Kafkas Universitesi Veteriner Fakultesi Dergisi
Journal Home-Page: http://vetdergikafkas.org
E-ISSN: 1309-2251

Kafkas Univ Vet Fak Derg
29 (1): 71-77, 2023
DOI: 10.9775/kvfd.2022.28624

RESEARCH ARTICLE

Diagnostic Value of Serum H-FABP and NT-proBNP Levels in Determining Cardiac Damage in Cattle with Bovine Respiratory Disease Complex

Şükrü DEĞİRMENÇAY [1 (*)]

[1] Atatürk University, Faculty of Veterinary Medicine, Department of Internal Medicine, TR-25240 Erzurum - TÜRKİYE

ORCID: Ş.D. 0000-0002-3920-6343

Article ID: KVFD-2022-28624 Received: 08.10.2022 Accepted: 02.01.2023 Published Online: 16.01.2023

Abstract: Cardiac complications associated with respiratory diseases are well-documented in humans, but there are not many studies with cattle. Therefore, this study aimed to investigate cardiac damage in cattle with bovine respiratory disease complex (BRDC) with serum heart-type fatty acid-binding protein (H-FABP), N-terminal pro-peptide natriuretic type B (NT-proBNP) and other known cardiac damage biomarkers [cardiac troponin I (cTnI), creatine kinase-myocardial band (CK-MB), creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH)]. The material of this study consisted of 20 cattle, aged 4-6 months with BRDC (infected group) and 10 healthy cattle aged 4-6 months (control group). The study findings revealed that leukocyte parameters and serum H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH, and AST levels were higher in cattle with BRDC (P=0.000). Heart rate and respiratory rate showed a strong positive correlation with cardiac damage markers. ROC analysis revealed that serum H-FABP levels with a cut-off value of 0.45 ng/ml were more sensitive (100%) and specific (100%) than the rest in determining cardiac damage. It was concluded that cardiac damage occurred in cattle with BRDC, and H-FABP was more sensitive and specific in detecting cardiac damage. It is anticipated that the use of biomarkers to detect cardiac injury in BRDC will be important for determining prognosis and guiding treatment.

Keywords: *BRDC, Cardiac damage, Cattle, cTnI, H-FABP, NT-proBNP*

Sığırların Solunum Sistemi Hastalığı Kompleksinde Kardiyak Hasarın Belirlenmesinde Serum H-FABP ve NT-proBNP Düzeylerinin Tanısal Değeri

Öz: Solunum yolu hastalıkları ile ilişkili kardiyak komplikasyonlar insanlarda iyi tanımlanmasına rağmen sığırlarda bu alanda çok az çalışma yapılmıştır. Bu nedenle, bu çalışmada sığır solunum hastalığı kompleksi (BRDC) olan sığırlarda serum kalp tipi yağ asidi bağlayıcı protein (H-FABP), N-terminal pro-peptid natriüretik tip B (NT-proBNP) ve bilinen diğer kardiyak hasar biyobelirteçleri [kardiyak troponin I (cTnI), kreatin kinaz-miyokardiyal band (CK-MB), kreatin kinaz (CK), aspartat aminotransferaz (AST) ve laktat dehidrogenaz (LDH)] ile kardiyak hasarın araştırılması amaçlandı. Çalışmanın materyalini BRDC'li (enfekte grup) 4-6 aylık 20 sığır ve 4-6 aylık 10 sağlıklı sığır (kontrol grubu) oluşturdu. Verilerimiz, BRDC'li sığırlarda lökosit parametreleri ve serum H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH ve AST düzeylerinin daha yüksek olduğunu ortaya koydu (P=0.000). Kalp ve solunum hızı, kardiyak hasar belirteçleri ile güçlü pozitif korelasyon gösterdi. ROC analizi, 0,45 ng/ml eşik değerine sahip serum H-FABP düzeylerinin kardiyak hasarı belirlemede diğer tanısal belirteçlere göre daha duyarlı (%100) ve özgül (%100) olduğunu ortaya çıkardı. Sonuç olarak, BRDC'li sığırlarda kardiyak hasarın meydana geldiği ve H-FABP'nin kardiyak hasarı tespit etmede daha duyarlı ve özgül olduğu sonucuna varıldı. BRDC'de kardiyak hasarı saptamak için biyobelirteçlerin kullanılmasının, prognozu belirlemek ve tedaviyi yönlendirmek için önemli olacağı tahmin edilmektedir.

Anahtar sözcükler: *BRDC, Kardiyak hasar, Sığır, cTnI, H-FABP, NT-proBNP*

How to cite this article?

Değirmençay Ş: Diagnostic value of serum H-FABP and NT-proBNP levels in determining cardiac damage in cattle with bovine respiratory disease complex. *Kafkas Univ Vet Fak Derg*, 29 (1): 71-77, 2023.
DOI: 10.9775/kvfd.2022.28624

(*) Corresponding Author

Tel: +90 442 231 7156
E-mail: s.degirmencay@atauni.edu.tr

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Introduction

Bovine respiratory disease complex (BRDC) is a well-defined multifactorial disease as a complex or syndrome involving the interaction of viruses, bacteria, and stress factors [1]. It is the most ubiquitous and severe disease in calf-rearing herds, with significant rates of morbidity (65-80%) and mortality (47-75%) [2,3]. *Mannheimia haemolytica*, *Pasteurella multocida*, *Histophilus somni*, and *Mycoplasma bovis* are common bacteria associated with BRDC [4]. Among the most significant viral pathogens linked to BRDC are infectious bovine rhinotracheitis virus (IBRV), bovine viral diarrhea virus (BVDV), parainfluenza-3 virus (PIV3), and bovine respiratory syncytial virus (BRSV) [5-7]. Due to the production losses and high treatment costs associated with BRDC, it is a financially significant disease in calves [8].

For the identification of BRDC agents, whole blood, nasal swab samples, nasopharyngeal swab samples, and bronchoalveolar lavage fluid can be used [9,10]. However, regular surveillance of infectious organisms is impractical and expensive for many farms. Because of this, clinical scoring systems-one of the more practical techniques for BRDC diagnosis-have been created [11-13]. Characteristic clinical signs are traditionally used to make the clinical diagnosis of BRDC [11]. Fever, cough, ocular or nasal discharge, abnormal breathing, and auscultation of abnormal lung sounds are the symptoms that are used to diagnose respiratory disease in calves [12]. Clinical scoring methods assign various values to some of these symptoms, and animals with a total score of 4 or higher are referred to as "BRDC positive." Usually, 90% of positive cases and controls are correctly classified by these techniques [12].

Our key hypothesis for this investigation was that respiratory system infections would cause cardiac damage from tachycardia and hypoxia. The information that follows is also relevant to our hypothesis. Increased blood cardiac troponin I (cTnI) concentrations have been associated with severe BRDC in weaned calves [14] and with increased disease severity in community-acquired pneumonia in humans [15]. Lung abscesses, consolidation, vasculitis, fever, hypoxia, septicaemia, complement activation, initiation of coagulation, increased acute phase proteins, exo- and endotoxin generation, and other conditions can all develop in BRDC that may cause cardiac damage [16-18].

The most often utilized biochemical indicators for identifying cardiac damage are cTnI, creatine kinase-myocardial band (CK-MB), creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) [19]. A novel cardiac marker called heart-type fatty acid-binding protein (H-FABP) is utilized to diagnose acute myocardial infarction in its early stages (within the first two hours) and to detect myocyte damage. In comparison to CK-MB and troponin, studies on humans have shown that H-FABP is a better diagnostic marker for early diagnosis (6 hours), with high sensitivity (79%) and specificity (93%) [20]. Natriuretic peptides have become crucial diagnostic and therapeutic monitoring tools for cardiac problems in recent years [21,22]. In the event of pressure and volume overload, the ventricular myocardium responds by releasing the hormone N-terminal pro-peptide natriuretic type B (NT-proBNP) and remains elevated in the blood for up to 60-120 minutes [23]. The most often utilized natriuretic peptide at the moment, more specifically in veterinary medicine, is NT-proBNP [21,22].

Studies in human medicine have demonstrated that cardiac problems are frequent in community-acquired pneumonia, are related to more severe illness, and may predict prognosis [18,24-26]. There are also studies in veterinary medicine evaluating heart damage in respiratory system diseases [14,27]. This study's main goal was to detect cardiac damage in calves with BRDC using serum levels of H-FABP, NT-proBNP, and other known cardiac biomarkers (cTnI, CK-MB, CK, AST and LDH). This study also aims to assess, using ROC analysis, the performance of these cardiac biomarkers in detecting cardiac damage.

Material and Methods

Ethical Approval

This study was performed in accordance with the approved ethical rules of Atatürk University (protocol no. 2022/6, decision number: 109) and for each cattle written informed consent was obtained from the owner.

Animals and Protocol Design

The study material included 30 cattle of 4-6 months old, Simmental breed and both genders. The cattle were divided into two groups as BRDC (infected, n=20) and healthy (control, n=10) based on clinical examination and complete blood count findings. During the clinical examination, the rectal temperature (RT), heart rate (HR) and respiratory rates (RR) of all calves were measured and noted. Animals that received a total score of 5 or higher under the scoring system created by Love et al.[12] were recognized as BRDC. Calves with abnormal ear or head carriage (normal, ear flick or head shake: 0, ear droop or head tilt: 5), calves with nasal discharge (none: 0, any: 4) and one other clinical finding [cough (none or induced cough: 0, spontaneous cough: 2), ocular discharge (none: 0, any: 4), rectal temperature (<39.2°C: 0, ≥39.2°C: 2), and abnormal respiration (absent: 0, present: 2)], or calves that have any three clinical signs are defined as BRDC cases according to this scoring system.

Blood Sampling

Blood samples from all the calves were taken from *v. jugularis externa* and collected into tubes with EDTA (Vacutainer, K2E 3.6 mg, BD, UK) and gel (Vacutainer, BD, UK) for haematological and biochemical analyses. Blood samples in gel tubes were kept at room temperature and centrifuged at 3000 rpm for 10 min. The obtained serum samples were stored at -80°C until the day of the biochemical analysis. Haematological analyses were finished right away.

Haematological Analyses

White blood cell (WBC), lymphocyte (LYM), monocyte (MON), neutrophil (NEU), eosinophil (EOS), basophil (BAS), and platelet (PLT) levels of the cattle were determined by a haematology analyser (Abacus Junior Vet5, Hungary).

Biochemical Analyses

Using approved commercial bovine-specific enzyme-linked immunosorbent assay (ELISA) kits, the manufacturer's recommendations were followed to assess the serum concentrations of H-FABP and NT-proBNP (Sunred Biological Technology, Shanghai, China). The intra-assay and inter-assay coefficients of variation (CV) for H-FABP were found to be 10% and 12%, respectively, with a minimum detectable concentration (MDC) of 0.08 ng/mL. The MDC for NT-proBNP was 10 ng/mL, and the intra-assay and inter-assay CVs were 10% and 12%, respectively. A commercial immunoassay system was used to measure the levels of cTnI in the serum in accordance with the one-step sandwich method (Unicel Beckman Coulter Access II, USA). The similarity of the troponin I sequence between cattle and humans is > 96%, allowing for the reliable application of this assay in cattle [28]. Troponin can be measured by the immunoassay system between 0.01 and 100 ng/mL. Serum CK, CK-MB, LDH, and AST activities were determined using a biochemistry autoanalyzer (Beckman Coulter, AU5800, USA) employing commercial enzyme kits.

Statistical Analyses

For statistical analysis, SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA) was utilized. A Shapiro-Wilk test was used to assess the data distribution between the groups (BRDC and Healthy groups). The Independent-Samples t-Test was used to compare parametric variables (LYM, PLT, H-FABP, NT-proBNP, CK-MB, AST, RT, HR, and RR). The Mann-Whitney U test was used to compare nonparametric variables (WBC, MON, NEU, EOS, BAS, cTnI, CK, and LDH). The correlation among parameters was measured by the Pearson Correlation test. The diagnostic efficacy of serum H-FABP and NT-proBNP in identifying cardiac damage was assessed using Receiver Operating Characteristic (ROC) analysis. For parametric variables, all results were shown as mean ± standard deviation (SD), and for nonparametric variables, median and range (min, max). All statistical comparisons were performed at the significance level of $P<0.05$.

Results

Clinical Findings

High temperature (T: 39.44±0.74), tachycardia (149.6±22.72 beats per minute), tachypnea (50.4±9.39 breaths per minute), anaemic and moderately cyanotic mucosa, cough, dyspnoea, nasal and ocular discharge, and anorexia were common clinical signs in cattle with BRDC. When compared to the control group, the infected cattle's RT ($P< 0.019$), HR, and RR ($P=0.000$) were significantly higher *(Table 1)*.

Haematological Findings

According to the haematologic findings, the WBC, LYM, BAS, and PLT values of the BRDC group were higher than those of the healthy group ($P<0.05$) *(Table 1)*.

Biochemical Findings

The mean H-FABP, NT-proBNP, CK-MB, and AST concentrations and the median cTnI, CK and LDH concentrations in the BRDC group were significantly higher than the healthy group ($P=0.000$) *(Table 1)*.

Serum H-FABP levels were very strongly positively correlated with LDH ($r=0.831$, $p=0.000$), strongly correlated with NT-proBNP ($r=0.733$, $P=0.000$) and AST ($r=0.659$, $P=0.000$), and moderately positively correlated with cTnI ($r=0.559$, $P=0.001$), (CK-MB ($r=0.531$, $P=0.003$) and CK ($r=0.489$, $P=0.006$). Serum NT-proBNP levels were strongly positively correlated with LDH ($r=0.724$, $P=0.000$), moderately positively correlated with CK-MB ($r=0.561$, $P=0.001$), AST ($r=0.538$, $P=0.002$), and CK ($r=0.462$, $P=0.010$), and weakly positively correlated with cTnI ($r=0.370$, $P=0.044$) *(Table 2)*.

There was a very strong positive correlation between heart rate and H-FABP ($r=0.855$, $P=0.000$) and LDH ($r=0.828$, $P=0.000$). Heart rate was strongly positively correlated with NT-proBNP ($r=0.633$, $P=0.000$), CK ($r=0.600$, $P=0.000$), and AST ($r=0.755$, $P=0.000$) whereas moderately positively correlated with cTnI ($r=0.537$, $P=0.002$) and (CK-MB ($r=0.476$, $P=0.008$). Respiration rate was moderately positively correlated with H-FABP ($r=0.570$, $P=0.001$) and NT-proBNP ($r=0.531$, $P=0.003$) whereas strongly positively correlated with CK ($r=0.640$, $P=0.000$), LDH ($r=0.705$, $P=0.000$), and AST ($r=0.766$, $P=0.000$) *(Table 2)*.

Serum H-FABP levels were moderately positively correlated with WBC ($r=0.409$, $P=0.025$) and LYM

Table 1. *Comparing haematological, biochemical and some clinical results between infected and control groups of cattle*

Parameters	Healthy	BRDC	P Value
WBC (x10³/µL)	6.95 (4.45-8.33)	9.97 (5.45-25-89)	0.014
LYM (x10³/µL)	3.32±1.41	4.82±0.80	0.009
MON (x10³/µL)	0.21 (0.08-0.71)	0.12 (0.06-0.38)	0.170
NEU (x10³/µL)	2.54 (0.52-5.34)	4.22 (1.63-21)	0.053
EOS (x10³/µL)	0.1 (0.05-0.20)	0.06 (0.02-0.10)	0.006
BAS (x10³/µL)	0.0 (0.00-0.01)	0.03 (0.01-0.07)	0.000
PLT (x10³/µL)	284±112	494±174	0.002
H-FABP (ng/mL)	0.37±0.79	0.65±0.81	0.000
NT-proBNP (ng/mL)	0.19±0.43	0.41±0.12	0.000
cTnI (ng/mL)	0.0398 (0.0196-0.0536)	0.0685 (0.0437-0.1512)	0.000
CK-MB (U/L)	136±45.2	382±113	0.000
CK (U/L)	122.5 (66-351)	318 (174-384)	0.000
LDH (U/L)	499 (270-1364)	2683 (2093-2971)	0.000
AST (U/L)	33±21.85	121±35.25	0.000
RT (°C)	38.97±0.28	39.44±0.24	0.019
HR (beats/min)	79±9.58	149.6±22.72	0.000
RR (breaths/min)	32.40±9.32	50.4±9.39	0.000

WBC: white blood cell; LYM: lymphocyte; MON: monocytes; NEU: neutrophil; EOS: eosinophil; BAS: basophil; PLT: platelet; H-FABP: heart type fatty acid binding protein; NT-proBNP: N-terminal pro-peptide natriuretic type B; cTnI: cardiac troponin I; CK-MB; creatine kinase myocardial band; CK; creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; RT: Rectal temperature; HR: Heart rate (per min); RR: Respiratory rate (per min). Data are presented as mean ± standard deviation and or median (range).

Table 2. *Correlation results of some haematological, clinical and cardiac damage parameters of cattle in the infected and control groups (Pearson Correlation)*

Parameters	WBC	LYM	RR	HR	H-FABP	NT-pro BNP	cTnI	CK-MB	CK	LDH	AST
WBC	1.000	0.449*	0.713**	0.626**	0.409*	0.295	0.063	0.088	0.344	0.483**	0.647**
LYM		1.000	0.327	0.550**	0.552**	0.551**	0.304	0.354	0.144	0.562**	0.355
RR			1.000	0.703**	0.570**	0.531**	0.157	0.321	0.640**	0.705**	0.766**
HR				1.000	0.855**	0.633**	0.537**	0.476**	0.600**	0.828**	0.755**
H-FABP					1.000	0.733**	0.559**	0.531**	0.489**	0.831**	0.659**
NT-proBNP						1.000	0.370*	0.561**	0.462*	0.724**	0.538**
cTnI							1.000	0.490*	0.248	0.413*	0.259
CK-MB								1.000	0.645**	0.743**	0.563**
CK									1.000	0.766**	0.860**
LDH										1.000	0.897**
AST											1.000

WBC: White blood cell; LYM: lymphocyte; RR: Respiratory rate (per min); HR: Heart rate (per min); H-FABP: heart type fatty acid binding protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTnI: cardiac troponin I; CK-MB; creatine kinase myocardial band; CK; creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase

(r=0.552, P=0.002). Serum NT-proBNP levels were moderately positively correlated with LYM (r=0.551, P=0.002) *(Table 2)*.

ROC analysis results of cardiac biomarkers were shown in *Table 3* and *Fig. 1*. The areas under the ROC curves (AUC) were found to be 1.000 for the H-FAB, 0.975 for the NT-proBNP, 0.970 for the cTnI, and 0.950 for the CK-MB parameter. The cut-off values of H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH, and AST parameters in showing cardiac damage were 0.45 ng/mL, 0.27 ng/mL, 0.0435 ng/mL, 185.9 U/L, 201 U/L, 1364 U/L and 63 U/L, respectively. The sensitivity and specificity values of the proposed diagnostic cut-off point for demonstrating cardiac injury were found to be 100% and 100% for H-FABP, 90% and 100% for NT-proBNP and CK-MB, and 100% and 90% for cTnI.

Table 3. ROC analysis results of H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH, and AST

Parameters	H-FABP (ng/mL)	NT-proBNP (ng/mL)	cTnI (ng/mL)	CK-MB (U/L)	CK (U/L)	LDH (U/L)	AST (U/L)
Area	1.000	0.975	0.970	0.950	0.900	1.000	0.990
Cut-off	>0.45	>0.27	>0.0435	>185.9	>201	>1364	>63
Sensitivity (%)	100	90	100	90	90	100	100
Specificity (%)	100	100	90	100	90	100	90
SEM	0.000	0.023	0.032	0.039	0.071	0.000	0.013
P value	0.000	0.000	0.000	0.000	0.000	0.000	0.000

H-FABP: heart type fatty acid binding protein; NT-proBNP: N-terminal pro-B-type natriuretic peptide; cTnI: cardiac troponin I; CK-MB; creatine kinase myocardial band; CK; creatine kinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase

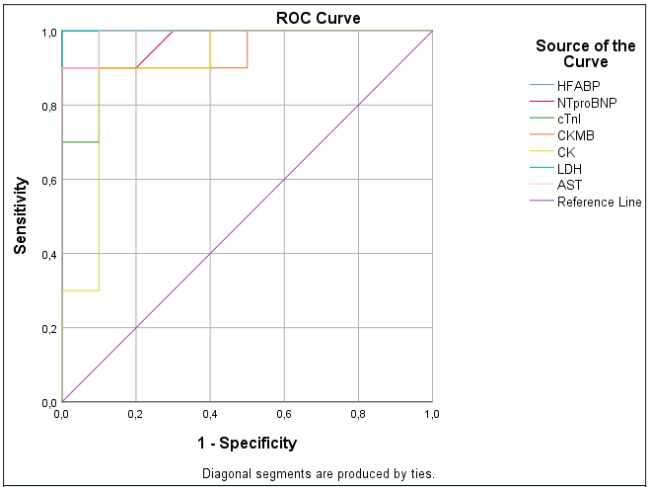

Fig 1. ROC curve analysis of H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH, and AST parameters

Discussion

In this study, we investigated changes in the levels of cardiac damage markers in cattle with BRDC. Consistent with our hypothesis, we found that cardiac damage occurred in cattle with BRDC with elevated H-FABP, NT-proBNP, cTnI, CK, AST and LDH levels. High respiratory and heart rates were also noticed and found to be strongly positively correlated with heart damage markers. H-FABP was found to be more sensitive (100%) and specific (100%) than other diagnostic markers in identifying the cardiac injury.

Cardiovascular problems such as cardiac arrhythmias [25] might arise in cases of pneumonia [18]. Serum cardiac troponin levels may rise due to bacterial endotoxins, cytokines, increased cardiac oxygen demands due to inflammation, ventilation-perfusion mismatches in acute pneumonia, myocardial contractility depression, catecholamine release, and tachycardia [18,29]. Hypoxia can affect heart function by leading to impaired oxygen delivery to cells and decreased tissue perfusion [30]. Myocardial oxygen demand increases when tachycardia develops as a result of hypoxemia in pneumonia cases [31], which may contribute to acute myocardial damage [15]. In this study, the BRDC group showed higher cardiac and respiratory frequency than the control group (P=0.000). Respiratory frequency was moderately positively correlated with H-FABP and NT-proBNP, on the other hand, heart rate was very strongly correlated with H-FABP and strongly positively correlated with NT-proBNP. These findings suggest that BRDC-induced hypoxia and tachycardia caused cardiac damage in cattle. Similar to this, Hanedan et al.[14] reported elevated heart and respiratory frequency in cattle with BRDC and verified heart damage with high cTnI.

In the early diagnosis of the acute coronary syndrome, it was found that H-FABP was more sensitive and specific than troponin I and CK-MB. The rapid release of H-FABP into the bloodstream following myocardial injury has made it a valuable early and accurate diagnostic marker for myocardial infarction in humans [32]. Similarly, in this study, we found that H-FABP was superior to NT-proBNP, cTnI and CK-MB in detecting cardiac damage by ROC analysis, and a similar feature may exist in cattle. Pharmaceutical treatments, such as anti-tachycardic drugs, were observed to lower H-FABP plasma levels [33]. In our study, the marker with the highest positive correlation coefficient with heart rate was H-FABP (r=0.855, P=0.000). Therefore, tachycardia may play a role in finding H-FABP as the most sensitive marker for detecting heart damage in cattle with BRDC. According to a study that evaluated the levels of H-FABP, NT-proBNP, and cTnI in dogs with dilated cardiomyopathy and degenerative valve disease, H-FABP may be a helpful marker because it was shown to be high, linked with the severity of the disease, and tended to predict a shorter survival time [34]. The importance of such sensitive markers in the veterinary field was emphasized after it was shown that H-FABP levels were high in a different study's assessment of heart damage in cattle with traumatic pericarditis [35]. The second most sensitive marker in BRDC for identifying cardiac damage, according to ROC analysis, was NT-proBNP. As a result of both acute and chronic pneumonia in cattle, pulmonary artery pressures have been shown to rise [36]. Considering that NT-proBNP is released into the blood circulation in

case of pressure and volume overload [23], we speculate that pneumonia, tachycardia and possible pulmonary hypertension are effective in finding NT-proBNP as a high and second sensitive marker in cattle with BRDC.

As is generally known, BRDC is a condition characterised by severe inflammation [37]. In calves with BRDC, leucocytosis and neutrophilia connected with acute respiratory inflammation have been documented [38-40]. Similarly, in this study, the BRDC group had higher WBC (P=0.014), LYM (P=0.009), and BAS (P=0.000) values than that of the healthy group. Serum NT-proBNP levels were shown to be moderately positively correlated with WBC and LYM, but serum H-FABP levels only with WBC. As a result, infection-related cardiac damage occurs in BRDC. To support this inference, it has been reported that pulmonary interstitial disease or severe pneumonia may cause cardiac damage [41]. Additionally, *Histophilus somnus* has been linked to endocarditis [42,43]. This study's shortcoming is the lack of detection of etiological agents in animals with BRDC. However, the study primarily aimed to reveal whether cardiac damage occurred in BRDC-affected animals. I recommend that future studies should investigate how cardiac damage varies depending on the etiological agents in animals with BRDC.

In conclusion, this study demonstrated that cardiac damage occurred in cattle with BRDC with elevated levels of H-FABP, NT-proBNP, cTnI, CK-MB, CK, LDH and AST. In addition, H-FABP and NT-proBNP were superior to other markers in showing this damage, respectively. Cardiac damage markers in BRDC may be elevated as a result of increased cardiac oxygen demands caused by inflammation, ventilation-perfusion mismatches, hypoxia, tachycardia, and pulmonary hypertension due to acute respiratory distress syndrome. It is important to understand the role of cardiac dysfunction in BRDC as this would help clinicians both assess the risk of death in BRDC cases and determine their treatment accordingly.

Availability of Data and Materials

On reasonable request, the corresponding author will provide the data provided in this study.

Acknowledgements

The author would like to thank Assoc. Prof. Dr Sefa Küçükler for performing the biochemical analysis for the study.

Funding Support

The study was self-funded.

Competing Interests

The author declares no conflict of interest.

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