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Further characterization of computed tomographic and clinical features for staging and prognosis of idiopathic pulmonary fibrosis in West Highland white terriers

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In Memoriam of Lesley G. King.

Abstract

Idiopathic pulmonary fibrosis is an interstitial lung disease of unknown etiology resulting in progressive interstitial fibrosis, with a known predilection in West Highland white terriers. In humans, computed tomography (CT) is a standard method for providing diagnostic and prognostic information, and plays a major role in the idiopathic pulmonary fibrosis staging process. Objectives of this retrospective, analytical, cross-sectional study were to establish descriptive criteria for reporting CT findings and test correlations among CT, clinical findings and survival time in West Highland white terriers with idiopathic pulmonary fibrosis. Inclusion criteria for affected West Highland white terriers were a diagnosis of idiopathic pulmonary fibrosis and available CT, bronchoscopy, bronchoalveolar lavage, echocardiography, and routine blood analysis findings. Clinically normal West Highland white terriers were recruited for the control group. Survival times were recorded for affected dogs. The main CT lung pattern and clinical data were blindly and separately graded as mild, moderate, or severe. Twenty-one West Highland white terriers with idiopathic pulmonary fibrosis and 11 control West Highland white terriers were included. The severity of pulmonary CT findings was positively correlated with severity of clinical signs ($\rho = 0.48$, $P = 0.029$) and negatively associated with survival time after diagnosis ($\rho = -0.56$, $P = 0.025$). Affected dogs had higher lung attenuation (median: −563 Hounsfield Units (HU)) than control dogs (median: −761 HU), ($P < 0.001$). The most common CT characteristics were ground-glass pattern (16/21) considered as a mild degree of severity, and focal reticular and mosaic ground-glass patterns (10/21) considered as a moderate degree of severity. Findings supported the use of thoracic CT as a method for characterizing idiopathic pulmonary fibrosis in West Highland white terriers and providing prognostic information for owners.

KEYWORDS
dog, idiopathic pulmonary fibrosis, interstitial pneumonia

1 | INTRODUCTION

Idiopathic pulmonary fibrosis has been described as an interstitial lung disease of unknown etiology resulting in progressive and fatal interstitial fibrosis.[1,2] Several factors are known to trigger interstitial lung diseases such as infectious agents, toxin exposure, drug reaction, immunologic condition, or neoplastic disease.[1] In human medicine, idiopathic pulmonary fibrosis has been well characterized histologically as usual interstitial pneumonia.[2–4] Dogs with idiopathic pulmonary fibrosis commonly present in middle to old age with clinical findings including inspiratory crackles, cough, exercise intolerance, dyspnea, and eventually cyanosis, and West Highland white terriers

have a high predisposition.[2,5] The disease is progressive with a protracted history. While definitive diagnosis is achieved on histopathology in human patients, this is rarely undertaken in dogs where idiopathic pulmonary fibrosis is commonly a diagnosis of exclusion. Canine idiopathic pulmonary fibrosis lesions are characterized by an accumulation of collagen in the interstitial space, type II pneumocyte hyperplasia and alveolar septal fibrosis.[5,6] However, the pathological description in the dog does not match that required for a diagnosis of usual interstitial pneumonia in most cases, and is more reminiscent of that seen with nonspecific interstitial pneumonia in humans.[2] The exact relationship, if any, between nonspecific interstitial pneumonia and usual interstitial pneumonia in human patients is unknown, but may represent a spectrum of idiopathic interstitial lung disease that eventually results in end-stage fibrosis.[7] Computed tomography (CT) findings are commonly used as the basis for disease classification and prognosis in people. Human patients with nonspecific interstitial pneumonia have a better prognosis than those with usual interstitial pneumonia.[7]

Computed tomography features of canine idiopathic pulmonary fibrosis have been previously described, with common findings including ground-glass pattern, reticular abnormalities, traction bronchiectasis, and honeycombing in the later stage.[8–11] These characteristics are somewhat similar to high resolution CT findings in human idiopathic pulmonary fibrosis except there appears to be a greater degree of ground-glass attenuation in the dog that is reported to equate with human nonspecific interstitial pneumonia.[7,8,10] Hematology and biochemistry profiles, bronchoscopy, and bronchoalveolar lavage are often unremarkable in affected dogs. Chronic bronchitis can be a common comorbidity that complicates diagnosis, but also the main reason for the presence of a highly cellular bronchoalveolar lavage.[8,9] According to the American Thoracic Society and European Respiratory Society 2011 consensus statement on human idiopathic pulmonary fibrosis the appearance of the lung on CT has both diagnostic and prognostic value that plays a major role in disease staging and decision making for patient care.[12] A correlation between CT findings and clinical signs has not been reported for the dog. An American Thoracic Society workshop report on comparative idiopathic pulmonary fibrosis (2013) highlighted the need for further descriptive research in order to better define the clinical and imaging presentation of dogs with idiopathic pulmonary fibrosis.[13]

Aims of the current study were to establish CT descriptive terms for characterizing idiopathic pulmonary fibrosis in West Highland white terriers and determine whether CT characteristics are correlated with clinical signs or survival time. The study hypothesis was that the severity of the lesions on CT would be positively correlated to the severity of clinical signs, thus supporting the use of CT as a prognostic tool for affected dogs.

2 | MATERIALS AND METHODS

2.1 | Dogs

The study was a retrospective, analytical, cross-sectional design. Databases of the following three referral hospitals were searched for West Highland white terriers with a diagnosis of interstitial pulmonary fibrosis: University of Edinburgh, University of Glasgow, and University of Pennsylvania. For purposes of this study, the diagnosis of interstitial pulmonary fibrosis was based on clinical presentation, results from bronchoscopy, and bronchoalveolar lavage with mild changes, and an interstitial pulmonary abnormality on CT images. Inclusion criteria for participation in the study consisted of available thoracic CT images, hematology and biochemistry, and bronchoscopy performed at the time of diagnosis. Decisions for study inclusion for dogs in the affected group were made by the first author (F.T.). The database of the University of Edinburgh teaching hospital was also searched from July 2009 to November 2015 for West Highland white terriers without respiratory disease that had thoracic CT scans. Dogs for this control group were excluded from the study if any pulmonary pathology or significant lung atelectasis was noted on CT, or if there was any history of respiratory disease in the database. Decisions for inclusion or exclusion for the control group were made by the first author (F.T.).

2.2 | Computed tomography data recorded

All CT studies from dogs with idiopathic pulmonary fibrosis and control patients were randomised and blinded reviewed by a board-certified veterinary radiologist (T.S.) and an imaging resident (F.T.), and scored by consensus. All assessments and measurements were performed using dedicated DICOM viewer software (OsiriX v5.8.5 64-bit, Geneva, Switzerland). A window width of 1400 Hounsfield units (HU) and a window level of –500 HU were used. Each hemithorax was divided into two zones: the upper lung zone dorsal to the level of the ventral wall of the trachea and the lower lung zone ventral to it. Each of the four lung zones were then graded on a scale from 0 to 3 by taking into account the main lung pattern (Table 1). The severity of each lung pattern was based on previously published data in human literature.[4,14,15] A grade 0 was equivalent to a normal pulmonary parenchyma, grade 1 (mild severity) equivalent to a ground-glass pattern defined as hazy increased attenuation with preservation of the bronchial and vascular margins. A grade 2 (moderate severity) was given if there was a ground-glass mosaic pattern (patchwork of regions of differing attenuation) or focal reticular pattern (complex network of curvilinear opacities) or any pulmonary consolidation or bronchiectasis defined as a lack of tapering of the bronchi. A grade 3 (marked severity) was equivalent to a generalized reticular pattern or honeycombing (subpleural cystic airspaces) or traction bronchiectasis (irregular bronchial dilatation with abnormal surrounding parenchyma) or nodular pattern. The four scores given for each study were then averaged and named as "CT score". Tracheal or main stem bronchial collapse was also recorded for each tomographic study.

Computed tomographic lung attenuation was objectively assessed by the first author (F.T.) by performing Hounsfield unit measurements. A total of 14 regions of interest of 4 mm^2 were placed in the pulmonary parenchyma of each tomographic study and Hounsfield units were recorded. The regions of interests were placed by avoiding any vascular structure and choosing the least affected or least consolidated area of the lung. One regions of interest was placed in the upper lung zone and lower lung zone of each hemithorax within the cranial

TABLE 1 Criteria used for grading severity of computed tomographic lung patterns in sampled dogs

Grade	Lung pattern
Grade 0 (normal)	Normal lung
Grade 1 (mild severity)	Ground glass pattern
Grade 2 (moderate severity)	Mosaic ground glass pattern, focal reticular pattern, pulmonary consolidation, or bronchiectasis
Grade 3 (marked severity)	Generalized reticular pattern, honeycombing, traction bronchiectasis, or nodular pattern
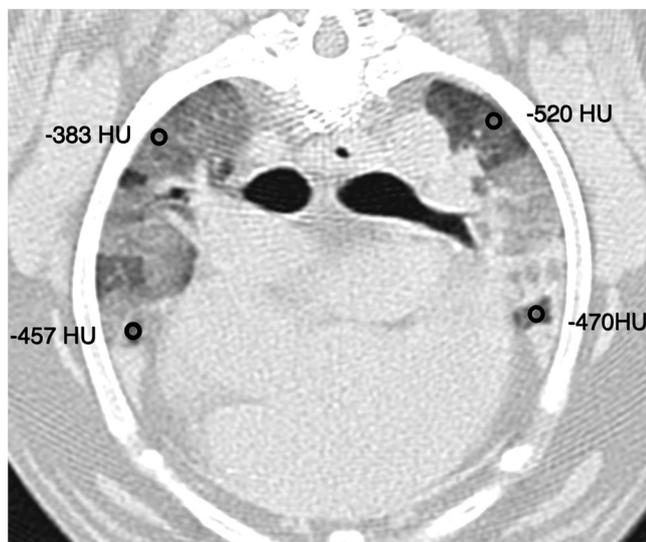
FIGURE 1 Thoracic computed tomographic images with four regions of interest placed within the pulmonary parenchyma at the level of the carina in a dog with idiopathic pulmonary fibrosis. Lung attenuation is specified in Hounsfield units (HU)

thorax (at level of 2nd rib), middle thorax (at level of carina), caudal thorax (at level of 8th rib), and within the accessory lung lobe (Fig. 1). A second set of regions of interest placements and Hounsfield unit measurements were performed by the same operator two months after the first set of measures in order to assess the intraobserver variability.

2.3 | Clinical data recorded

All clinical data were reviewed by a veterinary cardiopulmonary clinician (B.M.C.) unaware of the CT findings. Age, sex, duration of the clinical signs, previous treatment, results from clinical, echocardiographic, and radiographic examinations were recorded. Bronchoalveolar lavage with cytology and culture findings were also recorded. Postmortem histology of the lung, cause, and time of death were registered when available. Each clinical sign (cough, dyspnoea, exercise intolerance, and crackles) was scored for each animal. The scoring of exercise intolerance was based on anamnesis and scoring of dyspnoea and crackles was based on clinical examination. The scoring of cough relied on both information. For each of these clinical signs a score of 0–3 was assigned as follows: 0 = absence of the sign, 1 = mild severity of this sign, 2 = moderate severity, and 3 = marked severity. The four grades were then taken into account to establish the "clinical score", a whole number from 0 to 3.

2.4 | Data analyses

Statistical analyses were performed by two authors using commercial software [(SPSS 20 software for Macintosh, SPSS Inc, USA (F.T.) and R Core Team 2016, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria (I.H.)]. An intraclass correlation coefficient was computed to assess the reproducibility of the Hounsfield unit measurements with a confidence interval of 95%. Since the sample size was small, nonparametric tests were used. The Spearman rank correlation coefficient test was used to assess the correlation between the clinical, CT scores and survival time from diagnosis. The difference of lung attenuation in dogs with idiopathic pulmonary fibrosis compared to control dogs was assessed with a Mann–Whitney U test. The area under the receiver operating characteristic curve was calculated as a measure of diagnostic performance. To estimate uncertainty in this measure two approaches were used: a simulation of 10,000 data sets from the original data adding normally distributed noise using the variance estimated in the repeatability study, and a parametric estimation of the area under the receiver operating characteristic curve assuming idiopathic pulmonary fibrosis scores from case and control dogs were normally distributed with means from the observed data and variance adding the observed variance and repeatability variance. The critical significance level for statistical tests was set at 0.05.

3 | RESULTS

3.1 | Dogs

A total of 21 West Highland white terriers diagnosed with idiopathic pulmonary fibrosis were sampled. Six dogs were retrieved from the University of Edinburgh database over a 6-year period, 12 dogs were retrieved from the University of Glasgow database over a 3-year period, and three dogs were retrieved from the University of Pennsylvania database over a 3-year period. The clinical features (excluding survival time) of 15 dogs included in this study had been previously presented in a short communication.[9] In the group of West Highland white terriers diagnosed with idiopathic pulmonary fibrosis, the median age was 10 years old (N = 21, range: 7–14 years). A total of 11 West Highland white terriers were included in the control group (seven females and four males). These dogs presented for staging of pathology unrelated to respiratory disease and had no sign of respiratory disorder. The median age was 10 years (N = 11, range: 4–11 years).

3.2 | Computed tomography image acquisition parameters

Computed tomography images were acquired with third-generation helical and axial CT scanners [University of Edinburgh – helical slice CT unit (Somatom Volume Zoom, Siemens, Germany; University of Glasgow – axial CT unit (Exel 2400 elite, Elscint Automation, Surrey, UK); University of Pennsylvania – helical CT unit (GE ProSpeed, General Electric, Milwaukee, WI)]. Scan settings included slice thicknesses from 1 to 3 mm for all studies except one with 5 mm slice thickness, pitch between 1 and 2, X-ray tube potential 120 kVp, tube current 116–279 mAs, matrix 512 × 512, reconstructed with a high frequency algorithm (lung). High resolution CT images consisting of 1 mm slice-thickness, small field of view and high frequency algorithm were available in eight animals with idiopathic pulmonary fibrosis. Images were acquired under anesthesia during apnea following hyperventilation in order to avoid motion artifact.

3.3 | Descriptive computed tomographic and clinical findings

A total of 15/21 affected dogs presented with cough, 19/21 with exercise intolerance, 20/21 with dyspnoea, and all dogs had crackles on thoracic auscultation. The duration of clinical signs varied between 1 month and 4 years for 20 dogs (median: 6 months). Only one dog presented acutely with no previous history of respiratory disease. The median clinical score was 2 ($N = 21$, range: 1–3). 76% of dogs had concurrent signs of chronic bronchitis on bronchoscopy (16/21). Eleven dogs had mild changes on bronchoscopy, three had moderate changes, and two had marked nodular and oedematous changes within the bronchial mucosa. Bronchiectasis (6/21), tracheal collapse (13/21), and bronchial collapse (5/21) were also commonly documented on bronchoscopy. Bronchoalveolar lavage procedure was abandoned in one dog due to anesthetic complications. The cytology of bronchoalveolar lavage revealed chronic active inflammation in 17 dogs, defined as an increase in neutrophils and macrophages, and was normal in three animals. The clinical score in these last three dogs was respectively mild, moderate, and severe. The culture from bronchoalveolar lavage was positive with *Pasteurella multocida* in 3/20 dogs. The CT findings of these dogs with a positive culture were all graded as mild (CT score < 1.25). Three dogs presented with a neutrophilia ($N = 21$, range: 9.7 to 24.4 × 10^9 /L, range interval (RI) 6.6–12 × 10^9 /L). Biochemistry demonstrated raised alkaline phosphatase in most dogs ($N = 18/21$, range: 91–4948 U/L, RI: 20–60 U/L) among which at least eight dogs had previously received steroids, raised alanine aminotransferase ($N = 4/21$, range: 177–393 U/L, RI: 21–102 U/L), and raised urea ($N = 7/21$, range: 8.8–13 mmol/L, RI: 1.7–7.4 mmol/L). Twelve dogs had a normal venous blood gas (12/13) and one animal demonstrated a metabolic alkalosis secondary to respiratory acidosis. Arterial blood gas was performed in one dog that was hypoxemic (arterial partial pressure of oxygen at 55 mmHg). Four dogs examined had sign of mild pulmonary hypertension on echocardiography with a tricuspid regurgitation velocity superior to 2.8 m/s ($N = 12$, range: 3–3.6 m/s). These four

dogs presented with clinical signs of 2–9 months of duration, a clinical score varying from 1 to 3 and a CT score up to 1.25. On radiography, the most common finding was a generalized interstitial to bronchointerstitial pattern (17/17). On CT evaluation, the most common feature reported was ground-glass attenuation (16/21). A focal reticular pattern was noted in seven animals, a mosaic ground-glass in four dogs, and honeycombing pattern noted in two animals (Fig. 2). Parenchymal bands were visible in four animals, bronchiectasis in three and nodules in two others. Traction bronchiectasis was described in two animals. The median CT score was 1.25 ($N = 21$, range: 0–3). Time of death was available for 76% of dogs with idiopathic pulmonary fibrosis (16/21). Two dogs were still alive at the time of writing (113 and 453 days after diagnosis). The median survival time after diagnosis was 255 days ($N = 16$, range: 1–1375 days). The cause of death was known in six dogs and was related to respiratory failure for two of them. Postmortem histology of the lung was available in six dogs. Chronic interstitial fibrosis with type II pneumocyte hyperplasia was noted in three dogs, pleural or subpleural fibrosis in two, and chronic interstitial pneumonia in three. Alveolar macrophages were described in three dogs and alveolar thickening in two others.

3.4 | Comparisons between computed tomographic findings and clinical findings

Nine of the control dogs had mild pulmonary atelectasis on CT evaluation. All dogs of the control group were blindly given a CT score of 0. Among the dogs with idiopathic pulmonary fibrosis, the clinical score showed a moderate positive correlation to the CT score (Spearman, $N = 21$, $\rho = +0.48$, $P = 0.029$) (Fig. 3). We did not establish a correlation between the survival time and clinical score (Spearman, $N = 16$, $\rho = -0.35$, $P = 0.180$), but did find a moderate negative correlation between survival time and CT score (Spearman, $N = 16$, $\rho = -0.56$, $P = 0.025$).

The median lung attenuation in dogs with idiopathic pulmonary fibrosis was –563 HU ($N = 21$, range: –696 to –425 HU) and –761 HU ($N = 11$, range: –842 to –708 HU) in the control group (Fig. 4). The lung attenuation in dogs with idiopathic pulmonary fibrosis was significantly different from control dogs (Mann–Whitney U, $N_{IPF} = 21$, $N_{control} = 11$, $U = 231$, $P < 0.001$). By choosing a cut-off value of –702 HU over which all dogs are considered affected by idiopathic pulmonary fibrosis, we estimated the false positive rate as up to 7% with a sensitivity of 97%. An intraclass correlation coefficient was computed to assess the reliability of the lung attenuation measurements for the 32 dogs included in the study. This produced excellent intraobserver agreement for the lung densitometry measurements (ICC = 0.984, 95% confidence interval 0.967–0.992). The median difference between two measurements was 14HU ($N = 32$, range: 0–53 HU). There was no lung density overlap between the two populations of dogs and hence the empirical estimate of area under the receiver operating characteristic curve was 1.0. The simulation (adding repeatability noise) estimated the area under the receiver operating characteristic curve to be 0.994 (95% confidence interval 0.978–1.00) and the parametric estimate assuming normal distributions for idiopathic pulmonary fibrosis estimated the area under the receiver operating characteristic curve to be 0.985.
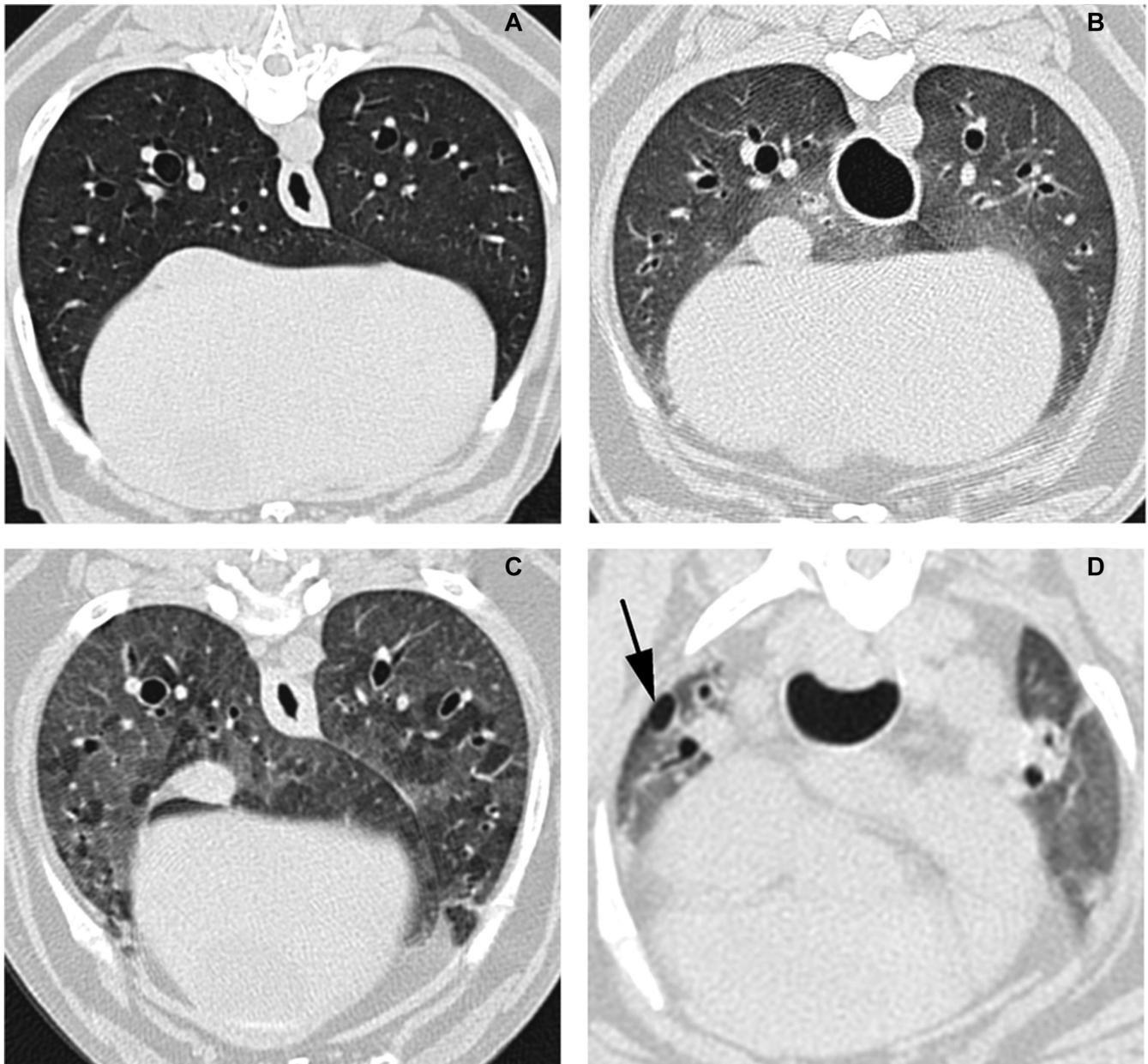
FIGURE 2 Thoracic computed tomographic images. (A) Normal dog graded as 0. (B) Generalized ground-glass attenuation graded as 1 (mild severity). (C) Generalized mosaic ground-glass pattern graded as 2 (moderate severity). (D) Focal honeycombing pattern in periphery of right cranial lung lobe (arrow) graded as 3 (marked severity) associated with focal adjacent bronchiectasis

4 | DISCUSSION

This is the first cross-sectional study demonstrating the correlation between the severity of the clinical signs of canine idiopathic pulmonary fibrosis and the severity of the abnormalities on CT. We also established that dogs with mild changes on CT are more likely to have a longer survival time. In human patients, the lung patterns on CT have been well classified depending on their specificity for usual interstitial pneumonia.[4,12,14,15] We based our grading scale on these previously published data. The appearance of idiopathic pulmonary fibrosis on CT in the dog is often described as a ground-glass pattern with a generalised hazy pattern.[8,10,11,16] This was confirmed in our study with 16 animal presenting this tomographic

feature. Focal reticular pattern and mosaic ground-glass pattern were common findings (10/21) and were considered as a feature of moderate severity (CT score of 2). Mosaic ground-glass pattern has not been previously described for the appearance of idiopathic pulmonary fibrosis on CT in West Highland white terriers and was present in 19% of the affected dogs in this study. Honeycombing is a severe reticular pattern commonly illustrated in advanced cases of human and canine idiopathic pulmonary fibrosis with subpleural location being most commonly described.[8,12,15] Compared to honeycombing observed in humans, the degree was very mild in our study population, consistent with a previous canine idiopathic pulmonary fibrosis study.[8] Nodules scattered throughout the lung parenchyma are described as well with canine idiopathic pulmonary fibrosis although appears less common.[5,8]
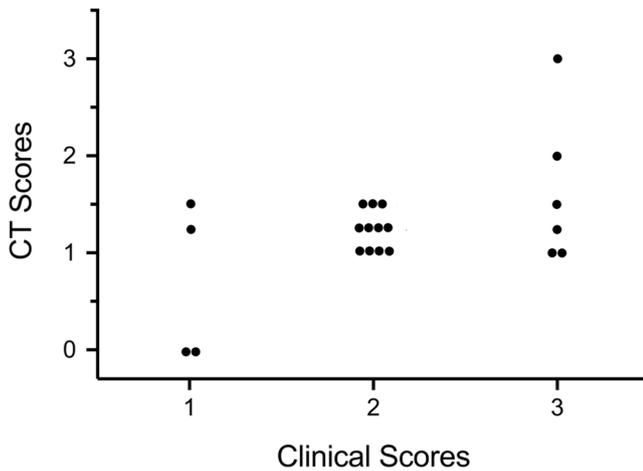
FIGURE 3 Clinical score and averaged CT score given for 21 West Highland white terriers with idiopathic pulmonary fibrosis as described in Table 1
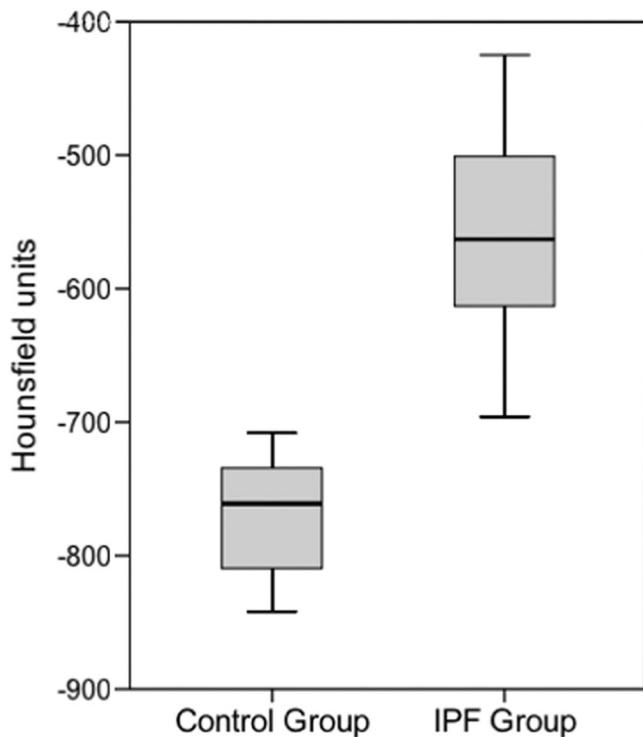
FIGURE 4 Box-plots representing the lung attenuation on CT (in Hounsfield units) in West Highland white terriers with idiopathic pulmonary fibrosis and in unaffected West Highland white terriers (P < 0.001)

Parenchymal bands representing atelectasis or fibrosis are common, but nonspecific findings within the pulmonary parenchyma on tomographic images. In a previous report the dorsal aspect of the lung parenchyma was reported to be more affected in dogs with idiopathic pulmonary fibrosis, but the current data identified more diffuse changes.[10]

There was a moderate positive association between the severity of the clinical signs and the severity of the lesions within the pulmonary parenchyma on CT, and this finding has not been demonstrated previously. While in human idiopathic pulmonary fibrosis, lung atten-

uation measurement is not considered reliable due to its dependence to the respiratory phase, the affected dogs had higher lung attenuation than control dogs.[10] Apnea following manual hyperventilation was induced in all dogs before scan acquisition, which may explain the good reliability of lung attenuation in our study. We chose to establish the cut-off value at −702 HU over which all dogs are considered affected by idiopathic pulmonary fibrosis. A previous study reported lower lung attenuation in dogs with idiopathic pulmonary fibrosis (mean: −735 HU, standard deviation: 55) compared to our data (mean: −563 HU, standard deviation: 74) but the measurement method was not described.[16] High lung attenuation in dogs with idiopathic pulmonary fibrosis is unfortunately not specific for this disorder, but we believe it can be used as an additional tool in the diagnostic process.

In this study, the survival time from diagnosis of dogs with idiopathic pulmonary fibrosis was not correlated to the severity of the clinical signs, but was negatively associated to the severity of the imaging findings. Indeed, advanced lesions on tomographic images tended to occur in dogs with shorter survival time. The median survival time after diagnosis was 8.5 months, which is slightly less than the previously published 13 months.[6] Due to the retrospective nature of the study, the cause of death was known in only a small number of dogs (6/16). It is possible the absence of correlation with the clinical signs could be related to the subjective nature of establishing a clinical score based on retrospective data. Computed tomographic findings are used in human medicine as a prognostic factor and it does appear to be feasible to do the same for idiopathic pulmonary fibrosis in West Highland white terriers.[4] Further studies with larger sample size are needed to confirm our preliminary findings.

In one-third of the dogs that underwent echocardiography (4/12), there were signs of mild pulmonary hypertension. This proportion is slightly lower than the previously reported prevalence of 44% in West Highland white terriers with interstitial disease.[17] These dogs with mild pulmonary hypertension appeared to have a wide range of severity of clinical signs from mild to severe but all of them had mild changes on tomographic images.

In the current study, 76% of dogs (16/21) had concurrent signs of chronic bronchitis. This comorbidity has previously been reported and is likely at the origin of the chronic active inflammation of the bronchoalveolar lavage fluid samples.[8,19-21] Determining if abnormalities on CT were attributed to another inflammatory process than idiopathic pulmonary fibrosis is an important issue. Most dogs had mild changes on bronchoscopy (11/16), which alone was not sufficient to explain the clinical signs of the animals of this study, and on that basis it was not unreasonable to decide that idiopathic pulmonary fibrosis was the primary diagnosis of clinical significance. In animals, the most common causes of interstitial lung disease are infectious agents, toxin exposure, high dose irradiation, immunologic, and neoplastic disorders, making tentative diagnosis much easier than for the same class of interstitial lung disease in human patient.[1] Additional risk factors have been described in human idiopathic pulmonary fibrosis such as smoking, or environmental exposures to specific dusts.[12] In the case of idiopathic pulmonary fibrosis-like diseases in people several are described based on histological appearance such as

usual interstitial pneumonia, acute interstitial pneumonia, desquamative interstitial pneumonia, or organising pneumonia.[5,15] Inflammation and fibroblast proliferation are common histologic features of these disorders.[5] Human usual interstitial pneumonia has been suggested to resemble idiopathic pulmonary fibrosis in West Highland white terriers, but the preponderance of ground glass opacity on CT, suggests early canine idiopathic pulmonary fibrosis more resembles human nonspecific interstitial pneumonia.[2,3,7] The limited histopathology from cases in this series and other reports would tend to support that assertion.[2,3,7] Histology findings in dogs include accumulation of alveolar macrophages, alveolar luminal changes, honeycombing of the alveolar architecture, thickening of the alveolar septa with oedema, fibroblast proliferation, proliferation of alveolar type II pneumocytes, but no evidence of myofibroblast foci (except in a few cases) that is diagnostic feature of true usual interstitial pneumonia.[2,5] A mosaic ground-glass and laterally a honeycombing pattern is found in moderate and severe forms of the canine disease, and more likely equates with usual interstitial pneumonia in human patients. In canine idiopathic pulmonary fibrosis there is overexpression of the cytokine chemokine ligand-2 (CCL2).[1,22,23] This cytokine acts on fibroblasts via an increased expression of transforming growth factor TGF-β, which then leads to accumulation of extracellular matrix and fibrosis.[2,3,23,24]

The retrospective nature of the study was a limitation. Some investigations such as echocardiography or arterial blood gases were not performed in all dogs. The unstable nature of the animals was the main reason for the missing data. High-resolution CT is recommended in human and veterinary literature for diagnosis of idiopathic pulmonary fibrosis.[8,14] This technique does not require specialised CT equipment but is a technique with thin slice thickness, a small field of view and high frequency reconstruction algorithm to maximise spatial resolution. Such tomographic acquisition was not available for all dogs in our study, which represents another limitation. A linear pattern with interlobular septal thickening superimposed on ground-glass opacity (so-called "crazy paving" appearance) has previously been reported on CT in dogs with idiopathic pulmonary fibrosis but was not seen in our study.[8] This type of pattern may only be highlighted by high resolution CT, which would explain its absence in our study. The absence of lung histology in 15 dogs is another limitation. We could not examine the association between pathological and CT features because of the small number of histology results. The nature of the pulmonary nodules detected on CT was not investigated due to their small size precluding a safe sampling. Performing lung biopsy is the gold standard for diagnosis of idiopathic pulmonary fibrosis but the invasiveness of the procedure makes its feasibility difficult.[18] Furthermore, this technique only allows assessing a small portion of the lung parenchyma, which may not be representative. The diagnosis of idiopathic pulmonary fibrosis is challenging. It is common practice to perform a diagnosis of exclusion from other cardiac or respiratory pathology (as has been done in this study).[8] The human 2011 idiopathic pulmonary fibrosis guidelines states that for patients not available for lung biopsies, a diagnosis of idiopathic pulmonary fibrosis only requires the exclusion of other known cause of interstitial lung disease and the presence of usual interstitial pattern on high resolution CT.[12]

In conclusion, findings from the current study support the use of thoracic CT as a diagnostic tool for grading of canine idiopathic pulmonary fibrosis and developing clinical prognoses. The severity of the clinical signs of canine idiopathic pulmonary fibrosis was correlated to the severity of the abnormalities on CT in this sample of dogs. A generalized ground-glass pattern was determined to be a sign of a mild form of canine idiopathic pulmonary fibrosis, whereas mosaic ground-glass and mild honeycombing patterns was identified in moderate and severe forms of the disease. Dogs with mild changes on CT were more likely to have a longer survival time. Future investigations are needed to more definitively characterize the benefits of CT as a prognostic tool and method for assessing treatment response in dogs with idiopathic pulmonary fibrosis.

LIST OF AUTHOR CONTRIBUTIONS

Category 1

(a) Conception and Design: Thierry F, Handel I, Hammond G, Corcoran BM, Schwarz T

(b) Acquisition of Data: Thierry F, Hammond G, King LG†, Corcoran BM, Schwarz T

(c) Analysis and Interpretation of Data: Thierry F, Handel I

Category 2

(a) Drafting the Article: Thierry F

(b) Revising Article for Intellectual Content: Thierry F, Handel I, Hammond G, Corcoran BM, Schwarz T

Category 3

(a) Final Approval of the Completed Article: Thierry F, Handel I, Hammond G, Corcoran BM, Schwarz T

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CONFLICT OF INTEREST

There are no conflicts of interest or disclaimers to report.

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