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Evaluation of Hematology and Blood Gas Parameters in Calves with Sepsis *

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In this study, it was aimed to conduct diagnostic evaluation of hematological indices (monocyte/lymphocyte ratio (MLR), erythrocyte distribution width (RDW), mean platelet volume (MPV)) and blood gas parameters (partial oxygen pressure (pO_2), partial carbon dioxide pressure (pCO_2), lactate, sodium (Na^+), potassium (K^+), chlorine (Cl^-), bicarbonate (HCO_3^-) pH, anion gap (AG) and base excess (BE)) in calves with diarrhea associated sepsis. The study material consisted of two groups, 20 calves with sepsis (sepsis) which were 1-28 days old and presented with diarrhea and 10 healthy calves (control). Fecal samples obtained from calves diagnosed with systemic inflammatory response syndrome (SIRS) were analyzed for Rotavirus, Coronavirus, *Escherichia coli*, *Cryptosporidium parvum* and *Giardia lamblia* using immunochromatographic test kits. Total leukocyte count (WBC), lymphocyte (LYM), monocyte (MON), hematocrit (HCT), RDW and MPV, pO_2, pCO_2, lactate, Na^+, K^+, Cl^-, HCO_3^-, pH, AG and BE parameters were measured. WBC (P<0.010), MON (P<0.001), MPV (P<0.001) and MLR (P<0.001) values of the sepsis group were statistically higher than the control group. In the sepsis group, pH (P<0.001), HCO_3^- (P<0.001) and BE (P<0.001) values were significantly lower than in the control group. K^+ (P<0.003) and AG (P<0.001) concentrations were significantly higher in the sepsis group compared to the control group. In the diagnosis of sepsis, the area under the curve for MON was 0.895, with a sensitivity of 80% and specificity of 75%; for RDW, the area under the curve was 0.840, with a sensitivity of 80% and specificity of 75%; for MPV, the area under the curve was 0.915, with a sensitivity of 100% and specificity of 90%; for MLO, the area under the curve was 0.910, with a sensitivity of 80% and specificity of 80%. In conclusion, MPV and MLR parameters are considered to be valuable in the diagnosis of sepsis in calves.

Key Words: *Calf, sepsis, MPV, MLR, diarrhea*

Sepsisli Buzağılarda Hematoloji ve Kan Gazı Parametrelerin Değerlendirilmesi

Bu çalışmada ishale bağlı sepsis gelişen buzağılarda hematolojik indeksler (monosit/lenfosit oranı (MLO), eritrosit dağılım genişliği (RDW), ortalama trombosit hacmi (MPV)) ve kan gazı (kısmi oksijen basıncı (pO_2), kısmi karbondioksit basıncı (pCO_2), laktat, sodyum (Na^+), potasyum (K^+), klor (Cl^-), bikarbonat (HCO_3^-) pH, anyon açığı (AG) ve baz fazlalığı (BE)) parametrelerinin diagnostik olarak değerlendirilmesi amaçlanmıştır. Çalışma materyalini ishal şikâyeti ile getirilen 1-28 günlük 20 sepsisli (sepsis) ve 10 sağlıklı buzağı (kontrol) olmak üzere iki grup oluşturdu. Sistemik inflamatuar yanıt sendromu (SIRS) tanısı konan buzağılardan alınan dışkı örnekleri Rotavirüs, Koronavirüs, *Escherichia coli*, *Cryptosporidium parvum* ve *Giardia lamblia* yönünden immunokromatografik test kitleri ile analiz edildi. Total lökosit sayısı (WBC), lenfosit (LYM), monosit (MON), hematokrit (HCT), RDW ve MPV, pO_2, pCO_2, laktat, Na^+, K^+, Cl^-, HCO_3^-, pH, AG ve BE parametrelerinin ölçümü yapıldı. Sepsis grubunun WBC (P<0.010), MON (P<0.001), MPV (P<0.001) ve MLO (P<0.001) değerleri kontrol grubuna göre istatistiksel olarak yüksek bulundu. Sepsis grubunda pH (P<0.001), HCO_3^- (P<0.001) ve BE (P<0.001) değerleri kontrol grubuna göre anlamlı olarak düşük bulundu. Sepsis grubunda K^+ (P<0.003) ve AG (P<0.001) konsantrasyonları kontrol grubuna göre anlamlı olarak yüksek bulundu. Sepsis tanısında MON'da eğri altındaki alan 0.895, duyarlılık %80, özgüllük %75; RDW'de eğri altındaki alan 0.840, duyarlılığı %80 ve özgüllüğü %75'tir; MPV için 0,915 eğri altındaki alan, %100 duyarlılık ve %90 özgüllük; MLO için eğri altındaki alan 0.910, %80 duyarlılık ve %80 özgüllük olarak belirlendi. Sonuç olarak, buzağılarda meydana gelen sepsisde MPV ve MLO parametrelerinin tanıda değerli olduğu düşünülmektedir.

Anahtar Kelimeler: *Buzağı, sepsis, MPV, MLO, ishal*

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Introduction

The 1-28-day period, defined as the neonatal period in calves, is important in protecting calf health. During this period, diarrhea, pneumonia, and sepsis, which occur due to various reasons, cause high morbidity and mortality in calves (1, 2). Neonatal sepsis, which occurs due to diarrhea in calves, allows opportunistic intestinal pathogens to enter the systemic circulation, causing bacterial, viral, or parasitological factors to damage the intestinal mucosa (3). Systemic inflammatory response syndrome (SIRS) occurs with the activation of acute endogenous mediators as a defense response against the inflammatory situation caused by these infectious agents (2). The most common causes of death from sepsis include nonspecific clinical symptoms and

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delayed diagnosis of sepsis (1). Definitive antemortem diagnosis of sepsis is made with positive blood cultures. However, it is known that results can be obtained after 48-72 hours and false negative culture findings are common (3). Various biomarkers, such as tumor necrosis factor-alpha, interleukin-6, procalcitonin, haptoglobin, and fibrinogen, have been investigated to diagnose sepsis in calves (2). However, it is not yet widely used in clinical settings due to reasons such as its high cost and the need for a laboratory environment and personnel to implement it (4).

Hematological and blood gas analysis are economically affordable analysis methods that can be easily applied at the bedside in the clinic and provide rapid results (5, 6). The first changes that respond to any disruption in homeostasis related to the blood and hematopoietic system are hematological parameters. Identifying these changes guides the search for diagnosis and plays a key role in monitoring the effectiveness of treatment (7, 8). With the developments in medical technologies in recent years, automatic hematology devices analyze many different parameters such as WBC, LYM, MON, HCT, erythrocyte distribution width RDW and MPV (4, 9). These parameters are used frequently in the evaluation of the diagnosis and prognosis of different disease conditions in cats and dogs. Unfortunately, no study has evaluated or revealed the specified hematological index in calves with sepsis.

Blood gas analysis is an auxiliary diagnostic method for detecting metabolic or respiratory disorders that cause pH changes in the blood, determining their severity, and facilitating follow-up after treatment (10). Electrolyte and acid-base imbalances due to calf diarrhea are inevitable. For this reason, blood gas analysis are one of the most important auxiliary tools for management of treatment and monitoring of the disease, especially in calves with diarrhea (5, 6). In calves with sepsis, the diagnostic significance of hematological index (MLR, RDW, MPV) and blood gas parameters (pO_2, pCO_2, lactate, Na^+, K^+, Cl^-, HCO_3^-, pH, AG, and BE) have not been investigated. For this reason, the present study aimed to evaluate hematological and blood gas parameters in calves that developed sepsis due to diarrhea.

Materials and Methods

Research and Publication Ethics: This study was started after the approval of Bingöl University Animal Experiments Local Ethics Committee (Bingöl University HADYEK Meeting Number: 2024/01 Decision No: 01/07).

Animal Selection and Grouping: It consists of a total of 30 calves aged between 1 and 28 days, brought to Bingöl University Veterinary Faculty Animal Hospital Internal Medicine Department Polyclinic with complaints of diarrhea. The sepsis group consists of 20 calves with acute diarrhea, while 10 calves determined to be healthy constitute the control group.

Clinical Examination and Sepsis Diagnosis: After systematic clinical examinations of all animals (rectal temperature, heart rate, and respiratory rate), body temperature was more than 39.5 °C or less than 38.5 °C, heart rate was more than 160/min or less than 100/min, respiratory rate was more than 36/min, and total leukocyte count was more than 12.000/mm^3 or less than 4000/mm^3. SIRS was considered positive in the presence of at least two of the existing criteria (1, 11-13). SIRS is defined as infection or suspected infection leading to the onset of sepsis (11, 14). In order to diagnose sepsis, the patient must have at least 2 SIRS criteria and a confirmed etiological factor (11, 14, 15). Fecal samples taken from calves were analyzed with immunochromatographic test kits (Anigen Rapid BoviD-5 Ag, Bionote, Inc. Korea) for Rotavirus, Coronavirus, Escherichia coli, Cryptosporidium parvum and Giardia lamblia. Calves with SIRS-positive diarrhea were considered to have sepsis in the presence of the agent in the feces and were included in the study. Calves outside the age range of 1-28 days, calves with chronic diarrhea, those receiving antibiotic treatment, those with congenital diseases, those not receiving colostrum, calves with diarrhea but no causative agent identified were excluded from the study. The control group calves were composed of animals that did not have any problems in clinical examination findings, hematological, biochemical and blood gas analyses.

Sample Collection, Hematology and Blood Gas Analysis: From all animals included in the study, 3 mL blood samples were taken into EDTA (BD Vacutainer®, Plymouth, UK) tubes for hematological examinations, and 2 mL blood samples were taken into heparin syringes for blood gas analyses. An automated hematology device (Benesphera H-31, USA) performed WBC, LYM, MON, HCT, RDW, and MPV analyses, while a blood gas device (Wondfo BGA-102) measured the parameters pCO_2, lactate, Na^+, K^+, Cl^-, HCO_3^-, pH, AG, and BE.

Statistical analysis: Statistical analysis of the data was performed using SPSS 26 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Data are presented as mean ± standard deviation, minimum-maximum values. Whether the data had a normal distribution was evaluated with the Shapiro-Wilk test. To determine the differences between the sepsis group and the control group, the Mann-Whitney U test was applied for data showing a nonparametric distribution, and the independent sample T test was applied for data showing a parametric distribution. Receiver Operating Characteristic (ROC) analysis was performed to determine under the curve (AUC), sensitivity, specificity and cut-off values of the parameters. According to the AUC values of the parameters, 0.500 was considered non-diagnostic, 0.600-0.700 was considered to have poor diagnostic performance, 0.700-0.800 was considered to be in the acceptable diagnostic range, 0.800-0.900 was considered good, and above 0.900 was considered to have very good diagnostic performance (16). The statistical significance level between groups was accepted as P value <0.05.

Results

Table 1 presents the etiological factors and their percentages detected in the calves in the sepsis group. In the presented study, rotavirus was seen in 50%, coronavirus in 20%, Cryptosporidium parvum in 15%, *Giardia lamblia* in 10%, and coronavirus + *Cryptosporidium parvum* + *Giardia lamblia* in 5%. It was determined that the sepsis group of calves in the study was 12.05±1.33 days old on average, while the control group calves were 10.70±0.66 days old. Table 2 presents the statistical analysis of the clinical examination findings. Heart rate (P<0.011) and respiratory rate (P<0.009) were found to be significantly higher in the sepsis group compared to the control group. Body temperature did not differ significantly between the sepsis and control groups (P>0.690). Table 3 displays the statistical significance levels and minimum-maximum values of the hematological analysis results for calves in the sepsis and control groups. The WBC (P<0.010), MON (P<0.001), MPV (P<0.001), and MLR (P<0.001) values of the sepsis group were found to be statistically higher than the control group. Blood gas analysis results for sepsis and control group calves are presented in Table 4. pH (P<0.001), HCO_3^-(P<0.001), and BE (P<0.001) values were found to be significantly lower in the sepsis group than in the control group. K^+ (P<0.003) and AG (P<0.001) concentrations were found to be significantly higher in the sepsis group than in the control group. No statistically significant difference was detected between the sepsis and control groups in terms of pCO_2 (P>0.322), pO_2 (P>0.627), Na^+ (P>0.628), Cl^- (P>0.192), and lactate (P>0.792) parameters.

Table 1. Etiological factors detected in calves with sepsis

Etiological factors	Number	%
Rotavirus	10	50
Coronavirus	4	20
Cryptosporidium parvum	3	15
Giardia lamblia	2	10
Coronavirus+Cryptosporidium parvum+Giardia lamblia	1	5

Table 2. Clinical examination findings and statistical significance of calves with sepsis and control groups

Variable	Sepsis (Ort±SD) (Min-Max)	Control (Ort±SD) (Min-Max)	p value
Body Temperature (°C)	37.90±1.47 (35.70-40.00)	38.49±0.20 (38.20-38.80)	0.690
Heart Frequency (Beats/minute)	127.75±35.85 (35.00-180.00)	100.60±19.61 (68.00-130.00)	0.011
Respiratory Frequency (Beats/minute)	40.85±10.93 (20.00-60.00)	30.00±4.89 (20.00-36.00)	0.009

Mean±SD: mean±standard deviation, Min-Max: minimum-maximum

Table 3. Descriptive statistics and significance levels of hematology analyzes in sepsis and control group calves

Variables	Group	Mean±SD	Min-Max	P value
WBC ($\times10^9$/L)	Sepsis	20.52±12.82	3.00-48.20	0.010
	Control	10.18±3.05	7.10-16.50	
MON ($\times10^9$/L)	Sepsis	4.00±6.97	0.90-33.20	0.001
	Control	0.99±0.61	0.34-1.90	
LYM ($\times10^9$/L)	Sepsis	6.43±9.41	1.30-45.90	0.140
	Control	5.47±1.21	3.70-7.70	
RDW (%)	Sepsis	42.77±9.33	17.00-53.40	0.003
	Control	38.45±3.06	33.30-43.60	
HCT (%)	Sepsis	32.71±9.06	21.00-50.00	0.082
	Control	26.70±3.50	22.00-32.20	
MPV (fL)	Sepsis	14.23±3.29	5.00-17.80	0.001
	Control	5.64±0.34	4.90-6.00	
MLR	Sepsis	0.87±1.30	0.04-6.26	0.001
	Control	0.19-0.13	0.06-0.40	

Mean±SD: mean±standard deviation, Min-Max: minimum-maximum, WBC: white blood cells, MON: monocytes, LYM: lymphocytes, RDW: red blood cell distribution width, HCT: hematocrit, MPV: Mean platelet volume, MLR: monocyte lymphocytes ratio.

Table 4. Descriptive statistics and significance levels of blood gas analyzes in sepsis and control group calves

Variables	Group	Mean±SD	Min-Max	P value
pH	Sepsis	7.05±0.18	6.69-7.40	0.001
	Control	7.46±0.04	7.40-7.51	
pCO_2 (mmHg)	Sepsis	45.69±16.66	19.70-82.50	0.322
	Control	46.28±5.05	41.10-59.30	
pO_2 (mmHg)	Sepsis	29.85±10.90	18.00-67.00	0.627
	Control	27.50±3.39	22.00-34.00	
Na^+ (mmol/L)	Sepsis	136.45±7.19	119.00-156.00	0.628
	Control	135.30±2.26	132.00-139.00	
K^+ (mmol/L)	Sepsis	5.84±1.60	3.70-9.40	0.003
	Control	4.59±0.20	4.30-5.00	
Cl^- (mmol/L)	Sepsis	105.65±8.58	95.00-127.00	0.192
	Control	101.80±1.75	100.00-104.00	
HCO_3^- (mmol/L)	Sepsis	12.84±5.98	6.50-29.70	0.001
	Control	32.41±2.04	29.60-35.00	
AG (mmol/L)	Sepsis	-17.25±9.97	-29.10-6.40	0.001
	Control	8.77±2.88	5.80-14.10	
Lac (mmol/L)	Sepsis	23.65±6.38	11.00-36.00	0.001
	Control	4.40±3.97	-1.00-11.00	
BE (mmol/L)	Sepsis	2.32±2.24	0.30-8.11	0.792
	Control	1.49±0.57	0.80-2.38	

Mean±SE: mean±standard deviation, Min-Max: minimum-maximum, pCO_2: partial pressure of carbon dioxide, pO_2: partial pressure of oxygen, Na: sodium, K: potassium, Cl: chlorine, HCO_3^-: bicarbonate, BE: base excess, AG: anion Gap, Lac: lactate

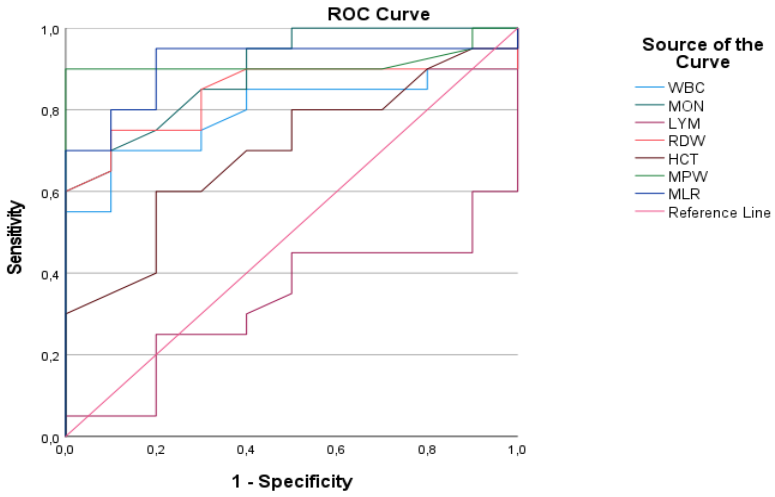

Figure 1. ROC analysis of hematological parameters

Table 5. ROC analysis of hematological parameters

Variables	AUC	Sensitivity (%)	Specificity (%)	Cut-Off	P value
WBC	0.793	70	70	11.75	0.010
MON	0.895	80	75	1.65	0.001
LYM	0.332	50	45	5.20	0.141
RDW	0.840	80	75	41.05	0.003
HCT	0.698	60	70	28.00	0.082
MPV	0.915	100	90	9.35	0.000
MLR	0.910	80	80	0.37	0.000

WBC: white blood cells, MON: monocytes, LYM: lymphocytes, RDW: red blood cell distribution width, HCT: hematocrit, MPV: Mean platelet volume, MLR: monocyte lymphocytes ratio

The ROC analysis of hematological parameters is presented in Table 5 and Figure 1. The AUC value of WBC in calves with sepsis was determined to be 0.793, with a with a sensitivity 70%, a specificity 70%, and a cut-off 11.75.In the diagnosis of sepsis, the MON AUC value was determined to be 0.895, the sensitivity was 80%, the specificity was 75%, and the cut-off was 1.65. The AUC of RDW in the diagnosis of sepsis was determined as 0.840, sensitivity 80%, specificity 75%, and cut-off 41.05. In the HCT diagnosis of sepsis, the AUC was determined to be 0.698, the sensitivity was 60%, the specificity was 70%, and the cut-off was 28.00. An AUC of 0.915, 100% sensitivity, 90% specificity, and a cut-off value of 9.35 were determined for MPV in the diagnosis of sepsis. In the diagnosis of sepsis, MLR, 0.910 AUC, 80% sensitivity, 80% specificity, and 0.37 cut-off values were determined.

Discussion

Early recognition of sepsis-related problems in calves before they become irreversible is vital for the life of the calf and is very important in preventing or reducing sepsis-related diseases and deaths. However, sepsis biomarker research and development studies are considered an important priority due to the fact that sepsis symptoms in newborn calves are nonspecific and blood cultures are obtained after 48–72 hours (1, 3, 17). Blood gas and hematological analyses provide useful information in the diagnosis of diseases affecting many organs and systems (5, 18). In this regard, the aim of the present study was to investigate the diagnostic utility of hematologic indices and blood gas parameters in calves with sepsis.

Monocytes are a subset of circulating white blood cells that can differentiate into macrophages and dendritic cells (19). Monocytes and macrophages are known to play an important role in the immune response against microorganisms as well as in the pathogenesis of sepsis (20). Studies have also demonstrated that monocytes actively initiate cellular immune responses and participate in the humoral response in hosts infected with enteric pathogens (21, 22). Activation of different receptors (Toll-like receptors 1-2) that play a part the inflammation of monocytes in sepsis has also been seen in humans (19, 23). In the presented study, it was determined that the number of monocytes in the sepsis group was significantly high and showed good diagnostic performance (AUC = 0.895, sensitivity = 80%, specificity = 75%) in the recognition of sepsis. The monocyte values obtained in this study are similar to the results of Chae et al. (24), Naseri et al. (25) and Kim and al. (22) and are different from those of Naseri and İder (26) and Akyuz et al. (27). The reason for the differences between studies may be related to the immune system of the animals and the variable course of monocyte numbers in cattle (18).

RDW is the coefficient of variation of erythrocyte (RBC) volume and reflects the heterogeneity of RBC size (28). Increased RDW in cattle is associated with other trace mineral deficiencies associated with iron deficiency and macrocytic/microcytic anemia (18). However, studies have shown that the RDW value

indicates systemic inflammation in horses (28), dogs (29), and humans (30) and can be used diagnostically in determining infectious conditions. In recent years, studies have been conducted on the RDW parameter in calves with diarrhea, but the change in RDW concentration in calves developing sepsis due to diarrhea has not been evaluated. In studies conducted on calves with diarrhea by many researchers (31, 32, 33), it has been reported that the RDW value does not show a statistically significant difference between groups. However, in this study, it was determined that the RDW value of the sepsis group was significantly higher than the control group. Additionally, the RDW variable showed good diagnostic properties (AUC = 0.840, sensitivity = 80%, specificity = 75%) in determining sepsis. Proinflammatory cytokines suppress erythropoietin-induced erythrocyte maturation and proliferation and downregulate erythropoietin receptor expression, which may be the cause of the increase in RDW in sepsis (30, 34). Therefore, in the presented study, it is thought that the increase in RDW is due to the inflammatory response caused by sepsis.

Platelets are important for stopping bleeding, but they are also inflammatory cells that can connect the immune system's humoral and cellular responses with molecular pathways and synthetic abilities that have not been known before (35). The MPV value obtained from the platelet histogram shows the average volume of platelets. It is known that in cases where platelet production decreases, such as sepsis, younger platelets, which are larger and more active, enter the circulation, and therefore MPV levels increase (36). Significant increases in MPV levels have been in dogs with various inflammatory diseases (37), horses (38) and humans (39). In cattle infected with the Bovine viral diarrhea virus (40) and sepsis infected cattle (41) MPV is said to be used as a diagnostic and prognostic marker. In this study, consistent with previous studies, it was determined that the MPV level was significantly higher in the sepsis group and that MPV showed very good diagnostic performance (AUC = 0.925, sensitivity = 100%, specificity = 90%) in the diagnosis of sepsis.

In inflammatory diseases, a variety of hematological rates can be used both for diagnosis and prognosis. (41). An increase in the thrombocyte/lymphocyte ratio (PLR) in cats and dogs with acute pancreatitis has been attributed to the ability of the platelets to modulate phagocytosis and leukocyte function. (42). By Gavazza et al. (43) in lymphoma dogs, neutrophil-lymphocyte ratio (NLR), thrombocytes/neutrophils (PNR), MLR, thrombocyte volume/thrombocyte (MPV/PLT) ratio have been to be useful parameters in the early diagnosis of a subclinical condition.

Aydın (9) reported that NLR, lymphocyte/monocyte ratio (LMR) in calves with diarrhea, Yanar et al. (41) evaluated NLR and PLR values may have potentials as indicators of inflammation in calves with sepsis. Likewise, in the presented study, it was determined that the MLR value of the sepsis group was significantly higher and showed very good diagnostic performance (AUC = 0.910, sensitivity = 80%, and specificity = 80%) in the recognition of sepsis.

Determination of acid-base balance is determined by changes in pH, HCO_3^-, BE and AG in plasma (44-46). Metabolic acidosis classically results from an initial loss of intestinal HCO_3^- as well as a decrease in glomerular filtration rate in response to severe dehydration (6, 45, 47). In the presented study, consistent with the data in the literature (6, 46, 48), pH, HCO_3^- and BE concentrations were found to be low and AG levels were high in the sepsis group compared to the control group. It is stated that changes in these blood gas parameters are caused by changes in dehydration and acidemia (6). In calves with diarrhea, changes in electrolyte concentrations occur, as well as acidemia and dehydration (6, 44). Although potassium loss occurs due to the increased amount of feces as a result of diarrhea, calves may be hyperkalemic, normokalemic or hypokalemic in this study, K^+ concentrations were found to be significantly higher in the sepsis group compared to the control group. It is reported that the increase in K^+ concentrations in the blood during metabolic acidosis is due to the buffering mechanism of hydrogen ions entering the cells (46). In addition, it is stated that hyperphosphatemia and the decrease in kidney function due to dehydration also contribute to hyperkalemia (48).

As a result, in this study, changes in hematological and blood gas analyzes in diarrhea calves that developed sepsis were determined. In the diagnosis of sepsis, it was determined that WBC had moderate diagnostic properties, monocyte and RDW had good diagnostic properties, and MPV and MLR had very good diagnostic properties. In future studies, it would be useful to classify hematological indices according to the etiology of sepsis and evaluate them in studies with a large population.

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