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GS Boluk, AS Ozturk, A Ozturk

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New cardiac biomarkers in dogs with parvoviral enteritis: galectin-3 and cardiotrophin-1

G.S. Boluk,[1] A. Sagkan Ozturk,[1,2*] A. Ozturk[3]

[1]Hatay Mustafa Kemal University, Veterinary Faculty, Department of Internal Medicine, Hatay, Turkiye.

[2]Hatay Mustafa Kemal University, Institute of Health Sciences, Department of Molecular Biochemistry and Genetic (Medicine), Hatay, Turkiye.

[3]Gaziantep Islam Science and Technology University, Medicine Faculty, Department of Physiology, Gaziantep, Turkiye.

ABSTRACT: Canine parvoviral enteritis remains a disease associated with high mortality and morbidity in puppies despite the availability of vaccination. Consequently, ongoing research into biomarkers for parvoviral enteritis is being conducted. This study aimed to evaluate, for the first time, cardiotrophin-1 (CT-1) and galectin-3 (GAL-3) as a cardiac biomarker in conjunction with routine parameters in dogs with parvoviral enteritis (PVE). The dog with PVE was subdivided into three categories: unvaccinated under 3 months of age dogs (n = 8), unvaccinated over 3 months of age dogs (n = 15), and dogs that had received vaccination (n = 10). Eight healthy dogs were included as A control group. Serum levels of GAL-3, CT-1, CK-MB, and CK were significantly elevated in all dogs with parvoviral enteritis (PVE) compared to the control group. The total leukocyte count was significantly reduced in all PVE groups. In dogs under 3 months of age, Packed Cell Volume (PCV) values were comparable to those of the control group. Creatinine levels were significantly reduced in all PVE groups. In conclusion, unlike routine biochemical parameters, elevated GAL-3, CT-1, and CK-MB and CK demonstrate satisfactory sensitivity and specificity, suggesting their potential as cardiac biomarkers for PVE. These biomarkers may also represent novel therapeutic targets.

Keyword: Cardiotrophin 1; Dog; Galectin-3; Parvoviral Enteritis.

Correspondence author:
A. Sagkan Ozturk,
Hatay Mustafa Kemal University, Veterinary Faculty, Department of Internal Medicine, Tayfur Sokmen Campus (31060) Alahan-Antakya/ Hatay, Turkiye
E-mail address: adurusua@gmail.com

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INTRODUCTION

Canine parvovirus is an important enteropathogen that results in high morbidity and mortality rates among susceptible dogs [1]. Parvovirus, initially designated CPV-1, was first identified in dogs in the late 1960s as a cause of gastrointestinal and respiratory infections. In the 1970s, a distinct mutating variant, CPV-2 was discovered, leading to the first pandemic that affected adult and juvenile dogs [2]. Vaccines targeting CPV-2 strains are still under development and are routinely administered [3].

CPV infection is transmitted through both fecal-oral (direct) and oral-nasal (indirect) routes, typically via exposure to substances contaminated with feces. The virus remains viable in the external environment for approximately one year under favorable conditions. It is ingested orally by puppies through exposure to feces or by ingesting material contaminated with the vomit of infected animals [4].

Canines infected with CPV exhibit two primary clinical manifestations: enteritis and myocarditis [5]. CPV-2 myocarditis is now exceedingly rare; however, it may still occur in puppies younger than 8 weeks of age or as a result of congenital infections transmitted from unvaccinated dams [4,6]. Although rapid faecal parvovirus antigen tests are typically negative in dogs with parvoviral myocarditis, some studies have reported the development of myocarditis in dogs with positive test results, often in conjunction with enteritis [7].

Galectin-3 (GAL-3) is a member of the β-galactoside-binding lectin family and has been detected in various cell types. It plays a significant role in the inflammatory process as well as in the viral life cycle, including replication, assembly, and release. Therefore, it is potentially a target for antiviral therapies [8]. On the other hand, GAL-3 is associated with left ventricular dilatation and serves as a valuable biomarker for monitoring patients with both acute and chronic heart failure [9,10].

Cardiotrophin-1 (CT-1), a cytokine related to interleukin 6, regulates the cardiovascular system. CT-1 is highly expressed in the heart, skeletal muscle, prostate, and ovary, with lower expression levels observed in the lung, kidney, pancreas, thymus, testis, and small intestine [11,12]. In addition, CT-1 plays a protective role in cardiac myocytes by preventing cytokine-induced apoptosis [13,14].

This study aimed to evaluate changes in GAL-3 and CT-1, known to be associated with inflammation, as new cardiac biomarkers for dogs, along with routine clinical parameters in dogs diagnosed with parvoviral enteritis.

MATERIALS AND METHODS

Animal management

The animal study protocol was approved by the Institutional Review Board (or Ethics Committee) of Animal Experiments Local Ethics Committee of the Hatay Mustafa Kemal University (approval reference number: 2018/6-1).

The subjects of this randomized controlled study included 33 dogs naturally infected with parvovirus and eight healthy dogs (control group), aged 1.5 to 6 months. The groups consisted of unvaccinated dogs under 3 months of age (n = 8), unvaccinated dogs over 3 months of age (n = 15), and dogs that tested CPV-positive approximately one month after their first or second vaccination (n = 10).

Clinical Examination

All dogs in the study underwent clinical examination. Fecal samples were collected using a rectal swab and evaluated with the rapid parvovirus antigen detection test (Canine Parvovirus Antigen Lateral Flow Assay Kit, Catalog No: E AD C023, Elabscience, USA). Dogs with positive test results were assigned to the PVE study group. The same tests were performed on the control group, and dogs with normal clinical findings and negative CPV antigen results in their feces were considered healthy.

Venous blood samples were collected from the cephalic veins of dog blood samples were centrifuged at 1,300×g for 15 minutes at 10°C, aliquoted, and stored at -80°C until biochemical analysis. Additionally, blood samples were placed in tubes containing K3EDTA for hematological testing (CBC – complete blood count)

Biochemical Analyses

Serum levels of total protein (TP), albumin (ALB), creatine kinase (CK), creatine kinase myocardial band (CK-MB), creatinine, blood urea nitrogen (BUN), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were measured using spectrophotometric methods with an autoanalyzer (Beckman Coulter LX-20, USA).

Canine Cardiotrophin-1 (CT-1) (BT-LAB, China, Cat.No E0461Ca) and canine Galectin-3 (GAL-3) (BT-LAB, China, Cat.No E0343Ca) concentrations

were measured using the ELISA method according to the manufacturer's instructions. The measurable sensitivity of CT-1 is 2.39 ng/L, with a test range from 5 ng/L to 1,000 ng/L. The measurable sensitivity of GAL-3 is 0.26 ng/mL, with a test range from 0.5 ng/mL to 200 ng/mL.

Statistical Analysis

Statistical analysis was conducted using the IBM SPSS Statistics 25 software. The Shapiro-Wilk test was first applied to assess the normality of the data distribution. For normally distributed data, one-way analysis of variance (ANOVA) was performed, and differences between groups were considered significant at $P < 0.05$. For data that did not follow a normal distribution, Kruskal-Wallis Test was used (for creatinine, BUN, TBIL, ALT, AST, and ALP). Differences between groups were considered significant at $P < 0.0125$ following Bonferroni correction for multiple comparisons of non-normally distributed parameters.

Receiver operating characteristic (ROC) analysis was conducted to determine the variables' diagnostic cut-off values, sensitivity, and specificity in the control and PVE groups. The Pearson correlation test was employed to assess the relationship between variables. Pairwise comparisons of ROC curves were conducted using the DeLong method with Bonferroni correction. The optimal cut-off point was determined as the value that maximized the sum of sensitivity and specificity. *p*-values < 0.05 were considered statistically significant.

RESULTS

Clinical examination of all parvovirus-positive dogs revealed anorexia, depression, lethargy, vomiting, and hemorrhagic diarrhea.

As shown in Table 1, dogs with PVE had significantly lower WBC counts compared to healthy dogs ($P < 0.01$). The granulocyte count was lower and statistically significant in dogs under 3 months of age compared to those in the other groups ($P < 0.01$). The number of monocytes was significantly decreased in the PVE groups compared to the control group ($P < 0.01$).

Serum concentrations of creatinine, CK, CK-MB, CT-1, and GAL-3 in dogs with PVE and healthy dogs are presented in Table 2. Serum levels of CK ($P < 0.05$), CK-MB ($P < 0.01$), CT-1 ($P < 0.05$), and GAL-3 ($P < 0.01$) were significantly higher in dogs with PVE compared to healthy dogs. On the other hand, serum creatinine levels ($P < 0.01$) were significantly lower in dogs with PVE compared to healthy dogs.

The ROC curve for CT-1 in positive parvoviral enteritis showed an area under the curve (AUC) of 0.818 (95% CI: 0.667–0.921), with a sensitivity of 70% and specificity of 88%. The optimal cut-off value for CT-1 in predicting PVE was > 45.1 ng/L. For GAL-3, the AUC (95% CI) was 0.848 (0.702–0.941), with a sensitivity of 85% and specificity of 75%. The optimal cut-off value for GAL-3 in predicting PVE was >10.07 ng/L. For CK, the AUC was 0.811 (95% CI: 0.658–0.916), with a sensitivity of 61% and a specificity of 100%. The optimal cut-off value for CK in predicting PVE was >276 μ/L. For CK-MB, the AUC was 0.902 (95% CI: 0.767–0.972), with a sensitivity of 79% and a specificity of 88%. The optimal cut-off value for CK-MB in predicting PVE was >286.2 U/L. (Fig. 1, Table 3).

Pairwise comparisons of ROC curves were performed using the DeLong method with Bonferroni

Table 1. Complete Blood Count (Hematological) analysis results of control and PVE groups*.

	Under 3 month Mean±SD	Over 3 month Mean±SD	Vaccine group Mean±SD	Control group Mean±SD	*p*-value
WBC (10^9/L)	6.03±3.11^b	8.63±5.65^b	5.89±3.45^b	13.91±2.52^a	0.004
Lym (10^9/L)	3.03±2.25	2.40±3.31	1.84±1.39	4.83±1.38	0.125
Gran (10^9/L)	2.70±1.28^c	6.05±3.02^{ab}	4.34±2.64^{bc}	8.28±2.41^a	0.002
Mon (10^9/L)	0.30±0.28^b	0.26±0.22^b	0.21±0.10^b	0.72±0.25^a	0.001
PCV %	36.84±8.83^b	47.70±7.28^a	47.06±12.55^a	37.75±4.43^b	0.027
PLT (10^9/L)	485.75±314.83	312.36±181.83	317.88±249.27	334.00±171.76	0.395
PCT %	0.35±0.16	0.33±0.15	0.24±0.16	0.29±0.15	0.435

*Data are expressed as mean±SD; means with different superscripts (a, b, c) within the same row are significantly different, at least at $P < 0.05$. SD: standard deviation; Values for total white blood cell count (WBC); lymphocytes (Lym); granulocytes (Gran) and monocytes (Mon); red blood cell (RBC); packed cell volume (PCV); platelet (PLT); plateletcrit (PCT).

Table 2. Biochemical analysis results of control and PVE groups*.

	Under 3 month Mean±SD	Over 3 month Mean±SD	Vaccine group Mean±SD	Control group Mean±SD	*p*-value
CT-1 (ng/L)	59.61±15.19[a]	48.09±17.44[a]	52.02±15.19[a]	33.43±13.05[b]	0.015
GAL-3 (ng/mL)	15.51±2.67[a]	13.17±3.06[a]	13.56±3.85[a]	9.97±1.69[b]	0.007
TP (g/dL)	4.78±0.94	4.99±0.50	5.38±0.77	5.00±0.69	0.331
ALB (g/dL)	2.72±0.44	3.02±0.32	3.13±0.35	3.19±0.39	0.055
CK (U/L)	248.00±142.17[ab]	346.43±166.48[a]	332.33±180.77[a]	150.07±75.98[b]	0.029
CK-MB (U/L)	329.00±200.65[ab]	527.70±246.79[a]	460.69±304.83[a]	156.27±99.13[b]	0.006
	Under 3 month Median (min-max)	**Over 3 month Median (min-max)**	**Vaccine group Median (min-max)**	**Control group Median (min-max)**	***p*-value**
Creatinine (mg/dL)	0.31 (0.12-0.87[b]	0.40 (0.15-0.68)[b]	0.53 (0.33-1.13)[ab]	0.74 (0.38-0.94)[a]	0.005
BUN (mg/dL)	14.50 (8.0-89.0)	14 (8.00-40.0)	21.5 (11.0-39.0)	16.50 (10-24)	0.221
TBIL (mg/dL)	0.04 (0.01-0.05)	0.06 (0.02-0.11)	0.07 (0.04-0.25)	0.04 (0.02-0.18)	0.073
ALT (U/L)	42 (11-114)	27 (7-85)	38.19 (11-83)	22 (12-40)	0.151
AST (U/L)	23.00 (9-54)	31 (11-89)	31 (11-174)	23 (15-32)	0.236
ALP (U/L)	166.5 (124-231)	166 (120-258)	169.5 (66-860)	12105 (24-285)	0.254

*Data are expressed as mean±SD; means with different superscripts (a, b, c) within the same row are significantly different, at least at P < 0.05. Abbreviations: SD: standard deviation; Cardiotrophin-1 (CT-1); Galectin-3 (GAL-3); total protein (TP); albumin (ALB); Creatine kinase (CK); creatine kinase myocardial band (CK-MB); blood urea nitrogen (BUN); total bilirubin (TBIL); alanine aminotransferase (ALT); aspartate transaminase (AST); alkaline Phosphatase (ALP).

correction (Table 4). Significant differences were observed between the AUC of CK and CK-MB (p = 0.0452), whereas no significant differences were found between the AUC of GAL-3 and CK-MB (p = 0.5489), GAL-3 and CK (p = 0.6418), CT-1 and CK-MB (p = 0.4393), CT-1 and CK (p = 0.9495), or GAL-3 and CT-1 (p = 0.7189).

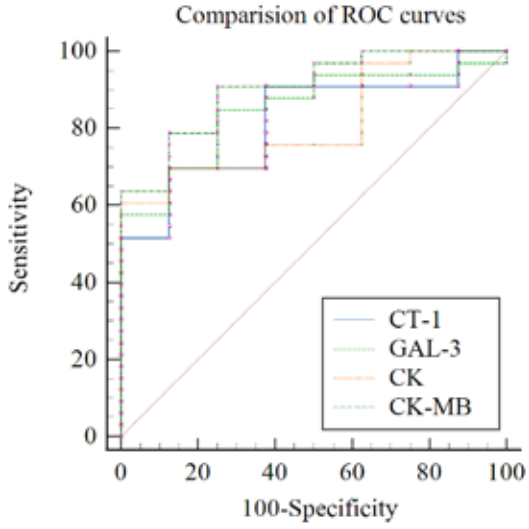

Figure 1. Receiver operating characteristic (ROC) curve analysis to discriminate between control and PVE groups based on serum concentrations of CT-1, GAL-3, CK and CK-MB.

The correlation between the concentrations of routine and selected biomarkers is displayed in Table 5. CK exhibits a positive correlation with CK-MB concentration (p < 0.01; Table 5; Fig. 2A). A positive correlation was observed between serum CT-1 and GAL-3 concentrations (p < 0.05; Table 5; Fig. 2B). No correlation was observed between CT-1 and CK, CT-1 and CK-MB, GAL-3 and CK, or GAL-3 and CK-MB (Table 5; Fig. 2C–F).

DISCUSSION

The present study, GAL-3 and CT-1 levels were investigated alongside other routine biochemical and hematological analyses in the blood serum of healthy dogs and dogs with PVE. Our results indicated that GAL-3, CT-1, CK, CK-MB, and creatinine were elevated in dogs with PVE.

The diagnosis of PVE is based on rapid and reliable lateral flow tests, which utilize the ELISA method to detect the viral antigen in stool samples. Fecal antigen tests in the myocardial form may yield negative results [15], although viruses isolated from myocardial tissues have been shown to cause enteritis experimentally [16, 17]. Er and Ok [7] suggested that myocarditis may develop in cases with positive test

Table 3. The area under the curve (AUC), standard error, confidence interval (95%), optimal cut-off values, and corresponding sensitivity and specificity for differential control and PVE groups.

Variable	AUC	Standard error	*P* value	Asymptotic 95% Confidence interval		Sensitivity %	Specificity %	Cut-off value
				Lower band	Upper band			
CT-1 (ng/L)	0,818	0,0742	<0.0001	0,667	0,921	69.70	87.50	>45.01
GAL-3 (ng/L)	0,848	0,0662	<0.0001	0,702	0,941	84.85	75.00	>10.07
CK (U/L)	0,811	0,0732	<0.0001	0,658	0,916	60.66	100	>276
CK-MB (U/L)	0.902	0,0542	<0.0001	0,767	0,972	78,79	87,50	>286.2

Table 4. The pairwise comparison includes the differences between areas, standard error, 95% confidence intervals, z-statistic, and *p*-values for CT-1, GAL-3, CK, and CK-MB.

	Difference between areas	Standard Error [a]	95% Confidence Interval	z statistic	*p*-value
CT-1/GAL-3	0.0303	0.0842	-0.135-0.195	0.360	0.7189
CT-1/CK	0.00758	0.120	-0.227-0.242	0.0633	0.9495
CT-1/CK-MB	0.0833	0.108	-0.128-0.295	0.773	0.4393
GAL-3/CK	0.0379	0.0814	-0.122-0.197	0.465	0.6418
GAL-3/CK-MB	0.0530	0.0885	-0.120-0.226	0.599	0.5489
CK/CK-MB	0.0909	0.0454	0.00194-0.180	2.003	0.0452

Table 5. Pearson correlation analysis between serum cardiac biomarkers in PVE groups.

Correlations				
	CT-1	GAL-3	CK	CK-MB
CT-1	1	.360*	.009	.075
GAL-3		1	.087	.071
CK			1	.750**
CK-MB				1

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

results associated with enteritis. Physical examination and information regarding the animal's vaccination schedule are not pathognomonic, and their diagnostic accuracy is only 58% [18]. The present study included vaccinated and unvaccinated dogs under one year of age, presenting to the clinic with gastrointestinal complaints and positive rapid parvovirus antigen detection test results. Hemorrhagic gastroenteritis is a common symptom of PVE [19, 20]. Depression, dehydration, mild to severe hemorrhagic diarrhea, anorexia, and fever were also present in all patient groups in this study, as reported by Er and Ok [7].

Creatine kinase (CK) is an enzyme found in three recognized isoforms: CK-MM (skeletal muscle), CK-MB (myocardium), and CK-BB (brain) [21]. CK-MB, an isoenzyme of creatine kinase, is a specific biomarker in cardiac myocytes. It is synthesized in damaged cells, increases in PVE, and leaks into the bloodstream, indicating heart muscle injury [7, 22, 23]. Approximately 90% of CK-MB is found in the myocardium, with trace amounts in the small intestine, tongue, diaphragm, and uterus. Plasma concentrations of CK-MB increased with the severity of the disease in dogs infected with the intestinal form of CPV-2 [24]. CK-MB is a suitable biomarker that decreases 72 hours after treatment to predict survival and disease outcomes [25].

In our study a significant increase in CK-MB and total CK was observed in the PVE groups. Additionally, CK concentrations, with 61% sensitivity and 100% specificity, and CK-MB concentrations, with 79% sensitivity and 88% specificity, were identified as important indicators of PVE. The increase in both parameters in the PVE groups showed a positive correlation between them. Although a positive correlation was observed between CK and CK-MB concentrations, this study demonstrated that CK concentrations had a stronger predictive ability for PVE than CK-MB concentrations ($p = 0.0452$). In the

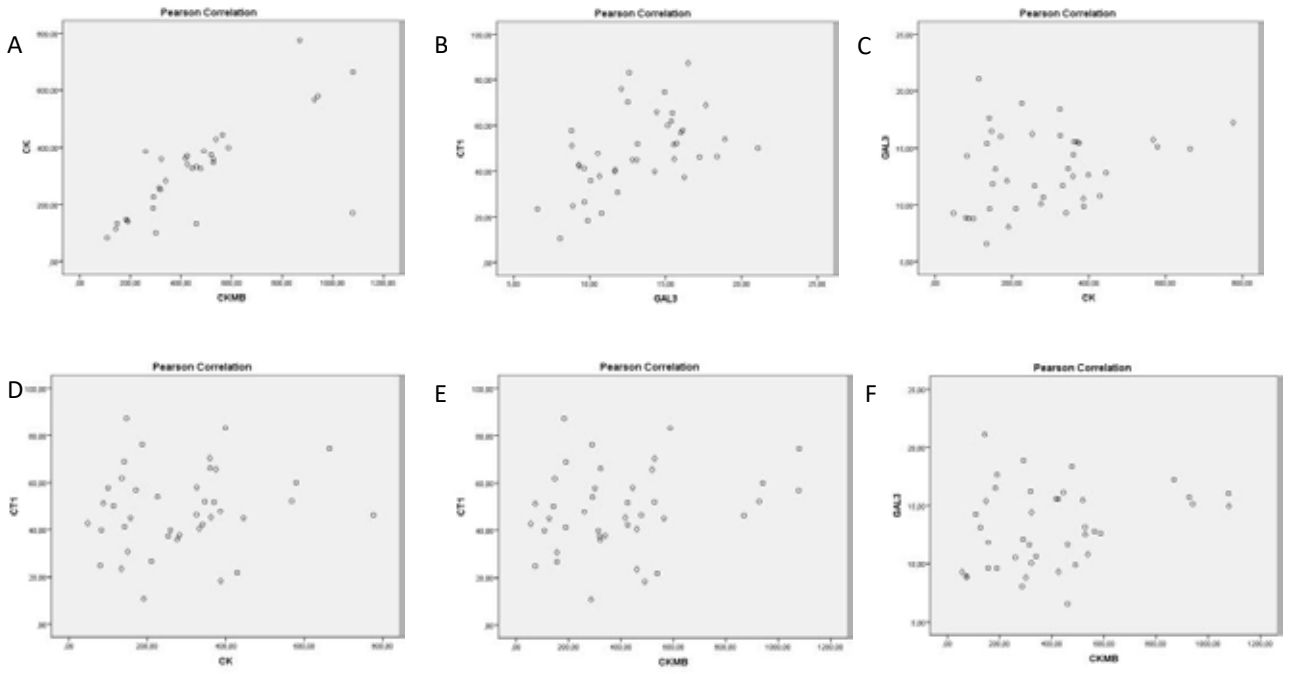

Figure 2. Correlation analysis graphs between CK and CK-MB (A), CT-1 and GAL-3 (B), GAL-3 and CK (C), CT-1 and CK (D), CT-1 and CK-MB (E), and GAL-3 and CK-MB (F) concentrations in PVE groups.

presence of elevated CK-MB levels exceeding total CK levels without accompanying cardiac findings, alternative pathologies should also be considered [26]. In our study, the observed elevation in CK-MB levels in the PVE groups, together with increased CK levels and their positive correlation, may point toward the possibility of a systemic inflammatory process that could extend beyond the gastrointestinal system. These findings raise the potential that parvoviral enteritis might be associated with involvement of not only intestinal tissues but also, perhaps, cardiac and/or systemic skeletal muscles.

CT-1 is a member of the IL-6 cytokine family, released from the myocardium, vascular endothelium, adipose tissue, and other tissues [27]. As a critical regulator of inflammation, recombinant CT-1 (rCT-1) may serve as a potential therapeutic molecule for inflammatory conditions [28]. In the current study, CT-1 levels were significantly higher in all PVE groups compared to the control group. Cardiotrophin-1 (CT-1) is known to have reno-protective effects in murine models, including the preservation of kidney function and the inhibition of renal inflammation and fibrosis [29]. Similarly, it was hypothesized that the increase in CT-1 levels was associated with the inflammatory response induced by PVE.

Galectin-3, a member of the lectin family, is primarily expressed by macrophages and plays a critical role in the pathophysiology of immune and inflammatory diseases (cancer and metabolic diseases). Galectin-3 is significantly elevated in cell adhesion, inflammation, tissue fibrosis, and viral myocarditis [30-32]. Our findings suggest that GAL-3 may be a useful biomarker for inflammation associated with PVE.

The current study revealed a positive correlation between CT-1 and GAL-3 concentrations. Galectin-3 promotes both acute and chronic inflammation through macrophage recruitment and pro-inflammatory signaling, while Cardiotrophin-1 exerts cytoprotective and metabolic effects that modulate the inflammatory response [33, 34]. In our study, the concurrent increase and positive correlation of Gal-3 and CT-1 in the PVE group suggest that both pro-inflammatory and anti-inflammatory responses are simultaneously activated in the host against the systemic inflammation caused by parvoviral enteritis. It is considered that this reflects the organism's attempt to restore homeostatic balance.

CT-1 concentrations, with 69.70% sensitivity and 87.5% specificity, and GAL-3 concentrations, with 84.85% sensitivity and 75% specificity, were iden-

tified as important indicators of PVE. Furthermore, the study demonstrated that the predictive abilities of GAL-3 and CT-1 for PVE were similar. Based on ROC analysis and correlation data, it is suggested that elevated concentrations of CT-1 and GAL-3 may be effective in predicting PVE and its associated inflammation in dogs.

Hematological changes are also observed in dogs with PVE, including a decrease in neutrophil count due to their migration to inflamed tissues [20, 35]. Additionally, leukopenia (including neutropenia and/or lymphopenia) is observed due to the destruction of progenitor cells. Monocytes, part of the mononuclear phagocyte system, show in-creased numbers (monocytosis) in acute and chronic inflammation [36]. However, monocytopenia is rare and of limited clinical significance. Goddard et al. [37] associated the monocytopenia observed in canine parvoviral enteritis with a poor prognosis. In the current study, monocyte counts were significantly reduced in all experimental groups compared to the control group. No significant difference was observed in lymphocyte counts between the groups, while granulocyte counts were decreased. Macartney et al. [38] reported that panleukopenia, characterized by lymphopenia and granulocytopenia, was a significant laboratory finding within the first 72 hours of the onset of clinical symptoms in dogs with parvoviral enteritis. The decrease in monocyte and granulocyte counts was consistent with the reduction in the total leukocyte count. This may reflect a decline in the macrophage function of monocytes in particular.

Septicemia associated with PVE increases the mortality rate by enhancing susceptibility to secondary bacterial infections in dogs [37-39]. Our findings are consistent with previous studies, showing a decrease in total leukocyte count in the PVE groups compared to the control group. Although this decrease was statistically significant, the results remained within the reference ranges. This variation can be attributed to individual differences within the patient group, as total leukocyte counts were below the reference values in some dogs while remaining within normal limits in others.

Changes in serum creatinine levels are primarily renal in origin. A decrease in serum creatinine is associated with an increase in packed cell volume (PCV) and plasma volume [40] and may also be influenced by factors such as age, body weight, and muscle mass [41]. However, the observed decrease in CPV-infected dogs is intriguing [42].

Serum creatinine production is decreased in animal models of sepsis and critically ill humans. This may be a more likely explanation for the lower serum creatinine concentrations observed in parvovirus-infected dogs [43]. In this study, serum creatinine levels were de-creased in infected dogs. In addition to the aforementioned factors, this may be associated with poor protein nutrition and malabsorption due to diarrhea [44]. On the other hand, normal BUN concentrations ruled out clinical kidney damage.

CONCLUSIONS

In conclusion, GAL-3, CT-1, CK, and CK-MB are valuable cardiac biomarkers for predicting PVE and inflammation, compared to routine biochemical and hematological parameters in dogs with PVE. Additionally, future studies should include larger sample sizes and post-mortem examinations to investigate the role of these biomarkers in the pathogenesis of PVE. Such studies could also focus on treatment trials aimed at reducing GAL-3 levels and promoting CT-1.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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