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RESEARCH ARTICLE

Thiol-Disulfide Homeostasis and Selected Biomarkers in Neonatal Calves with Rotavirus-Coronavirus Coinfection-Associated Diarrhea and Sepsis: Association with Colostrum Intake Status

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Abstract

This study included 20 Simmental calves (7-15 days old) presented with diarrhea and 10 healthy age- and breed-matched controls. Following clinical examination, mental status, dehydration score, respiratory rate, heart rate, and rectal temperature were recorded. Fecal samples were collected from diarrheic calves meeting sepsis criteria; calves positive for both rotavirus and coronavirus on a rapid immunochromatographic test were enrolled. The calves were hospitalized, treated, and monitored for 3 days. Blood samples were collected and clinical examinations were repeated before treatment (0 h) and during treatment (12, 24, 48, and 72 h). In septic calves, serum levels of reduced glutathione (GSH), total thiol (TT), native thiol (NT), endothelin-1 (ET-1), free triiodothyronine (fT3), free thyroxine (fT4), and insulin-like growth factor-1 (IGF-1), which were low before treatment, increased during therapy. Conversely, respiratory and heart rates and the levels of malondialdehyde (MDA), disulfide, and cortisol, which were high before treatment, decreased during therapy. Based on history, septic calves were further categorized as colostrum-fed or non-colostrum-fed, and group effects, time effects, and group x time interactions were evaluated. Among the evaluated parameters, MDA, IGF-1, and IgG showed the most pronounced group- and time-related differences. In conclusion, assessment of serum GSH, TT, NT, ET-1, fT3, fT4, IGF-1, MDA, disulfide, and cortisol (reflecting oxidative stress, endocrine response, and thiol-disulfide homeostasis) may contribute to the characterization and monitoring of systemic inflammatory, oxidative, endocrine, and immune alterations in neonatal calves with rotavirus-coronavirus coinfection-associated diarrhea and sepsis.

Keywords: Calf, Hormones, Immunoglobulin G (Ig-G), Neonatal period, Sepsis, Thiol-disulfide homeostasis

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INTRODUCTION

Calves are considered a fundamental stage in the livestock industry. Since calf rearing is crucial for the sustainability of the meat and dairy industry, obtaining and preserving high-quality genetic material is essential. This, in turn, depends on good hygiene management and nutrition [1]. The neonatal period is defined as the first 28 days after birth. Diarrhea is among the most important health problems encountered during this time [2]. Diarrhea is a clinical sign characterized by an increased frequency of defecation accompanied by changes in fecal consistency and increased fecal volume, typically resulting from inflammation of the gastrointestinal tract [3]. Bovine rotavirus and coronavirus are among the major infectious agents implicated in the etiology of neonatal calf diarrhea [4,5]. In diarrheic neonatal calves, sepsis is one of the leading causes of mortality [6]. Sepsis is a life-threatening systemic response to infection characterized by dysregulated host responses and organ dysfunction [7].

Reactive oxygen species (ROS) generated as a consequence of metabolic activity are neutralized by antioxidant defenses [8]. When the balance between oxidants and antioxidants is disrupted, oxidative stress occurs. Oxidative stress is associated with lipid peroxidation, DNA damage, and disturbances in enzymatic reactions, which may ultimately lead to immunosuppression [9]. Malondialdehyde (MDA) and reduced glutathione (GSH) are commonly measured biomarkers for assessing oxidative stress [10,11]. MDA is a secondary end product of

lipid peroxidation of polyunsaturated fatty acids (including arachidonic acid) and reflects free radical–induced damage to cell membranes [12]. In contrast, GSH protects cells from oxidative injury by detoxifying peroxides and scavenging free radicals [13]. Thiol-containing compounds are also organic molecules that contribute to cellular protection against oxidative stress. Oxidative products generated during metabolic processes can oxidize thiol groups, leading to the formation of disulfide bonds. This reversible process is referred to as dynamic thiol-disulfide homeostasis. Inflammation and oxidative stress contribute to disruption of this balance [14].

Due to their placental structure, cows cannot transplacentally transfer macromolecular components such as IgG to their calves during the intrauterine period. Therefore, calves are born with almost completely underdeveloped immune systems. Immune components received through colostrum are of great importance in the survival of newborn calves. This form of immunity transferred from the mother to the newborn via colostrum is called passive immunity transfer [15]. The response of the host to pathogenic agents is referred to as the immune response. It comprises two major arms: innate and adaptive immunity. As part of adaptive immunity, antibodies (immunoglobulins) are produced. Immunoglobulin G (IgG) is one of the predominant immunoglobulin classes and accounts for approximately 70-80% of circulating immunoglobulins. It is produced by plasma cells in the spleen, lymph nodes, and bone marrow [16]. In calves, IgG constitutes approximately 90% of the immunoglobulins transferred to the neonate [17].

Thyroid hormones are synthesized in the follicles of the thyroid gland and play essential roles in multiple physiological processes. These include regulation of oxygen consumption, maintenance of basal metabolic rate, modulation of energy, protein, and lipid metabolism, and control of cellular differentiation and proliferation [18]. Thyroid hormone concentrations may change in disease states, and such alterations have been suggested to have prognostic value. Thyroid function is commonly assessed by measuring serum triiodothyronine and thyroxine concentrations [19,20].

Glucocorticoids play a key role in the physiological adaptation to stress and severe inflammatory conditions [21]. During stress and severe illness, activation of the hypothalamic-pituitary-adrenal (HPA) axis stimulates cortisol secretion [22,23]. Insulin-like growth factor-1 (IGF-1) is a 70-amino acid polypeptide hormone primarily synthesized in the liver. Circulating IGF-1 concentrations can vary in response to immune activation and inflammatory status [24].

Endothelin-1 (ET-1) is a 21-amino acid peptide produced and released by endothelial cells. It is a potent vasoconstrictor, and its circulating concentrations may change under inflammatory conditions [25].

Neonatal enteric sepsis is accompanied by coordinated disturbances in redox homeostasis, endothelial regulation, endocrine and metabolic adaptation, stress responses, and passive humoral immunity. Thiol–disulfide homeostasis, GSH, and MDA serve as complementary indicators of redox status; ET-1 reflects endothelial–vascular regulation; fT3, fT4, cortisol, and IGF-1 indicate endocrine, metabolic, and stress-related adaptation; and IgG reflects passive humoral immune status. Because colostrum provides immunoglobulins and bioactive constituents that support neonatal immune competence, intestinal maturation, and metabolic adaptation, colostrum intake status may be associated with the magnitude and temporal course of these systemic responses. We hypothesized that calves with rotavirus–coronavirus coinfection-associated diarrhea and sepsis would exhibit coordinated multisystem biomarker alterations relative to healthy calves, that these biomarkers would change during the 72 h treatment and monitoring period, and that their temporal trajectories would differ according to colostrum intake status. Accordingly, this study aimed to compare the selected biomarkers between septic and healthy neonatal calves, characterize their longitudinal changes over 72 h, and evaluate whether their temporal patterns were associated with colostrum intake status.

Material and Methods

Ethical Approval

The study was conducted after approval was obtained from the Kafkas University Animal Experiments Local Ethics Committee (KAÜ-HADYEK/2025-009).

Animal Material

The study population consisted of 20 Simmental calves aged 7-15 days with diarrhea. All 20 diarrheic calves tested concurrently positive for both rotavirus and coronavirus. The Control group consisted of 10 clinically healthy, age and breed-matched calves.

Clinical Examination and Pathogen Detection

Clinical examinations were performed to record mental status, dehydration score, respiratory rate, heart rate, and rectal temperature. Fecal samples were obtained from calves that met the sepsis criteria *(Table 1)* and were tested according to the manufacturer's instructions using a rapid antigen test kit (BoviD-5 Ag Test Kit®; Bionote Inc., Korea). Diarrheic calves positive for both rotavirus and coronavirus were included. Calves meeting the sepsis criteria were subsequently hospitalized and treated. Blood samples were collected and clinical examinations were repeated at predefined time points (0, 12, 24, 48, and 72 h).

Table 1. The presence of at least two of the following criteria was considered sufficient for the diagnosis of sepsis

Parameters	Criteria
Total leukocyte count (x10^3/μL)	<5x10^3/μL or >12x10^3/μL
Respiratory rate (/min)	>45
Heart rate (/min)	<90 or >120
Band neutrophils (%)	>10%
Body temperature (°C)	>39.0 or <36.6

Treatment Protocol

Calves meeting the sepsis criteria were hospitalized in individual stalls and monitored for 72 h. During hospitalization, routine nursing care and feeding were provided, and treatment was administered as follows. Based on the degree of dehydration, intravenous fluid therapy consisted of 0.9% sodium chloride (PVC®, 1000 mL; Eczacıbaşı Baxter, Istanbul, Türkiye), 1.3% sodium bicarbonate (Bikarvil®; Vilsan, Ankara, Türkiye), and 5% dextrose (Polifleks®; Polifarma, Tekirdağ, Türkiye). Because blood gas analysis was not available, the sodium bicarbonate requirement was estimated using a pragmatic base-deficit calculation described by Gökce [26]. For antimicrobial therapy, enrofloxacin was administered parenterally at 2.5-5 mg/kg (Baytril® 10%; Bayer, Germany). In addition, sulfadoxine-trimethoprim was administered intravenously at 5 mL/40 kg body weight for 3 days (Animar®; Ceva, France). An oral powder containing sulfadimidine and oxytetracycline was administered for 3 days at 2.5 g/40 kg body weight (Tetramezathine®; Ceva, France). Supportive therapy included a parenteral B-complex vitamin preparation for 3 days at 8-10 mL/calf (Berovit B12®; Ceva, France), vitamin C at 4-6 mg/kg (Maxivit-C®; Bavet, Türkiye), vitamin AD_3E at 1 mL/50 kg (Ademin®; Ceva, France), and sodium selenite + vitamin E + vitamin B1 at 2 mL/calf (Yeldif®; Ceva, France). To control inflammation, meloxicam was administered once at 0.5 mg/kg (Bavet Meloxicam®; Bavet, Türkiye). All sick calves recovered following treatment, and no deaths occurred during the 72 h monitoring period.

Collection of Blood Samples

Blood samples were obtained from diseased calves via jugular venipuncture before treatment (0 h) and during treatment (12, 24, 48, and 72 h); healthy calves were sampled once. Sampling was performed using a holder with compatible sterile needles (Vacuette®, Greiner Bio-One GmbH, Austria) and serum separator (gel) tubes (BD Vacutainer®, BD, UK). Samples were centrifuged at 3000 rpm for 10 min (Rotina 380R®; Hettich, Germany), and serum was aliquoted and stored at −20°C until analysis.

Analyses

Serum GSH, MDA, and thiol-disulfide homeostasis parameters were assessed. Total thiol (TT) and native thiol (NT) concentrations were measured spectrophotometrically according to Erel and Neselioglu [27]. Disulfide concentration and derived indices (disulfide/TT x 100, disulfide/NT × 100, and NT/TT x 100) were calculated from TT and NT values as previously described [28]. Reduced glutathione (GSH) was determined using the method of Beutler et al.[29], and malondialdehyde (MDA) was measured according to Yoshioka et al. [30].

Serum immunoglobulin G (IgG; mg/dL), free triiodothyronine (fT3; ng/L), free thyroxine (fT4; ng/dL), cortisol (μg/dL), and insulin-like growth factor-1 (IGF-1; ng/mL) concentrations were measured using a chemiluminescence method (Snibe Diagnostics®, China). Based on the medical history obtained, septic calves were classified according to colostrum intake status. Study parameters were compared between colostrum-fed and non-colostrum-fed calves, and the results are presented in *Table 2*, *Fig. 1* and *Fig. 2*.

Serum endothelin-1 concentrations were determined using a commercial bovine-specific ELISA kit (Bovine ET-1 ELISA Kit®; BT Lab, China) according to the manufacturer's instructions. Absorbance was read at 450 nm using a microplate reader (Thermo Scientific®, USA). ET-1 concentrations were calculated from the standard curve using regression analysis.

Statistical Analysis

The distributional properties of continuous variables were assessed using the Shapiro-Wilk test. The normality of data distribution was evaluated separately for each variable within each study group [healthy Control group (n = 10), overall Sepsis group (n = 20), colostrum-fed subgroup (n = 10), and non-colostrum-fed subgroup (n = 10)] and at each measurement time point (0, 12, 24, 48, and 72 h). All data are presented as mean ± standard deviation (SD). Statistical analyses were performed using GraphPad Prism (version 10; GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). A two-sided P-value <0.05 was considered statistically significant for all analyses.

Blood samples from the healthy Control group were collected only once to provide baseline reference data. Therefore, this dataset was compared independently against each of the five sequential time points (0, 12, 24, 48, and 72 h) of the Sepsis group and its subgroups using independent comparisons. For normally distributed variables, an independent-samples t-test was used, and homogeneity of variances was assessed using Levene's test (Welch's t-test was applied when the homogeneity

Table 2. *Main effects of colostrum intake (group), time, and the group × time interaction for the evaluated parameters within the Sepsis group (colostrum-fed vs. non-colostrum-fed calves)*

Parameters	Colostrum Status	Sepsis				
		0 h	12 h	24 h	48 h	72 h
GSH (mg/dL)	C (+)	4.86±0.65	5.02±0.67	4.98±0.61	5.57±1.48	5.97±1.58
	C (-)	3.33±0.27	3.94±0.98	4.58±0.86	4.12±0.70	4.70±1.38
MDA (µmol/L)	C (+)	$2.06±0.52^{a**}$	$1.69±0.51^{ab***}$	$1.40±0.32^{ab***}$	$1.30±0.07^{b}$	$1.27±0.10^{b}$
	C (-)	$2.69±0.79^{a}$	$2.95±0.60^{a}$	$2.87±0.51^{a}$	$1.57±0.47^{b}$	$1.28±0.06^{b}$
TT (µmol/L)	C (+)	624.59±47.50	668.02±62.78	683.44±61.85	692.37±46.17	765.42±69.97
	C (-)	504.08±25.33	561.50±60.71	572.36±60.79	603.43±29.18	602.51±47.67
NT (µmol/L)	C (+)	207.64±61.94	306.95±107.24	320.75±53.27	302.52±47.19	513.11±120.65
	C (-)	156.15±43.97	221.84±75.82	236.61±31.85	237.60±33.60	313.79±80.63
Disulfide (µmol/L)	C (+)	208.47±29.95	180.53±29.21	181.34±26.20	194.92±29.80	126.15±29.53
	C (-)	173.96±17.32	169.82±20.80	167.87±25.32	182.91±24.83	144.35±30.39
Disulfide/NT (%)	C (+)	111.21±43.14	72.23±50.76	58.29±13.90	66.70±17.53	26.91±11.68
	C (-)	123.96±55.25	91.16±51.35	71.86±13.21	79.27±20.65	50.73±22.71
Disulfide/TT (%)	C (+)	33.44±4.59	27.42±6.18	26.56±3.13	28.11±3.60	16.83±5.01
	C (-)	34.59±3.88	30.60±5.54	29.26±2.42	30.24±3.08	24.12±5.60
NT/TT (%)	C (+)	33.12±9.17	45.16±12.35	46.88±6.27	43.78±7.21	66.34±10.02
	C (-)	30.81±7.76	38.79±11.08	41.48±4.83	39.51±6.16	51.76±11.21
Endothelin-1 (pg/mL)	C (+)	54.42±6.04	54.91±10.45	59.04±7.39	64.28±5.72	67.20±12.91
	C (-)	40.64±9.90	44.25±8.11	46.07±3.73	53.05±6.66	54.34±1.54
fT_3 (ng/L)	C (+)	5.96±2.12	5.64±1.60	6.12±2.35	6.40±1.46	8.83±3.03
	C (-)	3.78±2.29	4.42±0.65	5.29±2.05	5.05±1.95	8.58±3.23
fT_4 (ng/dL)	C (+)	1.45±0.35	1.61±0.42	1.48±0.50	1.54±0.33	2.07±0.48
	C (-)	1.36±0.38	2.02±0.59	1.65±0.33	1.87±0.51	1.94±0.38
IGF-1 (ng/mL)	C (+)	$296.50±14.41^{a**}$	$285.88±7.85^{ab**}$	$291.63±21.23^{ab***}$	$325.25±30.57^{c***}$	$335.75±42.84^{c*}$
	C (-)	$253.43±21.52^{a}$	$244.71±23.82^{a}$	$222.71±26.34^{b}$	$258.14±14.42^{a}$	$299.14±44.07^{c}$
IgG (mg/dL)	C (+)	$723±36.80^{a**}$	$711.75±23.41^{a**}$	$693±117.19^{a***}$	$722.63±77.54^{a***}$	$831.38±107.74^{b***}$
	C (-)	$609.14±73.10^{a}$	$581±72.48^{a}$	$513±16.15^{b}$	$516.57±81.67^{b}$	$634±86.49^{a}$
Cortisol (µg/dL)	C (+)	4.25±1.53	4.16±1.77	4.02±2.07	4.71±2.15	2.01±0.58
	C (-)	7.53±4.67	7.84±4.52	6.53±2.69	5.14±2.49	3.68±1.62

GSH: *Reduced glutathione,* ***MDA:*** *Malondialdehyde,* ***TT:*** *Total thiol,* ***NT:*** *Native thiol,* ***fT3:*** *Free triiodothyronine,* ***fT4:*** *Free thyroxine,* ***IGF-1:*** *Insulin-like growth factor-1,* ***IgG:*** *Immunoglobulin G,* ***C (+):*** *Colostrum-fed,* ***C (−):*** *Non-colostrum-fed. Significance notation: *P<0.05, **P<0.01, ***P<0.001. Asterisks indicate significant differences between C (+) and C (−) at the same sampling time point (pairwise comparisons). Different lowercase letters* ***(a–c)*** *indicate significant differences among time points within the Sepsis group*

assumption was violated). For variables that did not meet the normality assumption, between-group comparisons were performed using the Mann–Whitney U test.

To evaluate longitudinal (temporal) changes within the overall Sepsis group, repeated-measures analyses were performed on blood parameters measured sequentially in the same calves at 0, 12, 24, 48, and 72 h. For variables meeting parametric assumptions, a one-way repeated-measures ANOVA was performed, and the assumption of sphericity was evaluated using Mauchly's test; in cases of sphericity violation, degrees of freedom were corrected using the Greenhouse-Geisser correction. When a significant main effect of time was detected, Bonferroni-adjusted post-hoc multiple comparison tests were used to identify specific differences between time points. Temporal changes for parameters failing to meet normality assumptions were analyzed using the Friedman test, followed by post-hoc pairwise comparisons using Bonferroni-adjusted Wilcoxon signed-rank tests. Because all calves had complete repeated measurements at identical time points without missing observations, RM-ANOVA was considered an appropriate analytical approach for longitudinal analyses.

Additionally, a two-way mixed repeated-measures ANOVA was conducted to evaluate the longitudinal effects of

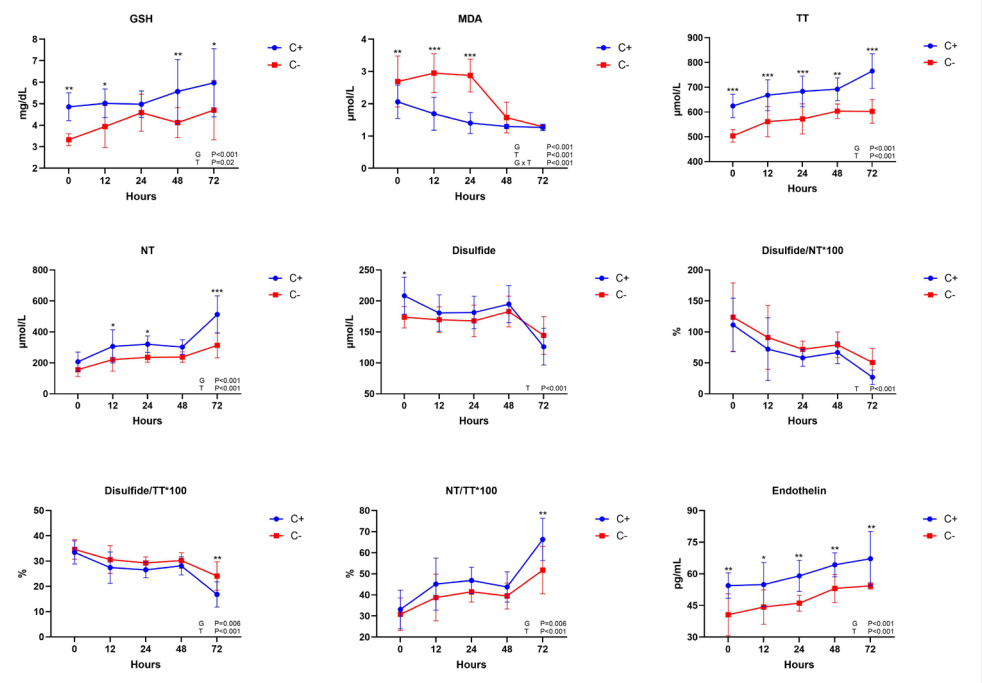

Fig 1. Longitudinal changes and time-course comparison of oxidative stress parameters, thiol-disulfide homeostasis variables, and endothelin-1 between colostrum-fed (C+) and non-colostrum-fed (C-) neonatal calves with sepsis secondary to rotavirus and coronavirus-associated diarrhea. The panels display reduced glutathione (GSH), malondialdehyde (MDA), total thiol (TT), native thiol (NT), disulfide, disulfide/NT ratio, disulfide/TT ratio, NT/TT ratio, and endothelin-1. Data are presented as mean ± standard deviation (SD). Asterisks (* P<0.05, ** P<0.01, *** P<0.001) indicate significant differences between the C+ and C- groups at the same sampling time point based on independent pairwise comparisons. G: Main effect of colostrum status (group); T: Main effect of time; G × T: Group × Time interaction effect determined by two-way mixed repeated-measures ANOVA

colostrum-feeding status (colostrum-fed vs. non-colostrum-fed), time, and their interaction (group x time) on the measured parameters within the Sepsis group. In this model, colostrum-feeding status was designated as the between-subjects factor, while time was defined as the within-subjects repeated factor. When significant main effects or group x time interactions were detected, post-hoc multiple comparisons were completed using Bonferroni-adjusted tests.

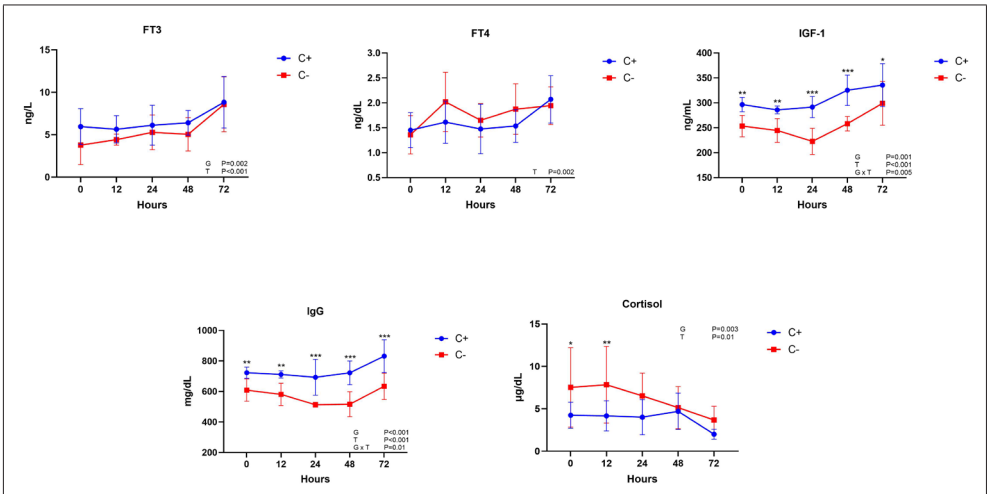

Fig 2. Longitudinal changes and time-course comparison of hormonal and immunological parameters between colostrum-fed (C+) and non-colostrum-fed (C-) neonatal calves with sepsis secondary to rotavirus and coronavirus-associated diarrhea. The panels display free triiodothyronine (FT3), free thyroxine (FT4), insulin-like growth factor-1 (IGF-1), immunoglobulin G (IgG), and cortisol. Data are presented as mean ± standard deviation (SD). Asterisks (*: P<0.05, **: P<0.01, ***: P<0.001) indicate significant differences between the C+ and C- groups at the same sampling time point based on independent pairwise comparisons. G: Main effect of colostrum-feeding status (group); T: Main effect of time; G × T: Group × Time interaction effect determined by two-way mixed repeated-measures ANOVA

Correlation analyses were conducted to evaluate associations among clinical, oxidative stress, hormonal, and immunological parameters. Pearson's correlation coefficient was used for normally distributed variables, whereas Spearman's rank correlation coefficient was used for non-normally distributed variables.

Results

Clinical Findings

Clinical examination of septic calves revealed severe enteritis and marked dehydration (10-12%), accompanied by enophthalmos, decreased skin turgor, weakness, severe depression, lateral recumbency, and absence of the suckling reflex.

Vital Findings

In the Sepsis group, respiratory rate at 0 h (pre-treatment) was higher than at subsequent time points. Between-group comparisons showed that respiratory rate at 0, 12, and 24 h was higher in the Sepsis group than in the Control group. Within the Sepsis group, heart rate at 0 h was higher than at 48 and 72 h; moreover, heart rate was higher in the Sepsis group than in the Control group at all assessed time points (0, 12, 24, 48, and 72 h). Rectal temperature at 0 h was lower in the Sepsis group than in the Control group *(Table 3)*.

Biochemical Findings

Effects of colostrum intake, time, and their interaction are summarized in *Table 2*. For GSH, TT, NT, ET-1, fT3, and cortisol, significant main effects of colostrum intake and time were observed, whereas the colostrum × time interaction was not significant. For fT4, disulfide, and disulfide/NT, only the main effect of time was significant. Similarly, for NT/TT, significant main effects of colostrum intake and time were detected, with no significant interaction.

For IGF-1 and IgG, significant main effects of colostrum intake and time were observed, and the colostrum × time interaction was also significant *(Table 2)*. Post hoc analyses indicated that IGF-1 differed between the Sepsis and Control groups at all assessed time points (0, 12, 24, 48, and 72 h). Within the sepsis subgroups, IGF-1 in colostrum-fed calves at 0 h differed from values at 48 and 72 h. In non-colostrum-fed calves, IGF-1 at 0, 12, and 48 h was higher than at 24 h and lower than at 72 h.

For IgG, significant differences compared with the control group were observed at all sampling time

Table 3. *Within-group comparisons across time points in the Sepsis group and between-group pairwise comparisons of the Sepsis and Control groups at corresponding time points*

Parameters	Sepsis					Control
	0 h	12 h	24 h	48 h	72 h	
Respiratory rate (/min)	44.93±18.87^{Aa}	33.23±7.70^{Ab}	28.93±7.48^{Ab}	27.07±6.32^{Bb}	26.80±8.74^{Bb}	22.93±5.12^{B}
Heart rate (/min)	141.73±18.16^{Aa}	132.53±23.12^{Aab}	127.73±11.63^{Aab}	122.40±13.82^{Ab}	121.33±17.95^{Ab}	99.33±6.26^{B}
Rectal temperature (°C)	37.04±2.34^{A}	38±0.75^{B}	37.89±1.14^{B}	38.21±0.86^{B}	38.72±0.67^{B}	38.37±0.30^{B}
GSH (mg/dL)	4.15±0.93^{Ab}	4.51±0.97^{Aab}	4.79±0.74^{Aab}	4.89±1.37^{Aab}	5.38±1.58^{ABa}	6.28±1.30^{B}
MDA (µmol/L)	2.35±0.71^{Aa}	2.28±0.84^{Aa}	2.09±0.86^{Aa}	1.42±0.35^{ABb}	1.27±0.08^{ABb}	1.20±0.32^{B}
TT (µmol/L)	568.35±72.64^{Ab}	618.31±81.09^{Aab}	631.60±82.38^{Aab}	650.87±59.50^{Aab}	689.39±102.47^{Aa}	986.62±202.67^{B}
NT (µmol/L)	183.61±58.77^{Ac}	267.23±100.72^{Abc}	281.48±61.17^{Ab}	272.22±52.16^{Abc}	420.09±143.73^{Aa}	788.39±205.62^{B}
Disulfide (µmol/L)	192.37±29.91^{Aa}	175.54±25.36^{Aa}	175.06±25.82^{Aa}	189.32±27.33^{Aa}	134.65±30.34^{Ab}	99.12±26.64^{B}
Disulfide/NT (%)	117.16±47.77^{Aa}	81.06±50.14^{Ab}	64.62±14.85^{Abc}	72.57±19.46^{Abc}	38.02±20.99^{Ac}	13.52±5.6^{4B}
Disulfide/TT (%)	33.98±4.16^{Aa}	28.91±5.91^{Ab}	27.82±3.06^{Ab}	29.10±3.43A^{ab}	20.23±6.34^{Ac}	10.35±3.46^{B}
NT/TT (%)	32.04±8.32^{Ac}	42.19±11.82^{Ab}	44.36±6.12^{Ab}	41.79±6.86^{Abc}	59.54±12.68^{Aa}	79.29±6.92^{B}
Endothelin-1 (pg/mL)	46.16±10.26^{Ab}	51.77±10.20^{Aab}	52.98±8.84^{Aab}	59.04±8.31^{Aa}	61.19±11.34^{ABa}	72.04±20.25^{B}
fT_3 (ng/L)	4.94±2.40^{Ab}	5.07±1.37 ^{Ab}	5.73±2.18 ^{Ab}	5.77±1.78 ^{Ab}	8.71±3.02^{ABa}	11.17±3.9^{4B}
fT_4 (ng/dL)	1.41±0.36^{Ab}	1.80±0.53^{Aab}	1.56±0.42^{Ab}	1.69±0.44^{Aab}	2.01±0.42^{Aa}	2.66±0.74^{B}
IGF-1 (ng/mL)	276.40±28.23^{Ab}	266.67±26.94^{Ab}	259.47±42.30^{Ab}	293.93±41.92^{Aab}	318.67±45.90^{ABa}	325.80±35.47^{B}
IgG (mg/dL)	669.87±80.15^{Aab}	650.73±84.17^{Aab}	609±124.98^{Ab}	626.47±131.10^{Aab}	739.27±139.28^{ABa}	823.93±128.73^{B}
Cortisol (µg/dL)	5.78±3.66^{Aa}	5.88±3.73^{Aa}	5.19±2.63^{Aab}	4.91±2.24^{Aab}	2.79±1.43^{ABb}	2.02±0.77^{B}

GSH: *Reduced glutathione,* ***MDA:*** *Malondialdehyde,* ***TT:*** *Total thiol,* ***NT:*** *Native thiol,* ***fT3:*** *Free triiodothyronine,* ***fT4:*** *Free thyroxine,* ***IGF-1:*** *Insulin like growth factor-1,* ***IgG:*** *Immunoglobulin G. Different lowercase letters* ***(a–c)*** *indicate significant differences among time points within the Sepsis group. Different uppercase letters* ***(A–B)*** *indicate significant differences between each Sepsis time point and the Control group (pairwise comparisons)*

Table 4. *Correlations among the parameters evaluated in the study*

Parameters	GSH	MDA	TT	NT	Disulfide	ET-1	fT3	fT4	IGF-1	IgG
GSH										
MDA	-0.334**									
TT	0.283**	-0.352**								
NT	0.342**	-0.471**	0.866**							
Disulfide	-0.393**	0.424**	-0.387**	-0.735**						
ET-1	0.264*	-0.457**	0.251*	0.298**	-0.265*					
fT3	0.336**	-0.424**	0.419**	0.522**	-0.474**	0.199				
fT4	0.152	-0.250*	0.428**	0.498**	-0.425**	0.170	0.481**			
IGF-1	0.253*	-0.392**	0.217*	0.311**	-0.373**	0.191	0.459**	0.210*		
IgG	0.303**	-0.332**	0.276**	0.318**	-0.287**	0.238*	0.360**	0.191	0.314**	
Cortisol	-0.242*	0.376**	-0.490**	-0.502**	0.422**	-0.206	-0.296**	-0.239*	-0.194	-0.285**

GSH: *Reduced glutathione,* ***MDA:*** *Malondialdehyde,* ***TT:*** *Total thiol,* ***NT:*** *Native thiol,* ***fT3:*** *Free triiodothyronine,* ***fT4:*** *Free thyroxine,* ***IGF-1:*** *Insulin-like growth factor-1,* ***IgG:*** *Immunoglobulin G; ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed)*

points. Within the sepsis subgroups, IgG in colostrum-fed calves at 0 h differed from 72 h, whereas in non-colostrum-fed calves, IgG at 0, 12, and 72 h was higher than at 24 and 48 h.

Correlations among the evaluated parameters are summarized in *Table 4*. Overall, the analysis suggested that thiol–disulfide homeostasis was closely associated with the hormonal response. GSH, TT, and NT were positively correlated with fT3, fT4, and IGF-1 and negatively correlated with disulfide. Conversely, disulfide showed significant negative correlations with fT3, fT4, and IGF-1 and a positive correlation with cortisol. Notably, the positive association between NT and fT3 and the strong negative association between NT and disulfide suggest that, in sepsis, shifts in redox balance occur in parallel with hormonal regulation.

Discussion

Diarrheic neonatal calves commonly exhibit lethargy/mental depression, tachycardia associated with reduced arterial pressure (often with a weak pulse), tachypnea, loss of the suckling reflex, enophthalmos, and decreased skin turgor [31]. In the present study, clinical findings in the Sepsis group were consistent with these reports. These signs likely reflect circulatory compromise secondary to diarrhea-induced fluid losses. Following treatment including fluid therapy with supportive medications (anti-inflammatory agents, antimicrobials, and vitamins) clinical status improved, and the initially elevated respiratory and heart rates in the Sepsis group declined toward control values.

Rotavirus and coronavirus are among the principal viral pathogens responsible for neonatal calf diarrhea. Coronavirus can cause marked injury to the gastrointestinal tract, particularly the intestinal villi, where it may induce epithelial alterations (including a shift from cuboidal to squamous morphology) and reduce the villus-to-crypt ratio, thereby substantially compromising absorptive capacity. Moreover, coronavirus may exacerbate diarrhea by impairing fluid absorption in the large intestine [31,32]. In contrast, rotavirus primarily targets the brush border of small-intestinal villous epithelial cells, leading to villous atrophy and compensatory crypt hyperplasia [31,33]. As a consequence, severe dehydration and electrolyte disturbances in diarrheic calves may promote oxidative stress and are associated with an increased risk of mortality [34].

Fu et al.[35] reported increased serum MDA concentrations in diarrheic calves accompanied by reduced antioxidant capacity, and Sağıroğlu et al.[34] similarly observed increased MDA together with decreased GSH. These alterations were attributed to oxidative injury associated with fluid electrolyte imbalance and metabolic acidosis. In calves with SIRS, also found elevated MDA levels, consistent with previous reports [36,37], and this has been linked to infectious inflammation driven release of proinflammatory cytokines that promote oxidative stress and lipid peroxidation. In addition, Terzi et al.[38] with Koçak and Duru [39] reported reductions in total thiol and native thiol levels in diarrheic calves, and Terzi et al. [38] further reported increased disulfide concentrations, supporting disruption of thiol-disulfide homeostasis under oxidative stress. In the present study, serum MDA and disulfide were elevated, whereas GSH, total thiol, and native thiol were reduced before

treatment, consistent with oxidative stress accompanying gastrointestinal injury and fluid electrolyte derangements. Following treatment, MDA and disulfide decreased and GSH, total thiol, and native thiol increased, suggesting partial restoration of redox balance in parallel with clinical stabilization.

Thyroxine (T4) and triiodothyronine (T3) are synthesized in thyroid follicles and regulate a wide range of physiological processes, including oxygen consumption, basal metabolic rate, macronutrient metabolism, and cellular differentiation and maturation [18]. In clinical settings, thyroid status is commonly assessed by measuring circulating free T3 (fT3) and free T4 (fT4), which represent the biologically available (unbound) fractions. Alterations in thyroid hormone concentrations have been reported in systemic illness, supporting their potential prognostic relevance [19,20]. In severe inflammatory conditions, decreases in fT3 and fT4 may occur and are commonly described as nonthyroidal illness syndrome [40]. Proposed mechanisms include reduced thyroid-stimulating hormone (TSH) secretion, anorexia-associated fasting, and impaired thyroid hormone binding and metabolism during systemic disease [41]. In severely dehydrated diarrheic calves, Hajimohammadi et al. [20] and Çorapsız and Birdane [42] reported decreased fT3 and fT4, which they attributed to endotoxemia- and cytokine-mediated disruption of thyroid function [43]. Cytokines can reduce peripheral conversion of T4 to T3 by suppressing pituitary TSH release and by impairing thyroxine 5′-deiodinase activity in thyroid and hepatic tissues [44]. Moreover, in acute severe illness such as sepsis, reductions in thyroxine-binding globulin (TBG) have been implicated in lower circulating free hormone concentrations [43]. In the present study, serum fT3 and fT4 were decreased in diarrheic neonatal calves before treatment and increased during therapy. These findings may reflect combined effects of disease severity (including reduced TSH secretion), anorexia-associated fasting, endotoxemia/cytokine-mediated alterations in thyroid function and deiodination, and changes in thyroid hormone binding proteins such as TBG.

In severe inflammatory disease, activation of the hypothalamic pituitary adrenal (HPA) axis increases adrenal glucocorticoid output. Hypothalamic stimulation of the pituitary promotes adrenocorticotropic hormone (ACTH) release, which in turn stimulates the adrenal cortex to secrete cortisol [22,23]. Cortisol exerts pleiotropic effects that are particularly relevant during systemic inflammation, including modulation of the inflammatory response, support of cardiovascular homeostasis through permissive effects on vascular tone and fluid balance, and regulation of intestinal barrier function [45,46]. In circulation, cortisol is largely bound and transported by corticosteroid-binding globulin, a liver-derived plasma protein [47]. In sepsis, increased ACTH and cortisol concentrations have been reported and are commonly attributed to cytokine-driven inflammatory stress [48]. Accordingly, monitoring adrenal axis hormones has been suggested to provide prognostic information in septic patients and in conditions characterized by marked stress and inflammation [21,45,49]. In the present study, serum cortisol concentrations were elevated in diarrheic calves before treatment and decreased during therapy. These changes may reflect attenuation of systemic stress and inflammation as dehydration and circulatory compromise improved with treatment.

Insulin-like growth factor-1 (IGF-1) is produced primarily by the liver, acts in concert with growth hormone, and contributes to growth and tissue development, including the maturation of the small intestine and skeletal muscle. During the neonatal period, IGF-1 is abundant in the intestinal epithelium and supports enterocyte proliferation and maturation. It has also been suggested to enhance barrier integrity during gastroenteritis, thereby limiting the effects of enteric pathogens and their toxins [50,51]. Colostrum contains substantial amounts of IGF-1 and IGF-binding proteins, which may support neonatal growth and gastrointestinal development [50]. In neonatal ruminants, circulating IGF-1 concentrations can fluctuate, and previous studies have reported a tendency for initially higher concentrations early in life to decline over time. Malabsorption, maldigestion, and endotoxemia have been proposed as contributing factors to reduced IGF-1 concentrations [52,53]. Decreased IGF-1 has also been reported in sepsis, potentially reflecting intestinal barrier dysfunction and systemic inflammation. An increased intestinal bacterial load may promote epithelial apoptosis and facilitate bacterial translocation to mesenteric lymph nodes, the liver, and the bloodstream. In addition, mucosal permeability increases during systemic illness, and both inflammatory activation and hypoperfusion can further compromise barrier integrity, which has been associated with reductions in IGF-1 [54]. In the present study, serum IGF-1 concentrations were lower in diarrheic septic calves with rotavirus/coronavirus infection than in controls. This decrease may be attributable to multiple concurrent factors, including insufficient colostrum intake in a subset of calves, impaired hepatic synthetic capacity during systemic

illness, and inflammation-associated increases in intestinal permeability with secondary effects on gut bacterial burden. Furthermore, virus-induced gastrointestinal injury with malabsorption, together with dehydration-related circulatory compromise, may have contributed to the observed reduction in serum IGF-1.

Immunoglobulins (Ig), which are abundant in colostrum, are antibody proteins produced primarily by B lymphocytes. Their principal functions are to recognize and bind antigens such as bacteria, viruses, and other potentially harmful foreign substances and to facilitate their neutralization or clearance [55]. Immunoglobulin G (IgG) is a predominant immunoglobulin isotype and plays a pivotal role in host defense against invading pathogens. IgG mediates protection by engaging Fc receptor bearing innate immune effector cells and by activating the complement cascade [56,57]. In the present study, IgG concentrations were lower in diarrheic septic calves that did not receive colostrum than in those that received colostrum, most likely reflecting absent and/or inadequate colostrum intake.

During sepsis, reactive oxygen species (ROS) are generated by both the vascular endothelium and activated inflammatory cells, including neutrophils and macrophages. Excessive ROS in the setting of insufficient antioxidant defenses can disrupt endothelial homeostasis, alter vascular tone, promote platelet and leukocyte aggregation, increase vascular permeability, and shift the hemostatic balance toward a procoagulant state collectively contributing to endothelial dysfunction [58]. Endothelin-1 (ET-1), a potent vasoconstrictor peptide, is produced primarily by vascular endothelial cells [59]. In the present study, ET-1 concentrations were lower than controls at early time points, and the difference appeared to attenuate by 72 h. These results suggest impaired endothelial function associated with sepsis-related oxidative stress, which could attenuate ET-1 production and/or release.

In conclusion, thiol-disulfide homeostasis, endothelin-1, IgG, and the selected endocrine and oxidative biomarkers exhibited temporal alterations during the 72-h treatment and monitoring period in neonatal calves with rotavirus- and coronavirus-associated diarrhea and sepsis. The longitudinal profiles of several parameters also varied according to colostrum intake status. Collectively, these findings suggest that the simultaneous evaluation of redox, endothelial, humoral immune, endocrine, metabolic, and stress-related biomarkers may contribute to a more comprehensive characterization and monitoring of the systemic response associated with neonatal enteric sepsis. However, given the observational design, history-based classification of colostrum intake, limited sample size, and absence of different clinical outcome groups, the findings should be interpreted cautiously. Further prospective studies involving larger populations and clearly defined clinical outcomes are required to establish the clinical monitoring utility and potential prognostic relevance of these biomarkers.

Declarations

Availability of Data and Materials: The data that support the findings of this study are available from the corresponding author (M.S.) upon reasonable request.

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Ethical Approval: The study was conducted after approval was obtained from the Kafkas University Animal Experiments Local Ethics Committee (KAÜ-HADYEK/2025-009).

Competing Interests: The authors declare that they have no competing interests.

Generative Artificial Intelligence (AI): The authors declare that no generative artificial intelligence (AI) was used in the preparation of this manuscript

Authors Contribution: MK and MS conceived and designed the study. MS, YUB, KK, NY, MM, and EA executed the experiment and analyzed the sera samples. MM, MK analyzed the data. All authors interpreted the data, critically revised the manuscript for important intellectual contents and approved the final version.

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