

Περιοδικό της Ελληνικής Κτηνιατρικής Εταιρείας

Τόμ. 75, Αρ. 1 (2024)



Cardiac Biomarkers in Calves with Diarrhea-Induced Neonatal Sepsis

C Ayvazoğlu, E Akyüz, A Harmankaya, M Sezer, YU Bati, T Gezer, M Kuru

doi: [10.12681/jhvms.32664](https://doi.org/10.12681/jhvms.32664)

Copyright © 2024, C Ayvazoğlu, E Akyüz, A Harmankaya, M Sezer, YU Bati, T Gezer, M Kuru



Άδεια χρήσης [Creative Commons Αναφορά-Μη Εμπορική Χρήση 4.0.](https://creativecommons.org/licenses/by-nc/4.0/)

Βιβλιογραφική αναφορά:

Ayvazoğlu, C., Akyüz, E., Harmankaya, A., Sezer, M., Bati, Y., Gezer, T., & Kuru, M. (2024). Cardiac Biomarkers in Calves with Diarrhea-Induced Neonatal Sepsis. *Περιοδικό της Ελληνικής Κτηνιατρικής Εταιρείας*, 75(1), 6871-6878. <https://doi.org/10.12681/jhvms.32664>

Cardiac Biomarkers in Calves with Diarrhea-Induced Neonatal Sepsis

C. Ayvazoğlu^{1*}, E. Akyüz², A. Harmankaya³, M. Sezer⁴, Y.U. Bati⁵, T. Gezer⁶,
M. Kuru⁷

¹*Nihat Delibalta Göle Vocational High School, Ardahan University, Ardahan, 75100, Türkiye*

^{2,4,5,6}*Department of Internal Diseases, Faculty of Veterinary Medicine, Kafkas University, Kars, 36100, Türkiye*

³*Department of Biochemistry, Faculty of Science and Letter, Kafkas University, Kars, 36100, Türkiye*

⁷*Obstetrics and Gynecology of Department, Faculty of Veterinary Medicine, Kafkas University, Kars, 36100, Türkiye*

ABSTRACT: In this study; it was aimed to determine the levels of cardiac biomarkers [cardiac troponin I (cTnI), atrial natriuretic peptide (ANP), N-terminal pro-brain natriuretic peptide (NT-proBNP), homocysteine (HCY), creatine kinase-myocardial band (CK-MB)] and C-reactive protein (CRP), and the correlations between the semarkers in calves with diarrhea-induced neonatal sepsis, which causes great economic losses, especially genetic material. In the study, 40 neonatal calves with diarrhea-induced neonatal sepsis and 10 clinically healthy neonatal calves aged 0-14 days were used. The study revealed that the serum cTnI, ANP, NT-proBNP, HCY, CK-MB and CRP levels of the calves with neonatal sepsis were statistically significantly higher than those in the control group ($P<0.001$). The correlation study also showed that there was a high correlation between the cardiac markers here of and the highest correlation was found between ANP and CK-MB ($R=0.836^{**}$). In conclusion, cTnI, ANP, NT-proBNP, HCY and CK-MB can be suggested as useful prognostic and diagnostic biomarkers of cardiac dysfunctions in calves with suspected sepsis. Furthermore, according to the results of the study; although the suggest that an approximately 10-fold increase in ANP level would be the best marker for early diagnosis of sepsis, ANP may not be an ideal marker due to its short half-life and instability. Therefore, we believe that NT-proBNP, which correlates very significantly with all other markers and increases approximately 7-fold in calves with sepsis, is an important marker in the detection and early diagnosis of sepsis.

Keywords: homocysteine; natriuretic peptide; neonatal calves; sepsis; troponin

Corresponding Author:

C. Ayvazoğlu, Nihat Delibalta Göle Vocational High School, Ardahan University, Ardahan, Türkiye.

E-mail address: cemayvazoglu@hotmail.com

Date of initial submission: 08-01-2023

Date of acceptance: 09-03-2023

INTRODUCTION

Digestive system diseases and neonatal diarrhea have an important impact on calves in postpartum period between 0-28 days (Pardon and Depres, 2018; Akyüz and Küktürk, 2021) and bacteremia or viremia develops as a result of infection and causes sepsis (Gökçe et al., 2021). Systemic inflammatory response syndrome (SIRS), triggered by infection and affecting the whole body, is a result of severe sepsis (Beydilli and Gökçe, 2020; Gökçe et al., 2021; Naseri et al., 2021; Akyüz and Gökçe, 2021). Therefore, SIRS findings (where SIRS criteria ≥ 2) can be used to define sepsis (Gökçe et al., 2021). Sepsis and its complications progress rapidly in the body, causing serious damage and almost making treatment impossible, often leading to the death of the patient (Kakihana et al., 2016; Akyüz et al., 2022). Therefore, early diagnosis and treatment of sepsis is very important to reduce the mortality rate in patients. Because, it has been reported that each one-hour delay in treatment increases the mortality rate by 6% (Levy et al., 2003).

The most important cause of death in sepsis, which has a mortality rate of approximately 30% in humans and animals, is organ failure, with the heart being the leading cause (Başoğlu et al., 2018; Naseri et al., 2019; Beydilli and Gökçe, 2020). In human studies, cardiac dysfunction was reported in 66% of sepsis cases and approximately 70% of these patients died (Landesberg et al., 2015; Kakihana et al., 2016). Studies in calves have also reported that sepsis causes cardiac dysfunction (Beydilli and Gökçe, 2020; Kırbaş et al., 2021; Naseri et al., 2021).

Different studies have reported that various biomarkers [cardiac troponin I (cTnI), atrial natriuretic peptide (ANP), N-terminal pro-brain natriuretic peptide (NT-proBNP), homocysteine (HCY), creatine kinase-myocardial band (CK-MB), C-reactive protein (CRP), etc.] can be used to detect myocarditis and cardiac dysfunction (Aydoğdu et al., 2016; Labonté et al., 2018; Aygün and Yıldız, 2018; Beydilli and Gökçe, 2020; Ogawa et al., 2021; Kozat et al., 2021).

The aim of this study was to determine the levels of cardiac biomarkers (cTnI, ANP, NT-proBNP, HCY, CK-MB) and CRP, and the correlations between these markers in sepsis, which causes great economic losses, especially in terms of genetic material. In this way, it was aimed to increase the use of biomarkers for the prognosis, early diagnosis and treatment of the disease and to reduce the mortality rate by performing a comprehensive examination of sepsis.

MATERIAL AND METHODS

This study was carried out after the approval (KAÜ-HADYEK 2022-069) received from Kafkas University Animal Experiments Local Ethics Committee.

Animals

The animal material of this study consisted of 0-14 days old Simmental and Simmental crossbred calves with sepsis brought to Kafkas University Faculty of Veterinary Medicine, Department of Internal Medicine clinics with diarrhea complaints. In the study, 40 sick animals (sepsis group) and 10 healthy calves of the same age group constituted the control group. Healthy animals consisted calves born at Kafkas University Faculty of Veterinary Medicine Prof. Dr. Ali Rıza Aksoy Research and Application Farm.

Procedures and evaluation of sepsis criteria

Calves with clinical signs of depression, diarrhea, low or absent sucking reflex, dehydration, and constant desire to lie down were examined and SIRS/sepsis criteria were evaluated. According to this evaluation, SIRS criteria for neonatal calves include body temperature $>39.5^{\circ}\text{C}$ or $<37^{\circ}\text{C}$, pulse rate <100 or >160 per minute, respiratory rate >45 per minute, leukocyte count $>12 \times 10^3/\mu\text{L}$ or $<4 \times 10^3/\mu\text{L}$ (Akyüz and Gökçe, 2021; Akyüz et al., 2022). The presence of at least 2 of the specified criteria was considered as sepsis and included in the study. In addition, a rapid test kit (BoviD-5 Ag Test Kit®, Bionote Inc., Korea) was used for the detection of etiologic agent in feces of calves with suspected neonatal sepsis meeting SIRS criteria.

Blood collection

From the calves in the sepsis and control groups, 8 mL blood samples were taken once from *V. jugularis* using a retainer and compatible sterile needle tip (Vacuette®, Greiner Bio-One GmbH, Austria). Vacuum gel serum tubes were used for serum samples and vacuum EDTA blood tubes were used for hematological measurements (BD Vakutainer®, BD, UK). Blood samples taken into vacuum gel serum tubes were kept at room temperature for about 1 hour and then centrifuged at 3500 rpm for 10 minutes (Hettich Rotina 380R®, Hettich, Germany). Serum samples were stored at -20°C until cTnI, ANP, NT-proBNP, HCY, CK-MB and CRP levels were measured. Although troponin concentrations can remain stable for a long time at $-70/-80^{\circ}\text{C}$, it has been reported that they remain sta-

ble for a maximum of 3 months at -20°C (Langhorn and Willesen, 2016). Therefore, serum samples used in this study were stored for a maximum of 60 days.

Measurement of cardiac markers and CRP

Serum cTnI, ANP, NT-proBNP, HCY CK-MB and CRP levels were determined with an ELISA device (ELISA Reader®-DAS Italy and ELISA Reader-Elecsys® 2010-Roche) and calculated with a commercial test kit (ELK Biotechnology, P.R.C.) as indicated by the manufacturer (ng/mL, pg/mL, pg/mL, μ mol/L, U/L, μ g/mL, respectively).

Hematological analysis

White blood cell ($\times 10^3/\mu\text{L}$) count was determined from the whole blood samples obtained by using a complete blood count device (VGMS4e®, Melet Schloesing, France)

Statistical analysis

The statistical comparison of the data was performed using the SPSS® software program (SPSS 26.0, Chicago, IL, USA). The distribution of the data was tested for conformity to a normal distribution by the Shapiro-Wilk test. Calves were grouped as sepsis and control. Then, the healthy versus ill were compared using an independent sample T test. Pearson correlation coefficients were calculated to define the correlation between variables. Data are expressed as Mean \pm SE (standard error) and the statistical significance was set at $P<0.05$.

RESULTS

In our study, 40 calves with sepsis (20 females, 20 males) and 10 healthy calves (5 females, 5 males) between 0-14 days postpartum were used.

As a result of the causative agent detection in feces with a rapid test kit, Rotavirus was detected in 10% (4/40), Coronavirus in 15% (6/40), *E. coli* K99 in 35%

(14/40), *E. coli* K99+Coronavirus in 20% (8/40), *E. coli* K99+Rotavirus in 10% (4/40), Rotavirus+Coronavirus in 7.5% (3/40) and *E. coli* K99+Coronavirus in 10% (4/40) of calves with sepsis (Table 1).

Physical examination findings and evaluation of the levels of cardiac biomarkers in calves with sepsis and control group calves in the study are presented in Table 2. Among the physical examination findings, respiratory rate (RR; $P<0.001$), heart rate (HR; $P=0.006$) and capillary refill time (CRT; $P=0.002$) were statistically significantly higher in calves with sepsis compared to the control (Table 2). White blood cells (WBC) level was statistically significantly higher in calves with sepsis compared to the control ($P<0.001$, Table 2). In addition, biomarkers cTnI, NT-proBNP, ANP, HCY, CK-MB and CRP were significantly higher in calves with sepsis compared to the control ($P<0.001$, Table 2).

Table 3 shows the Pearson correlation of the data in the study. The study revealed a high correlation between cardiac markers and the most significant correlation was found between ANP and CK-MB ($R=0.836^{**}$, Table 3).

DISCUSSION

Sepsis encountered during the neonatal period leads to serious economic losses in cattle breeding. The most important economic losses in this regard include the death of the calf, loss of genetic material, treatment costs or performance and yield failures despite recovery (Tokgöz et al., 2013; Demir et al., 2019). Cardiac markers (cTnI, ANP, NT-proBNP, NT-proBNP, HCY and CK-MB) and CRP, are important biomarkers that assist in the detection of cardiac diseases by increasing in serum concentrations even before the symptoms thereof (Mellanby et al., 2009; El-Ashker et al., 2013; Neamat-allah, 2015; Attia, 2016; Kılıçalp and Kozat, 2017; Ogawa et al., 2021). Our study aimed to determine the importance and ef-

Table 1. Enteropathogens evaluated in calfdiarrhea with sepsis and their prevalence

Disease Agent	N	Rate (%)
Rotavirus	4	10
Coronavirus	6	15
<i>E. coli</i> K99	14	35
<i>E. coli</i> K99+Coronavirus	8	20
<i>E. coli</i> K99+Rotavirus	4	10
Rotavirus+Coronavirus	3	7.5
<i>E. coli</i> K99+Rotavirus+Coronavirus	1	2.5
TOTAL	40	100

Table 2. Physical Examination Findings and Levels of Cardiac Biomarkers in Calves with Sepsis and Healthy Calves

Parameters	Groups	N	Mean±SE	P Value
RT (°C)	Sepsis	40	38.54±0.29	0.299
	Control	10	38.21±0.12	
RR (breaths/min)	Sepsis	40	43.13±3.10	<0.001
	Control	10	23.80±1.67	
HR (beats/min)	Sepsis	40	104.40±6.42	0,006
	Control	10	82.80±3.73	
CRT(sec)	Sepsis	40	2.93±0.24	0.002
	Control	10	1.50±0.17	
WBC(x10 ³ /µL)	Sepsis	40	16.66±1.77	<0.001
	Control	10	9.23±0.66	
cTnI (ng/mL)	Sepsis	40	0.19±0.01	<0.001
	Control	10	0.04±0.00	
NT-proBNP (pg/mL)	Sepsis	40	405.94±16.19	<0.001
	Control	10	60.02±3.06	
ANP (pg/mL)	Sepsis	40	228.35±10.75	<0.001
	Control	10	21.21±0.87	
Homocysteine (µmol/L)	Sepsis	40	26.38±1.04	<0.001
	Control	10	14.17±0.34	
CRP (µg/mL)	Sepsis	40	52.07±1.65	<0.001
	Control	10	24.05±1.83	
CK-MB (U/L)	Sepsis	40	139.18±3.36	<0.001
	Control	10	65.31±1.98	

RT: Rectaltemperature; RR: Respiration rate; HR: Heart rate; CRT: Capillaryrefill time WBC: White bloodcells; cTnI: cardiotroponin I; ANP: atrialnatriureticpeptide; NT-proBNP: N-terminal pro-brainnatriureticpeptide; HCY: Homocysteine; CRP: C-reactive protein; CK-MB: creatinekinase-myocardialband; P<0.05 indicates statistical significance between groups.

Table 3. Pearson Correlation of all data in the study

Parameters	RT (°C)	RR	HR	CRT	WBC	cTnI	NT-proBNP	ANP	HCY	CRP
RR (breaths/min)	0.023									
HR (beats/min)	-0.077	0.039								
CRT (sec)	0.124	0.281	0.100							
WBC (x10³/µL)	-0.216	0.196	0.163	0.405**						
cTnI (ng/mL)	0.048	0.467**	0.333*	0.409**	0.203					
NT-proBNP (pg/mL)	0.069	0.434**	0.295	0.427**	0.373*	0.685**				
ANP (pg/mL)	0.155	0.333*	0.264	0.507**	0.230	0.751**	0.743**			
Homocysteine (µmol/L)	0.155	0.364*	-0.009	0.332*	0.186	0.535**	0.623**	0.596**		
CK-MB (U/L)	0.025	0.522**	0.240	0.415**	0.254	0.786**	0.797**	0.836**	0.654**	0.722**

RT: Rectaltemperature; RR: Respiration rate; HR: Heart rate; CRT: Capillaryrefill time WBC: White bloodcells; cTnI: cardiotroponin I; ANP: atrialnatriureticpeptide; NT-proBNP: N-terminal pro-brainnatriureticpeptide; HCY: Homocysteine; CRP: C-reactive protein; CK-MB: creatinekinase-myocardialband; **:Correlation is significant at the 0.01 level (2-tailed); *: Correlation is significant at the 0.05 level (2-tailed).

fectiveness of biomarkers in early diagnosis of sepsis by identifying the changes in cTnI, ANP, NT-proBNP, HCY, CK-MB, CRP levels and Pearson correlations between these cardiac markers in calves with diarrhea-induced neonatal sepsis. In this way, early diagnosis of sepsis will become possible and economic losses due to unconscious treatment practices and drug/veterinary costs will be avoided.

Recently, immunochromatographic test kits have been used in the diagnosis of pathogenic agents causing diarrhea (Çitil et al., 2004). The sensitivity of these test kits has been reported to be between 60-94.9% for coronavirus, 93% for *E. coli* K99, 70-100% for rotavirus and 75-100% for *C. parvum* (Klein et al., 2009; Altuğ et al., 2013). In different studies conducted with immunochromatographic test kits, it has been reported that the highest diarrhea agent is *E. coli* at rates ranging from 24% to 40% (Sezer, 2021; Akyüz et al., 2022). In addition, it has been reported that *E. coli* causes 40% of the disease in the first week of the postpartum period (Al and Balıkçı, 2012). In our study, in parallel with the literature, the rate of *E. coli* in calves with sepsis was determined as 35%.

It is very difficult to establish sepsis criteria in calves due to the variability of clinical findings in sepsis (Pardon and Depres, 2018; Beydilli and Gökçe, 2020). However; depression, weak sucking reflex, changes in CRT, tachycardia, tachypnea, hypovolemia, hypotension and dehydration are clinically evident in sepsis (Çitil and Gökçe, 2013; Bonelli et al., 2018). Nevertheless, it has also been reported that rectal temperature (RT) is variable (Kırbaş et al., 2021). Different studies have reported that HR, RR, CRT and hematocrit levels are high in calves with sepsis (Aydoğdu et al., 2018; Yıldız et al., 2018; Akyüz and Gökçe, 2021). Our study also found that HR, RR, CRT and WBC were significantly elevated which was in line with the literature. However, in our study, although RT was found to increase numerically in our study, it was not statistically significant. Increased RR in calves with sepsis indicates a decrease in the vital capacity of the lungs (Poulsen et al., 2010). The possible reason for the increase in WBC values is thought to be due to the increase in the defense mechanism against infectious agents and hemoconcentration due to dehydration (Asati et al., 2008; Brar et al., 2015). Prolonged CRT in sepsis is a result of multiple organ dysfunction and the resulting negative effects on the cardiovascular system (Fecteau et al., 2009).

The most important cause of death in sepsis is or-

gan failure, and cardiac dysfunctions are the leading cause (Fecteau et al., 2009; King et al., 2014; Beydilli and Gökçe, 2020). Studies on humans have reported that cardiovascular abnormalities are common in sepsis cases, resulting in myocardial damage due to non-coronary artery disease (Fenton and Parker, 2016). In different studies, it has been reported that serum activities of cTnI and CK-MB increase during myocardial damage (Kemp et al., 2004; Aydoğdu et al., 2016), but CK-MB expression is not limited to the heart but can also be expressed in other tissues such as skeletal muscle and gastrointestinal system (Babuin and Jaffe, 2005; Hanedan et al., 2015). This explains why cTnI is more sensitive and specific than CK-MB for myocardial damage (Tunca et al., 2008; Akasha et al., 2015; Hanedan et al., 2015). When cardiac injury occurs, cTnI peaks in the blood within 6-12 hours and remains constant at this point for 14-21 days (Undhand et al., 2012; Chow et al., 2017). In addition, cTnI remains in circulation longer than CK-MB (Leonardi et al., 2008) and gives accurate results although CK-MB value returns to normal in the advanced stages of the disease (Başbuğan et al., 2010). In different studies, it was reported that cTnI and CK-MB levels were significantly increased in calves with sepsis (Beydilli and Gökçe, 2020; Kırbaş et al., 2021; Naseri et al., 2021). In our study, similar to the literature, cTnI and CK-MB levels were found to be significantly increased. In addition, cTnI has been reported to be the gold standard for cardiac damage (Langhorn and Willesen, 2016), and the elevation of cTnI and CK-MB in animals with sepsis indicates that myocardial damage occurs in these animals. On the other hand, the pathophysiology of troponin elevation in sepsis is thought to be due to myocardial dysfunction (Kırbaş et al., 2021).

The ANP concentration, which reflects the clinical stages of mitral valve disease (Ruskoaho, 2003), has a half-life of approximately 4 minutes and has no stability (Ogawa et al., 2021). Whereas NT-proBNP is released into the bloodstream mainly in response to ventricular myocyte stretch and has a long half-life (Kellihan et al., 2011). In addition, plasma ANP levels were found to be quite high in calves with congenital heart failure and it was suggested that it could be used for diagnostic purposes (Hori et al., 2009). In healthy calves; ANP level was reported as 36 ± 8.16 pg/mL (Hori et al., 2009) and NT-proBNP level was reported as 131.32 ± 13.1 pg/mL (Beydilli and Gökçe 2020). In our study, ANP and NT-proBNP levels in healthy calves were 21.21 ± 0.87 pg/mL and 60.02 ± 3.06 pg/

mL, respectively. In a study conducted on mice with sepsis, it was reported that ANP levels increased significantly (Li et al., 2014). However, no data on ANP levels in calves with sepsis were found in the literature review. Therefore, our study is the first in this field. Our study reported that the ANP level in calves with sepsis was 228.35 ± 10.75 pg/mL and the 10-fold increase in ANP level compared to healthy calves was statistically very significant ($P < 0.001$). A study conducted on calves with sepsis reported that NT-proBNP level increased significantly (Beydilli and Gökçe, 2020). Moreover, a study on the use of NT-proBNP in the determination of heart failure stated that values up to 300 pg/mL could not be a marker for the disease (Mueller et al., 2007). Our study, on the other hand, showed that NT-proBNP level in calves with sepsis was approximately 7 times higher (405.94 ± 16.19 pg/mL) compared to healthy calves and this result was statistically significant. This indicates that sepsis causes myocardial damage.

In human medicine, HCY is used to assess complications of renal, cardiovascular and other diseases (Amin et al., 2016; Long and Nie, 2016). HCY is an independent risk factor for cardiovascular disease in renal patients (Kavaklı et al., 2010) and a study on calves with diarrhea reported that HCY levels were significantly increased compared to healthy calves (Kozat et al., 2021). Furthermore, in a study conducted by Kılıçalp and Kozat (2017), it was reported that serum HCY values obtained from healthy cows can be used for the diagnosis of cardiovascular diseases. In our study, HCY level was found to be significantly increased in calves with diarrhea-induced sepsis compared to healthy calves. This increase may be caused by increased production rate of HCY (transmethylation), decreased HCY excretion, decreased HCY remethylation or transsulfuration rate (Kozat et al., 2021).

C-reactive protein is a positive acute phase protein that is often used as a biomarker of general inflammation and infection (Maglìulo et al., 2016). Acute phase proteins are plasma proteins whose production and serum concentrations are up-regulated in response to inflammation, infection, cardiovascular disease, cancer and tissue damage (Bradford, 2019). A study conducted in calves with suspected sepsis reported that CRP levels increased (Akgül et al., 2019). Our study also showed results parallel to the study by Akgül et al. and significant increases were observed in CRP levels. In addition, in a study conducted on middle-aged people, it was reported that CRP levels > 10 μ g/mL were associated with cardiovascular diseases (Dhingra et al., 2007). However, it is not possible to determine whether the elevation of CRP levels in calves with sepsis is due to infection or cardiac damage. Therefore, it is thought that more detailed studies on the subject are needed.

CONCLUSIONS

In conclusion, cTnI, ANP, NT-proBNP, HCY and CK-MB can be suggested as useful prognostic and diagnostic biomarkers of cardiac dysfunctions in calves with suspected sepsis. Furthermore, according to the results of the study; although the suggest that an approximately 10-fold increase in ANP level would be the best marker for early diagnosis of sepsis, ANP may not be an ideal marker due to its short half-life and instability. Therefore, we believe that NT-proBNP, which correlates very significantly with all other markers and increases approximately 7-fold in calves with sepsis, is an important marker in the detection and early diagnosis of sepsis.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

Akasha R, Mohammed A, Syed PA, Sirageldin E, Mohammed E, Al-lah MG (2015) Assessment of acute myocardial infarction by the use of special biochemical markers. *UMJ* 1:68-73. <https://doi.org/10.5455/umj.20150416122936>

Akgül Y, Akgül Ö, Kozat S, Özkan C, Yılmaz N (2019) Evaluation of intercellular adhesion molecule-1 (ICAM-1), Tumor necrosis factor α (TNF- α), Interleukins (IL-6, IL-8) and C-reactive protein (CRP) levels in neonatal calves with presumed septicemia. *Van Vet J* 30:167-173. <https://doi.org/10.36483/vanvetj.577392>

Akyüz E, Gökçe G (2021) Neopterin, procalcitonin, clinical biochemistry, and hematology in calves with neonatal sepsis. *Trop Anim Health Prod* 53:354. <https://doi.org/10.1007/s11250-021-02779-z>

Akyüz E, Kükkürt A (2021) Evaluation of oxidative stress index and some biochemical parameters in neonatal calves with diarrhea. *Acta Sci Vet* 3:58-63.

Akyüz E, Sezer M, Kuru M, Naseri A (2022) Changes in hematology, some clinical biochemical parameters and mineral levels in neonatal calves with sepsis due to diarrhea. *Van Vet J* 33:26-30. <https://doi.org/10.36483/vanvetj.1066050>

Al M, Balıkçı E (2012) Neonatal ishalli buzağılarda rotavirus, coronavirüs, *E. coli* K99 ve *Cryptosporidium parvum*'un hızlı test kitleri ile teşhis ve enteropatojen ile maternal immünite ilişkisi. *FÜ Sağ Bil Vet Derg* 26:73-78.

Altuğ N, Yüksek N, Özkan C, Keleş İ, Başbuğan Y, AĞAOĞLU ZT, Kaya

A, Akgül Y (2013) Neonatal buzağıshalerininimmunokromotografik test kitleri ile hızlı etiyolojik teşhisi. *Van Vet J* 24:123-128.

Amin HK, El-Sayed MIK, Leheta OF (2016) Homocysteine as a predictive biomarker in early diagnosis of renal failure susceptibility and prognostic diagnosis for end stages renal disease. *Ren Fail* 38:1267-1275. <https://doi.org/10.1080/0886022X.2016.1209382>

Asati CK, Roy S, Roy M (2008) Hemato-biochemical study and diagnosis of colibacillosis in calves. *Intas Polivet* 9:245-248.

Attia NE (2016) Cardiac biomarkers and ultrasonography as tools in prediction and diagnosis of traumatic pericarditis in Egyptian buffaloes. *Vet World* 9:976. <https://doi.org/10.14202/vetworld.2016.976-982>

Aydogdu U, Coskun A, Yıldız R, Guzelbektes H, Sen I (2018) Clinical importance of lipid profile in neonatal calves with sepsis. *J Hellenic Vet Med Soc* 69:1189-1194. <https://doi.org/10.12681/jhvms.15926>

Aydogdu U, Yıldız R, Guzelbektes H, Coskun A, Sen I (2016) Cardiac biomarkers in premature calves with respiratory distress syndrome. *Acta Vet Hung* 64:38-46. <https://doi.org/10.1556/004.2016.004>

Aygün O, Yıldız R (2018) Evaluation of thrombomodulin and pentraxin-3 as diagnostic biomarkers in calves with sepsis. *Vet Med* 63:313-320. <https://doi.org/10.17221/159/2017-VETMED>

Babuin L, Jaffé AS (2005) Troponin: the biomarker of choice for the detection of cardiac injury. *CMAJ* 173:1191-1202.

Başbuğan Y, AĞAOĞLU Z, YÜKSEK N (2010) An investigation on serum troponin concentration in healthy ruminants. *Kafkas Univ Vet Fak Derg* 16:641-645. <https://doi.org/10.9775/kvfd.2009.1358>

Basoglu A, Sen I, Meoni G, Tenori L, Naseri A (2018) NMR-based plasma metabolomics at set intervals in newborn dairy calves with severe sepsis. *Mediators Inflamm* 2018. <https://doi.org/10.1155/2018/8016510>

Beydilli Y, Gökçe Hİ (2020) Investigations of cardiac functions and organ damages in neonatal calves with suspected sepsis. *MAE Vet Fak Derg* 5:140-145. <https://doi.org/10.24880/maevf.815632>

Bonelli F, Meucci V, Divers TJ, Boccardo A, Pravettoni D, Meylan M, Sgorbini M (2018) Plasma procalcitonin concentration in healthy calves and those with septic systemic inflammatory response syndrome. *Vet J* 234:61-65. <https://doi.org/10.1016/j.tvjl.2018.02.003>

Bradford DJ (2019) The development of a medical biomarker test to aid in rapid screening for the presence of infectious diseases. PhD Thesis. Stellenbosch University, Institute of Health Science, 2019.

Brar TK, Singh KD, Kumar A (2015) Effect of different phases of menstrual cycle on heart rate variability (HRV). *J Clin Diagnostic Res* 9:CC01. <https://doi.org/10.7860/JCDR/2015/13795.6592>

Chow SL, Maisel AS, Anand I, Bozkurt B, De Boer RA, Felker GM, Zile MR (2017) Role of biomarkers for the prevention, assessment, and management of heart failure: a scientific statement from the American Heart Association. *Circ J* 135:e1054-e1091. <https://doi.org/10.1161/CIR.0000000000000490>

Çitil M, Arslan MÖ, Güneş V, Erdogan HM (2004) Neonatal buzağı shallerinde Cryptosporidium ve Eimeria enfeksiyonlarının rolü. *Kafkas Univ Vet Fak Derg* 10:59-64.

Çitil M, Gokce E (2013) Neonatal septicemia. *Türk Klin J Vet Sci* 4:62-70.

Demir PA, Aydin E, Ayvazoğlu C (2019) Estimation of the Economic Losses Related to Calf Mortalities Kars Province, in Turkey. *Kafkas Univ Vet Fak Derg* 25:283-290. <https://doi.org/10.9775/kvfd.2018.20471>

Dhingra R, Gona P, Nam BH, D'Agostino Sr RB, Wilson PW, Benjamin EJ, O'Donnell CJ (2007) C-reactive protein, inflammatory conditions, and cardiovascular disease risk. *Am J Med* 120:1054-1062. <https://doi.org/10.1016/j.amjmed.2007.08.037>

El-Ashker M, Salama M, El-Boshy M (2013) Traumatic reticuloperitonitis in water buffalo (Bubalus bubalis): Clinical findings and the associated inflammatory response. *J Vet Med* 808656:1-6. <http://dx.doi.org/10.1155/2013/808656>

Fecteau G, Smith BP, George LW (2009) Septicemia and meningitis in the newborn calf. *Vet Clin North Am Food Anim* 25:195-208. <https://doi.org/10.1016/j.cvfa.2008.10.004>

Fenton KE, Parker MM (2016) Cardiac function and dysfunction in sepsis. *Clin Chest Med* 37:289-298. <https://doi.org/10.1016/j.ccm.2016.01.014>

Gökçe E, Sözmen M, Gülmез C, Bozukluhan K, Gökçe G, Ataklı E, Erdogan HM (2021) Carnitine concentrations in healthy and septicemia suspected neonatal calves and its relation to passive immunity. *Turkish J Vet Anim Sci* 45:229-237. <https://doi.org/10.3906/vet-2011-49>

Hanedan B, Kirbas A, Dorman E, Mehmet OT, Kandemir MF, Alkan O (2015) Cardiactroponin-I concentration in weaned calves with bovine respiratory disease. *Acta Vet* 65:454-462. <https://doi.org/10.1515/actv-2015-0038>

Hori Y, Kikuchi M, Nakagawa A, Yonezawa T, Miura H, Ohnami Y (2009) Plasma atrial natriuretic peptide in healthy calves and calves with congenital heart disease. *J Vet Intern Med* 23:653-656. <https://doi.org/10.1111/j.1939-1676.2009.0293.x>

Kakihana Y, Ito T, Nakahara M, Yamaguchi M, Yasuda T (2016) Sepsis-induced myocardial dysfunction: pathophysiology and management. *J Intensive Care* 4:1-10. <https://doi.org/10.1186/s40560-016-0148-1>

Kavaklı HS, Altıntaş ND, Tanrıverdi F (2010) Homocysteine Levels in Acute Ischemic Stroke Patients. *Eurasian J Emerg Med* 9:169-171. <https://doi.org/10.5152/jaem.2010.007>

Kelliher HB, MacKie BA, Stepien, RL (2011) NT-proBNP, NT-proANP and NT-procTnI concentrations in dogs with pre-capillary pulmonary hypertension. *J Vet Cardiol* 13:171-182. <https://doi.org/10.1016/j.jvc.2011.04.003>

Kemp M, Donovan J, Higham H, Hooper J (2004) Biochemical markers of myocardial injury. *Br J Anaesth* 93:63-73. <https://doi.org/10.1093/bja/aeh148>

Kılıçkap A, Kozat S (2017) Research of serum homocysteine levels in healthy cows. *J Vet Sci Anim Husb* 5:103.

Kırbaş A, Değirmençay Ş, Kılinc A, Eroğlu M (2021) Evaluation of serum cardiactroponin-I concentration and cardiac enzyme activities in neonatal calves with sepsis. *Israel J Vet Med* 76:4-11.

King EG, Bauzá GJ, Mella JR, Remick DG (2014) Pathophysiological mechanisms in septic shock. *Lab Invest* 94:4-12. <https://doi.org/10.1038/labinvest.2013.110>

Klein D, Kern A, Lapan G, Benetka V, Möstl K, Hassl A, Baumgartner W (2009) Evaluation of rapid assays for the detection of bovine coronavirus, rotavirus A and Cryptosporidium parvum in faecal samples of calves. *Vet J* 182:484-486. <https://doi.org/10.1016/j.tvjl.2008.07.016>

Kozat S, Özkan C, Okman EN (2021) Evaluation of homocysteine levels in neonatal calves with diarrhea. *Kafkas Univ Vet Fak Derg* 27:271-277. <https://doi.org/10.9775/kvfd.2020.24894>

Labonté J, Dubuc J, Roy JP, Buczinski S (2018) Prognostic value of cardiactroponin I and l-lactate in blood of dairy cows affected by owner-cow syndrome. *J Vet Intern Med* 32:484-490. <https://doi.org/10.1111/jvim.14874>

Landesberg G, Levin PD, Gilon D, Goodman S, Georgieva M, Weissman C (2015) Myocardial dysfunction in severe sepsis and septic shock: no correlation with inflammatory cytokines in real-life clinical setting. *Chest* 148:93-102. <https://doi.org/10.1378/chest.14-2259>

Langhorn R, Willeson JL (2016) Cardiactroponins in dogs and cats. *J Vet Intern Med* 30:36-50. <https://doi.org/10.1111/jvim.13801>

Leonardi F, Passeri B, Fusari A, De Razza P, Beghi C, Lorusso R, Botti P (2008) Cardiactroponin I (cTnI) concentration in an ovine model of myocardial ischemia. *Res Vet Sci* 85:141-144. <https://doi.org/10.1016/j.rvsc.2007.09.010>

Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Ramsey G (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Intensive Care Med* 29:530-538. <https://doi.org/10.1007/s00134-003-1662-x>

Li X, Jiang L, Lin S, He Y, Shen G, Cai Z, Zhang M (2014) Inhibition of mTORC1 renders cardiac protection against lipopolysaccharide. *Int J Clin Exp Pathol* 7:8432.

Long Y, Nie J (2016) Homocysteine in renal injury. *Kidney Dis* 2:80-87. <https://doi.org/10.1159/000444900>

Magliulo M, De Tullio D, Vikholm-Lundin I, Albers WM, Munter T, Manoli K, Torsi L (2016) Label-free C-reactive protein electronic detection with an electrolyte-gated organic field-effect transistor-based immunosensor. *Anal Bioanal Chem Res* 408:3943-3952. <https://doi.org/10.1007/s00216-016-9502-3>

Mellanby RJ, Henry JP, Cash R, Ricketts SW, Bexiga R, Truyers I, Mellor DJ (2009) Serum cardiactroponin I concentrations in cattle with cardiac and non-cardiac disorders. *J Vet Intern Med* 23:926-930. <https://doi.org/10.1111/j.1939-1676.2009.0330.x>

Mueller C, Breidhardt T, Laule-Kilian K, Christ M, Perruchoud AP (2007) The integration of BNP and NT-proBNP into clinical medicine.

SwissMedWkly 137:4-12.

Naseri A, Sen I, Turgut K, Guzelbektes H, Constable PD (2019) Echocardiographic assessment of left ventricular systolic function in neonatal calves with naturally occurring sepsis or septic shock due to diarrhea. *ResVetSci* 126:103-112. <https://doi.org/10.1016/j.rvsc.2019.08.009>

Naseri A, Şen I, Turgut K, Guzelbektes H (2021) Evaluation of coagulation abnormalities and cardiac biomarkers in calves with naturally occurring severe sepsis or septic shock. *Van Vet J* 32:28-32. <https://doi.org/10.36483/vanvetj.855449>

Neamat-Allah ANF (2015) Alterations in some hematological and biochemical parameters in Egyptian buffaloes suffering from traumatic reticuloperitonitis and its sequelae. *Bull UASVM VetMed* 72:117-122. <https://doi.org/10.15835/buasvmcn-vm:11021>

Ogawa M, Hori Y, Kanno N, Iwasa N, Toyohuku T, Isayama N, Takemura N (2021) Comparison of N-terminal pro-atrial natriuretic peptide and three cardiac biomarkers for discriminatory ability of clinical stage in dogs with myxomatous mitral valvedisease. *J VetMedSci* 83:705-715. <https://doi.org/10.1292/jvms.20-0629>

Pardon B, Deprez P (2018) Rational antimicrobial therapy for sepsis in cattle in face of the new legislation on critically important antimicrobials. *VlaamsDiergeneskd. Tijdschr* 87:37-46.

Poulsen KP, Foley AL, Collins MT, McGuirk SM (2010) Comparison of passive transfer of immunity in neonatal dairy calves fed colostrum-bovine serum-based colostrum replacement and colostrum supplement products. *J AmVetMed* 237:949-954. <https://doi.org/10.2460/javma.237.8.949>

Ruskoaho H (2003) Cardiac hormones as diagnostic tools in heart failure. *EndocrRev* 24:341-356. <https://doi.org/10.1210/er.2003-0006>

Tokgöz BS, Özdemir R, Turut N, Mıroğlu M, İnce H, Mahanoğlu B, Tuzcu N (2013) Adana Bölgesinde görülen neonatal buzağı enfeksiyonlarının morbidite ve mortaliteleri ve risk faktörlerinin belirlenmesi. *AVKAE Derg* 3:7-14.

Tunca R, Sozmen M, Erdogan H, Cıtil M, Uzlu E, Ozen H, Gokçe E (2008) Determination of cardiotroponin I in the blood and heart of calves with foot-and-mouth disease. *J Vet Diagn Invest* 20:598-605. <https://doi.org/10.1177/104063870802000510>

Undhad VV, Fefar DT, Jivani BM, Gupta H, Ghodasara DJ, Joshi BP, Prajapati KS (2012) Cardiotroponin: an emerging cardiac biomarker in animal health. *Vet. World* 5:508-511. <https://doi.org/10.5455/vet-world.2012.508-511>

Yıldız R, Beslek M, Beydilli Y, Ozcelik M, Bicici O (2018) Evaluation of platelet activating factor in neonatal calves with sepsis. *J Turkish Vet Med Soc* 89:66-73.