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Article

# Computed Tomography-Measured Cranial Mediastinal Lymphadenomegaly Is Associated with Elevated C-Reactive Protein in Small Dogs with Non-Neoplastic Disorders

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**Simple Summary:** Dogs often show enlarged lymph nodes, or lymphadenomegaly, when they have cancer or inflammatory conditions. Veterinarians can examine lymph nodes close to the body surface by touch, but they need to use imaging techniques like computed tomography or ultrasonography to examine deeper lymph nodes. As a preliminary step in investigating how deeper lymph enlargement may be linked to inflammation, we targeted three areas of lymph nodes (sternal, cranial mediastinal, and internal iliac), and checked how node size relates to the level of C-reactive protein, which is known to increase with the onset of inflammation. We evaluated data on lymph node diameter and C-reactive protein level in small dogs with diseases other than cancer. We found that the cranial mediastinal lymph node was significantly larger in dogs with increased C-reactive protein level, and that the size of this lymph node correlated with the level of this protein overall. However, we found no such pattern for the sternal or internal iliac lymph nodes. We thus suggest that measurements of cranial mediastinal lymph nodes made with computed tomography may be useful for evaluating systemic inflammation. Further research could confirm the broader use of such measurements for assessing inflammation through lymph node size.

**Abstract:** Lymphadenomegaly is well described in dogs with neoplastic diseases, but it can also reflect inflammation. However, its role in assessments of inflammation is little reported in the veterinary literature. Lymph nodes are most easily assessed superficially through palpation, but computed tomography (CT) enables evaluation of deep lymph nodes. Accordingly, we investigated associations between maximal lymph node diameter and plasma concentrations of C-reactive protein (CRP), a sensitive inflammatory marker, targeting three deep lymph nodes (sternal, cranial mediastinal, and internal iliac). We evaluated data from small dogs with non-neoplastic diseases that underwent synchronous CT and blood biochemistry at our institution. We found that cranial mediastinal lymph node diameter was significantly greater in dogs with clinically elevated CRP than those with clinically unremarkable CRP (CRP 0.7–7.0 < mg/dL vs. <0.7 mg/dL: 5.28 vs. 4.17 mm;  $p=0.04$ ) and significantly correlated with CRP (adjusted  $R^2 = 0.15$ ;  $p < 0.01$ ) in multiple regression analysis. We found no significant association with CRP for the sternal or internal iliac lymph node. We thus consider that CT-measured cranial mediastinal lymphadenomegaly could be a clinically useful finding for comprehensive evaluation of systemic inflammation. We anticipate further research may highlight the utility of CT lymph-node measurements for such evaluations.

**Keywords:** computed tomography; C-reactive protein; lymphadenomegaly; cranial mediastinal lymphadenomegaly; canine

## 1. Introduction

Lymphadenomegaly, or the enlargement of lymph nodes, can occur in dogs suffering from various conditions, including neoplasms [1–3], infectious diseases, or idiopathic ailments [4,5], as well as inflammatory disorders [6,7]. In the realm of veterinary literature, the presence of enlarged lymph nodes frequently captures attention in oncological studies, particularly those focusing on lymphoma or lymph node metastasis [8–11]. Notably, neoplastic diseases have been found to be the most prevalent diagnosis in both dogs and cats presenting with radiologically enlarged lymph nodes [12]. As a result, lymph nodes are often targeted in oncological assessments, including procedures like sentinel lymph node biopsies [13]. In both veterinary and human medical literature [14], inflammatory disorders are also acknowledged as differential diagnoses for cases involving lymph node enlargement. However, the significance of such enlargement in the context of evaluating inflammatory conditions in dogs has been discussed rather infrequently. This lack of discourse may stem from the reality that during examinations of enlarged lymph nodes in canines, inflammation can coexist with neoplasia, making it challenging to differentiate between inflammatory and neoplastic disorders without observing significant lymphadenopathy. Therefore, there is a pressing need for thorough investigations focused on lymph node size in dogs that have exclusively non-neoplastic disorders. Such studies are essential to clarify the intricate relationship between lymphadenomegaly and inflammation, particularly in the context of systemic inflammation. Nonetheless, to the authors' knowledge, no previous investigations addressing this specific issue have been reported in the veterinary literature.

Dogs with neoplastic disorders may represent a valuable target population for research focused on lymphadenomegaly and systemic inflammation. However, this raises an important question regarding the most effective methods for evaluating lymph nodes in this group. Typically, lymph node enlargement is assessed clinically through the palpation of superficial lymph nodes, but this approach is inherently qualitative and does not provide insight into deeper lymph nodes, which may be more sensitive to systemic inflammation due to their anatomical positioning.

Ultrasonography has been proposed as a method for assessing deep lymph nodes in dogs. Although this technique has been utilized in oncological studies, it has proven to be somewhat problematic for diagnostics, often lacking the ability to effectively differentiate between malignant and benign deep lymph nodes based solely on hypoechoogenicity and other imaging findings [15]. Additionally, factors like gas-related distortion of sound waves can hinder accurate ultrasonographic visualization of these deeper structures [16].

As a potentially superior alternative, computed tomography (CT) offers a useful, non-invasive imaging modality for evaluating deeper lymph nodes. Unlike ultrasonography, CT provides robust visualization that is unaffected by respiratory gases. It also delivers high-resolution images quickly and accurately identifies lymph node locations [16]. The advantages of CT for deep lymph assessments have been demonstrated in various oncological investigations. For instance, it has enabled the differentiation between malignant and benign tumors based on characteristic imaging of sternal lymph nodes, and it has shown that a tracheobronchial lymph node diameter greater than 12 mm significantly increases the likelihood of metastatic tumors [17]. Moreover, CT facilitates accurate measurement of geometric parameters, including the diameters of deep lymph nodes, thereby generating quantitative data that can enhance statistical evaluations of neoplastic systemic inflammation and improve diagnostic accuracy for neoplastic disorders. This combination of factors underscores the potential for CT to play a pivotal role in the assessment and management of lymphadenomegaly in dogs with neoplastic diseases.

An evaluation of lymphadenomegaly in inflammatory disorders would benefit from evidence on associations between deep lymph node geometry and relevant biomarkers of systemic inflammation. In both veterinary and human medicine, C reactive protein (CRP) is widely used as one such marker. This acute phase protein also has utility in assessments of tumors and for post-surgical monitoring [19–21], and it is rapidly and markedly elevated at the onset of inflammation. CRP is a very sensitive, albeit not selective, marker of inflammation. Establishing associations between deep lymph node enlargement and plasma CRP concentration would thus provide useful

evidence on the sensitivity of the former in inflammatory conditions, but there is a paucity of reported evidence on any such association in dogs. We speculated that there would be a relationship between serum CRP levels and the maximal diameters of deep lymph nodes.

Accordingly, in this study, we aimed to investigate associations between lymphadenomegaly and levels of the inflammatory marker CRP, using CT images of deep lymph nodes (sternal, cranial mediastinal, and iliac) in small dogs with non-neoplastic disorders.

## 2. Materials and Methods

### 2.1. Study Population

For evaluation in this retrospective study, we targeted 369 dogs which underwent CT examinations and plasma CRP measurements on the same day, while receiving medical care at Kagoshima University Veterinary Teaching Hospital (Kagoshima, Japan) between January and December 2022. The inclusion criteria were a body weight not exceeding 10 kg, so as to minimize any bias in body weight or size (set in reference to a previous report [22]), and the presence of tomographically measurable sternal, cranial mediastinal, and/or internal iliac lymph nodes. Dogs were excluded from the study when their cases corresponded to any of the following conditions: diagnosis of a neoplasm, previous treatment for a neoplasm, and any evidence in their medical history that could give rise to suspicion of cancer and/or metastasis. These exclusion criteria were set to ensure that no cases of lymphadenomegaly due to lymph node metastasis or inflammatory reactive hyperplasia associated with the cancer were included in this study. Ethics approval was waived for this retrospective study, because it did not involve any procedures with experimental animals. It was conducted in accordance with the research ethics bylaws of Kagoshima University. The owner of each dog evaluated in this study had given consent to the use of the relevant data in research at the time of medical examinations.

### 2.2. Evaluation of Lymph Node Images

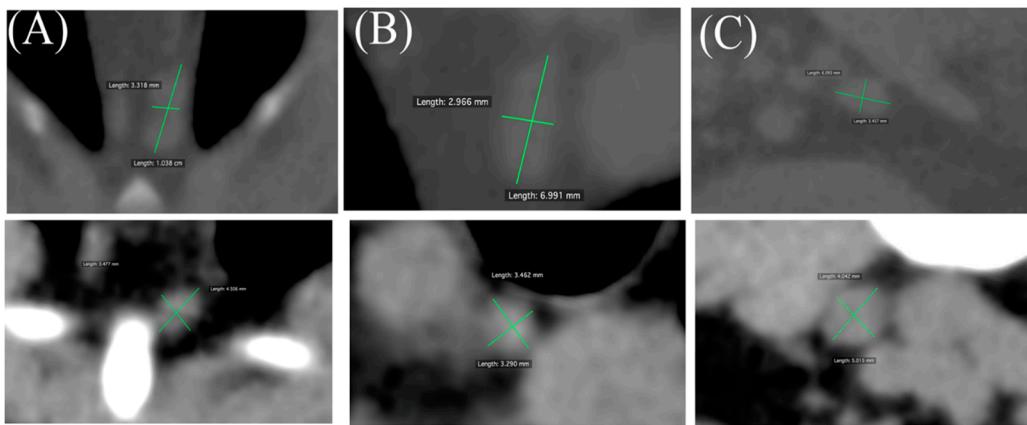
The dogs had undergone CT imaging with a dedicated 16-herical sliced CT scanner (Aquilion TSX-201A, Toshiba Medical Systems Corporation, Tochigi, Japan), with or without anesthesia. These CT images were acquired with reading and measurement under two conditions (soft tissue condition WL50:WW350; lung condition WL:-50WW:1500). Slice thickness was 1 mm. Blood was collected from each dog on the same day as the CT imaging, for standard blood chemistry examinations, which included measurement of CRP concentration in plasma with a clinical chemistry analyzer (Fuji DRI-CHEM NX500, Fujifilm Corporation, Japan).

In this study, the CT images for each dog were retrieved, for a determination of lymph node diameters in three target regions. All images were acquired in DICOM format and were read and measured using the DICOM viewer OsiriX Ver. 5.9. As target regions, those for the sternal and cranial mediastinal lymph nodes were selected as corresponding to the most commonly identified nodes by CT within the thoracic cavity [16], and that for the internal iliac lymph nodes was then selected as these nodes are adjacent to the abdominal aorta and are among the most easily assessable nodes in the abdominal cavity.

Transverse CT images of the thoracic and abdominal cavities of each dog were examined for the target lymph nodes. The sternal, cranial mediastinal, and internal iliac lymph nodes were identified on the relevant CT image, as structures of the expected appearance (spherical or oval in shape, with distinct margins) at their expected anatomical locations.

When target lymph nodes were identified, two notional, perpendicular lines were plotted through the center of the relevant lymph line extending to its border, and the longer of the two lines was regarded as its maximal diameter. Its measured length was read by the DICOM viewer scale function to the nearest mm and adopted as the value for evaluation (Figure 1). In cases of multiple lymph nodes at a given location, the maximal diameter of the largest node was adopted as the measurement result. Lymph nodes were considered unmeasurable and excluded from the analysis when CT images did not show a structure of the expected appearance at the expected anatomical

location, an occupying lesion was detected there, or there was evidence of pleural fluid or ascites. Measurements were performed by a single veterinarian (YI) and confirmed by a second veterinarian (NM) engaged at the Diagnostic Imaging Department of Kagoshima University Veterinary Teaching Hospital.



**Figure 1.** Measurable lymph nodes in computed tomography.

A measurable lymph node was regarded as a spherical or oval marginal structure with a well-defined boundary at an anatomically expected location. Two notional lines were drawn perpendicular to the boundary line, the longer of the two lines was considered the largest diameter, and the measured length was taken as the value for evaluation.

Representative examples of clinically enlarged (upper) and clinically unremarkable (lower) lymph nodes are shown for sternal (A), cranial mediastinal (B), and internal iliac (C) lymph nodes.

### 2.3. Other Data Retrieved

The medical records for each dog with measurable lymph nodes were retrieved, and demographic information (age, breed, sex, and body weight), and plasma CRP concentration and white blood cell count (WBC) were collated for evaluation in this study. Each medical record was also checked for any findings of superficial lymph node enlargement on palpation.

### 2.4. Associations between Lymph Node Enlargement and CRP Level

Lymph nodes were regarded as enlarged when their diameter exceeded a threshold value, set in reference to the literature (sternal lymph node: 7 mm; cranial mediastinal and internal iliac lymph nodes: 6 mm) [24–27]. Plasma CRP concentrations  $>0.7\text{mg/dL}$  were regarded as clinically elevated, based on the reference range at our institution. Lymph node diameters were compared between dogs with clinically elevated and clinically unremarkable plasma CRP, using Welch's t test.

### 2.5. Statistics Analysis

We evaluated the correlation between lymph node diameter and plasma CRP concentration in a single regression analysis, but the model showed poorness of fit. Thus, we also evaluated these parameters in multiple regression analyses, with WBC and the presence of intra-abdominal disease as independent variables, to obtain an adjusted  $R^2$  value derived from correlation coefficients for evaluation (intra-abdominal disease was regarded as a condition developing in an organ or structure within the abdominal cavity, based on the individual dog's medical record). All analyses were performed using a statistical software package (EZR version 1.64, Saitama Medical Center, Jichi Medical University, Japan) [27]. P values  $< 0.05$  were regarded as statistically significant.

## 3. Results

Demographic and clinical characteristics of the study population

A total of 40 dogs were included in the study population (mean age: 14.2 years; mean body weight 4.9 kg), of which 15 were neutered males, four were intact males, 14 were neutered females, and seven were intact females. The dog breeds encompassed in this study (in descending order of magnitude) were Miniature Dachshund (n = 11), Toy poodle (n = 9), Chihuahua (n = 7), Shih Tzu (n = 4), Papillon (n = 2), Yorkshire terrier (n = 2), French bulldog (n = 1), Miniature schnauzer (n = 1), Miniature pinscher (n = 1), Shiba Inu (n = 1), and mixed breed (n = 1). The diagnosed conditions for this study population (as determined by the relevant original attending veterinarian) encompassed Cushing's syndrome (n=4); single or multiple cervical disk herniation (n = 3); cystoliths, herniated disc, gallbladder mucocele, intestinal or small intestinal foreign body, and tracheal collapse (n = 2 each); and suspected pancreatitis, lesional adherence to the radial-ulnar ligament, immune-mediated neutropenia, chronic bronchitis, spinal osteoarthritis, rhinitis, encephalitis, idiopathic polyarthritis, cholelithiasis, aortic thrombus, polyarthritis, choledocholithiasis, duodenal polyposis, syncope, uterine cysticercosis, eosinophilic enteritis, laryngeal paralysis, megaesophagus, acute pancreatitis, hepatitis, diaphragmatic hernia, inflammatory polyps, and lymphocytic plasmatic rhinitis, and epilepsy (n = 1 each). Demographic and diagnostic data are presented in Table 1.

**Table 1.** Demographic and clinical characteristics of small dogs free of neoplasms.

Parameter	Value
Study population	N = 40
Male / Female	N = 19 / N = 21
Intact / Neutered	N = 12 / N = 28
Age	Mean 14.2y(max-min: 16y1m-1y4m 95%CI:0.46)
Sternal lymph nodes	
No. measurable	N = 34
Mean diameter	4.49±1.43mm (max-min : 8.1-2.9 95%CI:0.46)
Clinically enlarged	2/34(>7mm)
Cranial mediastinal lymph nodes	
No. measurable	N = 34
Mean diameter	4.62±1.46mm (max-min : 9.3-2.9 95%CI:0.47)
Clinically enlarged	4/34(>6mm)
Internal iliac lymph nodes	
No. measurable	N = 39
Mean diameter	5±1.2mm (max-min : 8.1-2.9 95%CI:0.39)
Clinically enlarged	9/34(>6mm)
CRP	2.3±2.65mg/dL(max-min:7.0-0.3 95%CI:0.85)
Clinically elevated	18/40(0.7mg/dL)

For these 40 dogs, the sternal, cranial mediastinal, and internal iliac lymph nodes were measurable in 34, 34, and 39 cases, respectively. Imaged lymph nodes measured were mostly of predefined morphology and enhanced shade. In some cases, low-absorption areas were visible within the lymph nodes, but they did not affect determination of nodal morphology or diameter. Representative CT images of measurable lymph nodes are shown in Figure 1.

Based on the measured diameter, the subpopulations with enlarged lymph nodes were as below. A total of 2/34 dogs (5.8%) showed enlarged sternal lymph nodes (7.4 or 8.1 mm). Both of these dogs were neutered females, one was a Miniature Dachshund (age: 1 year 5 months, body weight: 9.3 kg) diagnosed with an intestinal foreign body, and the other was a Toy Poodle (age: 10 months, body weight: 2.94 kg) diagnosed with diaphragmatic hernia.

A total of 4/34 dogs (11.7%) showed enlarged cranial mediastinal lymph nodes (range: 6.2 mm to 9.3 mm). These dogs comprised one intact and three neutered males (total: n=4; age: 2 years 6 months to 11 years 6 months), two of which were Toy Poodles, one was a Chihuahua, and one was a Miniature Pinscher. The diagnosed conditions for these dogs were duodenal intussusception, Cushing's syndrome, immune-mediated neutropenia, and cervical disc herniation (n = 1 each).

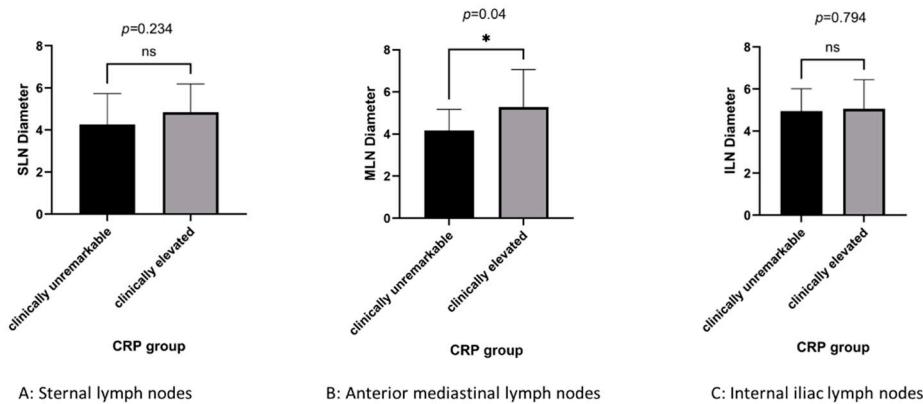
A total of 9/39 dogs (23.0%) showed enlarged internal iliac lymph nodes (range: 6.0 to 8.1 mm). These dogs comprised two intact and six neutered males and one neutered female (age: 2 years 4 months to 15 years 7 months). The diagnosed conditions for these dogs were epilepsy, syncope, gallbladder mucocele, cholelithiasis, Cushing syndrome, immune-mediated neutropenia, duodenal intussusception, and cervical disc herniation (n=1, each).

Blood chemistry revealed that 18/40 dogs (45%) had clinically elevated plasma CRP. Furthermore, 12/40 dogs (30%) showed elevated WBC counts (Table 1).

Palpably enlarged superficial lymph nodes were only noted in one case (an instance of enlarged mandibular lymph nodes).

#### Deep lymph node evaluation in dogs with elevated plasma CRP

Lymph node diameters were compared between dogs with clinically elevated and clinically unremarkable plasma CRP concentrations. Dogs with clinically elevated plasma CRP showed significantly greater cranial mediastinal lymph node diameter than dogs with clinically unremarkable plasma CRP concentration (5.28 vs. 4.17 mm;  $p = 0.04$ ), but no significant differences for the sternal (4.84 vs. 4.25 mm;  $p = 0.247$ ) or internal iliac (5.05 vs. 4.95 mm;  $p = 0.799$ ) lymph node (Figure 2).



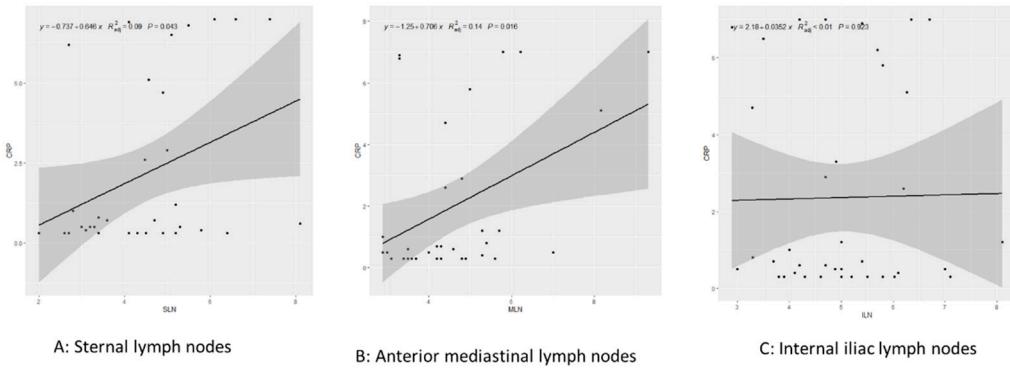
**Figure 2.** Lymph node diameters in dogs with clinically elevated and clinically unremarkable CRP.

Lymph node diameters (mm) in dogs with clinically elevated or clinically unremarkable plasma CRP levels. Based on the reference values testing companies provided, CRP was categorized as clinically unremarkable at concentrations <0.7 mg/dL, or elevated at concentrations of 0.7-7.0 mg/dL.

Associations between lymph node diameter and plasma CRP concentration in simple and multiple regression analyses.

Single regression analysis revealed that cranial mediastinal node diameter was significantly correlated with plasma CRP concentration (adjusted  $R^2=0.15$ ,  $p=0.01>a$ ), but we found no significant correlations for the sternal (adjusted  $R^2=0.09$ ,  $p=0.122$ ) or internal iliac (adjusted  $R^2=-0.005$ ,  $p=0.43$ ) lymph node (Figure 3).

In multiple regression analysis, neither WBC count nor the presence/absence of intraabdominal disease was significantly correlated with plasma CRP concentration. The variance inflation factor (VIF) was < 2 for all variables in the regression model (Table 2).



**Figure 3.** Single regression analysis targeting lymph node size and CRP concentration.

A: sternal lymph nodes; B: anterior mediastinal lymph nodes; C: internal iliac lymph nodes.

Each graph shows the relevant regression line, with the gray area representing the 95% confidence interval.

**Table 2.** Multiple regression analysis for WBC, abdominal disease, and CRP by lymph node.

	$\beta$	<i>t</i>	<i>p</i>	95%CI
Sternal lymph nodes				
CRP(mg/dL)	0.13	1.39	0.17	-0.06 – 0.34
WBC(k/ $\mu$ L)	0.01	0.72	0.47	-0.03 – 0.06
Abdominal disease (Yes=1, No=0)	0.57	1.14	0.26	-0.45 – 1.6
Cranial mediastinal lymph nodes				
CRP(mg/dL)	0.33	3.01	<0.01 *	0.10 – 0.56
WBC(k/ $\mu$ L)	-0.03	-1.35	0.18	-0.08 – 0.02
Abdominal disease (Yes=1, No=0)	-0.44	-0.87	0.38	-1.49 – 0.6
Internal iliac lymph nodes				
CRP(mg/dL)	-0.06	-0.72	0.475	-0.24 – 0.11
WBC(k/ $\mu$ L)	0.0032	1.65	0.107	-0.01 – 0.07
Abdominal disease (Yes=1, No=0)	0.026	0.06	0.949	-0.81 – 0.86

\* Statistically significant values ( $P < 0.05$ ).

#### 4. Discussion

In this study, we investigated associations between CT-measured canine lymphadenomegaly and elevated CRP in dogs without neoplastic disorders, targeting deep lymph nodes (cranial mediastinal, sternal, and internal iliac lymph nodes), based on our speculation that serum CRP levels would show associations with deep lymph node diameter in this population. Although this acute phase protein may not totally reflect an inflammatory condition, we consider that its utility for quantitative assessments make it a biologically relevant parameter for this study. To the authors' knowledge, this is the first report on such an association in the canine medical literature.

As a key finding, somewhat surprisingly, only the cranial mediastinal lymph node showed an association with CRP. Cranial mediastinal lymph node diameter was significantly correlated with plasma CRP concentration, and dogs with clinically elevated CRP showed a significantly greater cranial mediastinal lymph node diameter than dogs with clinically unremarkable CRP. Previously, mediastinal lymphadenomegaly has largely been reported in dogs with neoplastic diseases or heart failure [28–30], and in the human literature, it has also been associated with cystic fibrosis, cardiac disorders, and COVID-19 [32–34]. The dogs with enlarged mediastinal lymph nodes in this study had been diagnosed with a range of conditions (polyarthritis, idiopathic polyarthritis, disk herniation, and gallbladder mucocele; n=1 for each). Systemic inflammatory responses have been reported in dogs with idiopathic polyarthritis, disc herniation, and gallbladder mucocele. Since elevated serum CRP levels accompanying systemic inflammatory response have been reported in gallbladder mucocele and polyarthritis, [35–37], we consider that the cranial mediastinal lymph node enlargement in the corresponding cases in this study may well reflect systemic inflammation. On the other hand, more caution is required in interpreting the case of disk herniation in this study, since there are reports of no elevated serum CRP levels for this condition [38,39], and the cause of the elevated serum CRP levels in the relevant dog is unclear. Furthermore, the anatomical position of the cranial mediastinal lymph node lymph nodes [40,41], embedded in fat around central blood vessels such as the vena cava and aortic arch, indicates that these lymph nodes could be readily sensitive to systemic inflammatory responses. Our findings are thus not inconsistent with a phenomenon reflecting systemic inflammation. It is also noteworthy that our findings on cranial mediastinal lymph node enlargement came in a population with almost no palpably enlarged superficial lymph nodes (a single instance noted in 40 dogs).

In this study, we were unable to establish an association between sternal lymph node enlargement and systemic inflammation. The diameter of this lymph node did not differ significantly between dogs with clinically elevated CRP and those with clinically unremarkable CRP. Furthermore, sternal lymph node diameter and plasma CRP were not significantly correlated in multiple regression analysis, although we did note such a correlation in preliminary single regression analysis (which is not regarded as the major endpoint in this evaluation due to poorness of fit). Considering this preliminary finding, and the small number of dogs with enlarged sternal lymph nodes (n=2) in this study, we cannot exclude a potential association with CRP, which might emerge in analyses with a larger population. In previous reports in dogs, sternal lymphadenomegaly has been linked with lymphoma and metastatic tumors [12,22,42,43]; however, the dogs with enlarged sternal lymph nodes in this study were diagnosed with diaphragmatic hernia and an intestinal foreign body (n=1, each), and the authors are unaware of any reports on sternal lymphadenomegaly arising with these conditions in dogs.

This study provided no evidence that internal iliac lymph node enlargement reflects systemic inflammation, as we found no significant correlation with CRP in multiple regression analysis, or significant differences between dogs with clinically elevated and unremarkable CRP. The internal iliac lymph nodes are located within the hypogastric lymphosome, which occupies a relatively small region at the caudal end of the abdominopelvic cavity, indicating that these lymph nodes are potentially less sensitive to systemic inflammatory responses than the nodes in centers we investigated in the thoracic cavity.

Although lymph nodes are always likely to reflect localized inflammation, our findings suggest an interesting possibility that effects of systemic inflammation may vary in magnitude between

lymph nodes at different anatomical locations in dogs. Some caution is required in interpreting these results though, because of the possibility that localized inflammation-induced lymph node enlargement may have occurred without CRP elevation in some cases, which might have affected the statistical evaluation. Anatomically, sternal lymph nodes are drain by lymphatic vessels to the sternal skin, mammary glands, chest wall, and abdominal wall, whereas mediastinal lymph nodes are drain the neck and chest regions [44]. Accordingly, inflammation in these regions could be expected to cause reactive enlargement of these lymph nodes. Nevertheless, we speculate that lymph nodes such as the mediastinal lymph nodes, which are closer to the major blood vessels and thoracic ducts, may be more sensitive to systemic inflammation. Interestingly, almost no superficial lymph enlargement was reported in the dogs in this study, indicating potentially greater sensitivity for these deep lymph nodes and that images of deep lymph node enlargement may provide more useful clinical information on the lymphatic system than findings solely based on palpation.

Even with the caveats related to the interpretation of our findings, we suggest that CT findings of cranial mediastinal lymph node enlargement in dogs should prompt clinicians to consider inflammatory disorders, and this may illustrate one of the advantages of CT imaging. It is difficult to evaluate lymph node size using palpation or other imaging modalities such as ultrasonography. With CT, clinicians can accurately elucidate changes in lymph node size in a way that might otherwise not be possible. CT imaging has been proposed as a useful complementary technique for oncological evaluations [18,41], and we suggest it may have a similar potential utility for assessments of inflammation.

This study presents several limitations, partly due to its design as a hypothesis-generating investigation. Being a retrospective study, we could not confirm the pathological status of the lymph nodes directly; for superficial lymph nodes, we relied solely on information recorded in the medical records, which indicated whether they were enlarged. Additionally, our data were collected from dogs at a single time point—specifically, upon referral to our hospital—preventing us from exploring any temporal aspects of the relationship between CRP levels and lymph node diameter. Understanding this relationship over time would be valuable, particularly since CRP functions as an acute phase protein. Another limitation is the wide range of diagnoses represented among the dogs in this study, which complicates our ability to draw meaningful conclusions from a heterogeneous population. The hypotheses we are formulating regarding the potential utility of lymph node enlargement in evaluating inflammatory conditions will necessitate evidence from future studies conducted over extended periods, ideally within a more uniform population. Given that CRP has a relatively short half-life in the bloodstream, it is more likely to reflect inflammation close to its onset. Thus, it would be beneficial to establish the time course of systemic inflammation-related lymph node enlargement and compare it to the timeline of CRP elevation. Furthermore, our analysis was limited to one biomarker (CRP). Expanding this investigation to include a broader array of biomarkers could yield additional valuable insights into the associations between lymph node size and systemic inflammation. Such an approach would enhance our understanding of the dynamics of inflammation in dogs and could inform better clinical practices.

## 5. Conclusions

We demonstrated that CT-measured maximal cranial mediastinal lymph node diameter may have some potential utility in evaluations of systemic inflammation, based on its association with measured plasma CRP concentration, in small dogs free of neoplastic disease. We suggest that CT determinations of cranial mediastinal lymphadenomegaly may prove useful in holistic assessments of dogs with inflammatory conditions. Such determinations should give rise to clinical consideration of inflammatory disorders when noted, and may inform clinical decisions on further diagnostic testing.

**Author Contributions:** Conceptualization, Y.I. and N.M.; methodology, Y.I.; validation, Y.I., Y.F., T.S., K.T., T.K., A.N. and M.T.; formal analysis, Y.I. and N.M.; investigation, Y.I., Y.F., T.S., K.T., T.K., A.N. and M.T.; data curation, Y.I., Y.F., T.S., K.T., T.K., A.N. and M.T.; writing—original draft preparation, Y.I.; writing—review and editing, N.M.; visualization, Y.I.; supervision, N.M.; project administration, Y.I. and N.M.; All authors have read and agreed to the published version of the manuscript.

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**Institutional Review Board Statement:** Ethical review and approval were waived for this study because it did not involve any procedures with experimental animals. It was conducted in accordance with the research ethics bylaws of Kagoshima University. The owner of each dog evaluated in this study had given consent to the use of data in research at the time of medical examinations.

**Data Availability Statement:** The raw data supporting the conclusions of this article will be made available by the authors on request.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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