Feline Pleural Effusions: Prevalence and Radiographic Signs Predicting Disease Aetiology

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Abstract

Background:

The objectives of the study were to determine the prevalence of underlying conditions causing pleural effusion in cats and to calculate the positive predictive values, negative predictive values, sensitivity and specificity of radiographic signs.

Methods:

Data from 151 cats diagnosed with pleural effusion with known aetiologies were retrospectively analysed. Seventy-one patients' thoracic radiographs were available for a prospective, blinded evaluation by two radiologists.

Results:

Congestive heart failure (52.3%) was the most common diagnosis, followed by neoplasia (21.9%), pyothorax (10.6%), idiopathic chyloous effusion (5.3%), feline infectious peritonitis (1.3%) and Other or cats with multiple diagnoses (total 9.3%). Cats with an enlarged cardiac silhouette had a high positive predictive value of congestive heart failure (73% and 81% for radiologist 1 and 2 respectively). The presence of unilateral effusion was highly predictive of pyothorax (75%) for radiologist 1 and poorly predictive (20%) for radiologist 2. Mediastinal masses (100%, 83% for radiologist 1 and 2 respectively), pulmonary nodules (50%, 50%) and pulmonary masses (50%, 67%) had moderate probabilities of neoplasia. The remainder of the radiographic variables were not informative predictors of underlying disease.

Conclusions:

In our population of cats, congestive heart failure was the most common cause of pleural effusion. Radiographically enlarged cardiac silhouette, presence of a mediastinal mass and unilateral effusion may be useful predictors of aetiology. Limitations of radiography alone as a diagnostic tool are discussed.

Background

Pleural effusion can be a life-threatening condition caused by altered fluid dynamics leading to abnormal accumulation of fluid between the visceral and parietal pleura¹⁻⁴. Whilst pleural effusion may be straightforward to detect, understanding the primary cause may require multiple diagnostic tests including radiography, sonography, echocardiography, computed tomography (CT), biochemical and cytological assessment of pleural effusion¹. Rapidly determining the underlying cause allows for accurate prognostication and treatment, as these patients are considered acute emergencies which may require immediate thoracocentesis and prioritisation of diagnostics to prevent respiratory arrest.

Radiography remains an important and initial diagnostic tool to assess thoracic disease in cats. Studies in cats with pyothorax, chylothorax and neoplasia suggest that radiographic signs are generally non-specific⁴, but there are no structured investigations of the usefulness of radiographic signs in predicting disease type.

The aims of this study were to determine the prevalence of underlying conditions causing pleural effusions in cats and assess sensitivity, specificity, positive and negative predictive values of radiographic signs for the various underlying aetiologies.

Materials And Methods

Sampling strategy

Clinical records of cats with pleural effusion were recruited retrospectively from 2009 to 2020 across several referral Veterinary hospitals. All veterinary hospitals were located within a 10km radius of metropolitan Perth. Majority of the cases (n=138) were obtained from a single multi-disciplinary specialist hospital (Perth Veterinary Specialists, Perth, Western Australia, Australia). Inclusion criteria were the presence of pleural effusion (confirmed on thoracic ultrasound, CT, radiography or positive thoracocentesis) with a definitive or presumptive diagnosis documented by the primary clinician after assessment of all available diagnostic data (clinical parameters, cytology, histopathology, imaging modalities, treatment response). Exclusion criteria included any cat with thoracic disease without pleural effusion, and cats lacking comprehensive investigations into the cause of the pleural effusions with a lack of a presumptive or definitive diagnosis. Data collected for the study included signalment (age, breed, sex), diagnostic imaging results (radiography, echocardiography, thoracic ultrasound, CT assessment of the thorax), fluid analysis (cytological, biochemical, tissue histopathology, fluid culture). Due to the retrospective nature of the study, not all diagnostic tests were performed in every patient.

Cats were classified by underlying aetiology according to the following criteria:

1. Congestive heart failure (CHF): left atrium to aorta ratio larger than 1.64^{5,6} and/or left atrium on right parasternal long axis view >16.8mm diameter⁵, with the echocardiography performed by a board-certified or board-eligible radiologist, or by a resident in training with direct supervision. In some cases, these measurements were taken retrospectively from the echocardiogram reports and echocardiogram images.
2. Neoplasia: Either cytological or histopathological evidence of neoplasia or sonographic and/ or CT evidence of a solid and vascular mass. Cytology and histopathology of neoplastic disease was assessed by board certified pathologists and sonographic assessment of masses was performed by board certified or resident radiologists with direct supervision by a board-certified radiologist.
3. Pyothorax: detection of septic exudate on cytology and/or detection of intracellular bacteria on cytology or presence of a positive bacterial culture by an external Veterinary laboratory with board certified pathologists⁷.

4. Idiopathic chylothorax: cytological findings on effusion (predominance of small lymphocytes and non-degenerative neutrophils with background chylomicrons) and elevated triglycerides ($>1.13\text{mmol/L}$). All cats had an echocardiograms performed which did not identify cardiac disease, and without a history of trauma or evidence of neoplasia⁸.
5. Feline infectious peritonitis: presence of translucent, yellow protein-rich pleural effusion (positive on Rivalta's test), with pyrexia, non-specific lethargy, weight loss, and young age (less than 1 years old)⁹. Cats with positive immunohistochemical staining of FCoV antigen in tissue macrophages or fluid cytology (direct IFA), FIP RT-PCR assays were also included.
6. Other: cats not meeting the above criteria, with an alternative aetiology identified by the clinician or resolution of clinical signs after treatment trial on the presumed diagnosis.
7. Concurrent disease: two or more diseases as a potential cause of pleural effusion according to the above criteria.

Radiographic assessment

For inclusion into the study, patients must have at least two orthogonal projections of diagnostic quality. Radiographs were excluded if only a single projection was available, or if artefacts such as movement or poor collimation were present. Radiographs from each patient were reviewed by two boarded radiologists. Both radiologists' results were used in the assessments of predictive values, sensitivity, specificity, inter and intra-observer agreeability. All observers were blinded to the diagnosis(es) associated with the clinical record. The participants could select "cannot assess" if they deemed it not possible to visualise a particular radiographic sign (Figure 1 [Insert Figure 1]). For measurements of intra-observer agreement, participants were provided a randomised selection of 10 radiographs one month after the initial assessment for reassessment.

The reviewers evaluated the cardiac silhouette size, distribution of the pleural effusion and size of great vessels and pulmonary vasculature, and assessed the mediastinal, pleural space, thoracic wall, and extra-thoracic structures for abnormalities. An enlarged cardiac silhouette was defined using the vertebral heart score of VHS greater than 8¹⁰ (Figure 2 [insert Figure 2]), and/or comparisons of base to apex dimensions against the length of the sternbrae 2 to 4¹¹ (see Figure 2) and/or subjective assessment of left atrial dilation causing altered cardiac shape (e.g. valentine shaped heart and slipper shaped heart¹⁰). To date, there are no established objective measurements of radiographic left atrial dilation for cats. Pulmonary vasculature was assessed by comparing the relative size of the pulmonary artery to the pulmonary vein¹⁰ and/or by comparison to the width of the 4th rib on the lateral projection (cranial lobe vessels)¹² (Figure 3a [Insert Figure 3a]) and 9th rib on the VD or DV (caudal lobe vessels)^{12,13} (Figure 3b [Insert Figure 3b]). The cranial lobar vessels were enlarged if they were more than 0.7 times the proximal third of the fourth rib¹². The caudal lobar vessels were subjectively assessed (as there are no reported normals¹² in the feline patient) and were considered enlarged if they were more than 1:1 ratio of the 9th rib¹³ at their intersection. A mediastinal mass was suspected if there was widening of the mediastinum by a large soft tissue opacity that caused deviation of mediastinal structures (trachea, oesophagus), and focal lateral

and caudal displacement of the cranial lung margins from the thoracic inlet (Figure 4 [insert Figure 4]). Pulmonary parenchyma was assessed for any evidence of bronchial, alveolar, unstructured or structured interstitial patterns¹³. Lung 'nodules' were defined by the authors as rounded soft tissue opacity(ies) less than one intercostal space in diameter; a lung 'mass' was defined as soft tissue opacity(ies) more than one intercostal space diameter. The visceral pleura was considered abnormal if there were abnormally rounded or scalloped margins, focal indentations or irregularities. Distribution of effusions were assessed subjectively and categorised into unilateral, bilateral and 'cannot assess'. When there was presence of an unequal but bilateral presence of effusion, this was still considered a 'bilateral' distribution.

All radiographs were anonymised, randomly ordered (using a random number generator), and optimised for viewing in Powerpoint (Microsoft Powerpoint; Microsoft Corporation) slideshow. Participants read the studies from dual monitors, to allow simultaneous recording of responses on Forms (Microsoft Forms; Microsoft Corporation).

Statistical evaluation

Positive predictive values, negative predictive values, sensitivities and specificities of radiographic signs were calculated using the R package epiR¹⁴. To measure inter- and intra- observer agreement, kappa tests and observed agreement percentage were performed using SPSS (SPSS Inc, NY: IBM Corp).

Results

A total of 624 cats with pleural effusions were identified across the veterinary hospitals. 473 cases were excluded from the study (75.8%), as no further investigation was performed, or if the patient was immediately euthanised on discovery of pleural effusion. The remaining 151 cats met the inclusion criteria. The median age at initial consultation was 10 years (from 0.3 – 21years old). 86 cats (57.0%) were neutered males, 4 (2.6%) were non-neutered males, 59 (39.0%) were spayed females, 2 (1.3%) were non-neutered females. 149 patients had breed recorded; 70.2% were cross breeds and 28.8 % were pure breeds, with 24 breeds represented. The most common breeds in the study were domestic short hair (47.0%), domestic medium hair (11.9%), domestic long hair (6.6%), and Ragdoll (6.0%).

Prevalence of definitive diagnoses

The most common cause of pleural effusion was CHF (52.3%), followed by neoplasia (21.9%), pyothorax (10.6%) and idiopathic chylous effusion (5.3%) (Table 1). The 'FIP', 'other' category and 'concurrent disease' made up a small proportion of cases. The diagnosis of FIP cases were presumptive, as the owners of these cats did not pursue immunofluorescent staining or tissue biopsy. Both cats had fluid analysis performed which revealed a yellow, high protein exudate with a positive Rivalta test.

Table 1
Prevalence of disease aetiologies in 151 cats with pleural effusion

	Conditions	Number of cats	Percentage (95% CI)
	CHF	79	52.3 (44.0- 60.5)
	Neoplasia	33	21.9 (15.5-29.3)
	Pyothorax	16	10.6 (6.2-16.6)
	Idiopathic chylothorax	8	5.3 (2.3-10.2)
	Feline infectious peritonitis	2	1.3 (0.16-4.7)
Multiple diagnoses	CHF and neoplasia	4	2.6 (0.7-6.6)
	CHF and fluid overload	1	0.7 (0.02-3.6)
	Neoplasia and pyothorax	1	0.7 (0.02-3.6)
Other diseases	Inflammatory lung disease	4	2.6 (0.7-6.6)
	Post-operative fluid overload	1	0.7 (0.02-3.6)
	Granulomatous pericarditis	1	0.7 (0.02-3.6)
	Ketoacidotic diabetes mellitus	1	0.7 (0.02-3.6)

In the neoplastic disease group, a total of 4 cats did not have cytology or histology performed, with presumed diagnoses of neoplastic disease. One cat had a large cranial mediastinal mass confirmed on thoracic sonography, but the owners did not consent to sampling. One cat with multifocal lung nodules had confirmed nasal carcinoma with suspected metastatic disease and another had a large right caudal lung lobe mass confirmed on ultrasound by a radiologist but the patient was deemed too unstable to sample. The remaining case without cytology had a compressive heart base mass and a large gastric mass but owners did not wish to pursue sampling.

Radiographic interpretation

Radiographic studies of sufficient diagnostic quality and at least two orthogonal projections were available for 68 cats of various aetiologies (Table 2). Cats with multiple diagnoses were included in calculations for sensitivity, specificity, positive predictive and negative predictive values.

Table 2
Distribution disease for cats with radiographic studies available

	CHF	Neoplasia	Pyothorax	IdiopathicChylous	FIP	Other	Multiple diagnoses
Number of cats	27	15	13	4	2	4	3

Among certain radiographic signs, there was substantial variability between the radiologists in whether a structure could be perceived and assessed. When the observer judged that a structure could be assessed, and in consideration of error margins, the results were similar between observers, with one exception relating to the presence or absence of an unstructured interstitial pattern.

The results for radiologist 1 and 2 are displayed separately (Table 3). Sensitivity of each radiographic sign is the ability of a test to correctly identify the patients with a disease. Classification of cats with cardiomegaly for radiologist 2 yielded a 91% sensitivity for congestive heart failure, suggesting that 91% of cats with cardiomegaly would have congestive heart failure, where 9% of cats with congestive heart failure did not have radiographic cardiomegaly. Specificity is the ability to correctly identify cats without the disease. Radiologist 2 had a 69% specificity of cardiomegaly for CHF, meaning that 31% of the time, cats with cardiomegaly do not have congestive heart failure. An enlarged cardiac silhouette had both a high positive predictive value and high negative predictive value for CHF. The positive predictive value is the probability that following a positive test result the cat will have that specific disease. Radiologist 2 had 81% positive predictive value of cardiomegaly for congestive heart failure, meaning that any cat with radiographic cardiomegaly has 81% of congestive heart failure. A negative predictive value means that following a negative test, the individual will truly not have that disease. NPV of 85% when assessing cardiomegaly and congestive heart failure implies that cats without radiographic cardiomegaly had 85% probability of not being in congestive heart failure.

Enlarged pulmonary arteries and veins did not improve predictive values for congestive heart failure.

The identification of a mediastinal mass on radiographs entailed a high probability of neoplastic disease (100% for radiologist 1, 83% for radiologist 2) and a high specificity (1 and 0.98 for radiologist 1 and 2 respectively) with a low sensitivity (0.28 for both radiologists). Presence of a radiographic mediastinal mass was not predictive of congestive heart failure or chylothorax but had a low positive predictive value of 20% (radiologist 1) and 30% (radiologist 2) of pyothorax. Pulmonary nodules entailed a 50% probability of neoplasia for both radiologist 1 and 2. Pulmonary masses had a 50% probability of neoplasia for radiologist 1 and 67% probability for radiologist 2. Unilateral effusion was highly predictive of pyothorax (75% probability) for radiologist 1, but moderately low for radiologist 2 (20% probability). A flow diagram representation of these results is visible in figure 5.

Table 3 Sensitivity, specificity, positive predictive values and negative predictive values of various radiographic signs in identification of different pleural effusion aetiologies in cats for both radiologists

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Enlarged cardiac silhouette	Neoplasia	1	0.15 (0.04, 0.35)	0.63 (0.38, 0.84)	0.36 (0.11, 0.69)	0.35 (0.20, 0.54)
		2	0.12 (0.02, 0.30)	0.62 (0.32, 0.86)	0.38 (0.09, 0.76)	0.26 (0.12, 0.45)
	CHF	1	0.73 (0.52, 0.88)	0.79 (0.54, 0.94)	0.83 (0.61, 0.95)	0.68 (0.45, 0.86)
		2	0.81 (0.61, 0.93)	0.85 (0.55, 0.98)	0.91 (0.72, 0.99)	0.69 (0.41, 0.89)
	Pyothorax	1	0.04 (0.00, 0.20)	0.68 (0.43, 0.87)	0.14 (0.00, 0.58)	0.34 (0.20, 0.51)
		2	0.00 (0.00, 0.13)	0.77 (0.46, 0.95)	0.00 (0.00, 0.71)	0.28 (0.14, 0.45)
	Chylothorax	1	0.04 (0.00, 0.20)	0.95 (0.74, 1.00)	0.50 (0.01, 0.99)	0.42 (0.27, 0.58)
		2	0.04 (0.00, 0.20)	0.85 (0.55, 0.98)	0.33 (0.01, 0.91)	0.31 (0.16, 0.48)
Enlarged cardiac silhouette, PA and PV	Neoplasia	1	0.15 (0.02, 0.45)	0.77 (0.60, 0.90)	0.20 (0.03, 0.56)	0.71 (0.54, 0.85)
		2	0.06 (0.00, 0.30)	0.66 (0.49, 0.80)	0.07 (0.00, 0.34)	0.62 (0.46, 0.77)
	CHF	1	0.77 (0.46, 0.95)	0.69 (0.51, 0.83)	0.48 (0.26, 0.70)	0.89 (0.71, 0.98)
		2	0.75 (0.48, 0.93)	0.76 (0.60, 0.89)	0.57 (0.34, 0.78)	0.88 (0.72, 0.97)
	Pyothorax	1	0.00 (0.00, 0.25)	0.65 (0.45, 0.79)	0.00 (0.00, 0.25)	0.63 (0.45, 0.79)

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Chylothorax	2	0.00 (0.00, 0.21)	0.68 (0.51, 0.82)	0.00 (0.00, 0.26)	0.62 (0.46, 0.76)
		1	0.00 (0.00, 0.25)	0.94 (0.81, 0.99)	0.00 (0.00, 0.84)	0.72 (0.57, 0.84)
		2	0.06 (0.00, 0.30)	0.92 (0.79, 0.98)	0.25 (0.01, 0.81)	0.70 (0.55, 0.82)
PA and PV enlargement	Neoplasia	1	0.19 (0.05, 0.42)	0.77 (0.58, 0.90)	0.36 (0.11, 0.69)	0.57 (0.41, 0.73)
		2	0.05 (0.00, 0.26)	0.68 (0.50, 0.82)	0.08 (0.00, 0.36)	0.58 (0.42, 0.73)
	CHF	1	0.67 (0.43, 0.85)	0.70 (0.51, 0.85)	0.61 (0.39, 0.80)	0.75 (0.55, 0.89)
		2	0.63 (0.38, 0.84)	0.76 (0.59, 0.88)	0.57 (0.34, 0.78)	0.80 (0.63, 0.92)
	Pyothorax	1	0.05 (0.00, 0.24)	0.63 (0.44, 0.80)	0.08 (0.00, 0.38)	0.49 (0.32, 0.65)
		2	0.11 (0.01, 0.33)	0.68 (0.50, 0.82)	0.14 (0.02, 0.43)	0.60 (0.43, 0.74)
	Chylothorax	1	0.00 (0.00, 0.16)	0.93 (0.78, 0.99)	0.00 (0.00, 0.84)	0.57 (0.42, 0.71)
		2	0.05 (0.00, 0.26)	0.92 (0.78, 0.98)	0.25 (0.01, 0.81)	0.65 (0.51, 0.78)
	Neoplasia	1	0.21 (0.06, 0.46)	0.71 (0.56, 0.84)	0.24 (0.07, 0.50)	0.68 (0.53, 0.81)
		2	0.23 (0.10, 0.42)	0.74 (0.57, 0.87)	0.41 (0.18, 0.67)	0.55 (0.40, 0.69)

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	CHF	1	0.37 (0.16, 0.62)	0.51 (0.36, 0.66)	0.24 (0.10, 0.44)	0.66 (0.48, 0.81)
		2	0.30 (0.15, 0.49)	0.47 (0.31, 0.64)	0.31 (0.15, 0.51)	0.46 (0.30, 0.63)
	Pyothorax	1	0.32 (0.13, 0.57)	0.89 (0.76, 0.96)	0.55 (0.23, 0.83)	0.75 (0.62, 0.86)
		2	0.37 (0.20, 0.56)	0.92 (0.79, 0.98)	0.79 (0.49, 0.95)	0.65 (0.51, 0.77)
	Chylothorax	1	0.11 (0.01, 0.33)	0.98 (0.88, 1.00)	0.67 (0.09, 0.99)	0.72 (0.59, 0.83)
		2	0.10 (0.02, 0.27)	0.97 (0.86, 1.00)	0.75 (0.19, 0.99)	0.58 (0.45, 0.70)
Bilateral effusion	Neoplasia	1	0.28 (0.17, 0.41)	0.75 (0.19, 0.99)	0.94 (0.71, 1.00)	0.07 (0.01, 0.18)
		2	0.19 (0.10, 0.33)	0.50 (0.19, 0.81)	0.67 (0.38, 0.88)	0.11 (0.04, 0.23)
	CHF	1	0.45 (0.32, 0.58)	1.00 (0.40, 1.00)	1.00 (0.87, 1.00)	0.11 (0.03, 0.26)
		2	0.44 (0.30, 0.59)	0.70 (0.35, 0.93)	0.88 (0.70, 0.98)	0.19 (0.08, 0.36)
	Pyothorax	1	0.17 (0.09, 0.29)	0.25 (0.01, 0.81)	0.77 (0.46, 0.95)	0.02 (0.00, 0.11)
		2	0.23 (0.13, 0.37)	0.80 (0.44, 0.97)	0.86 (0.57, 0.98)	0.17 (0.07, 0.30)
	Chylothorax	1	0.07 (0.02, 0.17)	1.00 (0.40, 1.00)	1.00 (0.40, 1.00)	0.07 (0.02, 0.17)

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
		2	0.08 (0.02, 0.19)	1.00 (0.69, 1.00)	1.00 (0.40, 1.00)	0.17 (0.09, 0.29)
Unilateral effusion	Neoplasia	1	0.25 (0.01, 0.81)	0.72 (0.59, 0.83)	0.06 (0.00, 0.29)	0.93 (0.82, 0.99)
		2	0.50 (0.19, 0.81)	0.81 (0.67, 0.90)	0.33 (0.12, 0.62)	0.89 (0.77, 0.96)
	CHF	1	0.00 (0.00, 0.60)	0.55 (0.42, 0.68)	0.00 (0.00, 0.13)	0.89 (0.74, 0.97)
		2	0.30 (0.07, 0.65)	0.56 (0.41, 0.70)	0.12 (0.02, 0.30)	0.81 (0.64, 0.92)
	Pyothorax	1	0.75 (0.19, 0.99)	0.83 (0.71, 0.91)	0.23 (0.05, 0.54)	0.98 (0.89, 1.00)
		2	0.20 (0.03, 0.56)	0.77 (0.63, 0.87)	0.14 (0.02, 0.43)	0.83 (0.70, 0.93)
	Chylothorax	1	0.00 (0.00, 0.60)	0.93 (0.83, 0.98)	0.00 (0.00, 0.60)	0.93 (0.83, 0.98)
		2	0.00 (0.00, 0.31)	0.92 (0.81, 0.98)	0.00 (0.00, 0.60)	0.83 (0.71, 0.91)
Alveolar pattern	Neoplasia	1	0.27 (0.15, 0.42)	0.80 (0.56, 0.94)	0.76 (0.50, 0.93)	0.31 (0.19, 0.46)
		2	0.33 (0.15, 0.57)	0.82 (0.66, 0.92)	0.50 (0.23, 0.77)	0.70 (0.54, 0.82)
	CHF	1	0.35 (0.22, 0.51)	0.40 (0.19, 0.64)	0.59 (0.39, 0.76)	0.21 (0.09, 0.36)
		2	0.19 (0.05, 0.42)	0.41 (0.26, 0.58)	0.15 (0.04, 0.34)	0.48 (0.31, 0.66)

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Pyothorax	1	0.27 (0.15, 0.42)	0.95 (0.75, 1.00)	0.93 (0.66, 1.00)	0.35 (0.23, 0.49)
		2	0.29 (0.11, 0.52)	0.85 (0.69, 0.94)	0.50 (0.21, 0.79)	0.69 (0.54, 0.81)
	Chylothorax	1	0.06 (0.01, 0.17)	0.95 (0.75, 1.00)	0.75 (0.19, 0.99)	0.30 (0.19, 0.42)
		2	0.10 (0.01, 0.30)	0.95 (0.83, 0.99)	0.50 (0.07, 0.93)	0.66 (0.52, 0.78)
	CHF	1	0.46 (0.33, 0.60)	0.71 (0.42, 0.92)	0.86 (0.68, 0.96)	0.26 (0.13, 0.42)
		2	0.59 (0.41, 0.76)	0.71 (0.51, 0.87)	0.70 (0.50, 0.86)	0.61 (0.42, 0.77)
Unstructured interstitial pattern	Pyothorax	1	0.19 (0.09, 0.31)	0.71 (0.42, 0.92)	0.71 (0.42, 0.92)	0.19 (0.09, 0.31)
		2	0.16 (0.05, 0.33)	0.75 (0.55, 0.89)	0.42 (0.15, 0.72)	0.44 (0.29, 0.59)
	Chylothorax	1	0.07 (0.02, 0.18)	1.00 (0.77, 1.00)	1.00 (0.40, 1.00)	0.22 (0.13, 0.34)
		2	0.12 (0.04, 0.29)	1.00 (0.88, 1.00)	1.00 (0.40, 1.00)	0.50 (0.36, 0.64)
	Neoplasia	1	0.22 (0.12, 0.36)	0.64 (0.35, 0.87)	0.71 (0.44, 0.90)	0.18 (0.08, 0.31)
		2	0.06 (0.01, 0.21)	0.57 (0.37, 0.76)	0.14 (0.02, 0.43)	0.35 (0.21, 0.50)
Pulmonary nodules	Neoplasia	1	0.50 (0.16, 0.84)	0.78 (0.66, 0.88)	0.24 (0.07, 0.50)	0.92 (0.81, 0.98)

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	CHF	2	0.50 (0.16, 0.84)	0.79 (0.67, 0.89)	0.25 (0.07, 0.52)	0.92 (0.81, 0.98)
		1	0.12 (0.00, 0.53)	0.53 (0.40, 0.66)	0.03 (0.00, 0.18)	0.82 (0.66, 0.92)
		2	0.38 (0.09, 0.76)	0.55 (0.42, 0.68)	0.10 (0.02, 0.27)	0.86 (0.71, 0.95)
		1	0.12 (0.00, 0.53)	0.78 (0.66, 0.88)	0.07 (0.00, 0.34)	0.87 (0.75, 0.95)
	Pyothorax	2	0.00 (0.00, 0.37)	0.78 (0.65, 0.87)	0.00 (0.00, 0.25)	0.85 (0.72, 0.93)
		1	0.25 (0.03, 0.65)	0.97 (0.88, 1.00)	0.50 (0.07, 0.93)	0.91 (0.81, 0.96)
	Chylothorax	2	0.25 (0.03, 0.65)	0.97 (0.88, 1.00)	0.50 (0.07, 0.93)	0.90 (0.80, 0.96)
		1	0.50 (0.07, 0.93)	0.77 (0.64, 0.86)	0.12 (0.01, 0.36)	0.96 (0.87, 1.00)
	CHF	2	0.67 (0.09, 0.99)	0.78 (0.66, 0.87)	0.12 (0.02, 0.38)	0.98 (0.89, 1.00)
		1	0.25 (0.01, 0.81)	0.56 (0.43, 0.69)	0.03 (0.00, 0.18)	0.92 (0.79, 0.98)
Pulmonary masses	Neoplasia	2	0.33 (0.01, 0.91)	0.56 (0.42, 0.68)	0.03 (0.00, 0.18)	0.95 (0.82, 0.99)
		1	0.00 (0.00, 0.60)	0.78 (0.66, 0.87)	0.00 (0.00, 0.23)	0.93 (0.82, 0.98)
	Pyothorax	2	0.00 (0.00, 0.71)	0.79 (0.67, 0.89)	0.00 (0.00, 0.25)	0.94 (0.84, 0.99)
		1				
		2				
		1				

Radiographic sign(s)	Final diagnosis	Observer	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Chylothorax	1	0.00 (0.00, 0.60)	0.94 (0.85, 0.98)	0.00 (0.00, 0.60)	0.94 (0.85, 0.98)
		2	0.00 (0.00, 0.71)	0.94 (0.85, 0.98)	0.00 (0.00, 0.60)	0.95 (0.87, 0.99)
Mediastinal Mass	Neoplasia	1	1 (0.57, 1.00)	0.79 (0.68, 0.88)	0.28 (0.12, 0.51)	1 (0.93, 1.00)
		2	0.83 (0.44, 0.97)	0.79 (0.67, 0.87)	0.28 (0.12, 0.51)	0.98 (0.90, 1.00)
	CHF	1	0.00 (0, 0.43)	0.54 (0.42, 0.66)	0.00 (0.00, 0.12)	0.87 (0.73, 0.94)
		2	0.00 (0.00, 0.39)	0.53 (0.41, 0.65)	0.00 (0.00, 0.12)	0.85 (0.70, 0.93)
	Pyothorax	1	0.20 (0.04, 0.62)	0.79 (0.68, 0.88)	0.07 (0.01, 0.32)	0.93 (0.82, 0.97)
		2	0.33 (0.10, 0.70)	0.81 (0.69, 0.89)	0.14 (0.04, 0.40)	0.93 (0.82, 0.97)
	Chylothorax	1	0.00 (0.00, 0.43)	0.92 (0.83, 0.97)	0.00 (0.00, 0.43)	0.92 (0.83, 0.97)
		2	0.00 (0.00, 0.39)	0.92 (0.83, 0.97)	0.00 (0.00, 0.43)	0.91 (0.81, 0.96)

PPV = positive predictive values, NPV = negative predictive values, CHF = congestive heart failure, PV = pulmonary vein, PA = pulmonary artery

Inter-observer and intra-observer reliability

Between the radiologists, there was some variability in whether a specific radiographic structure could be assessed. When the observer was able to assess a structure, the radiologists had very similar results. Both Kappa statistics and observed agreement were used to measure interobserver and intra-observer reliability. Percent agreement is a direct measure of how many times the radiologists agreed divided by

the total observations. Cohen's kappa is interpreted as follows: values less than zero indicate no agreement; 0.01-0.2 as none to slight, 0.21 – 0.4 as fair, 0.41- 0.60 as moderate, 0.61 – 0.80 as substantial, 0.81 – 1.00 as perfect agreement¹⁵. Interobserver agreement of 88.2% corresponds to the radiologists reaching an identical radiographic conclusion 88.2% of the time and reached a disparate result 11.8% of the time. In observers that are well trained and 'guessing' is unlikely, percent agreement is often a better test of interrater reliability¹⁵.

Between the radiologists (supplementary Table 1) there was moderate to substantial agreement in cardiac size (κ 0.73, observed agreement 88.2%) and presence or absence of mediastinal masses (κ 0.57, 76.1%), pleural margins (κ 0.49, 76.6%), pulmonary vein (κ 0.52, 76.1%) and artery size (κ 0.52, 76.6%). There was only slight to fair agreement in alveolar (κ 0.17, 53.3%) and unstructured interstitial patterns (κ 0.23, 63.3%). Pleural effusion distribution had a high observed agreement (86.2%), but only fair agreement when measured by kappa (κ 0.27).

Intra-observer agreement (supplementary Table 2) was moderate to substantial for both radiologists when assessing cardiac silhouette size (κ 0.46, 1.00 respectively), mediastinal abnormalities (κ 1.00, 1.00), pleural effusion distribution (κ 0.46, 0.55) and presence or absence of an unstructured interstitial pattern (κ 0.6, 1.00). Assessment of pulmonary artery was slight to fair for both radiologists (κ 0.1, 0.2). There was marked variation in intra-observer agreement for assessing pulmonary veins (κ 0.33, 0.8), pleural margins (κ 0.00, 0.5) and alveolar patterns (κ 0.74, 0.00).

Discussion

In conducting this study, the authors aimed to combine information regarding the most common causes of pleural effusion and thoracic radiography to assist veterinarians with decision making in the instance of a respiratory emergency. The present study is the first to examine the positive and negative predictive values of radiographic signs in cats with pleural effusions. In our population of cats with pleural effusion, over half were caused by congestive heart failure, and the other half comprised of neoplasia, pyothorax, idiopathic chylous effusion, other causes. This is consistent with recent studies^{2,3,16} and in contrast to previous retrospective studies^{17–19} which identified that pleural effusions were more likely to be caused by neoplasia, pyothorax or FIP.

Radiographic assessment of the thorax with pleural effusion can be extremely challenging, due to obscuring of structures, including the cardiac silhouette and pulmonary parenchyma. The varied intra-observer and inter-observer measurements in assessing specific radiographic traits suggest radiographic assessment is difficult even for experienced radiologists. Of the radiographic variables assessed, we found that, by recognising an enlarged cardiac silhouette and presence of bilateral effusion on thoracic radiographs, clinicians should be strongly suspicious of CHF. A caveat to finding is that a small proportion of cats in congestive heart failure do not present with radiographic cardiomegaly (due to concentric hypertrophy being the most common cause of congestive heart failure^{10,20}). Therefore, echocardiography or other tests such as NT-proBNP are still recommended as an initial diagnostic test

when pleural effusion is identified. Cardiac biomarkers such as NT-proBNP can assist in differentiating cardiac versus non-cardiac disease through measurement of plasma²¹ or pleural effusion levels²². NT-proBNP is useful when comprehensive echocardiography is not available, or when there may be concurrent disease (i.e., cardiac disease and neoplasia) or for monitoring of cardiac disease progression.

There was minimal added benefit in assessing the pulmonary vasculature, as radiographic assessment of these structures was poorly reliable without significant improvement on PPV and NPV than cardiomegaly alone. The poor reliability is likely due to differences in subjective assessment of vessel size and also the difficulty of assessing pulmonary vessels in the presence of pleural effusion.

There were some discrepancies in assessing bilateral versus unilateral effusions by the two radiologists. On review of the 17 cases with discrepancies in fluid distribution, majority of the effusions (13/17) had trivial or a small volume of effusions in both hemithoraces. A trivial or small volume of effusion can be difficult to assess on radiographs and may be open to differences in subjective interpretation. The remainder of the 5/17 cases had unequal distributions of effusion, in one hemithorax there was a moderate to large volume of effusion, whereas the other hemithorax was had a trivial effusion. This slight difference in opinion and assessment of unilateral versus bilateral effusion likely the reason for the large disparity in positive predictive values of fluid distribution for pyothorax among the two radiologists (radiologist 1 PPV 75%, radiologist 2 PPV 20%). The difference in interpretation of bilateral and unilateral effusion suggests that the assessment of fluid distribution when there is a small or trivial effusion may not be a reliable criterion. In retrospect, the addition of a third observer may be beneficial to reduce these discrepancies.

In the literature, there are varying reports^{1-4, 7}, on whether neoplastic, chylous and pyothorax effusions cause unilateral or bilateral effusions. It is postulated that the mediastinum is fenestrated in cats⁴; however, an excessive fibrin may seal the mediastinum (i.e. rupture of abscess, unilateral pleuritis causing adhesions etc). Previous reports^{4,23} describe chylothorax and pyothorax to have unilateral effusions due to the highly inflammatory effusion. Other studies by Barrs and Beatty²⁴ and others^{19,25-27}, identified that most cats with pyothorax (70-90%) had bilateral effusions. It is not reported in detail how 'unilateral' and 'bilateral' effusions are interpreted in these studies. More importantly, our results suggest that cats with CHF or idiopathic chylothorax did not present with unilateral effusion. This finding may be important for ruling out these two diseases and prompt clinicians to perform thoracocentesis and fluid analysis or advanced imaging, as there is a higher likelihood of pyothorax or neoplastic disease when a unilateral effusion is identified.

The presence of a radiographic mediastinal mass had 83% and 100% positive predictive value for neoplasia with a low sensitivity and high specificity. Not all neoplastic disease was caused by mediastinal masses leading to a low sensitivity; however, when a mediastinal mass was radiographically diagnosed, there is a very high probability of neoplastic disease. There was one false positive case, where one cat assessed to have a radiographic mediastinal mass, had a diagnosis of pyothorax. This radiographic appearance may be due to loculated fluid within the mediastinum, causing an appearance

of a mediastinal mass secondary to the exudative nature of the fluid. This case was reviewed and no post mortem or thoracic ultrasound was available to confirm this speculation. No cats with CHF and idiopathic chylothorax had radiographic mediastinal mass(es). Limitations of this finding are associated with the low sample size (only a total of 5 cats with confirmed mediastinal masses had radiographs available for assessment).

Radiographic pulmonary nodules only predicted neoplastic disease 50% of the time and masses from 50–67% of the time. Of the cats diagnosed with neoplastic disease, a small portion did not have sonographic or radiographic pulmonary nodules or masses, these included two cats with heart base and myocardial neoplasms, and three cats with neoplastic pleural effusions without a primary mass identified (supplementary table I). The variable neoplastic processes that were present in the population examined could be one reason for the low predictive value pulmonary nodules and masses. In addition. Some cats with congestive heart failure and chylothorax were interpreted to have radiographic nodules. On review of the congestive heart failure cases, it is speculated that cardiogenic oedema infiltrates and peri-bronchial infiltrates may mimic nodules or masses (Figure 6 [Insert Figure 6]). Several cats with pyothorax and chylothorax had radiographic nodules and this may be due to a combination of atelectasis and retraction of the lung margins causing regions of patchy consolidation. Unfortunately, these cats did not have a CT, post mortem or biopsy to confirm these speculations. No chylous and pyothorax cases had radiographic pulmonary masses.

In previous studies, cats with chylothorax have been described to have rounded pleural contours due to chronic fibrosing reaction of visceral pleura^{27,28} (Figure 7 [Insert Figure 7]), exerting a constrictive and restrictive effect on lung lobes. It was found that pleural abnormalities were not useful as a predictor, and only had a 30% positive predictive value for chylous effusion. This suggests that chylothorax may not always cause a constrictive and fibrosing effect to the pleura; however, the sample size examined was small and these results may not generalise to other populations. An additional finding from this cohort is that idiopathic chylous effusion never presented with unilateral effusion or presence of a mediastinal mass.

There are many limitations to this study, particularly pertaining to the retrospective access to cases. Not every patient had radiographs recorded which may create bias from missing data. Although we have accounted for multiple diseases in a single patient, it is possible that some cats had more than one disease causing pleural effusion that we were unaware of, with a potential for misclassification bias. In addition, not every patient had histopathology or cytology performed in the neoplasia group; although this was a small proportion of patients (n=4), this may reflect some inaccuracies in classification. Despite collecting data across 10 years, the sample sizes in the non-CHF groups were small, which may cause the lack of precision in the predictive values, sensitivity and specificity estimates. In particular, the FIP group had very small sample size; the data was collected prior to the widespread availability of Remdesivir and many owners with suspected FIP did not pursue further diagnostics. In addition, not all FIP cases with further diagnostics had pleural effusion and therefore not included in this study. A larger scale study

examining more cases (pyothorax, neoplasia, idiopathic chylothorax, feline infectious peritonitis) would allow for more accurate results, therefore although this study is novel, it is preliminary.

All cases were obtained in practices in metropolitan Western Australia and the practices were within a 10km radius from the referral hospital. When interpreting the data, clinicians should be aware of the effects of disease prevalence on test results, which may affect the accuracy of the results, as the PPV and NPV results assume the prevalence of the disease aetiologies are similar in all populations. Several radiographic parameters were interpreted differently with some performed a priori as there are some radiographic parameters that could not be objectively measured (such as interstitial and alveolar patterns and small volumes of pleural effusion), leading to inconsistent application of measurement techniques. Although, inter-observer agreement was moderate to substantial for majority of the radiographic signs, several radiographic signs only had slight to fair agreement (distribution of pleural effusion, pulmonary parenchymal abnormalities) between the radiologists, which partly reflects the challenges of interpreting thoracic structures in the presence of pleural effusion, even among experienced operators.

Conclusions

The results from the current study provides an estimate of four common causes of pleural effusion, which may assist in treatment decisions. In our population of cats with pleural effusions, cardiomegaly is the most reliable predictor of CHF; mediastinal mass can predict neoplastic disease and unilateral pleural effusion may be useful at predicting pyothorax. Cats with chylothorax never presented with unilateral pleural effusion. Radiography alone is helpful but inadequate at differentiating underlying disease aetiologies, particularly for idiopathic chylothorax and non-mediastinal neoplasms. The authors would like to reiterate, although radiographs can be beneficial for confirmation and diagnosis of thoracic disease, stabilising the patient prior to performing diagnostics is always indicated. Severely dyspnoeic cats can acutely deteriorate when stressed and radiographic positioning can further exasperate clinical signs and lead to respiratory failure. Therefore, although radiographs may be beneficial for the diagnostic process, this should always be weighed against each patient's clinical status and only performed if deemed clinically safe. Teaching practitioners to recognize cardiomegaly and mediastinal masses on thoracic radiographs are beneficial for differentiating cardiac versus non-cardiac causes of pleural effusion and may prioritise further diagnostics, particularly where a comprehensive investigation of aetiology is not possible (for example, due to financial constraints).

Abbreviations

CHF: congestive heart failure; CT computed tomography; FIP feline infectious peritonitis; PPV: positive predictive values; NPV: negative predictive values; PV: pulmonary vein; PA: pulmonary artery

Declarations

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Author's contributions

Concept and study design by all authors. BJH and ZL interpreted the radiographs and statistical analysis was performed by AH and LH. All authors contributed to, read, and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/ or analysed during the current study are available from the corresponding author on reasonable request.

Ethical Approval

This is a retrospective study. No live animals were recruited for this study. The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Ethical approval from a committee was therefore not specifically required for publication.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

A patient with a large volume of pleural effusion with complete effacement of cardiac silhouette, indistinct pulmonary vasculature and marked difficulty assessing pleural margins and mediastinum.

Figure 2

Cardiac silhouette size was measured using two methods. The first method was the vertebral heart score. The base apex length and craniocaudal length were transposed onto the vertebral column and recorded as the corresponding number of vertebrae measured from the cranial edge of T4 vertebral body. VHS more than 8 was considered enlarged and likely in heart failure. The base apex length was measured from the ventral wall of the carina to apex (orange solid line). The craniocaudal length was measured perpendicular to the base-apex length, at the widest width of the cardiac silhouette (green solid line). The second method used the base apex length and compared this against the length of sternebrae 2 to 4. If the length extended beyond three sternebrae, the cardiac silhouette was considered enlarged (dashed orange line). This patient has VHS of 9 and an elongated base-apex length suggestive of congestive heart failure.

Figure 3

a VD projection. Caudal lobar vein (depicted by orange solid line) and veins at where they intersect with the 9th rib (depicted by green solid line) were considered enlarged if they were more than 1:1 ratio. This cat had bilateral enlarged caudal pulmonary veins and arteries with a scant volume of pleural effusion. b Lateral projection. Cranial lobar veins (depicted by orange solid line) were considered enlarged if it was more than 0.7 times the proximal third of the 4th rib (depicted by green solid line). This cat had enlarged cranial lobar veins and arteries, severely enlarged globoid cardiac silhouette with a scant volume of pleural effusion.

Figure 4

The mediastinum has a large soft tissue mass with rounded caudal and lateral margins causing severe deviation of the mediastinal structures (trachea, oesophagus) and lung lobes with complete effacement of the cardiac silhouette. This patient had mediastinal lymphoma.

Figure 5

A flow diagram representing highest positive predictive values among different radiographic signs for prediction of specific disease aetiologies for both radiologists.

Figure 6

A pulmonary nodule was defined in this study as a soft tissue nodule less than one intercostal space. This cat had multiple radiographic soft tissue nodules but was diagnosed with congestive heart failure (no neoplasms were identified). The cause of the soft tissue opacity is likely secondary to pulmonary oedema.

Figure 7

Rounded and contracted pleural margins secondary to chronic fibrosis is often described in cats with pyothorax. This cat represents the classic chronic chyllothorax pleural margin abnormalities; however, this was not a predictive sign of chyllothorax in our cohort, and only one cat showed this radiographic pattern.

Supplementary Files

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