ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article / Araştırma Makalesi DOI: 10.5152/VetSciPract.2022.222745

Evaluation of CBC, Lipid Profile, Oxidative Stress Biomarkers, Total Thiol, Native Thiol, and Disulfide Levels in Dogs Diagnosed with Parvoviral Enteritis Without Clinical Findings

Klinik Bulgular Görülmeden Parvoviral Enteritis Tanısı Konulan Köpeklerde, CBC, Lipid Profili, Oksidatif Stres Biyobelirteçleri, Total Thiol, Native Thiol ve Disülfid Düzeylerinin Değerlendirilmesi

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Received/Geliş Tarihi: 28.07.2022
Accepted/Kabul Tarihi: 14.12.2022
Publication Date/Yayın Tarihi: 29.12.2022

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Cite this article as: Kurtdede E, Börkü MK, Gür B, Doğan Y, Sevim K, Gülendağ E. Evaluation of CBC, lipid profile, oxidative stress biomarkers, total thiol, native thiol, and disulfide levels in dogs diagnosed with parvoviral enteritis without clinical findings. *Vet Sci Pract.* 2022; 17(3), 98-102.

Atıf: Kurtdede E, Börkü MK, Gür B, Doğan Y, Sevim K, Gülendağ E. Klinik bulgular görülmeden parvoviral enteritis tanisi konulan köpeklerde, CBC, lipid profili, oksidatif stres biyobelirteçleri, total thiol, native thiol ve disülfid düzeylerinin değerlendirilmesi. *Vet Sci Pract.* 2022; 17(3), 98-102.

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ABSTRACT

In this study, whole blood cell count, metabolic and inflammatory biomarkers, and oxidative stress parameters were evaluated in dogs diagnosed with canine parvoviral enteritis by stool antigen testing performed 24-48 hours before any clinical findings arose. This study aimed to conduct effective evaluations of the status of the disease, the selection of treatment methods, and the prognosis of the disease. Thirty dogs with canine parvoviral enteritis positivity according to stool antigen test results 24-48 hours before the appearance of any clinical signs associated with parvoviral enteritis (lethargy, vomiting, diarrhea, dehydration) were evaluated together with 10 healthy dogs. In analyses of the dogs with canine parvoviral enteritis, significant decreases were found for white blood cell ($P < .001$), neutrophil ($P < .001$), and monocyte ($P = .011$) counts and significant increases were found for alanine aminotransferase and aspartate aminotransferase ($P < .001$ for both). Significant increases ($P < .001$) were also determined for high-density lipoprotein, cholesterol, and triglyceride levels among the studied lipid metabolites and C-reactive protein, malondialdehyde, and paraoxonase-1 among inflammatory biomarkers. Significant decreases were found for total thiol ($P = .002$) and native thiol ($P < .001$), with which antioxidant levels were evaluated, and a significant increase was found for disulfide ($P < .001$), with which oxidation was evaluated. It was concluded that early changes in blood samples taken 24-48 hours before the onset of clinical symptoms in dogs with CPV, as reflected by values of CBC and metabolic and inflammatory biomarkers, may provide information about the severity of the disease, the choice of medical treatments to be applied, and prognosis.

Keywords: Canine parvoviral enteritis, disulfide, malondialdehyde, paraoxonase-1, thiol

ÖZ

Bu çalışmada, klinik bulgular görülmeden 24-48 saat önce, dışkıda yapılan antijen testi ile parvoviral enteritis (CPV) tanısı konulan köpeklerde, tam kan hücreleri (CBC) sayıları, metabolik ve inflamasyon biyobelirteçleri ve oksidatif stres parametreleri birlikte değerlendirilerek; hastalığın durumu, sağaltım yöntemlerinin seçimi ve hastalığın prognozu hakkında etkin değerlendirmelerin yapılması amaçlandı. Çalışmada, parvoviral enteritis ile ilişkili klinik belirtilerin (durgunluk, kusma, ishal, dehidratasyon) görülmesinden 24-48 saat önceki dışkı antijen testi sonucuna göre CPV pozitif olan 30 köpek ile, 10 sağlıklı köpek değerlendirildi. CPV'li köpeklerde yapılan analizlerde, WBC ($P < ,001$), nötrofil (neut) ($P < ,001$) ve monosit (mono) ($P = ,011$) sayılarında anlamlı düşüşler, ve alanin aminotransferaz (ALT) ve aspartat aminotransferaz (AST) değerlerinde anlamlı artışlar ($P < ,001$) saptandı. Lipid metabolitlerinden yüksek dansiteli lipoprotein (HDL), kolesterol (Chl) ve trigliserit (Tg) düzeylerinde ve inflamasyon biyobelirteçlerinden C-reaktif protein (CRP), malondialdehit (MDA) ve paraoksanaz-1 (PON-1) değerlerinde anlamlı artışlar ($P < ,001$) belirlendi.

Antioksidan düzeyinin değerlendirildiği total thiol (*P*=,002) ve native thiol (*P* < ,001) değerlerinde anlamlı düşüşler, ve oksidasyonun değerlendirildiği disülfit düzeyinde anlamlı (*P* < ,001) artış saptandı. CPV'li köpeklerde klinik semptomların başlangıcından 24-48 saat önce alınan kan örneklerinde, CBC sayısında ve metabolik ve inflamasyon biyobelirteçlerinin düzeylerinde meydana gelen erken dönem değişikliklerin hastalığın şiddetine, uygulanacak tıbbi tedavilerin seçimine ve prognoza yön verebileceği sonucuna varıldı.

Anahtar Kelimeler: Canine parvoviral enteritis, disulfide, MDA, PON-1, thiol

INTRODUCTION

Canine parvoviral enteritis (CPV) infection is an important disease that is commonly seen in domestic and wild dogs, especially between the ages of 6 weeks and 6 months, in Turkey and around the world. It is characterized by high morbidity and mortality rates despite vaccination. Sivas Kangal, Rottweiler, Doberman, Pincher, Labrador Retriever, and German Shepherd dogs are particularly susceptible to this disease.[1,2]

Some pathophysiological disorders developing in the course of the disease include intravascular coagulopathy, the death of myeloproliferative cells and immunosuppression due to thymic lymphocytosis, septicemia due to intestinal mucosal destruction, malabsorption due to villus atrophy, and dehydration and shock due to diarrhea and vomiting.[3-5] Good response to treatment is directly proportional to effective treatment in the early period and the speed of the patient's recovery from intestinal disorders.[6,7]

Determination of whole blood cell count (CBC) parameters including lymphocyte (Lym), monocyte (Mono), and neutrophil (Neut) counts together with oxidative stress status, some liver parameters, and lipid profile is important in evaluating the pathophysiological status of patients. In dogs with CPV, systemic inflammation as reflected by C-reactive protein (CRP) and procalcitonin (PCT); liver parameters including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), and albumin (Alb); lipid profile as reflected by high-density lipoprotein (HDL), cholesterol (Chol), and triglyceride (Tg); and biomarkers associated with oxidative stress such as malondialdehyde (MDA) and paraoxonase-1 (PON-1) can be evaluated and treatment protocols that will help clinical veterinarians in choosing treatment practices can be recommended.[2,6,8,9]

One of the most important findings in the early period of CPV infection is the increase in serum CRP, which is an acute-phase protein.[10,11] It is also recommended to evaluate the changes in serum MDA resulting from the peroxidation of polyunsaturated fatty acids abundant in erythrocyte membranes, the changes in PON-1 and HDL levels associated with redox status and degradation of oxidized lipids, and oxidative pathobiological changes in dogs with CPV.[12,13] Since plasma thiols contain sulfhydryl groups with antioxidant/prooxidant properties, determining the level of thiol and disulfide hemostasis in patients is also valuable in the evaluation of oxidative stress.[14,15] The plasma thiol level in the body is often affected by oxidative stress and other disorders. When subjected to oxidation reactions, thiol compounds form disulfide bonds, which have important functions in the response to upregulated oxidative stress markers, metabolic functioning, and the maintenance of hemostasis.[16,17] The plasma thiol pool, reflecting thiol/disulfide homeostasis, is evaluated based on the levels of Alb and thiols (proteins and compounds of low molecular weight).[18] Molecules found in the dynamic plasma thiol pool are affected by oxidative stress and other disease processes, triggering changes in thiol/disulfide homeostasis. In addition to their antioxidant effects, these molecules also have important effects on metabolic reactions, signal transduction, the scavenging of toxins, gene expression, and cell signaling.[19]

In this study, dogs diagnosed with CPV were evaluated according to stool antigen test results obtained 24-48 hours before the appearance of clinical findings. Whole CBC results, liver parameters (ALT, AST, TP, and Alb), metabolic (HDL, Chol, and Tg) and inflammatory biomarkers (CRP, PCT, and PON-1), and oxidative stress (MDA, total thiol, native thiol) and oxidation (disulfide) parameters were considered together with the aim of performing effective evaluations of the status of the disease, the selection of treatment methods, and the prognosis of the disease.

METHODS

Ethical approval of this study was obtained from the Ankara University Animal Experiments Local Ethics Committee with decision number 2020-5-43 and decision date 04-03-2020. Forty owned dogs of different breeds and both sexes, ranging in age between 6 weeks and 6 months and brought to the Animal Hospital of Ankara University's Veterinary Faculty for general health examinations and vaccination purposes, were included in the study after obtaining written permission and approval from their owners.

Thirty dogs with positive fecal CPV antigen test results in the first examination and the beginning of clinical signs of CPV (lethargy, vomiting, diarrhea, dehydration) 24-48 hours after that initial examination constituted the group of dogs with CPV infection. Ten dogs determined to be healthy according to clinical and laboratory examination findings constituted the control group. In dogs with suspected CPV, the diagnosis was confirmed by detecting the CPV antigen in stools with a rapid test kit (Canivet CPV-CCV Ag Combo Test, Vet Diagnostix, China).

Blood samples were collected from the cephalic vein for all dogs included in the study, with 1 mL obtained for each tube with anticoagulant and 5 mL for each tube without anticoagulant.

Whole blood cell count values were determined from blood samples with anticoagulant using an automatic hematology analyzer (Mindray BC 5000). Within 2 hours after blood collection, blood samples without anticoagulant were centrifuged at 3000 rpm for 10 minutes and serum was obtained. These samples were placed in small containers and kept at −20°C until biochemical analysis was performed. The levels of ALT, AST, TP, Alb, urea, and creatinine in blood serum samples thawed at room temperature before analysis were determined spectrophotometrically with an autoanalyzer (Mindray BS-120) using the relevant kits.

Blood serum MDA level was calculated according to the method specified by Draper and Hadley.[19] For this, 2.5 mL of 10% trichloroacetic acid was mixed with 0.5 mL of serum in a tube. The reaction

solution was kept in a hot water bath for 15 minutes. The solution was then held at room temperature and centrifuged at 400× g for 10 minutes. The supernatants were removed in volumes of 2 mL and combined with 1.0 mL of 0.67% TBA in separate tubes, and those mixtures were incubated in boiling water baths for 15 minutes. The mixtures were brought to room temperature and absorbance was measured at 532 nm. Malondialdehyde activity was expressed as nmol/g protein.

Paraoxonase-1 activity was determined by the method developed by Eckerson et al.[20] This method is based on the conversion of paraoxon (diethyl p-nitrophenyl phosphate) to diethyl phosphate and p-nitrophenol with the effect of paraoxonase in the serum with measurement of the absorbance of the formed p-nitrophenol using a spectrophotometer at a wavelength of 412 nm. Paraoxonase-1 activity was expressed as U/L.

Thiol-disulfide levels (thiol [–SH] and disulfide [–S–S]) were determined separately spectrophotometrically according to the method specified by Erel and Neselioglu.[15] With this method, $NaBH_4$ is used to reduce sulfide bonds in serum samples and form thiol groups in the free functional state. Formaldehyde was used to remove the unused portion of $NaBH_4$, and with DNTB, thiol groups were determined at 415 nm as total thiol and native thiol. The disulfide value (μmol/L) was calculated with the following formula: (total thiol [μmol/L] – native thiol [μmol/L])/2.

Statistical Analysis

Results were analyzed using the Shapiro-Wilk test for normality and the Levene test for homogeneity of variances. One-way analysis of variance and Kruskal-Wallis tests were conducted accordingly to determine the presence of similarities and differences between experimental groups. The differences between the groups were identified by Tukey HSD and Dwass-Steel-Critchlow-Fligner pairwise tests. All data were analyzed using IBM Statistical Package for Social Sciences Statistics 26.0 (IBM Corp., Armonk, NY, USA). Values of $P < .05$ were considered significant for all analyses.

RESULTS

In this study, CBC results, ALT and AST levels, metabolic biomarkers (HDL, Chol, and Tg), systemic inflammatory biomarkers (CRP, PCT, and PON-1), and oxidative stress (MDA, total thiol, and native thiol) and oxidation (disulfide) parameters were obtained as presented in Tables 1-3.

DISCUSSION

Canine parvoviral enteritis is a highly contagious disease involving acute hemorrhagic enteritis in dogs with high morbidity and mortality rates. Veterinary clinicians use blood cell counts and some laboratory analysis results obtained from blood serum in evaluating the severity of this disease, choosing the treatment options to be applied, and determining the prognosis of the patient. For this reason, it is important to consider analytical results that reveal the levels of systemic inflammation, metabolic processes, and oxidative stress in dogs with CPV.[10] It is necessary to evaluate CBC values and parameters related to systemic inflammation, metabolic processes, and oxidative stress.[20,21]

Previous studies have noted the importance of determining the values of certain hematological parameters in cases of CPV and monitoring them throughout the treatment process. Kocatürk et al[22] reported that determining the level of CRP, an acute-phase protein, in the evaluation of systemic inflammation is important in predicting the severity and prognosis of the disease, and a direct correlation was found between the severity of the disease and increased CRP levels in dogs with CPV. Şimşek et al[23] stated that CRP levels were statistically significantly increased in dogs with this disease, while Dinler et al[24] found PCT and CRP levels to be higher in cases of CPV compared to a control group. Similarly, in the present study, a significant increase ($P < .001$) was found in CRP levels in dogs with CPV compared to the healthy control group, revealing inflammation, while the increase in PCT was not statistically significant.

Many other studies have reported the importance of determining the values of hematological parameters and monitoring them during the treatment of dogs with CPV. Şimşek et al[23] and Goddard et al[10] found WBC, Lym, Mono, and granulocyte counts to be significantly lower in cases of CPV compared to healthy dogs.

Table 1. WBC, Lym, Mono, and Neut Counts of the CPV and Control Groups

	Hematological Parameters (10^9/L)			
Groups	WBC	Lym	Mono	Neut
Control (n = 10)	8.41 ± 0.41	2.12 ± 0.5	0.47 ± 0.06	5.52 ± 0.31
CPV (n = 30)	4.714 ± 0.59**	1.774 ± 0.23	0.28 ± 0.04*	2.47 ± 0.31**
P	<.001		.011	<.001

*The Mono counts of the CPV and control groups were significantly different ($P = .011$).
**The WBC and Neut counts of the CPV and control groups were significantly different ($P < .001$).
CPV, canine parvoviral enteritis; Lym, lymphocytes; Mono, monocytes; Neut, neutrophils; WBC, white blood cell count.

Table 2. ALT, AST, TP, Alb, Chol, Tg, and HDL levels of the CPV and control groups

	Biochemical Parameters						
Groups	ALT (U/L)	AST (U/L)	TP (g/dL)	Alb (g/dL)	Chol (mg/dL)	Tg (mg/dL)	HDL (mg/dL)
Control (n = 10)	40.68 ± 4.04	48.15 ± 0.83	5.23 ± 0.15	2.90 ± 0.17	234.5 ± 3.81	57.75 ± 1.4	49.25 ± 0.96
CPV (n = 30)	61.48 ± 1.04	61.23 ± 1.01	5.17 ± 0.11	2.84 ± 0.06	237.77 ± 4.92	72.45 ± 1.35	56.636 ± 0.64
P	<.001	<.001				<.001	<.001

*The ALT, AST, Tg, and HDL levels of the CPV and control groups were significantly different ($P < .001$).
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Chol, cholesterol; CPV, canine parvoviral enteritis; HDL, high-density lipoprotein; TP, total protein.

Table 3. CRP, PCT, MDA, PON-1, total thiol, disulfide, and native thiol levels of the CPV and control groups

	Biochemical Parameters						
Groups	CRP (mg/L)	PCT (%)	MDA (nmol/g protein)	PON-1 (U/L)	Total Thiol (μmol/L)	Disulfide (μmol/L)	Native Thiol (μmol/L)
Control (n = 10)	9.84 ± 0.26	0.18 ± 0.05	1.878 ± 0.03	157.05 ± 2.9	236 ± 1.34	12.037 ± 0.21	204.299 ± 1.82
CPV (n = 30)	103.5 ± 1.84	0.28 ± 0.04	2.9 91 ± 0.04	118.883 ± 2.46	217.767 ± 4.92	15.307 ± 0.25	169.907 ± 1.91
P	<.001		<.001	<.001	.002	<.001	<.001

* The total thiol levels of the CPV and control groups were significantly different ($P = .002$).
**The CRP, MDA, PON-1, disulfide, and native thiol levels of the CPV and control groups were significantly different ($P < .001$).
CPV, canine parvoviral enteritis; CRP, C-reactive protein; MDA, malondialdehyde; PCT, procalcitonin; PON-1, paraoxonase-1.

Kubesy et al[25] found decreased WBC, Neut, and Lym counts and increased Mono counts in dogs with CPV compared to a control group. Arora et al[26] determined decreases in total leukocyte and Neut counts in dogs with CPV. Decreases in WBC, Lym, and Neut counts, which are common findings in studies of dogs with CPV, were also determined in this study. The decrease in Mono count obtained here is consistent with the findings of Şimşek et al[23] and Goddard et al.[10] Alves et al[27] stated that increases in total leukocyte, Lym, and Mono counts in dogs with CPV are signs that the prognosis of the patient will be good. In the present study, the significant decreases in WBC count ($P = .011$) and Neut and Mono counts ($P < .001$) and insignificant decrease in Lym count in dogs with CPV were thought to be due to the destruction of the bone marrow and lymphoproliferative organs, together with the development of the inflammatory response.

In dogs with CPV, it is important to determine the levels of serum ALT, AST, TP, and Alb, which are some of the liver parameters used to evaluate metabolic profiles. Serum urea and creatinine levels should also be used to evaluate kidney function. Öcal and Ünsüren[28] reported that dogs with CPV had lower serum TP and Alb levels and higher serum blood urea nitrogen, creatinine, ALT, and AST levels compared to healthy dogs. Abdullaziz et al[29] found significant decreases in TP and Alb values and significant increases in ALT, AST, urea, and creatinine values in dogs with CPV compared to healthy dogs. Thakur and Thakur[30] found increases in serum AST and ALP levels and decreases in Alb levels in dogs with CPV. Arora et al[26] found increases in AST and ALP values and decreases in Alb values in dogs with CPV. Abdullaziz et al[29] and Khare et al[21] concluded that increased ALT and AST levels in dogs with CPV were related to the absorption of toxic substances resulting from hepatic hypoxia caused by hypovolemia or intestinal barrier disorders. In the present study, on the other hand, mild increases in serum ALT and AST were seen in dogs whose physical clinical examinations did not reveal any signs of disease but whose fecal CPV screening test results were positive. This finding suggests that hypovolemia began to form in these dogs together with deterioration of the intestinal barrier.

Metabolic, systemic inflammatory, and oxidation processes of dogs with CPV are evaluated by monitoring the levels of HDL, Tg, and Chol, which are biomarkers of lipid metabolism. Salarpour et al[31] found statistically insignificant increases in HDL and Tg levels and insignificant decreases in Chol levels in 27 dogs with CPV. Yılmaz and Senturk[32] found significant decreases in HDL and Chol levels and significant increases in Tg levels in dogs with CPV compared to healthy dogs. In the present study, significant increases ($P < .001$) in HDL and Tg levels in dogs with CPV were evaluated as indications that the level of Chol transport was high in these animals and the effective prevention of lipid peroxidation was increased. Furthermore, this result highlights the necessity of evaluating the effects of oxidative stress in relation to the severity of CPV, and at the same time, the effects of increased HDL and Chol levels on liver performance, changes in protein structure,[33] and the development of inflammatory and oxidative stress responses[22,23] with the beginning of the deterioration of the intestinal barrier.

Serum MDA, PON-1, total thiol, disulfide, and native thiol levels, which reveal oxidative stress, should also be determined in order to evaluate the oxidative balance in patients and to identify the necessary medical applications.[22,34-36] In comparative studies with healthy dogs, Kocatürk et al[22] reported that PON-1 levels were lower in dogs with CPV, while Harizan et al[34] found that MDA levels were higher. Panda et al[35] found a significant difference in MDA levels in dogs with CPV. Değirmençay et al[36] determined that the levels of total thiol, disulfide, and native thiol of infected dogs were lower than those of healthy dogs. In the dogs with CPV in this study, significant increases ($P < .001$) in MDA, PON-1, and disulfide were detected, while significant decreases in total thiol ($P = .002$) and native thiol ($P < .001$) showed that noteworthy levels of oxidative stress had developed in the dogs with CPV. The decrease in PON-1 activity is thought to occur in response to the occurrence of lipid peroxidation via HDL oxidation. Kocatürk et al[22] emphasized that determining the level of CRP, one of the acute-phase proteins that reveal the degree of systemic inflammation in dogs with CPV, is important in terms of evaluating the severity and prognosis of the disease, and they found a direct correlation between the severity of CPV and the increase in CRP. Şimşek et al[23] stated that CRP levels were statistically significantly higher in dogs with parvoviral enteritis, while Dinler et al[24] found PCT and CRP levels to be higher in dogs with parvoviral enteritis compared to a control group. In the present study, a significant increase ($P < .001$) in CRP, revealing inflammation, was found in dogs with CPV compared to the control group, while the increase in PCT was not statistically significant.

Based on the findings of the present study, it is clear that the evaluation of changes in inflammatory, metabolic, and oxidative stress parameters in the early phase of CPV will provide important data for clinical veterinarians. In the early phase of CPV infection, the increase in disulfide level, which indicates increased oxidation, and the decrease in total thiol and native thiol levels, which indicate decreased antioxidant levels, are particularly noteworthy. In addition, the increase in the level of MDA, which is the end product of lipid peroxidation, and the decrease in the level of PON-1, which protects lipid metabolites from oxidation, indicate that significant oxidative stress develops in dogs in the early stage of CPV without clinical signs of the disease. Other indicators of oxidative stress that developed in dogs with CPV in this study were increased HDL, Chol, and Tg, which are lipid metabolites.

In conclusion, the data obtained in this study by evaluating the changes in the levels of CBC results, metabolic and inflammatory biomarkers, and oxidative stress-related parameters that show the pathophysiological status of dogs 24-48 hours before the appearance of clinical findings of CPV suggest that these variables can provide guidance in determining the seriousness of the disease in the early period and selecting the treatment methods to be applied. This study was carried out with a limited number of dogs. If similar studies are conducted in the future with more dogs with CPV, it will be possible to make more comprehensive generalizations of the obtained data.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara University (Date 04.03.2020, Decision No: 2020-5-43).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Design – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Supervision – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Resources – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Materials – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Data Collection and/or Processing – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Analysis and/or Interpretation – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Literature Search – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Writing Manuscript – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Critical Review – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Other – E.K., M.K.B., B.G., Y.D., K.S., E.G.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: The authors declared that this study has received no financial support.

Etik Komite Onayı: Bu çalışma için etik komite onayı Ankara Üniversitesi'nden alınmıştır. (Tarih: 04.03.2020, Karar No: 2020-5-43)

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Tasarım – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Denetleme – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Kaynaklar – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Malzemeler – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Veri Toplanması ve/veya İşlemesi – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Analiz ve/veya Yorum – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Literatür Taraması – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Yazıyı Yazan – E.K., M.K.B., B.G., Y.D., K.S., E.G.; Eleştirel İnceleme – E.K., M.K.B., B.G., Y.D., K.S., E.G.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

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