Acta Scientiae Veterinariae, 2026. 54: 2013.

RESEARCH ARTICLE
Pub. 2013

ISSN 1679-9216

Meningoencephalomyelitis of Unknown Origin in Dogs: Utility of S100B as a Diagnostic Biomarker

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ABSTRACT

***Background*:** Meningoencephalomyelitis of unknown origin (MUO) is an immune-mediated, noninfectious inflammatory disease of the canine central nervous system (CNS). Despite its clinical importance, diagnosis remains presumptive, as definitive confirmation requires histopathology. Therefore, reliable biomarkers are required to improve diagnostic accuracy. Astrocytic S100B, which contributes to neuroinflammation and oxidative stress, may serve as a potential biomarker for MUO. This study aimed to evaluate S100B in dogs with MUO compared to healthy controls (HC) and those with idiopathic epilepsy (IE).

***Materials, Methods & Results*:** This study included 43 client-owned dogs: 16 with MUO, 13 with IE, and 14 HC based on clinical records, cerebrospinal fluid (CSF) analysis, and magnetic resonance imaging (MRI) findings. Blood and CSF samples were collected on the day of MRI and S100B concentrations were measured. Nonparametric and inferential statistical analyses were performed. CSF and serum S100B levels were significantly higher in dogs with MUO than in HC or IE. S100B levels were not significant between HC and IE groups in either CSF or serum. A significant correlation was found between S100B levels in CSF and serum. Receiver operating characteristic curve analysis for MUO versus control indicated that a CSF S100B cutoff of 699.11 pg/mL yielded 85.7% sensitivity and 84.2% specificity, whereas 835.82 pg/mL provided 71.4% sensitivity and 100% specificity. For serum S100B, a cutoff of 782.39 pg/mL showed 100% sensitivity and 84.2% specificity, whereas 977.06 pg/mL had 85.7% sensitivity and 100% specificity.

***Discussion*:** Both CSF and serum S100B concentrations were significantly elevated in dogs with MUO compared with healthy and epileptic controls, supporting the involvement of S100B in the neuroinflammatory pathogenesis of the disease. This finding aligns with previous evidence from human neuroinflammatory conditions such as multiple sclerosis, suggesting a conserved mechanism of astrocytic activation and S100B overexpression during central nervous system inflammation. The strong correlation between CSF and serum S100B levels further demonstrates that peripheral S100B reflects intracranial pathology and blood-brain barrier disruption, providing a feasible and minimally invasive diagnostic approach. These results indicate that measuring S100B could improve diagnostic confidence when MRI or CSF analysis yields inconclusive results, reducing reliance on invasive procedures. Moreover, the availability of a serum-based assay may enhance its translational potential and feasibility within veterinary diagnostic applications. In addition, the absence of elevated S100B in idiopathic epilepsy emphasizes its diagnostic specificity for inflammatory rather than non-inflammatory neurological disorders, reinforcing its potential utility in differentiating neuroinflammation from seizure disorders without structural lesions. Although the study was limited by small sample size and the lack of other structural CNS disease controls, the consistent increase in both serum and CSF S100B provides compelling evidence that this astrocytic protein represents a promising diagnostic and possibly therapeutic biomarker for MUO. Future large-scale investigations incorporating disease severity, treatment monitoring, and other CNS pathologies are warranted to confirm its clinical applicability and explore the benefits of targeting S100B-mediated neuroinflammatory pathways.

Keywords: cerebrospinal fluid, dog, idiopathic epilepsy, meningoencephalomyelitis of unknown origin, S100B.

DOI: 10.22456/1679-9216.151302

Received: 24 November 2025 Accepted: 20 February 2025 Published: 21 March 2026

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INTRODUCTION

Meningoencephalomyelitis of unknown origin (MUO) is an immune-mediated, noninfectious inflammatory disease of the canine central nervous system (CNS) [10]. Although common and potentially life-threatening, its etiology and pathophysiology remain poorly understood, making diagnosis and treatment challenging as definitive confirmation relies on histopathology [8-10]. Clinically, diagnosis is based on neurological findings, imaging, and cerebrospinal fluid (CSF) analysis, which are often inconclusive, highlighting the need for reliable biomarkers [8,9].

S100B is a Ca^{2+}-binding protein predominantly expressed in astrocytes within the brain [15,16]. Under neuroinflammatory conditions, astrocytes release S100B at micromolar levels, where it acts as a damage-associated molecular pattern (DAMP) molecule by activating the receptor for advanced glycation end products (RAGE) and inducing oxidative stress [15,16]. In humans with multiple sclerosis (MS), the most common neuroinflammatory disease, elevated S100B levels have been reported in the CSF and serum, and inhibition of S100B in its experimental model, experimental autoimmune encephalomyelitis (EAE), improves clinical outcomes [6,10]. Thus, S100B is gaining recognition as a promising diagnostic and therapeutic biomarker for MS [3,6].

MUO is often considered a canine counterpart to MS due to their similar neurological and pathological characteristics [10]. Based on this parallel, we hypothesized that S100B levels would be elevated in dogs with MUO. This study aimed to measure S100B concentrations in the CSF and serum of dogs with MUO, comparing them with those of healthy controls (HC) and dogs with idiopathic epilepsy (IE).

MATERIALS AND METHODS

Animals and grouping

The dogs included in this case-control study were client-owned patients at the Chungnam National University (CNU) between 2021 and 2024. They were divided into following 3 groups: HC, MUO, and IE. Diagnoses were based on their medical records, including signalment, medical history, physical and neurological examination findings, laboratory results, CSF analysis, and advanced imaging findings, such as magnetic resonance imaging (MRI).

The HC group presented no abnormalities on physical or neurological examinations, complete blood count, serum biochemical analysis, serum electrolyte analysis, urinalysis, radiography, abdominal ultrasonography, or MRI.

The MUO group was classified according to the guidelines from a previous study [9]. Dogs were considered to have MUO if they were older than 6 months and presented with focal or multifocal CNS signs, evidence of multiple, single, or diffuse intra-axial hyperintensities on T2-weighted MRI, and pleocytosis in CSF analysis (total nucleated cell count >5 nucleated cells/μL; erythrocyte count <4,000 cells/μL), with >50% mononuclear cells and negative results for infectious etiological agents.

The IE group was classified as having recurrent seizures with no abnormal findings in physical examination, neurological examinations, blood analysis, CSF analysis, and MRI of the prosencephalon [18].

Data and sample collection

Medical records, including age, sex, and weight, were collected at the patient's 1st visit. Blood samples for serum separation were collected on the same day as the MRI scans in all the groups. Blood was obtained via jugular venipuncture using a 22-gauge needle and placed directly into a 3 mL serum-separating tube. The serum was separated by centrifugation at 3,500 *g* and 4°C for 10 min within 1 h of sample collection. CSF samples were collected on the same day as the MRI scans in all groups. CSF was obtained from the cerebellomedullary cistern via atlanto-occipital puncture using a 22-gauge needle and placed directly into 1 mL plain tubes. If evidence of blood contamination was found in the CSF analysis, samples were excluded from the study. Both serum and CSF samples were stored at -80°C in a microcentrifuge tube within 1 h of sampling. Samples not collected or stored according to the study design were excluded. All samples were thawed immediately before use.

Assay

Serum and CSF concentrations of S100B were estimated using a canine-specific enzyme-linked immunosorbent assay (ELISA) kit[1] (Dog S100 calcium-binding protein B ELISA kit) according to the manufacturer's protocol. The detection range was 150-2,500 pg/mL. The intra-assay coefficient of variation (CV) was <8% and the inter-assay CV was <10% across the measurement range. Optical density was measured at 450 nm with an automated microplate reader[2] (Epoch).

Statistical analysis

The Mann-Whitney U test was used to compare serum S100B and CSF S100B levels between the groups. Spearman's correlation (rs) assessed the relationship between serum S100B and CSF S100B levels, with rs < 0.4 indicating a weak correlation, 0.4 ≤ rs < 0.6, a moderate correlation, and rs ≥ 0.6, a strong correlation. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the optimal cutoff values of serum and CSF S100B concentrations and differentiate between the HC and MUO groups.

For all analyses, $P < 0.05$ was considered statistically significant. Data analyses were performed using the Statistical Package for Social Sciences software[3] (SPSS 26.0.0 Windows).

RESULTS

Animals and sample collection

A total of 43 dogs were recruited and divided into 3 groups: 14, 16, and 13 in the HC, MUO, and IE group, respectively. Among them, 27 were males (88.9% neutered, 11.1% intact) and 16 were females (81.2% spayed, 18.8% intact). The median age was 7.9 years (range, 1-15). The breeds included Maltese Terrier (n=12), mixed breed (n=9), Pomeranian (n=6), Labrador Retriever (n=5), Beagle (n=4), Poodle (n=2), Jindo dog (n=2), Italian Greyhound (n=1), Welsh Corgi (n=1), and Pug (n=1).

Of the 43 serum samples, 2 were excluded because of poor storage, leaving 41 samples in this study. For the CSF samples, 8 were excluded (4 for poor storage and 4 for blood contamination), leaving 35 samples in this study.

In the HC group, 14 serum and 13 CSF samples were collected, with a median age of 7 years (range: 2-15) and median weight of 6 kg (range: 2.8-30). In the MUO group, 14 serum and 14 CSF samples were included. The median age was 6 years (range: 1-8) and median weight was 4.1 kg (range: 2.8-9). In the IE group, 13 serum samples and 8 CSF samples were included, with a median age of 7 years (range: 3-10) and median weight of 12 kg (range: 3.9-37).

S100B concentration

The CSF and serum S100B concentrations in each group are shown in Figure 1. The mean (± SD) CSF S100B concentration was 538.23 ± 163.69 pg/mL (median: 532.02; range: 238.96-735.94) in the HC group, 1,062.49 ± 331.62 pg/mL (median: 1,055.74; range: 570.01-1,633.74) in the MUO group, and 607.38 ± 123.49 pg/mL (median: 588.29; range: 459.44-753.58) in the IE group. The mean (±SD) serum S100B concentration was 705.40 ± 254.27 pg/mL (median: 694.94; range: 274.63-1,270.12) in the HC group, 1,328.12 ± 448.16 pg/mL (median: 1,300.72; range: 803.39-2,198.17) in the MUO group, and 576.97 ± 209.05 pg/mL (median: 488.07; range: 303.26-995.66) in the IE group. CSF S100B levels were significantly higher in the MUO group than in the HC group ($P < 0.001$) and the IE group ($P = 0.005$). Serum S100B levels were also significantly higher in the MUO group than in the HC group ($P < 0.001$) and IE group ($P < 0.001$). However, no significant difference in S100B levels was found between the HC and IE groups in either the CSF ($P = 0.323$) or serum ($P = 0.155$).Correlation analysis

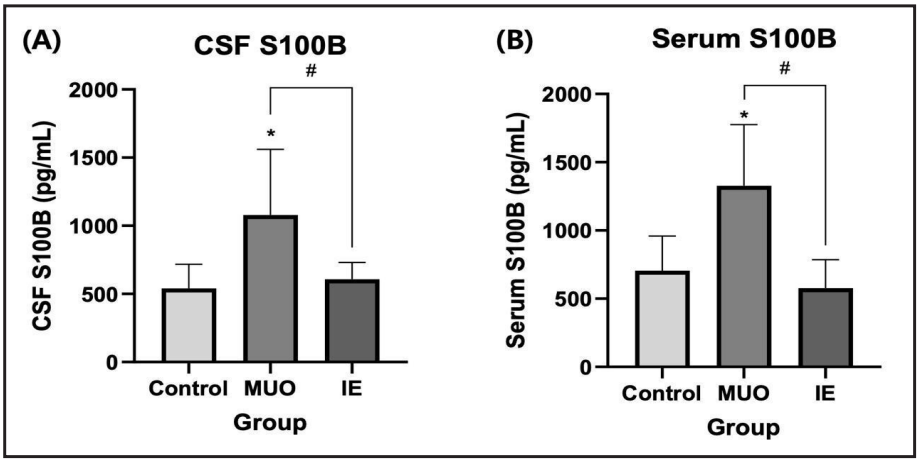

Figure 1. Box-whisker plots showing the concentration of CSF S100B and serum S100B in each group. A- CSF S100B. B- serum S100B. The middle line of the boxplot represents the median value of the group, and the lower and upper lines represent the first and third quantiles, respectively. The whiskers represent 1.5 times the interquartile range. Mann-Whitney U test was performed. The asterisk and hashtag indicate a statistically significant difference. (*$P < 0.001$, #$P = 0.005$). CSF: cerebrospinal fluid.

Figure 2 shows the correlation between the CSF and serum S100B levels. A significantly strong positive correlation was found between S100B levels in CSF and serum (rs = 0.652; $P < 0.001$).

ROC analysis

To discriminate dogs with MUO from other dogs, optimum cutoff values, sensitivities, specificities, and area under the curve (AUC) for CSF S100B and serum S100B were calculated, and the ROC curves are presented in Figure 3.

The AUC for CSF S100B was 0.92 (95% confidence interval [CI]; 0.83-1.00). For serum S100B, the AUC was 0.97 (95% CI; 0.93-1.00). In the ROC curve analysis to distinguish MUO using CSF S100B, a cutoff value of 699.11 pg/mL showed 85.7% sensitivity and 84.2% specificity. At 835.82 pg/mL, the sensitivity and specificity were 71.4% and 100%, respectively. For serum S100B, a cutoff value of 782.39 pg/mL showed 100% sensitivity and 84.2% specificity, and at 977.06 pg/mL, the sensitivity was 85.7% with specificity of 100%

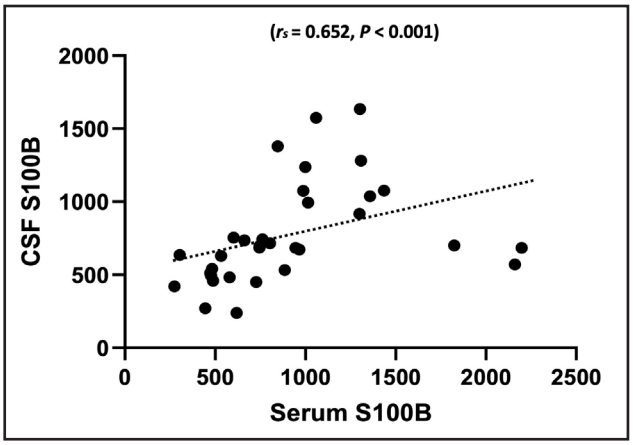

Figure 2. A scatterplot showing the correlation between serum S100B and CSF S100B. The correlation (rs) and associated statistical significance (*P*-value) are displayed at the top of the graph. (rs = 0.652, $P < 0.001$). CSF: cerebrospinal fluid.

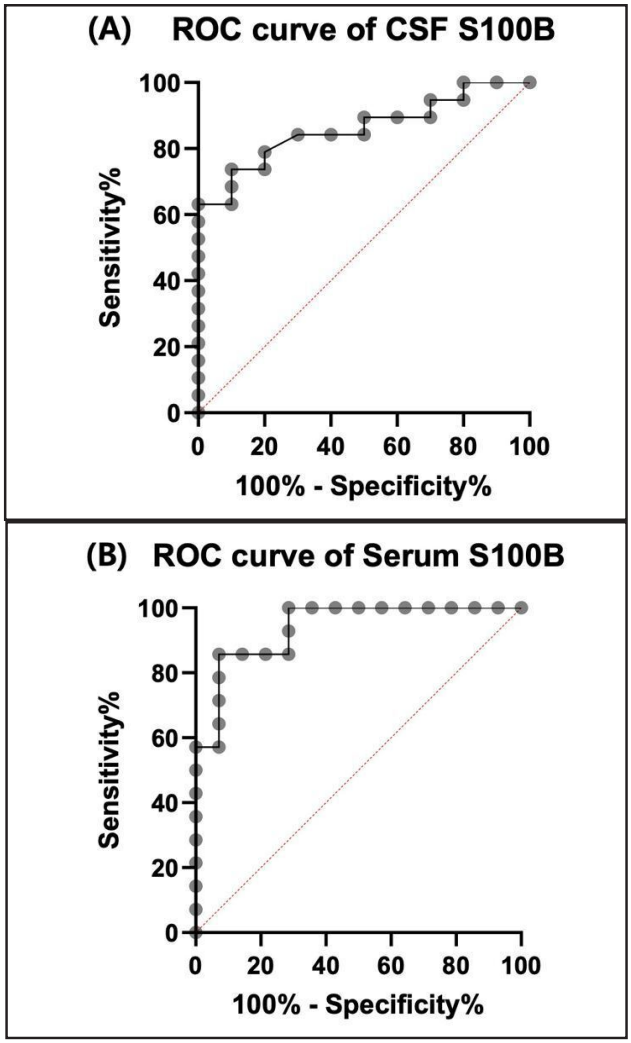

Figure 3. ROC curves illustrate the sensitivity and specificity of CSF S100B and serum S100B. A- CSF S100B. B- serum S100B. This analysis distinguished dogs with meningoencephalitis of unknown origin (MUO). The area under the ROC curve for CSF S100B (A) was 0.92 (95% CI, 0.83-1.00). The area under the ROC curve for serum S100B (B) was 0.97 (95% CI, 0.93-1.00). CI: confidence interval; CSF: cerebrospinal fluid; ROC: receiver operating characteristics.

DISCUSSION

CSF and serum S100B concentrations were significantly higher in the MUO group than in the HC and IE groups. Thereby supporting the hypothesis that S100B is associated with neuroinflammation in dogs. In humans, S100B is directly correlated with neuroinflammation, with elevated levels observed in various CNS diseases [3,6,15]. S100B is predominantly produced by astrocytes, the most abundant cell types in the CNS [15], which play critical roles in maintaining CNS homeostasis and act as immune-competent cells involved in neuroinflammation [22]. Astrocyte-secreted S100B has dual actions: neurotrophic at low concentrations and neurotoxic at high concentrations [12,22]. During stress conditions such as neuroinflammation, astrocytes secrete S100B at the micromolar level, potentially causing neurotoxic effects and acting as a DAMP molecule [15]. S100B mainly interacts with target cells by activating RAGE, a ubiquitous transmembrane immunoglobulin-like receptor that acts as an inflammatory intermediary and a critical inducer of oxidative stress [15]. Previous studies in humans have indicated that S100B is a key molecule in pathogenic processes and a reliable biomarker for various neural disorders, including acute brain injury, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and MS [6,8,11,15,17,23]. MS is the most common form of noninfectious menin-

goencephalitis in humans and parallels MUO because of their clinical and pathological similarities [6]. S100B is a key molecule in MS pathogenic processes and its levels in biological fluids are reliable biomarkers of MS [3,6]. Previous studies have shown elevated S100B levels in the CSF and serum during the acute phase of MS, with levels decreasing during the stationary phase [6]. Increased S100B expression is observed in chronically active MS plaques [6]. In EAE, a laboratory model of MS, S100B levels increased markedly during demyelination, whereas inhibiting S100B action reduces demyelination and the expression of inflammatory molecules [6]. MUO, characterized by astrocyte-specific inflammation, may share mechanistic similarities with MS [1]. As the disease progresses, astrocytes release S100B, a key biomarker associated with neuroinflammation and tissue damage. Consequently, S100B likely plays a critical role in MUO pathogenesis and holds potential as a diagnostic and prognostic biomarker. To the best of our knowledge, this study is the 1st to measure the S100B levels in dogs with MUO.

The blood-brain barrier (BBB) consists of microvascular endothelial cells and glial endfeet [14]. Microvascular endothelial cells are connected by tight junctions that prevent molecular communication between the blood and the brain [14]. Perivascular glia, particularly astrocytes, and their processes contribute to the unique properties of the BBB, investing more than 90% of the endothelial capillaries, with their endfeet tightly projected around the endothelial cells [14]. CSF proteins extravasate into the serum only when the BBB is compromised because of its low transendothelial permeability to proteins [11,14,23]. Previous studies have shown that with intact BBB, serum S100B levels remain low despite ongoing CNS damage, whereas CSF S100B levels may increase [14,16]. Therefore, neuronal damage precedes the appearance of any protein marker of brain damage in the peripheral blood, which extravasates into the plasma at later times if the BBB is compromised [14]. Since astrocytes are the most abundant cell type in the CNS and a key component of the BBB, we hypothesized that S100B, as an astrocytic protein, can be used to detect damage occurring in the brain parenchyma with high sensitivity. This study found a linear correlation between S100B levels in the blood and CSF, supporting our hypothesis that S100B could be an effective tool for guiding further diagnostic evaluations of intracranial diseases that may cause BBB disruption. Additionally, serum S100B can be isolated from extracranial sources [11,19]. Among them, muscles and fat are the primary extracranial sources of S100B protein; however, previous studies have shown that S100B from these sources does not significantly elevate serum levels, in contrast to intracranial sources [11,19]. Therefore, changes in serum S100B levels are likely strongly related to CNS damage, making S100B an established peripheral biomarker of BBB permeability associated with various forms of CNS damage in humans [11,14]. In this context, the results of this study suggest that elevated serum S100B levels in dogs may indicate CNS damage. However, further research is required to examine other potential S100B sources and their influence on serum levels in dogs, which will help us understand how S100B changes correlate with CNS damage.

Biomarkers are substances, either endogenous or introduced, that can be measured in the body to predict the incidence or outcome of a disease [1,7]. Currently, a presumptive diagnosis of MUO is based on MRI findings, CSF analysis, and the exclusion of infectious agents. However, this method is expensive and not commonly accessible. Both advanced imaging and CSF analysis sometimes fail to identify these conditions, as MRI can be normal in up to 7% of cases, and CSF analysis can be normal in 3-57% of dogs with MUO [8]. Therefore, as a diagnostic biomarker, S100B may improve the sensitivity and specificity of the presumptive diagnosis of MUO. Additionally, the cut-off values for distinguishing dogs with MUO from healthy individuals were determined as 699.11 pg/mL for CSF and 782.39 pg/mL for serum S100B, as it exhibited superior AUCs (CSF: 0.92; serum: 0.97), sensitivities (CSF: 85.7%; serum: 100%), and specificities (CSF: 84.2%; serum: 84.2%). These findings suggest that S100B may be a useful diagnostic biomarker for screening for MUO in dogs.

In our study, the IE group showed no significant difference in S100B levels compared with the HC group, consistent with previous human studies on IE [2,20]. However, some studies have reported elevated S100B levels in patients with epilepsy [4,5,13], suggesting that S100B might contribute to epileptogenesis by disrupting the BBB and inducing neuroinflammation processes [12,16,21]. Based on our results, the absence of elevated S100B levels in dogs with IE without suspected CNS problems indicates that S100B

could be a useful initial screening tool for distinguishing between primary and secondary epilepsy. However, the small number of cases and CSF samples may have contributed to these negative results. Therefore, further investigations involving a larger number of cases are required to clarify the differences in epilepsy.

Our study has a few limitations. First, although we successfully supported the hypothesis that CSF and serum S100B levels were elevated in the MUO group, the small sample size raises the possibility of type 1 error. Second, 8 CSF samples were excluded because of storage issues and blood contamination, which may have affected the reliability of the assessment of linearity between serum and CSF. Therefore, additional well-controlled studies with larger sample sizes are required to accurately evaluate the relationship between MUO and S100B levels. Third, we did not analyze S100B levels in relation to MUO severity or treatment. Therefore, this does not provide information on whether S100B levels reflect MUO progression or treatment response, indicating the need for further research. Fourth, a conclusive diagnosis could not be established for dogs that did not survive, as an accurate diagnosis of MUO usually relies on histopathological analysis. Despite this, the inclusion criteria applied in our study suggested that other differential diagnoses were unlikely. Fifth, the study lacked comparative controls for other structural CNS diseases (e.g., neoplasia, infectious encephalitis, and trauma) that disrupt the BBB, limiting the specificity of S100B for MUO. We also acknowledge that using IE as the sole disease control limits the ability to differentiate MUO from other structural brain pathologies. Inclusion of other structural CNS disease controls in future work is essential to establish the discriminatory value of S100B as a biomarker.

CONCLUSIONS

This preliminary study demonstrates that dogs with MUO exhibit higher CSF and serum S100B concentrations than HC and IE cases, with a strong correlation between blood and CSF levels. Additional large-scale studies including diverse structural brain disease controls are needed to further validate S100B as a specific biomarker for MUO. Furthermore, the ease of detecting S100B in peripheral blood supports its translation into a rapid point-of-care assay, and pharmacological inhibition of S100B-mediated pathways may offer novel strategies for early intervention and improved management of MUO.

MANUFACTURERS

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***Acknowledgements*.** This study was supported by the National Research Foundation (NRF) of Korea and funded by a grant from the Korean Government (NRF-2022R1G 1A1003682113148209264010 1) and the Basic Science Research Program through the NRF funded by the Ministry of Education (RS-2023-00219710314820926400 01).

***Ethical approval*.** This study was approved by the Chungnam National University Ethics Committee, approval number (protocol 202311-CNU-374). Additionally, informed consent was obtained from all the dog owners.

***Declaration of interest*.** The authors report no conflicts of interest. The authors are solely responsible for the content and writing of the article.

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