

Evaluation of some acute phase proteins in calves naturally infected with cryptosporidiosis

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ABSTRACT

Diarrhea is a leading cause of neonatal calf mortality, resulting in substantial economic losses in the livestock industry. Cryptosporidiosis, a major infectious etiology of diarrhea in neonatal calves, is characterized by high morbidity. This study aimed to evaluate the acute-phase response in calves with cryptosporidiosis, with a particular focus on the roles of haptoglobin (Hp) and serum amyloid A (SAA) in disease prognosis. A total of 15 calves diagnosed with cryptosporidiosis and 10 healthy calves were included in the study. Clinical assessments and oocyst scoring were conducted on days 0, 3, 5, and 7, alongside evaluation of the hematological and serum biochemical parameters. A standard treatment protocol was administered to calves diagnosed with cryptosporidiosis. The results indicated a significant reduction in oocyst shedding by the end of the study period, following treatment. The mean Hp levels in the infected calves exhibited an increasing trend. However, SAA levels demonstrated fluctuations throughout the monitoring period. In conclusion, while Hp and SAA play roles in the acute-phase response, their utility as prognostic biomarkers for cryptosporidiosis in neonatal calves appears to be limited. Comprehensive studies are needed to better understand the inflammatory process in naturally infected cryptosporidiosis..

Key words: calf; cryptosporidiosis; haptoglobin; serum amyloid A

Introduction

Calf diarrhea may result from both infectious and non-infectious factors, including nutritional, toxic and allergic causes. Infectious agents implicated in calf diarrhea include *Bovine Rotavirus*, *Bovine Coronavirus*, *Bovine Viral Diarrhea Virus* (BVDV), *Escherichia coli*, *Salmonella spp.*, *Cryp-*

tosporidium spp., and *Clostridium spp.* (CHOI et al., 2021). *Cryptosporidium spp.* is one of the most prevalent pathogens responsible for diarrhea in neonatal calves. *Cryptosporidium parvum* (*C. parvum*) is the main causative agent of cryptosporidiosis (OK et al., 2021). Clinical signs typically appear 3-5 days post-exposure and may persist for 4-17

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days, with oocyst shedding peaking between days 7 and 14 ([SARI and ARSLAN, 2012](#)).

The acute phase response (APR) is the organism's systemic reaction to infection, inflammation, trauma, injury and neoplastic processes ([PEETSALU et al., 2022](#); [TÓTHOVÁ et al., 2014](#)). Clinically, acute phase proteins (APPs) serve as valuable biomarkers for monitoring treatment efficacy and predicting disease prognosis and for assessing the severity of both clinical and subclinical conditions ([KABU et al., 2023](#)). In ruminants, haptoglobin (Hp) and serum amyloid A (SAA) are the major APPs, although their induction may differ according to the nature, course and etiology of inflammation ([SACO and BASSOIS, 2022](#)). In cryptosporidiosis, infection severity correlates with the extent of pathogen dissemination ([DINLER et al., 2017](#)). Intestinal mucosal damage triggers the release of inflammatory mediators that contribute to enteritis, while elevated levels of Hp and SAA play protective roles in restoring homeostasis and enhancing host defense ([CECILIANI et al., 2012](#); [DINLER et al., 2017](#); [PEETSALU et al., 2022](#)).

A study investigating fecal consistency in calves infected with *Cryptosporidium spp.* found significantly higher serum concentrations of SAA and Hp in calves with watery diarrhea compared to those with normal feces ([AL-ZUBAIDI, 2015](#)). Furthermore, [CENESIZ et al. \(2017\)](#) observed elevated SAA and Hp levels in calves infected with *C. parvum* prior to treatment. However, no statistically significant difference in SAA levels was detected between the pre- and post-treatment periods. Studies in calves have also reported elevated serum Hp and SAA levels ([EL-DEEB et al., 2022](#)), with Hp showing a greater increase than SAA during the disease course ([ERLING, 2022](#)).

This study aimed to characterize the acute-phase response in calves with cryptosporidiosis, and to evaluate the role of Hp and SAA levels in the disease.

Materials and methods

Formation of groups. The sample collection schedule, microscopic examination of fecal samples, and treatment process in the study are

schematized in Fig. 1. Animal material comprised twenty-five calves, aged 5-15 days. Fifteen naturally infected calves (10 Holstein (3 male, 7 female), 2 Jersey (2 male), 2 Simmental (2 female), and 1 Brown Swiss (1 female)) were presented to the Burdur Mehmet Akif Ersoy University Veterinary Clinics with clinical signs of diarrhea. Ten healthy control calves (5 male and 5 female Holstein) were obtained from the University's research farm. Immunochromatographic test kits (Bovid-5 Ag, Bionote, Korea) were used on the calves to eliminate *Escherichia coli*, *Giardia spp.*, *Rotavirus*, and *Coronavirus*. Fecal samples from calves that tested positive for *Cryptosporidium spp.* were stained with carbol fuchsin and examined microscopically. Calves with confirmed *Cryptosporidium spp.* oocysts under microscopy were included in the infected group. The clinical score parameters of the calves in the infected group were recorded throughout the duration of the study. Calves classified as healthy on the basis of clinical score parameters and showing no pathogen presence in the immunochromatographic test were included in the healthy group. The clinical score parameters of the calves in the healthy group were recorded throughout the study period. Infected calves were housed individually in calf hutches at the University Veterinary Hospital and fed a total of 4 L/day of calf milk replacer (Optimilk®, Optima, Turkey), divided into two equal feedings, throughout the study.

Clinical scoring. Clinical scoring was adapted from the literature ([ÖZKAN and AKGÜL, 2004](#); [AYDOĞDU et al., 2018](#)). The parameters evaluated included body temperature, degree of dehydration, capillary refill time (CRT), sucking reflex, mental status, skin elasticity, eye recession, fecal consistency, mucosa and body condition. Clinical scores were assigned on a scale of 0 to 3 on the basis of the severity of clinical signs. According to the total score, the calves were classified as mildly affected (1-10 points), moderately affected (11-20 points), or severely affected (21-30 points).

Oocyst detection and scoring. Fecal samples were obtained directly from the rectum, placed in sterile plastic containers, and transported to the laboratory under appropriate conditions. Ho-

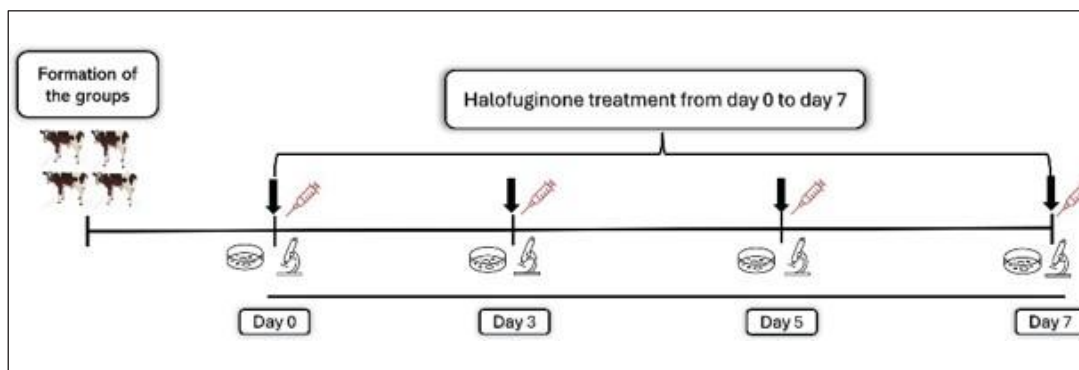


Fig. 1. The formation of groups and sample collection schedule

Following clinical examination in diarrheic calves, pathogen detection was performed using an immunochromatographic test kit. Blood and fecal samples were collected from both infected and healthy calves on the follow-up days. Stool samples were examined under a microscope on the same day using the carbol fuchsin staining method. The standard treatment protocol was administered to calves in the infected group, including on days 0 and 7.

mogenized smears (50 μ L feces + carbol fuchsin) were prepared on ether alcohol-cleaned slides, air-dried, and examined microscopically (100x, oil immersion). The oocyst count was evaluated semi-quantitatively by examining 20 randomly selected microscopic fields. The scoring system was adapted to align with the parameters of our study, incorporating methodologies from prior research. Oocyst counts were categorized as follows: no oocysts observed (negative); a single oocyst in a few fields (rare, score 1); 1-5 oocysts (low, score 2); 6-10 oocysts (moderate, score 3); and >10 oocysts (high, score 4) ([CASTRO-HERMIDA et al., 2001](#); [SAKARYA et al., 2010](#), [AYDOGDU et al., 2018](#)).

Hematological and serum biochemical analysis. Blood samples were collected from the jugular vein of each calf on days 0, 3, 5, and 7 using both EDTA tubes (BD Vacutainer, United Kingdom) and activator-gel, anticoagulant-free tubes (BD Vacutainer, United Kingdom). Total leukocyte (WBC), erythrocyte (RBC), hemoglobin (HGB), and hematocrit (HCT) levels were measured using the Abacus Junior Vet analyzer (Diatron MI Ltd., Hungary). Following centrifugation at 5000 rpm for 10 minutes, serum samples were stored at -20°C until further analysis. Serum albumin (Alb), total protein (TP), and creatinine levels were determined spectrophotometrically using an autoanalyzer (Randox, Monaco, United Kingdom).

Measurement of acute phase proteins. Hp and SAA levels were analyzed using the existing serum samples with commercial ELISA kits (Bovine Haptoglobin: BT LAB, Cat. No. E2263Bo; Bovine SAA: BT LAB, Cat. No. E2264Bo), following the manufacturer's protocol. The optical densities of each well were determined using a microplate reader (Biotek, 800TS) set at 450 nanometers.

Treatment protocol. Following baseline (Day 0) sample collection, all *Cryptosporidium spp.*-infected calves received standardized treatment. Halofuginone lactate (Halocur®, Intervet, France) was administered orally at 0.1 mg/kg for 7 days. Intravenous fluid therapy with 0.9% isotonic sodium chloride (Polifleks®, Polifarma, Tekirdağ) and 8.4% sodium bicarbonate (Carbotek®, Teknovet, Tekirdağ) was provided to correct dehydration and bicarbonate deficits.

Statistical analyses. Statistical analyses were performed using IBM SPSS Statistics software (Version 26.0, Armonk, NY: IBM Corp.). Normality of data distribution was assessed using the Kolmogorov-Smirnov test, and parametric tests were applied as the data met normality assumptions. Healthy and infected cases were compared using the independent samples t-test, while within-group comparisons were analyzed using one-way ANOVA. The statistical significance threshold was set at $P < 0.05$. The data obtained were presented as mean

± standard deviation. The correlation and regression analyses were performed using the JAMOVI ([THE JAMOVI PROJECT, 2024](#); [R CORE TEAM, 2024](#); [FOX and WEISBERG, 2023](#)) statistical software. To explore the relationships between factors, a correlation test conducted between follow-up days, Hp and SAA. A correlation matrix was made from these results and using this matrix, factors with significant correlation were detected along with their direction. From the results of these calculations, a linear regression analysis was performed done for factors with significant correlation to quantify their association.

Results

Clinical findings. Clinical scoring for both groups was performed as detailed in Table 1. The temporal evolution of total clinical scores in the infected calves over the follow-up period is illustrated in Fig. 2. All calves were aged 5-15 days, with mean ages of 9.87 ± 3.11 days in the infected group and 10.40 ± 2.84 days in the healthy group. The clinical scores of the animals in the healthy

group remained zero throughout the study and all animals appeared clinically healthy. On day 3 of follow-up, a 3-point increase in the clinical score was observed in calf number eleven. However, a decrease in its clinical score was noted on the subsequent days. By day 5, two calves had achieved a clinical score of 0, indicating full recovery, while the remaining calves exhibited mild clinical signs with scores ranging between 2 and 10. On day 7, eleven calves had a clinical score of 0, indicating complete recovery. However, on day 7, one calf exhibited a clinical score of 3, another a score of 2, and two calves scored 1, indicating a mild degree of illness.

Oocyst scoring findings. The oocyst shedding of the calves in the infected group during the study period is illustrated in Fig. 3. A statistically significant decrease and a variation in oocyst scores across different days were observed within the infected group of calves ($P < 0.05$). When day 0 was compared to subsequent days, the reduction in oocyst shedding was statistically significant on day 3 ($P < 0.01$) and highly significant on days 5 and 7 ($P < 0.001$). A significant difference ($P < 0.01$) was observed between

Table 1. Clinical score

	Healthy (0)	Mild (1)	Moderate (2)	Severe (3)
Body temperature(°C)	38-39,5	39,6-40	40,1-41	<38 or >41
Dehydration(%)	None	4-6	8-10	>10
Capillary refill time (sec.)	1-2	3-4	5-6	>7
Sucking reflex	Normal	Unwilling	Weak	None
Mental status	Normal	Mildly depressed	Depressed	Unconscious
Skin elasticity (sec.)	<1	1-2	2-5	5-10 or >10
Eye recession (cm)	Normal	Slightly sunken (0,5 cm)	Moderately sunken (0,5-1 cm)	Severely sunken (>1 cm)
Mucosa	Normal	Hyperemic	Pale	Cyanotic
Fecal consistency	Normal	Doughy	Watery	Very watery
Body condition	Standing	Immobile, lethargic	Lying on the sternum	Lateral recumbency

sec.: second; cm: centimeter

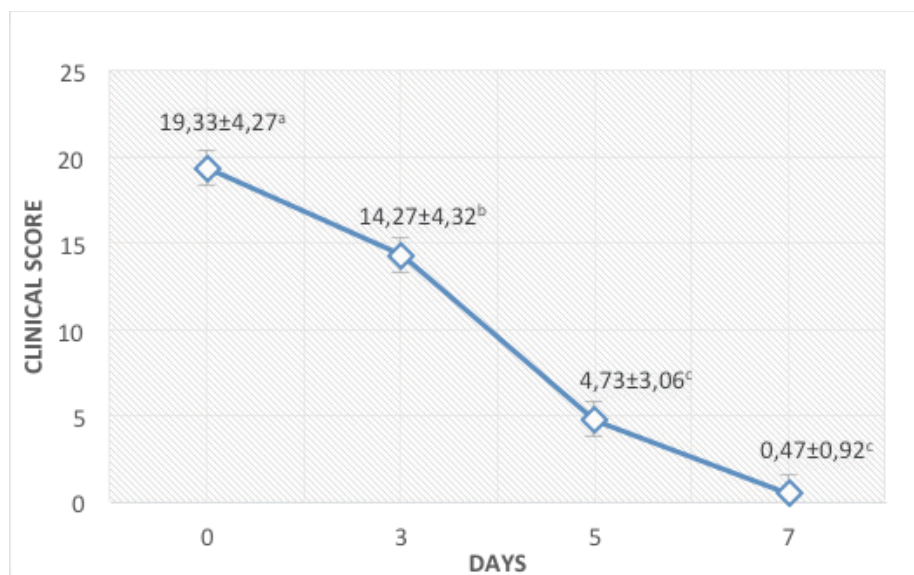


Fig. 2. The changes in the total clinical scores of the animals in the infected group over the follow-up days
abc: There is a statistically significant difference between the days marked with different superscript letters

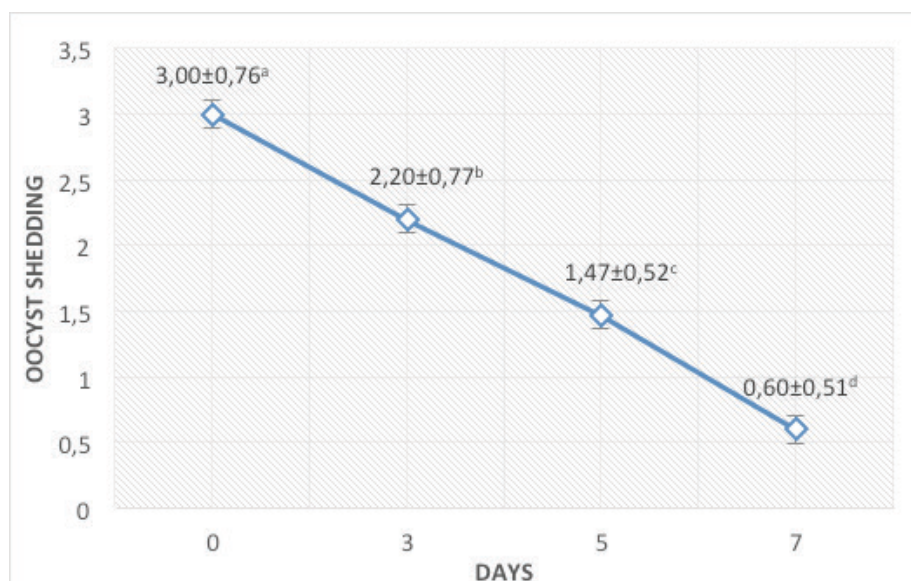


Fig. 3. Changes in oocyst scores of calves over the follow-up days
abcd: There is a statistically significant difference between the days marked with different superscript letters ($P<0.05$)

days 3 and 5, while the reduction between days 3 and 7 was highly significant ($P<0.001$). Similarly, a significant decrease in oocyst shedding was detected between days 5 and 7 ($P<0.01$).

Hematological findings. The values of WBC, RBC, HGB, and HCT in the infected and healthy groups are presented in Table 2, along with statistical evaluations of these parameters. A statistically

significant difference in mean WBC between the infected and healthy groups was only detected on day 0 ($P<0.05$). Within the infected group, WBC values on day 0 were statistically significantly higher than at all subsequent time points ($P<0.05$), whereas no statistically significant within-group variation was observed in the healthy group. Mean RBC values in healthy calves were significantly higher than in the infected group on days 5 and 7 ($P<0.05$). However, neither group exhibited significant within-group changes in mean RBC values over the followup period ($P>0.05$). Although mean HGB values were higher in the infected group, no significant differences were found between or within groups ($P>0.05$). Mean HCT values were significantly higher in the infected group on days 0, 3, and 7 ($P<0.05$), but no significant within-groups variations were observed over time.

Serum biochemical and acute phase proteins findings. The values of TP, Alb, creatinine, Hp and SAA for the calves in the healthy and infected groups, along with the statistical evaluations of these parameters, are presented in Table 3. TP concentrations were higher in the infected calves on day 0 but lower on subsequent days, with no significant between- or within-group differences ($P>0.05$). Mean albumin levels remained stable over the follow-up period in both groups, with no significant differences detected ($P>0.05$). Likewise, no significant differences were observed in mean creatinine values between the groups ($P>0.05$). Although creatinine levels declined over time in the infected group, within-group comparisons showed no statistical significance ($P>0.05$).

Table 2. Hemogram findings of animals in the infected and healthy groups

	Days	Infected (Mean±S.d.)	Healthy (Mean±S.d.)	P value
WBC ($\times 10^9/l$)	0	13.37±5.29 ^A	10.14±2.45	$P<0.05$
	3	9.81±1.83 ^B	10.15±2.84	$P>0.05$
	5	8.72±1.90 ^B	9.86±2.31	$P>0.05$
	7	9.06±2.29 ^B	10.33±2.35	$P>0.05$
RBC ($\times 10^{12}/l$)	0	7.65±1.09	7.87±1.26	$P>0.05$
	3	7.56±1.18	7.95±1.15	$P>0.05$
	5	7.39±1.24	8.53±1.41	$P<0.05$
	7	7.35±1.45	8.39±1.24	$P<0.05$
HGB (g/dl)	0	7.82±1.13	7.41±0.78	$P>0.05$
	3	7.61±1.40	7.30±0.89	$P>0.05$
	5	7.43±1.28	7.39±1.10	$P>0.05$
	7	7.56±1.81	7.37±0.92	$P>0.05$
HCT (%)	0	31.67±7.74	25.56±3.63	$p<0.05$
	3	30.43±7.15	25.28±3.68	$P<0.05$
	5	29.15±6.32	25.02±4.08	$P>0.05$
	7	29.77±6.23	24.86±3.69	$P<0.05$

S.d.: Standard deviation; P value: Statistical significance between groups across follow-up days; ^{AB}: Within group comparisons, differences between days marked with different superscript letters in the same column are statistically significant ($P<0.05$); WBC: White blood cell count; RBC: Red blood cell count; HGB: Hemoglobin; HCT: Hematocrit

Table 3. Biochemical and acute phase protein findings of animals in the Infected and healthy groups

	Days	Infected (Mean±S.d.)	Healthy (Mean±S.d.)	P value
Albumin (g/dl)	0	3.02±0.41	2.93±0.14	P>0.05
	3	2.87±0.27	2.86±0.22	P>0.05
	5	2.78±0.32	3.43±1.49	P>0.05
TP (g/dl)	7	2.96±0.30	3.03±0.20	P>0.05
	0	5.48±0.80	5.35±0.91	P>0.05
	3	5.06±0.79	5.42±1.01	P>0.05
	5	5.06±0.68	5.78±1.33	P>0.05
Creatinine (mg/dl)	7	5.15±0.69	5.60±0.98	P>0.05
	0	1.11±0.39	0.99±0.16	P>0.05
	3	1.02±0.29	1.08±0.24	P>0.05
	5	0.97±0.22	1.06±0.28	P>0.05
Hp (µg/ml)	7	0.94±0.26	1.08±0.20	P>0.05
	0	167.78±29.73 ^A	179.00±24.32 ^A	P>0.05
	3	198.41±38.96 ^B	214.89±29.88 ^B	P>0.05
	5	226.77±53.00 ^C	247.03±37.64 ^C	P>0.05
SAA (µg/ml)	7	233.99±49.62 ^C	229.89±22.37 ^B	P>0.05
	0	11.45±2.48	10.50±3.20 ^A	P>0.05
	3	12.49±2.26	12.50±2.03 ^B	P>0.05
	5	11.88±2.57	13.74±1.46 ^B	P<0.05
	7	12.40±2.82	12.80±1.26 ^B	P>0.05

S.d.: Standard deviation; P value: Statistical significance between groups across follow-up days; ^{ABC}: Within group comparisons, differences between days marked with different superscript letters in the same column are statistically significant (P<0.05); TP: Total protein; Hp: Haptoglobin; SAA: Serum amyloid A.

In the statistical evaluation of the mean Hp values in the infected group, significant differences were observed between day 0 and day 3 (P<0.05), day 5 (P<0.01), and day 7 (P<0.001). Additionally, significant differences were observed between day 3 and days 5 and 7 (P<0.05), while no difference was found between days 5 and 7. In the statistical evaluation of mean Hp values in the healthy group, significant differences were observed between day 0 and day 3 (P<0.05), day 5 (P<0.001), and day 7 (P<0.01). Statistical analysis of the mean Hp values in the healthy group revealed a significant difference between day 3 and day 5 (P<0.05), but

no significant difference was detected between day 3 and day 7 (P>0.05). In the comparison between infected and healthy groups, no statistically significant differences were observed in mean Hp values over the follow-up days (P>0.05). In the infected group, no significant change was observed in the mean SAA levels over the follow-up days (P>0.05). In the healthy group, however, SAAs exhibited an increasing trend starting from day 0, with significant differences detected between day 0 and days 3, 5, and 7 (P<0.05). The mean SAA values of the infected and healthy groups were similar over the follow-up days. In the com-

parison between infected and healthy groups, no statistically significant differences were observed in mean SAA values on days 0, 3, or 7 ($P>0.05$). However, a statistically significant difference was detected on day 5 ($P<0.05$), with calves in the infected group exhibiting lower mean SAA values compared to the healthy group.

Correlations between clinical score and acute phase proteins. The Pearson correlation analysis indicated a significant moderate negative correlation between serum Hp and clinical score ($r=-0.543$, $P<0.001$), alongside a significant strong negative correlation between follow-up days and Hp ($r=-0.915$, $P<0.001$). In contrast, SAA demonstrated no significant correlation with follow-up days ($r=0.11$, $P=0.401$) or clinical score ($r=-0.069$, $P=0.599$). Subsequent linear regression analysis, based on 60 measurements from 15 calves, established a statistically significant model ($P<0.001$) explaining 29.5% of the variance in serum Hp concentrations ($R^2=0.295$, Adjusted $R^2=0.283$). Within this model, the clinical score emerged as a significant negative predictor of serum Hp levels ($\beta=-2.84$, $SE = 0.577$, $P<0.001$). Fig. 4 presents a matrix of scatter plots visually illustrating the pairwise correlations between Hp concentrations, SAA levels, clinical score, and follow-up days (days). Each individual scatter plot depicts the relationship between two variables, with fitted trend lines and corresponding 95% confidence intervals overlaid to aid in the interpretation of these associations. Notably, the plot visually confirms the moderate negative linear relationship observed between serum Hp and clinical score, and the strong negative linear relationship between serum Hp and follow-up days. Conversely, the scatter plots for SAA against both follow-up days and clinical score demonstrate a dispersed pattern of data points, consistent with the reported lack of significant correlations for these pairs. The Normal Q-Q plot of standardized residuals (fig. 5) indicated that the residuals were approximately normally distributed, with points generally following the diagonal reference line.

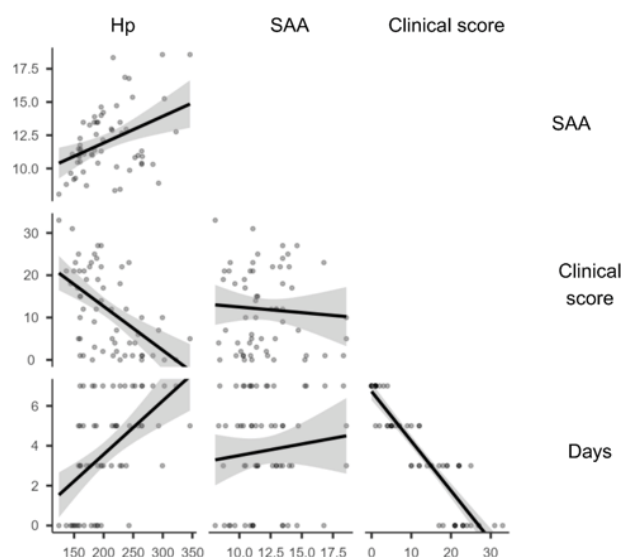


Fig. 4. Pairwise correlation matrix of Hp, SAA, clinical score, and follow-up days

Individual scatter plots show the data points, with the black line representing the linear best fit and the gray shaded area indicating the 95% confidence interval for the fit

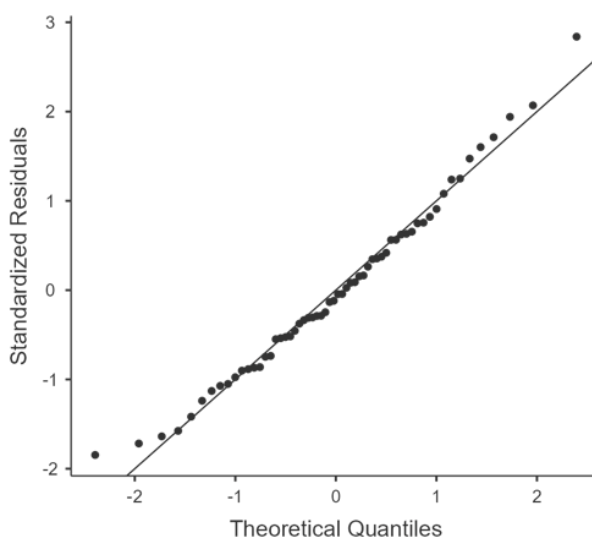


Fig. 5. Normal Q-Q plot of standardized residuals for the linear regression model predicting Hp concentrations

The plot compares the quantiles of the standardized residuals to the quantiles of a standard normal distribution. The points falling approximately along the diagonal line suggest that the residuals are reasonably normally distributed.

Discussion

This study aimed to evaluate the acute-phase response in calves infected with *Cryptosporidium* spp. and assess the roles of Hp and SAA parameters in the inflammatory process. No significant differences were observed between infected and healthy calves, although a mild increase in Hp levels was noted during the disease course. We anticipate that our findings will guide and contribute to the evaluation of the acute-phase response (APR) and acute-phase proteins (APPs) in future studies on cryptosporidiosis.

The primary agent of cryptosporidiosis in the neonatal period is *C. parvum* ([SANTÍN, 2013](#)). Neonatal diarrhea caused by *C. parvum* is globally prevalent and its significance is increasingly recognized ([BJÖRKMAN et al., 2018](#); [MALLINATH et al., 2009](#)). Clinical manifestations are nonspecific and include diarrhea, dehydration, depression and anorexia ([GAMSJÄGER et al., 2023](#)). Halofuginone lactate has been shown to reduce oocyst shedding, decrease diarrhea prevalence, and shorten recovery time, although oocyst excretion may resume after cessation of treatment ([BRAINARD et al., 2021](#)). In the present study, administration of routine halofuginone lactate therapy resulted in marked clinical improvement, as evidenced by declining disease scores; by day 7, most calves had recovered. Mean oocyst shedding scores in diarrheic calves fell from 3.0 to 0.6, confirming the cryptosporidiostatic efficacy of halofuginone.

In cryptosporidiosis, chemokines mediate the migration of inflammatory and adaptive immune cells, including neutrophils, natural killer cells, macrophages, and dendritic cells ([VESHKINI et al., 2024](#)). Leukocytosis in *cryptosporidium* infected calves likely reflects intestinal epithelial injury, co-infections or parasitic cytotoxicity ([SIACHOS et al., 2017](#)). Although elevated RBC, HGB and HCT are often attributed to dehydration-induced hemoconcentration ([ÖZKAN and AKGÜL, 2004](#); [ALAM et al., 2012](#)), other studies report no significant differences in RBC or HGB between diarrheic and healthy calves ([ALBAYRAK and KABU, 2016](#); [ATCALI and YILDIZ, 2020](#)). In this study, elevated WBC levels in infected calves aligned with gastrointestinal infection and epithelial cell

damage. RBC and HGB values mirrored prior findings, while HCT, though within reference ranges, was higher in the infected calves, likely due to fluid loss.

Serum albumin, a major negative acute-phase protein, has shown variable responses in diarrheic calves: decreased ([BOZUKLUHAN et al., 2016](#); [CHOI et al., 2021](#); [HA et al., 2022](#)), increased ([ALAM et al., 2012](#); [USTA et al., 2021](#)), or unchanged levels ([ALBAYRAK and KABU, 2016](#); [MERHAN et al., 2016](#); [KIM et al., 2021](#)). In our study, the albumin values of infected calves were found to be similar to those of healthy calves. It was concluded that the absence of severe inflammation and the lack of adverse effects on liver function in cryptosporidiosis contributed to the unchanged serum albumin levels.

Some studies have reported elevated TP in diarrheic calves, attributed to increased globulin synthesis, hepatic sialoprotein production, or hemoconcentration from extracellular fluid loss ([MERHAN et al., 2016](#); [USTA et al., 2021](#)), whilst others found no statistical differences between healthy and infected calves ([ALBAYRAK and KABU, 2016](#); [KIM et al., 2021](#); [CHOI et al., 2021](#)). In our study, the infected calves exhibited lower serum TP levels compared to the healthy calves, although no significant difference was observed. This reduction was attributed to inadequate colostrum intake and reduced appetite in infected animals, likely linked to compromised nutritional status.

While diarrhea associated with dehydration is reported to elevate creatinine concentrations due to reduced renal perfusion ([ÖZKAN and AKGÜL, 2004](#); [ALAM et al., 2012](#); [MERHAN et al., 2016](#); [KANG et al., 2020](#), [HA et al., 2022](#)). One study found no statistically significant increase in diarrheic or arthritic calves ([PEKCAN et al., 2012](#)). In our study, creatinine levels in the diarrheic calves remained comparable to the healthy controls, likely due to the absence of severe dehydration, suggesting preserved renal perfusion under mild fluid loss.

Colostrum intake and age have a significant impact on serum Hp and SAA levels in neonatal calves ([SEPPÄ-LASSILA et al., 2013](#)). Colostrum contains high amounts of cytokines such as IL-1 β ,

IL-6, TNF- α , and IFN- γ , and the concentrations of these cytokines are significantly higher in colostrum compared to mature milk ([PEETSALU et al., 2022](#)). In newborn calves, IL-6 is absent in blood plasma immediately after birth. Following colostrum intake, the concentrations of this cytokine increase, with the highest levels observed during the first 24 hours of life. Therefore, the pro-inflammatory cytokines absorbed from colostrum can directly stimulate the production of acute phase proteins or activate circulating lymphocytes and neutrophils ([TÓTHOVÁ et al., 2015](#)). In another study, colostrum proinflammatory cytokines were reported to regulate the neonatal calf immune system during the first week of life; however, colostrum SAA and Hp levels were not found to be directly associated with their corresponding serum concentrations. The same study reported that colostrum APPs may exert systemic effects through local or proinflammatory mechanisms within the gastrointestinal tract ([PEETSALU et al., 2022](#)). In neonatal calves, the lowest concentrations of SAA were observed shortly after birth, followed by a progressive increase after colostrum intake, extending up to the 7th ([ORRO et al., 2008](#)) or 14th ([SEPPÄ-LASSILA et al., 2013](#)) day of life. In another study, the lowest levels of Hp and SAA were observed after birth, with both APPs concentrations showing a gradual increase up to day 7. Furthermore, Hp levels remained elevated compared to day 1 throughout the observation period (up to day 30), while SAA levels began to decline from day 14 onwards. ([TÓTHOVÁ et al., 2015](#)). Another study reported that calves exhibited high Hp levels during the first two weeks of life ([KNOWLES et al., 2000](#)). Serum Hp and SAA levels in healthy calves exhibit broad reported ranges: 50-1090 $\mu\text{g/mL}$ for Hp and 1.11-178 $\mu\text{g/mL}$ for SAA ([HAJIMOHAMMADI et al., 2013](#); [BALIKCI and AL, 2014](#); [AL ZUBAIDI, 2015](#); [ALBAYRAK and KABU, 2016](#); [MERHAN et al., 2016](#); [BOZUKLUHAN et al., 2016](#); [DINLER et al., 2017](#); [NIINE et al., 2018](#); [KIM et al., 2021](#), [HA et al., 2022](#); [SALEH et al., 2022](#)). The changes in APPs concentrations in neonatal calves may vary independently of any disease processes, and may be influenced by stimulatory cytokines in colostrum, the processes of parturition, and the

calves' adaptation to extrauterine life ([ORRO et al., 2008](#); [TÓTHOVÁ et al., 2015](#); [KANG et al., 2020](#)). In our study, healthy calves exhibited mean Hp and SAA levels within the ranges reported by other researchers. It was concluded that the increase in the mean Hp and SAA levels observed in the healthy group of calves during the follow-up days was contributed by the cytokines received through colostrum and the calves' adaptation to extrauterine life.

Acute-phase protein elevations vary depending on inflammation type, disease chronicity, etiology and species ([DORBEEK-KOLIN et al., 2022](#)). Increased Hp and SAA levels were observed during intestinal mucosal damage and inflammation ([DINLER et al., 2017](#)), with higher concentrations reported in bacteria and mixed infections compared to viral or parasitic ones ([MURATA et al., 2004](#); [POURJAFAR et al., 2011](#)). Studies conducted on calves naturally infected with *C. parvum* ([NIINE et al., 2018](#); [EL-DEEB et al., 2022](#)) have reported elevated serum levels of Hp and SAA, while halofuginone treatment was found to reduce Hp levels ([NIINE et al., 2018](#)). In both experimental and naturally occurring cryptosporidiosis in lambs, increased Hp and SAA levels have been reported ([DINLER et al., 2017](#); [KABU et al., 2023](#)), with Hp suggested as a better biomarker for assessing disease severity ([DINLER et al., 2017](#)). In eimeriosis-affected calves, no significant differences in SAA concentrations were observed between infected and healthy groups, with researchers highlighting limitations in sample size for detecting subtle variations ([SEPPÄ-LASSILA et al., 2015](#)). In contrast, another study reported no statistical differences in Hp or SAA levels between diarrheic and non-diarrheic calves, suggesting APPs may not correlate with diarrhea severity, and could be influenced by confounding factors such as stress, trauma, or colostrum intake ([KANG et al., 2020](#)). A study analyzing serum protein profiles and acute-phase proteins in calves during the first month of life reported a five-fold increase in serum Hp levels in diarrheic calves, whereas SAA levels remained unchanged. The researchers attributed the lack of SAA response to the age of the calves (particularly those aged 1–10 days), and suggested that SAA may be a less sensitive indicator for assessing health status in cattle ([CHOI et al., 2021](#)). Several

studies have reported that the serum Hp levels in diarrheic calves range from 195-1600 µg/ml ([HAJIMOHAMMADI et al., 2013](#); [BALIKCI and AL, 2014](#); [AL ZUBAIDI, 2015](#); [MERHAN et al., 2016](#); [ALBAYRAK and KABU, 2016](#); [DINLER et al., 2017](#); [NIINE et al., 2018](#); [KIM et al., 2021](#); [HA et al., 2022](#); [SALEH et al., 2022](#)), while SAA levels range from 3-227 µg/ml ([HAJIMOHAMMADI et al., 2013](#); [BALIKCI and AL, 2014](#); [AL ZUBAIDI, 2015](#); [BOZUKLUHAN et al., 2016](#); [DINLER et al., 2017](#); [NIINE et al., 2018](#); [KIM et al., 2021](#); [HA et al., 2022](#)). Proteomic analyses of *C. parvum*-induced ileitis have revealed that the condition is characterized by leukocyte infiltration, activation of reactive oxygen pathways, proteins associated with hypochlorous acid biosynthesis, and lymphocyte aggregation. However, proinflammatory cytokine (IL-8, IL-10, IFN-γ, TNF-α) expression levels were similar between healthy and infected animals ([GAMSJÄGER et al., 2023](#)). In a study evaluating inflammatory and anti-inflammatory cytokines in diarrheic neonatal calves (aged 0-10 days), it was reported that levels of TNF-α, IL-5, and IL-6 were decreased in the *C. parvum* group, while no changes were observed in the levels of the other cytokines examined. The researchers noted that viral and protozoal diseases causing calf diarrhea may not lead to a severe inflammatory response, depending on the timing of sample collection ([CALISKAN et al., 2023](#)). The differences in the magnitude of response and the time taken to reach peak levels between Hp and SAA are associated with the diversity of the infectious agents and the kinetic characteristics of these APPs. Moreover, inflammatory processes in internal organs appear to trigger more pronounced reactivity patterns compared to diseases of the skin and the gastrointestinal system ([DINLER et al., 2017](#)). In our study, the mean Hp and SAA levels in diarrheic calves were within the range reported in previous studies. However, we determined that the Hp and SAA levels in the infected calves were similar to those in the healthy group. This condition may be attributed to the infection being limited solely to the gastrointestinal system, and to the inability of *Cryptosporidium* spp. infection alone to elicit a sufficient acute phase response. Additionally, fluctuations in APPs

during the adaptation process to extrauterine life in healthy calves, as well as cytokines transferred through colostrum, may also have contributed to the observed values.

Cryptosporidiosis may present asymptotically in calves, or with diarrhea and dehydration of varying severity ([VÉLEZ et al., 2019](#)). Severe clinical signs correlate with *C. parvum* localization in the proximal small intestine, while distal infection often results in subclinical cases ([THOMPSON, 2005](#)). Hp and SAA levels rise markedly in calves with bacterial/mixed infections, severe clinical signs, fever, or dehydration ([POURJAFAR et al., 2011](#); [HAJIMOHAMMADI et al., 2013](#)), and in those with watery feces ([AL-ZUBAIDI, 2015](#)). However, no significant differences in Hp and SAA levels were observed between calves exhibiting moderate clinical signs and those without any clinical signs ([HAJIMOHAMMADI et al., 2013](#)). In experimentally BRSV-infected calves with mild clinical signs, SAA levels did not correlate with the clinical findings. ([HEEGARD et al., 2000](#)). Detecting differences in APPs concentrations between healthy and diseased calves can be challenging under natural conditions, particularly when the differences are subtle. Moreover, study designs may not accurately capture the onset, duration, and acute nature of the inflammatory response ([SEPPÄ-LASSILA et al., 2015](#)). Although cryptosporidiosis outbreaks are observed in calves under farm conditions, the potential involvement of other pathogens in the process cannot be ruled out ([NIINE et al., 2018](#)). Halofuginone lactate has been shown to reduce oocyst shedding, diarrhea prevalence, recovery time, and alleviate clinical signs in calves ([SILVERLÅS et al., 2009](#); [SHAHIDUZ-ZAMAN and DAUGSCHIES, 2012](#); [BRAINARD et al., 2021](#)). In our study, a statistically significant inverse relationship was observed between Hp and clinical scores, whereas no significant correlation was found between SAA and clinical scores. Halofuginone treatment was found to reduce oocyst counts and make a significant contribution to clinical improvement. However, it was concluded that the disruption of the intestinal microbiota caused by cryptosporidiosis may have led to an increase in the mean Hp levels observed in the treatment group

during the follow-up period. Furthermore, the elevated levels of APPs, which are known to increase with postnatal age in calves, may also have contributed to this increase.

A study on *C. parvum* infection reported elevated acute-phase reactants (Hp, SAA), proinflammatory cytokines (IF- γ , IL-1 β , TNF- α), procalcitonin, neopterin, and oxidative stress markers (MDA), identifying procalcitonin and neopterin as potential diagnostic and prognostic biomarkers ([EL-DEEB et al., 2022](#)). Despite research, the immunopathogenesis of *C. parvum* remains unclear. Next generation sequencing may elucidate host-pathogen interactions in mucosal immunity ([VESHKINI et al., 2024](#)). *Cryptosporidium spp.* alters gut microbiota, reducing certain bacterial species, while others may mitigate infection severity. Tissue-based microbiome studies provide detailed insights into microbial communities but necessitate invasive sampling procedures, whereas fecal analysis facilitates non-invasive longitudinal monitoring of microbial dynamics ([HARES et al., 2025](#)). The combined evaluation of all these methodological approaches with acute phase proteins will contribute to a more comprehensive understanding and assessment of the inflammatory process.

Our study has several limitations. The diseased group in our study comprised diarrheic calves recruited from multiple farms. Selecting patients from a single farm or using an experimental approach to control external factors would enhance the interpretative strength of the results. Furthermore, extending the sampling period to encompass the neonatal phase may provide clearer insights into the dynamics of inflammatory processes. The small sample size may have obscured intergroup differences. Moderate APPs were not measured. While major APPs fluctuate rapidly, moderate APPs show gradual dynamics. Their inclusion would enhance understanding of the inflammatory processes ([DINLER et al., 2017](#)). In our study, the immunomodulatory effects of *Cryptosporidium spp.* on both the innate and adaptive immune systems were not evaluated. In cryptosporidiosis, investigating both innate (e.g., neutrophils, NK cells, chemokines, TLRs) and adaptive immune components (e.g., CD4⁺/CD8⁺ T cells, regulatory T cells)

will provide critical insights into how the parasite modulates the host's defense mechanisms.

Conclusions

This study assessed the inflammatory response in calves naturally infected with cryptosporidiosis and found no significant difference in serum Hp and SAA levels compared to healthy animals. However, a slight increase in Hp levels was observed over the follow-up period in the infected calves. These findings suggest that Hp and SAA have limited utility as prognostic biomarkers for evaluating disease progression in calves naturally infected with *Cryptosporidium spp.* A more comprehensive evaluation of these acute phase proteins appears to require additional studies with well-controlled experimental models.

Ethics approval

The study protocol received approval from the Local Board of Ethics Committee for Animal Experiments in Burdur Mehmet Akif Ersoy University (Decision No:2019/589).

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Declaration of competing interest

No potential conflicting interest was reported by the authors.

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SAŽETAK

Proljev je vodeći uzrok smrtnosti u novorođene teladi, što uzrokuje znatne ekonomske gubitke u stočarskoj proizvodnji. Kriptosporidioza, kao glavni čimbenik u infektivnoj etiologiji proljeva, uzročnik je velikog morbiditeta teladi. Istraživanje je provedeno kako bi se procijenio odgovor proteina akutne faze u teladi s kriptosporidiozom, s posebnim naglaskom na ulogu haptoglobina (Hp) i serumskog amiloida A (SAA) u prognozi bolesti. U istraživanje je uključeno 15 jedinki s kriptosporidiozom i 10 zdravih jedinki teladi. Klinička procjena i procjena broja oocista provedene su 0., 3., 5. i 7. dan, uz procjenu hematoloških i serumskih biokemijskih pokazatelja. U teladi s dijagnosticiranom kriptosporidiozom provedeno je standardno liječenje. Rezultati su pokazali da je provedenim liječenjem znakovito smanjeno izlučivanje oocista do kraja razdoblja istraživanja. Srednje vrijednosti haptoglobina u zaražene teladi pokazale trend porasta, dok su vrijednosti serumskog amiloida pokazale fluktuacije tijekom istraživnog razdoblja. Zaključuje se da iako haptoglobin i SAA mogu utjecati na odgovor proteina akutne faze, njihova je korisnost kao prognostičkog biomarkera kriptosporidioze u novorođene teladi ograničena. Potrebna su sveobuhvatna istraživanja kako bi se bolje razumio upalni proces u teladi prirodno zaražene kriptosporidijama.

Ključne riječi: telad; kriptosporidioza; haptoglobin; serumski amiloid A
