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Influence of concurrent lower respiratory tract disease on point-of-care lung ultrasound in small-breed dogs with myxomatous mitral valve disease

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Abstract

Background: Small-breed dogs commonly have concurrent myxomatous mitral valve disease (MMVD) and lower respiratory tract disease (LRTD).

Hypothesis: Small-breed dogs with preclinical MMVD and concurrent LRTD have more B-lines on point-of-care lung ultrasound (POC-LUS) compared to dogs without concurrent LRTD and are prone to misdiagnose as cardiogenic pulmonary edema (CPE).

Animals: A total of 114 small-breed dogs with preclinical MMVD.

Methods: A prospective study was conducted, in which POC-LUS was obtained and the number of B-lines was calculated by a single clinician using the Veterinary Bedside Lung Ultrasound Examination protocol. The presence/absence of LRTD was assessed by clinicians blinded to the POC-LUS results.

Results: Fifty and 64 dogs were in ACVIM stage B1 and B2, respectively. The presence of LRTD was prevalent in 74.6% (85/114) of small-breed dogs with preclinical MMVD. When a previously reported criterion for CPE diagnosis (≥2 sites with >3 B-lines/site) was applied, false-positive results were observed in 15.8% (18/114) of dogs with preclinical MMVD. The summated number of B-lines (3 vs. 1, $P = .003$), as well as the false-positive rate (20% vs 3%, $P = .04$), were significantly higher in dogs with LRTD compared with dogs without LRTD. Multivariable logistic regression showed the presence of abnormalities other than B-line on POC-LUS (eg, thickened pleura or consolidation) could predict false-positive results (odds ratio = 3.75, 95% confidence intervals 1.12-12.54; $P = .03$) after adjustment for other clinical and echocardiographic factors.

Conclusions and Clinical Importance: Concurrent LRTD and abnormalities other than B-lines should be considered in the interpretation of POC-LUS in MMVD dogs.

KEYWORDS
airway, canine, cardiogenic pulmonary edema, congestive heart failure, lower respiratory tract disease, lung ultrasound, mitral valve disease, small-breed dogs

Abbreviations: CI, confidence intervals; CPE, cardiogenic pulmonary edema; LA, left atrium; LRTD, lower respiratory tract disease; LV, left ventricle; MMVD, myxomatous mitral valve disease; OR, odds ratio; POC-LUS, point-of-care lung ultrasound; Vet BLUE, Veterinary Bedside Lung Ultrasound Examination.

1 | INTRODUCTION

Myxomatous mitral valve disease (MMVD) is the most common cardiovascular disease in small-breed dogs, and it might eventually progress to congestive heart failure in some affected dogs.[1-5] Thoracic radiography can be helpful to identify cardiogenic pulmonary edema (CPE), but the associated manipulation in emergency condition might exacerbate respiratory distress in critically ill animals. Instead, point-of-care lung ultrasound (POC-LUS) has the advantage to quickly assess animals with minimal restraint.[6-9] The Veterinary Bedside Lung Ultrasound Examination (Vet BLUE), a scanning protocol of POC-LUS modified from BLUE protocol in human medicine, has been studied for applications in small animals with respiratory distress.[8,10-15] By recognizing the presence and the pattern of B-lines (comet-tail-like vertical hyperechoic artifacts), Vet BLUE has been reported to be useful for differentiating CPE and noncardiac causes of respiratory distress in dogs and cats.[8,11-13,16]

The number of B-lines is commonly used to define the severity on POC-LUS.[8,10,17] The criteria for the diagnosis of CPE by POC-LUS in previous veterinary studies were developed using evidence-based recommendations in human medicine field.[18] A cutoff criterion to identify CPE in dogs or cats with respiratory distress is to have at least 2 strong-positive sites (defined as >3 B-lines in a scanning site) on each hemithorax, representing ≥4 strong-positive sites out of 8 Vet BLUE scanning sites.[12,13] Alternatively, the diagnostic cutoff value for B-lines in nonemergency dogs with cough was lower—having ≥2 strong-positive sites out of 8 Vet BLUE scanning sites.[19] However, it was reported in previous studies that various etiologies other than CPE can also produce increased B-lines on POC-LUS, such as acute respiratory distress syndrome, lung cancer, heartworm-associated pneumonitis, pneumonia, pulmonary hypertension, pulmonary thromboembolism, and airway disease.[12,14,19] Small-breed dogs are also well-known to have high prevalence of respiratory disease, thus it is not uncommon for geriatric small-breed dogs to suffer from concurrent cardiac and respiratory disease.[4,20-23] Currently, it is unclear how the presence or absence of lower respiratory tract disease (LRTD) would influence the assessment of CPE on POC-LUS in small-breed dogs with MMVD.

The objective of this study was to examine the influence of concurrent LRTD on the POC-LUS in small-breed dogs with MMVD. The findings of B-lines and a previously described POC-LUS scanning protocol for determining the presence of CPE[8,11-13,19] were evaluated in small-breed MMVD dogs that were not yet developed of congestive heart failure. It was hypothesized that the number of B-lines on POC-LUS in small-breed dogs with concurrent LRTD and preclinical MMVD would be significantly higher than in preclinical MMVD dogs without LRTD. It was also hypothesized that small-breed dogs with concurrent LRTD and MMVD are prone to misdiagnose as CPE by commonly used criteria of POC-LUS.

2 | MATERIALS AND METHODS

2.1 | Animals and study design

Client-owned dogs presented to the small animal respiratory medicine and cardiology service at a university teaching hospital for various purposes (eg, annual echocardiography follow-up, preanesthesia evaluation, new outpatients with signs of respiratory or cardiovascular disease, recheck visits, consultation requested by other specialists or general practitioners, or health examination) were prospectively recruited between August 2018 and June 2020. The following were the inclusion criteria for this study: (a) the breed should belong to small breeds of dogs or be a mongrel breed weighing less than 15 kg[24]; (b) the dog should be diagnosed with preclinical stage B MMVD based on ACVIM consensus statement guidelines[4] by senior clinicians who are experienced in echocardiography and cardiorespiratory specialty service at the time when POC-LUS scanning was performed; (c) a clinical assessment for the respiratory system including history evaluation, physical examination, thoracic radiography, and other advanced diagnostics whenever necessary (eg, bronchoscopy, endotracheal wash or bronchoalveolar lavage, thoracic computed tomography, or pulmonary function testing) made by senior clinicians who were unaware of the results of POC-LUS findings should be available; (4) the dog's owner must sign an informed consent and agree with the POC-LUS scanning, which was not associated with the dog's diagnostic workup. Dogs with a recent history of trauma, dogs with a condition associated with pain response that might disturb the assessment of their clinical signs, dogs that were not cooperative for ultrasonographic scanning, or cases without sufficient information for clinicians to make a judgment of the presence or absence of LRTD were excluded from the study. The study was approved by the Institutional Animal Care and Use Committee (Approval No: NTU106-EL-00209) at the authors' institutions.

The POC-LUS scanning using the Vet BLUE protocol[8,12,13,19] was performed by a single clinician (M-C Lam) who was unaware of the conclusion from clinical assessment at the time of scanning. This operator had completed training for the Vet BLUE protocol for LUS and had demonstrated adequate skill during 6 supervised examinations. In brief, the dog was scanned while standing or in sternal recumbency. The hair was not clipped before the examination, and a little sprayed water and then ultrasound gel were applied to ensure the probe contact. The ultrasound probe was held horizontally at each of the 4 Vet BLUE scanning sites (caudal, perihilar, middle, and cranial) on the left and the right thorax (Figure 1). Several ultrasound equipments (EPIQ 7, Philips; MyLab50, Esaote; C7 Vet, Clarius) were used in the cardiorespiratory service, and the transducer for POC-LUS scanning was chosen to use a convex type of probe with frequency of 5-10 MHz. For each scanning site, the imaging was optimized according to the instruction from previous studies,[8,10,12] such as adjusting depth, setting adequate total, near- and far-field gains, and placing the focal zone close to the pleural level. Cine loops were saved for the subsequent analysis.

The severity of B-lines at each scanning site was assessed and recorded as 0, 1, 2, 3, > 3, or confluent (multiple B-lines that no longer discernable as individual B-lines).[8,11,12,14,19] For the purposes of quantifying and comparing the previous and current study, > 3 and confluent B-lines were counted as 4 and 10 B-lines, respectively.[13,16,19] A site with >3 or confluent B-lines was defined as a strong-positive site, and a previous criterion for CPE diagnosis (with ≥2 strong-positive

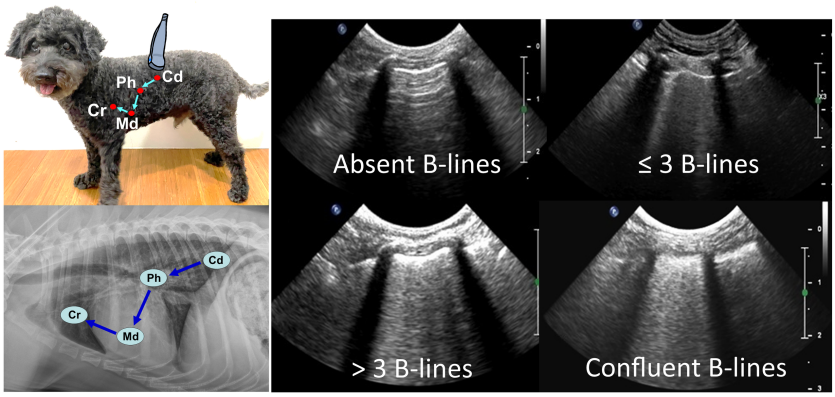

FIGURE 1 Illustration of the Vet BLUE scanning sites (Cd: caudal, Ph: perihilar, Md: middle, Cr: cranial) and the severity of B-lines

sites among a total of 8 scanning sites) with POC-LUS was used to examine the false-positive rate in dogs without CPE.[19] The presence of other abnormalities (eg, focal consolidation, irregular or thickened pleura) from the saved images was recorded as well.

Clinical assessment for the respiratory and cardiovascular systems was performed by 2 clinicians (C-H Lin and P-Y Lo) who were blind to the POC-LUS data. History-taking, physical examination, thoracic radiography, echocardiography, pulmonary function testing, and other necessary diagnostics were proceeded based on each dog's condition. The diagnosis and the categorization of preclinical stage B MMVD was made according to the recommendations from 2019 ACVIM consensus statement guideline[4]: Stage B1 MMVD was diagnosed by (a) auscultation of a heart murmur typical of mitral regurgitation; (b) medical history indicating that the dog is asymptomatic for MMVD and has never had clinical signs of heart failure (congestive heart failure from increased venous pressures or forward failure during exercise or at rest); and (c) imaging findings (thoracic radiography with or without echocardiography) suggesting that LA and LV are normal or not enlarged enough to meet criteria for medical treatment. Stage B2 MMVD was diagnosed by (a) auscultation of ≥3/6 intensity murmur typical of mitral regurgitation; (b) medical history indicating that the dog is asymptomatic for MMVD and has never had clinical signs of heart failure; and (c) echocardiographic evidence for left atrium (LA) and left ventricle (LV) enlargement (2D LA to aorta ratio ≥ 1.6 at right parasternal short-axis view; normalized LV diameter in diastole ≥1.7 with dimension measured by 2D short-axis-guided M-mode). These 2 clinicians were requested to complete a case report form regarding clinical signs, thoracic radiographic findings, echocardiographic data, the presence or absence of LRTD, and the stage of MMVD after assessing each case.

2.2 | Statistical analysis

Statistical analyses were performed using commercial software (MedCalc, version 19.6, MedCalc Software, Ostend, Belgium). Data with continuous variables were presented as median and range, and categorical data were reported as frequency rates and percentage. The numbers of B-lines on POC-LUS between preclinical MMVD dogs with and without LRTD were compared using the Mann-Whitney rank sum test. The definition of "misdiagnosis" or "false-positive POC-LUS result for CPE" in this study was a POC-LUS result matching the criterion for CPE diagnosis (with ≥2 strong-positive sites among a total of 8 scanning sites) in a dog without congestive heart failure. The proportion of false-positive results between dogs with and without LRTD were compared using the Mann-Whitney rank sum test. Logistic regression models employing Enter method as a direct approach (all variables are entered into the model at the same time and applies no assumptions about the ranking of the variables) were used to identify clinical, echocardiographic, and LUS factors that might help predict a false-positive POC-LUS result in MMVD dogs.[25] The factors with P value <.15 in the univariable logistic regression model were selected into the multivariable logistic regression model in 1 single step without elimination of variables that became non-significant. Statistical significance was defined as $P < .05$.

3 | RESULTS

Seven hundred sixty-four dogs were screened for enrollment during August 2018 and June 2020 (Figure 2). A total of 114 small-breed dogs with preclinical MMVD were enrolled in the final analysis, including 64 and 50 dogs in the ACVIM stages B2 and B1, respectively. Small breeds in this study consisted of 37 Maltese Terriers, 20 Miniature and Toy Poodles, 10 Pomeranians, 8 Yorkshire Terriers, 7 Miniature Schnauzers, 6 Shih Tzus, 6 cross-breeds, 5 Chihuahuas, 5 West Highland White Terriers, 5 Japanese Spitzs, 3 Miniature Dachshunds, and 1 each of Pug and Sheltie. There were 46 (40%) females. The ages ranged from 2.5 to 17 years with a median of 12 years. The body weight ranged from 1.2 to 10.2 kg with a median of 4.1 kg, and the median 9-point body condition score was 5 (range, 3-8).

Among the 114 small-breed dogs, 18 fit the criteria of CPE diagnosis with POC-LUS, representing a false-positive rate of 15.8% in MMVD dogs not yet developed congestive heart failure. Ninety-two percent of dogs had at least 1 clinical sign possibly associated with the respiratory or cardiovascular systems, including coughing (97, 85.1%), noisy breathing (36, 31.6%), excessive panting (15, 13.2%), labored breathing (15, 13.2%), cyanosis (8, 7.0%), tachypnea (6, 5.3%), nasal discharge (4, 3.5%), syncope (2, 1.8%), reverse sneezing (1, 0.9%), and hemoptysis (1, 0.9%). The presence of

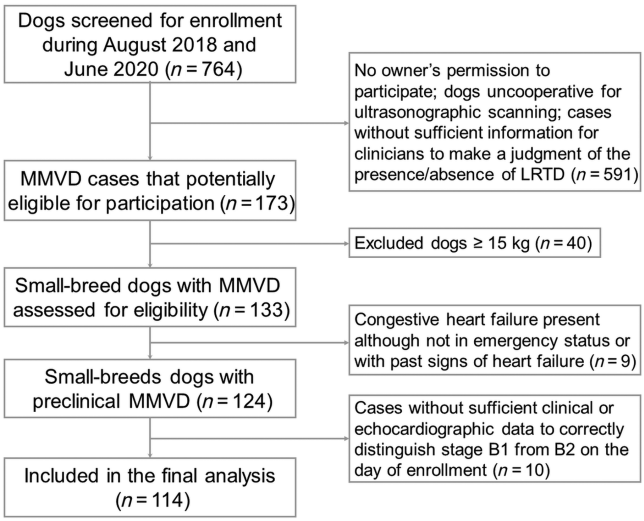

FIGURE 2 Flowchart illustrating the enrollment of the cases in the study. LRTD, lower respiratory tract disease; MMVD, myxomatous mitral valve disease

LRTD was diagnosed in 85 preclinical MMVD dogs with a prevalence of 74.6% after clinical assessment for the respiratory and cardiovascular system. Twenty-three of the 85 dogs with concurrent LRTD in the present study had diagnostic workups under general anesthesia for further clarifying the exact etiology of LRTD. The most common diagnoses were bronchomalacia (19/23) and inflammatory airway disease (IAD; 17/23), and >1 respiratory disease category was frequently seen in these dogs (eg, had both bronchomalacia and IAD).

The summated number of B-lines in 8 Vet BLUE scanning sites on POC-LUS was found to be significantly higher ($P = .003$) in stage B MMVD dogs with concurrent LRTD (3; range, 0-58) compared to stage B MMVD dogs without concurrent LRTD (1; range, 0-27; Table 1). The false-positive rate in stage B MMVD dogs was also significantly higher among dogs with concurrent LRTD than in dogs without concurrent LRTD (20.0% vs 3.4%, $P = .04$).

Considering clinical, echocardiographic, and LUS factors, univariable logistic regression revealed that the false-positive result on POC-LUS was significantly correlated with elevated transmitral E-wave velocity (≥ 1.2 m/s; $P = .01$) and the presence of

TABLE 1 Signalment and point-of-care lung ultrasound (POC-LUS) data in small-breed dogs with and without lower respiratory tract disease (LRTD)

	Small-breed dogs with preclinical stage B MMVD		
Variables	**Presence of LRTD (n = 85)**	**Absence of LRTD (n = 29)**	***P***
Age (years)	12.0 (6.0-17.0)	12.0 (2.5-16.0)	.2
Body weight (kg)	4.1 (1.2-9.8)	4.0 (2.0-10.2)	.56
Body condition score (9-point)	5 (4-7)	5 (3-8)	.13
Summated number of B-lines (sum of 8 sites)	3 (0-58)	1 (0-27)	.003*
Numbers of strong positive sites (8 scanning sites)	0 (0-7)	0 (0-2)	.003*
False-positive as CPE (≥2 sites with >3 B-lines/site; %)	20 (17/85)	3.4 (1/29)	.04*
With abnormalities other than B-line on POC-LUS (%)	25.9 (22/85)	0 (0/29)	<.001*

Note: Data are presented as median with range, or percentage with numbers. Significant differences ($P < .05$) are denoted with an asterisk (*).
Abbreviations: LRTD, lower respiratory tract disease; MMVD, myxomatous mitral valve disease; POC-LUS, point-of-care lung ultrasound.

TABLE 2 Logistic regression analyses of clinical, echocardiographic, and lung ultrasound (LUS) factors predictive of the false-positive result of cardiogenic pulmonary edema (CPE) on point-of-care lung ultrasound (POC-LUS)

	Univariable analysis			Multivariable analysis		
Clinical, echocardiographic, and LUS factors	**Crude OR**	**95% CI**	***P***	**Adjusted OR**	**95% CI**	***P***
Age (years)	1.07	0.89 to 1.29	.47	NA	NA	NA
Body weight (kg)	1.05	0.82 to 1.34	.7	NA	NA	NA
Body condition score (9-point)	0.79	0.39 to 1.60	.51	NA	NA	NA
With concurrent LRTD	7.0	0.89 to 55.2	.06	4.09	0.48 to 35.1	.2
MMVD stage B2 (vs B1)	2.40	0.85 to 6.73	.1	1.45	0.35 to 5.94	.61
Transmitral E velocity ≥ 1.2 m/s	4.06	1.33 to 12.4	.01*	2.33	0.20 to 26.7	.5
With pulmonary vein enlargement	2.86	1.00 to 8.15	.05	0.89	0.08 to 9.64	.93
With pulmonary hypertension	0.69	0.23 to 2.03	.5	NA	NA	NA
With abnormalities other than B-line	6.38	2.14 to 19.1	<.001*	3.75	1.12 to 12.5	.03*

Note: The factors with $P < .15$ in the univariable logistic regression model were selected into the multivariable logistic regression model. Significant differences ($P < .05$) are denoted with an asterisk (*).
Abbreviations: LRTD, lower respiratory tract disease; LUS, lung ultrasound; MMVD, myxomatous mitral valve disease; NA, Not applicable (not included in multivariable model).

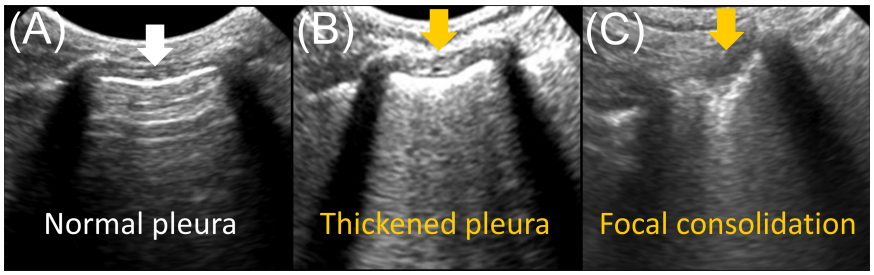

FIGURE 3 The presence of abnormalities other than B-line (eg, thickened/irregular pleura or consolidation) on point-of-care lung ultrasound (POC-LUS) was a significant factor for predicting the false-positive result when using a previously reported criterion (≥ 2 sites with >3 B-lines/site) for diagnosis of cardiogenic pulmonary edema (CPE) in small-breed dogs with preclinical myxomatous mitral valve disease (MMVD). (A) Normal pleura; (B) thickened pleura; and (C) focal consolidation

abnormalities other than B-line on POC-LUS (eg, thickened pleura or consolidation; $P = .0009$; Table 2). After adjustment for possible confounding factors through multivariable logistic regression, the presence of abnormalities other than B-line on POC-LUS (Figure 3; adjusted odds ratio (OR) = 3.75, 95% confidence interval (CI) 1.12-12.54; $P = .03$) was a significant factor for predicting the false-positive POC-LUS result in small-breed dogs with preclinical MMVD.

4 | DISCUSSION

The results of the present study support the hypothesis that small-breed dogs with concurrent LRTD and preclinical MMVD have higher numbers of B-lines on POC-LUS and are more likely to be misdiagnosed as CPE than in preclinical MMVD dogs without LRTD. This information is important when applying POC-LUS as a part of clinical assessment, especially in MMVD dogs that belong to ACVIM stage B2 but have a tendency to progress to stage C (congestive heart failure).

LUS profiles on MMVD dogs in a previous study showed that B-lines are only rarely present in stage B1 (n = 15) and B2 (n = 18); however, the body weight of those preclinical MMVD dogs ranged from 3.5 to 40 kg, which included not only small breeds.[26] The presence of B-lines is variably observed in dogs with a clinical history of cough, and the etiologies include tracheobronchomalacia, bronchitis, pneumonia, lung cancer, and CPE.[19] The prevalence of LRTD and MMVD are both relatively high in small-breed dogs, which leads to a diagnostic challenge in this cohort.[2,3,20,21,27-29] Based on our results, concurrent LRTD existed in 74.6% of small-breed dogs with preclinical MMVD. Therefore, the influence of LRTD on the findings of POC-LUS cannot be ignored, and it is probably more challenging to make a judgment in a dog with respiratory distress, LA enlargement, and the known progression of the previous MMVD. Clinicians should be aware that the increase of B-lines is not necessarily the evidence for CPE in small-breed MMVD dogs with history or physical examination findings suggestive of concurrent LRTD.

The so-called B-line is a type of artifact generated by the acoustic impedance gradient between tissue-air or fluid-air interface.[6,18,30,31] Except for pulmonary edema, B-lines are also well-known to be present in cases with lung contusion, pneumonia, and alveolar-interstitial syndrome.[12,14,19,30] Strong-positive B-line sites can be present in some coughing dogs with airway diseases in a recent study.[19] Considering the body size of small-breeds, it is suspected that the increased B-lines in our dogs with LRTD might be related to their smaller diameters of lower airways, which makes it easier to generate air-tissue/fluid interface in the presence of bronchial mucus or mucosal edema compared to larger-sized airways. However, this cannot be concluded from this study.

The most prevalent etiology of LRTD in our study cohort was bronchomalacia. Dynamic airway collapse (tracheal or bronchial collapse) was also 1 of the subgroups that showed B-lines on POC-LUS in a previous study, but it was unclear for the percentages of tracheomalacia, tracheobronchomalacia, and bronchomalacia in these dogs.[19] Although bronchomalacia is not currently known as a disease involving alveoli and interstitium, we suppose that the aeration in different parts of the lung lobes might be variably affected by the dynamic collapse of bronchi, resulting in the ongoing change of the acoustic impedance and subsequent B-line artifacts.

Concurrent occurrence of MMVD and LRTD is an unavoidable reality in small-breed dogs. Considering the existence of LRTD could increase the numbers of B-lines on POC-LUS, the next important question is how clinicians could actively lookout for the possibility of a false-positive result while applying POC-LUS for aiding CPE diagnosis. Our study results from multivariable logistic regression analysis revealed that the most important factor helping to predict a misdiagnosis is the finding of abnormalities other than B-line on POC-LUS. In small-breed dogs with MMVD, the finding of irregular/thickened pleura or focal consolidation on LUS indicates that it is 3.75 times more likely to be a misdiagnosis of CPE than in dogs without abnormalities other than B-lines. Focal consolidation, described as "subpleural shred sign" on POC-LUS, has also been found to be associated with non-CPE etiologies in previous studies.[12,13,15,19,32,33] Therefore, it should be brought in mind that recognizing abnormalities other than B-lines on LUS is critically important for an accurate assessment in small-breed dogs with MMVD.

This study has some limitations. First, not all dogs with LRTD received bronchoscopic examination because of the owners' concerns about anesthetic risk and cost. Consequently, although bronchomalacia was frequently observed in cases with bronchoscopy, its association

with the increase of comet tail artifacts needs further investigations. Second, all dogs were in preclinical stage B of MMVD in our study. It is unclear whether the findings of this study could be extrapolated to MMVD dogs with previously controlled CHF. Third, it is also unknown whether the phenomena found in this study would also occur in large-breed dogs or in dogs weighing greater than 15 kg. Finally, although all POC-LUS examinations were performed by 1 single clinician, > 1 ultrasound machines were used in our clinical settings. It has been introspected that the machine settings or different probes might affect the assessment of B-lines in recent studies.[34,35] However, this effect should have been minimized by the process of imaging optimization on each scanning in our study.

In conclusion, concurrent LRTD and abnormalities other than B-lines should be considered in the interpretation of POC-LUS in small-breed MMVD dogs that are likely to develop congestive heart failure.

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CONFLICT OF INTEREST DECLARATION

Authors disclose no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) APPROVAL DECLARATION

Approved by the National Taiwan University IACUC (Approval No: NTU106-EL-00209).

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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