Key words: antithrombin activity, colitis, Thoroughbred, thrombin-antithrombin complex

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Blood coagulopathy in horses is commonly caused by gastrointestinal disorders, along with other serious pathologic conditions such as severe infection, trauma, surgery, and neoplasia [15]. Conventionally, the representative coagulation parameter changes observed with the gastrointestinal diseases have been prolongation in clotting time (activated partial thromboplastin time and prothrombin time), decrease in plasma coagulation inhibitors (antithrombin and protein C), and increase in fibrin/fibrinogen degradation products [8, 10, 17, 24]. In addition, thrombin-antithrombin complex (TAT), which forms when thrombin is bound by antithrombin, has come into use as a molecular marker indicative of a hypercoagulative state, and an increase in TAT has been identified in horses with gastrointestinal disorders [6, 14, 23]. These hemostatic abnormalities are compatible with a consumption coagulopathy and disseminated intravascular coagulation (DIC) accompanying systematic inflammation and endotoxemia

[7, 15, 16]. The primary pathogenesis of DIC generally involves persistent and systematic coagulation activation, and the degree of fibrinolytic activation is dependent on the type of underlying disease [1]. Despite being a biophylactic mechanism of the body, severe DIC may cause multiple organ failure through ischemic circulation disorders, which may be fatal [5, 21].

In recent years, the number of cases of acute colitis at the Japan Racing Association (JRA) Ritto Training Center (RTC) has been increasing, with a very high mortality rate of 31.6% (unpublished data). Previously reported causes of acute colitis include stress factors such as shipping and surgical operations, as well as a shift in the intestinal microbial flora following administration of antibiotics [3]. Diarrhea and pyrexia are characteristic symptoms of acute colitis, and vast areas of necrotic mucous membrane in the colon and cecum were the primary findings of the cases on necropsy. Among a certain number of past reports on coagulopathy accompanying colitis, Dolente *et al.* reported that the occurrence of severe blood coagulopathy could be associated with poor prognosis in acute colitis cases [8]. However, most of the reports in the past have examined the correlation between the prognosis and the parameters related to coagulopathy focusing on a single point in time (e.g., the day of diagnosis as DIC) [10, 14, 16, 24]. In clinical practice, monitoring of parameters is often performed

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continuously from the day of diagnosis as acute colitis, and there is still much to be investigated concerning the fluctuation of these values, which may offer valuable insight that could be applied to clinical use. The purpose of the present study was to evaluate not only the most remarkable aberrations suggestive of DIC but also the fluctuations of blood coagulation parameters in Thoroughbred racehorses with acute colitis, as well as their relevance to clinical outcome. We hypothesized that there would be a correlation between the progression of coagulation disorders and poor outcome and that some parameters would be useful in assessing the severity of acute colitis.

Thoroughbred racehorses that were in full training for racing at the JRA RTC and were diagnosed with acute colitis between June 2014 and October 2015 were included in the study. For the diagnosis of acute colitis, in addition to pyrexia ($>38.5^{\circ}\text{C}$) with watery diarrhea, tachycardia (>60 bpm), prolongation of capillary refilling time (>2.0 sec), tachypnea (>30 bpm), leukopenia ($<5,000$ cell/ μl), and elevation of hematocrit ($>55\%$) were taken into account. Twenty clinically healthy Thoroughbred racehorses in full training for racing at the JRA RTC in November 2014 were assigned to the control group. Horses presenting with acute colitis were classified into 2 groups according to clinical outcome. The survivor group was defined as horses that recovered or those that survived the episode of diarrhea and pyrexia but were eventually euthanized. The non-survivor group was defined as horses that died from aggravation of the episode of diarrhea and pyrexia. Blood samples were collected for 5 consecutive days, except in the horses that died within 5 days, starting from the day the horse was hospitalized for isolation for infection control (defined as Day 1). For blood collection, 3.2% sodium citrate-containing tubes (5 mL; Venoject II, TERUMO, Tokyo, Japan) were used. Adjustments were made to set the ratio of sodium citrate to blood to 1:9. The tubes were immediately centrifuged at 3,000 rpm for 10 min after blood collection, and then the separated plasma samples were stored at -80°C in a freezer. Samples were sent to a laboratory (FUJIFILM Monolith Co., Ltd., Tokyo, Japan) and analyzed within 1 month of collection [18]. Samples were collected only when permitted by each horse's trainer. The following 6 parameters were selected as indicators to evaluate coagulation properties in reference to previous reports [6, 8, 14, 24]: activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB), antithrombin (AT) activity, fibrin degradation products (FDP), and thrombin and antithrombin complex (TAT). APTT, PT, and FIB were determined by light scattering method (CA-650, Sysmex Corp., Kobe, Japan), and AT activity was determined by chromogenic assay, in which plasma was incubated in the presence of bovine thrombin and excess heparin (BM6050, JEOL Ltd., Tokyo, Japan).

The concentration of FDP was determined using a latex turbidimetric immunoassay (BM6050, JEOL Ltd.), and TAT was determined using enzyme immunoassay (PATHFAST, LSI Medience Corp., Tokyo, Japan). All samples were collected and handled according to published recommendations [18] and the laboratory's instructions.

Values are shown as the mean \pm standard deviation (SD) when applicable. The most remarkable aberrations suggestive of DIC [15, 22] in the groups (control vs. survivors vs. non-survivors) during the measurement period were analyzed by one-way analysis of variance (ANOVA), with an additional Tukey-Kramer *post hoc* test to compare means among groups. For horses whose samples were obtainable for 4 days or more, statistical significance between the survivor group and the non-survivor group in the same time point was determined using the Welch's *t*-test. Fisher's exact test was performed to study the correlation between the coagulation profiles and prognosis. The results of coagulation profiles included the following: 1) whether the most remarkable aberrations throughout the measurement period were within the reference range (defined as the mean of the control groups ± 2 standard deviations) and 2) continuous changes (defined as a change in which the measured value either increased or decreased continuously compared with the previous day for 2, 3, or 4 consecutive measurement days starting from Day 1) in APTT, PT, FIB, AT activity, and FDP. Statistical analyses were performed with EZR (1.00, Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (version 2.13.0, the R Foundation for Statistical Computing, Vienna, Austria) [11]. *P* values <0.05 were considered statistically significant.

The values of parameters in control groups are summarized in Table 1. TAT was below detectable limits (<1.0 ng/mL) in all 20 horses. The reference ranges of the values for Thoroughbred racehorses at the JRA RTC were defined as the mean of the control group ± 2 standard deviations. Within the study period, 14 horses met the inclusion criteria (Table 2). The median age was 3 (range, 2–7) years, and there were 9 horses in the non-survivor group and 5 horses in the survivor group. All horses received continuous intravenous fluid therapy (lactated Ringer's solution and 6% hydroxyethyl solution), intravenous antiendotoxin therapy (low-dose flunixin meglumine and polymyxin B), and oral probiotics therapy, and some received systemic antibiotic therapy (oral administration of metronidazole or intravenous administration of cephalothin) as necessary. In the non-survivor group, the median number of survival days was 4 (range, 2–7). In the survivor group, all horses survived the episode of diarrhea and pyrexia and completed the treatment for acute colitis. Horses 11 and 13 were eventually euthanized due to laminitis (Day 80) and cecal impaction

(Day 14), as both were considered unlikely to recovery.

Parameters presenting with the most remarkable aberrations suggestive of DIC (prolongation of APTT and PT, decrease of FIB and AT activity, and increase of FDP and TAT) during the measurement period were compared between groups (Fig. 1). APTT and PT were both significantly prolonged in the survivor and non-survivor groups compared with the control group (105.2 ± 7.5 and 102.3 ± 22.0 sec for APTT and 12.5 ± 1.2 and 13.2 ± 2.8 sec for PT in the survivor and non-survivor groups, respectively), while a significant difference was not observed between the survivor and non-survivor groups. FIB showed no significant difference between the 3 groups (126.2 ± 19.7 and 135.7 ± 53.7 mg/dl in the survivor and non-survivor groups, respectively). There was a significant decrease in AT activity in both the survivor group and the non-survivor group compared with the control group ($203 \pm 53\%$ and $122 \pm 43\%$ in the survivor and non-survivor groups, respectively), and the values in the non-survivor group were significantly lower than those in the survivor group. Although FDP did not differ significantly between the control group and

the survivor group, FDP was significantly greater in non-survivors (7.5 ± 1.9 and 16.7 ± 8.3 $\mu\text{g/ml}$ in the survivor and non-survivor groups, respectively). TAT was detectable in Horses 1, 4, 5, 6, 7, and 9 (2.4, 4.9, 1.8, 3.1, 2.9, and 2.5 ng/ml, respectively), all of which belonged to the non-survivor group. The period from the detection of TAT (on Days 1, 1, 3, 3, 5, and 4, respectively) until death (on Days 2, 2, 4, 5, 7, and 4, respectively) comprised 2 days at most in these horses. These horses also had high FDP values (16.8, 10.6, 18.0, 21.1, 18.4, and 35.3 $\mu\text{g/ml}$, respectively). TAT was below detectable limits (<1.0 ng/ml) throughout the measurement period in the remaining 8 horses.

Samples were obtainable for 4 days or longer in 10 colitis horses; these included 5 horses that could be sampled until Day 4 in the non-survivor group (Horses 5–9) and 5 in the survivor group (Horses 10–14). The values for Day 5 were not included in the statistical analysis, because there were only 3 horses remaining in the non-survivor group on Day 5, as Horses 5 and 9 had died on Day 4. Figure 2 illustrates the changes in certain coagulation parameters over time by comparing the survivor and non-survivor groups. TAT is not included, as the mean could not be obtained because some values were below the detection limit (<1.0 ng/ml). In the survivor group, prolonged APTT and PT and decreased AT activity were most prominent on Day 2 or 3, and these parameters subsequently improved. On the other hand, the corresponding parameter values continuously deteriorated in the non-survivor group. Differences between the 2 groups became obvious on Day 4, at which time prolonged APTT (69.5 ± 13.7 and 108 ± 9.8 sec in the survivor and non-survivor groups, respectively) and PT (10.9 ± 1.2 and 14.3 ± 1.5 sec in the survivor and non-survivor groups, respectively), decreased AT activity ($215 \pm 57\%$ and $95.6 \pm$

Table 1. The coagulation profiles (mean \pm SD) and the reference ranges in 20 healthy Thoroughbred racehorses

	Measured values	Reference ranges ^a
APTT (sec)	43.6 ± 1.6	40.4–46.8
PT (sec)	7.8 ± 0.4	7.0–8.6
FIB (mg/dl)	124.6 ± 10.7	103.2–46.0
AT activity (%)	315 ± 17	281–349
FDP ($\mu\text{g/ml}$)	6.8 ± 0.5	5.8–7.8
TAT (ng/ml)	1.0 >	1.0 >

^aThe reference ranges were defined as the mean of the control group \pm 2 SD.

Table 2. Profiles and outcomes of 14 horses presented for acute colitis

Horse No.	Age	Sex	Events before development of colitis	Rectal temperature ($^{\circ}\text{C}$) (on admission)	Outcome (day of death)
1	7	Female	Surgery and injection of cephalothin	38.7	Died (2)
2	3	Female	Transportation (>20 hr) and oral administration of enrofloxacin	40.5	Died (3)
3	2	Male	Transportation (>20 hr)	40.8	Died (4)
4	3	Female	Nothing in particular	39.6	Died (2)
5	3	Male	All-out training	40.0	Died (4)
6	2	Male	All-out training	40.4	Died (5)
7	3	Male	All-out training	39.6	Died (7)
8	3	Female	Nothing in particular	40.2	Died (7)
9	2	Male	Nothing in particular	40.3	Died (4)
10	4	Male	Race	39.5	Survived
11	3	Male	Race	40.0	Survived ^a
12	3	Male	Race	40.0	Survived
13	2	Male	Nothing in particular	41.0	Survived ^b
14	3	Male	All-out training and injection of cephalothin	39.2	Survived

^aEuthanized due to laminitis 80 days after admission. ^bEuthanized due to cecal impaction 14 days after admission.

25% in the survivor and non-survivor groups, respectively), and increased FDP (6.5 ± 2.1 and $18.2 \pm 9.4 \mu\text{g}/\text{ml}$ in the survivor and non-survivor groups, respectively) were observed. No differences were observed in FIB between the 2 groups throughout the observation period. The correlation analysis performed between the results of coagulation profiles and prognosis are shown in Table 3. Continuous decrease in AT activity and continuous increase in FDP for 4 consecutive days starting from Day 1 and detection of TAT ($>1.0 \text{ ng}/\text{ml}$) during the measurement period were significantly correlated with poor prognosis. No correlation was found when the 5 parameters (except TAT) were tested for 2 or 3 consecutive days.

In this study, we evaluated the most remarkable aberrations suggestive of DIC and the fluctuations of blood coagulation parameters in Thoroughbred racehorses with

acute colitis, as well as their relevance to clinical outcome. Regardless of the severity, all the colitis cases in the present study showed some blood coagulation abnormalities compared with the control horses. However, there were some differences in the degree of coagulation disorders and the fluctuation of parameters between surviving and non-surviving cases. In the surviving cases, prolonged APTT and PT and decreased AT activity were most prominent on Day 2 or 3, after which they improved. On the other hand, in the non-surviving cases, AT activity and FDP continuously decreased and increased, respectively, during the measurement period, and TAT increased in the last 2 days before death, in addition to prolongation in APTT and PT. As a consequence, significant differences were observed between survivors and non-survivors in the values of APTT, PT, AT activity, and FDP on Day 4.

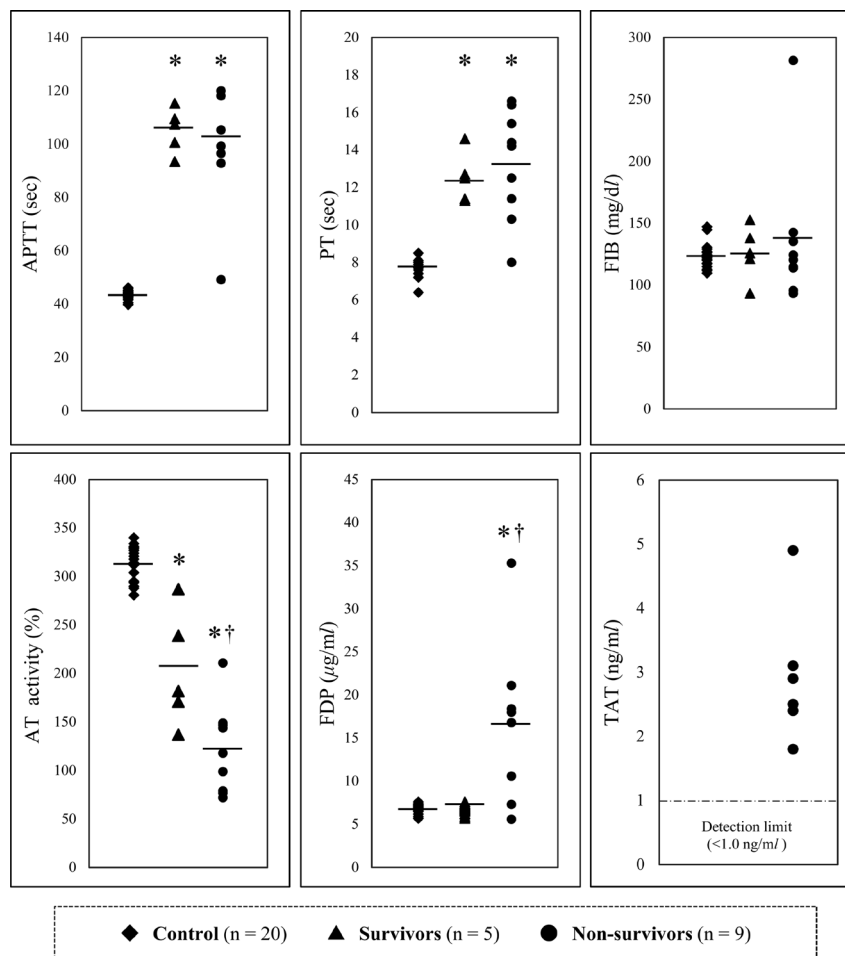


Fig. 1. Distributions of coagulation profiles presenting with the most remarkable aberrations suggestive of DIC during the measurement period for 14 horses with acute colitis grouped according to outcome of colitis and 20 control horses. Horizontal bars represent mean values. TAT was not detected ($<1.0 \text{ ng}/\text{ml}$) in the control and survivor groups during the measuring period. *Significantly different ($P<0.05$) from the control group. †Significantly different ($P<0.05$) between the survivor group and the non-survivor group.

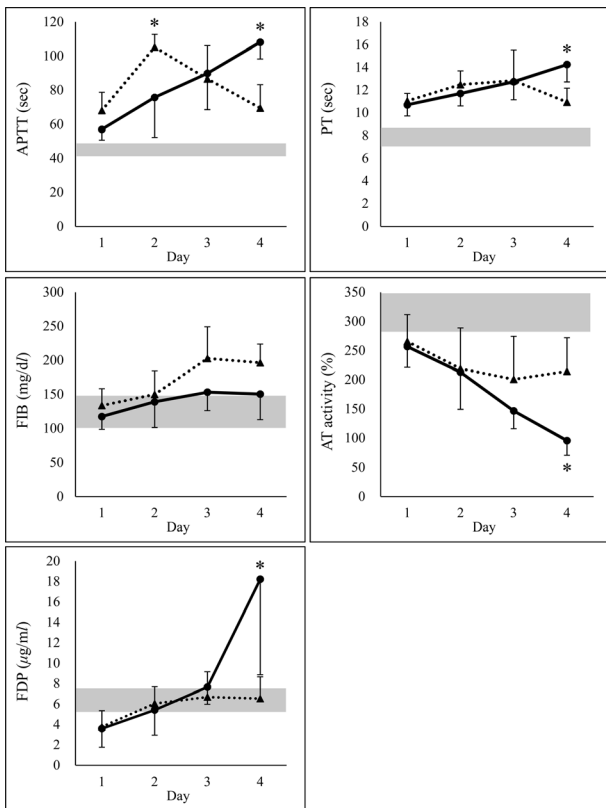


Fig. 2. Changes in each coagulation parameters (mean ± SD; APTT, PT, FIB, AT activity, and FDP) in the non-survivor group (●; solid line) and survivor group (▲; dashed line). Gray areas represent reference ranges at the JRA RTC (defined as the mean of the control groups ± 2 SD). *Significantly different ($P < 0.05$) between the survivor group and the non-survivor group.

Since there are no report available on the normal values for blood coagulation parameters in Thoroughbreds under training as racehorses, we first measured those of clinically healthy horses at the JRA RTC. The values of APTT, PT, FIB, and FDP were in the same ranges as in past reports [6]; however, the value for AT activity was higher, and that for TAT was lower. Although it should be noted that the values cannot simply be compared because the measurement methods were different among papers, in Thoroughbreds under training, AT activity and TAT may be high and very low, respectively, compared with horses in general.

TAT has been proposed as a direct indicator of an activated blood coagulation system [23]. In human medicine, TAT is considered useful for the detection of hypercoagulation in DIC [20]. In the present study, 6 horses presented with increased TAT (>1.0 ng/ml), and there was a significant correlation between the increase in TAT and poor prognosis. All of these horses also showed increased FDP, which reflects dissolution of microthrombi and is a fibrinolysis activation marker [1, 14, 24]. An increase in both TAT and FDP may indicate that both hypercoagulation and hyperfibrinolysis are activated to a greater extent, which could lead to terminal stages in horses affected with acute colitis. In other words, TAT may be useful as an indicator of poor prognosis, and past reports in which TAT was measured in colic cases in horses support this presumption as well [6, 14]. In our cases, the horses died approximately two days after the increase in TAT was seen. This may indicate that close and continued monitoring of TAT is crucial for observing the terminal stages of acute colitis cases.

Table 3. The correlations between coagulation profiles and clinical outcomes of acute colitis

a) The most remarkable aberrations during the measurement period			
	Survivors	Non-survivors	P value
Prolongation of APTT	5/5 (100%)	9/9 (100%)	N.S.
Prolongation of PT	5/5 (100%)	8/9 (89%)	N.S.
Decrease of FIB	1/5 (20%)	2/9 (22%)	N.S.
Decrease of AT activity	4/5 (80%)	9/9 (100%)	N.S.
Increase of FDP	2/5 (40%)	7/9 (78%)	N.S.
Increase of TAT	0/5 (0%)	6/9 (67%)	<0.05
b) Continuous changes ^a for 4 consecutive days starting from Day 1			
	Survivors	Non-survivors	P value
Continuous prolongation of APTT	0/5 (0%)	2/5 (40%)	N.S.
Continuous prolongation of PT	0/5 (0%)	2/5 (40%)	N.S.
Continuous decrease of FIB	0/5 (0%)	0/5 (0%)	N.S.
Continuous decrease of AT activity	1/5 (20%)	5/5 (100%)	<0.05
Continuous increase of FDP	0/5 (0%)	5/5 (100%)	<0.05

N.S.: Not significant. ^aDefined as a change in which the measured value either increased or decreased continuously compared with the previous day in horses whose samples were obtainable for 4 days or more.

In this study, FDP was significantly greater in non-survivors compared with survivors. Additionally, continuous increase of FDP is significantly correlated with poor prognosis. In non-surviving horses whose samples were obtainable for 4 days, the values on Day 4 were significantly higher compared with surviving horses. These fluctuation of FDP may be the defining feature in non-survivors. Although the degree of fibrinolytic activation does not always correspond to the progression of disease, depending on the type of underlying disease [1, 14], hyperfibrinolysis was directly correlated with progression of coagulopathy and poor outcome in this study population. Several pathologies including the development of septic and hypovolemic shock are thought to be the cause of DIC associated with acute colitis, but this mechanism has not been well documented. In addition to FDP, monitoring other markers of fibrinolysis activation (e.g., plasmin- α 2 plasmin inhibitor complex) may help clarify the mechanism of DIC in acute colitis in horses [1, 12].

AT activity decreased significantly in the survivor and non-survivor groups compared with the control group and in the non-survivor group compared with the survivor group. Further, the correlation between continuous decrease in AT activity and poor prognosis was significance, and the values on Day 4 in non-surviving horses whose samples were obtainable for 4 days were significantly smaller compared with those of surviving horses. This suggests that monitoring AT activity may facilitate identification of the progression of coagulopathy in acute colitis cases. Additionally, since antithrombin has the ability to bind with heparin and express directly anticoagulant effects *in vivo*, a decrease in AT activity may affect the choice of treatment for coagulopathy. It is known that antithrombin easily decreases with coagulopathy associated with sepsis because of enhanced vascular permeability and degradation by granulocyte esterase [4, 9], and antithrombin supplementation is suggested to be effective in the treatment of blood coagulopathy in cases with AT activity <70% of normal value in human medicine [13, 19]. To our knowledge, no antithrombin preparations are available in horses, but plasma contains various anticoagulant factors such as antithrombin; therefore, plasma transfusion may be one option in horses with severely reduced AT activity. Although further studies about the administration protocol and the risk of side effects with plasma transfusion in horses are needed, the authors propose that monitoring AT activity values may serve as a potential benchmark for clinical interventions including plasma transfusion.

APTT and PT are traditional parameters for evaluating blood coagulopathy [6, 8, 14, 15]. Although their maximum values were significantly different between colitis cases and healthy horses, there was no statistical difference between survivors and non-survivors. In non-survivors whose

samples were obtainable for 4 days, the values of APTT and PT on Day 4 were significantly higher compared with survivors, but continuous prolongation of APTT and PT was not always a feature of non-survivors in this study. It was difficult to distinguish survivors and non-survivors by measuring APTT and PT. In clinical use, if the values of APTT and PT are normal during the treatment period, cases might have a low possibility of acute colitis. FIB is known to decline in DIC [15, 22], but there were no differences between the groups in the present study. This result is consistent with the findings of other studies involving evaluation of coagulation parameters in horses with large colon volvulus and acute colitis [6, 8]. FIB is also known as indicator of local and systemic inflammation in horses [2]; therefore trends in the changes in FIB appear to be influenced by some inflammatory responses [7, 16], in addition to consumption coagulopathy, in acute colitis cases.

The Fisher's exact test using the parameters for continuous changes (2, 3, or 4 days starting from Day 1) revealed a significant correlation with prognosis only when the parameters were followed for up to 4 consecutive days. Monitoring parameters for 3 days or less may be insufficient to predict the prognosis, and we propose that a more accurate prognostic assessment would be possible by monitoring them for more than 4 days.

In conclusion, evaluating blood coagulopathy continuously has proven useful in assessing the severity of acute colitis in Thoroughbred racehorses. Although prolongation in APTT and PT were observed in all cases, noteworthy features of the coagulation parameters in the non-surviving cases were a continuous decrease in AT activity and continuous increase in FDP from the day of hospitalization and increased TAT in the terminal stages. It is important for these parameters to be continuously monitored to observe these fluctuation in acute colitis cases. In clinical practice, continuous monitoring of AT activity and TAT may allow them to serve as useful indicators, as a benchmark for the choice of treatment in coagulopathy cases and as an indicator of poor prognosis, respectively.

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