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TITLE: Prognostic value of mitral annular systolic plane excursion and tricuspid annular plane systolic excursion in cats with hypertrophic cardiomyopathy

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2
3 **Abstract**
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6 Introduction: Hypertrophic cardiomyopathy (HCM) has a variable prognosis; left atrial size,
7
8 presence of clinical signs and left ventricular (LV) systolic function have been shown to
9
10 predict outcome. Mitral annular plane systolic excursion (MAPSE) and tricuspid annular
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12 plane systolic excursion (TAPSE) assess longitudinal ventricular systolic function and are
13
14 decreased in cats with HCM. The aim of the study was to ascertain whether MAPSE and
15
16 TAPSE have prognostic value in HCM and if cats with pleural effusion have lower
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18 MAPSE and TAPSE than cats with pulmonary oedema.
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21
22 **Animals:** 184 client owned cats diagnosed with HCM.
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25 **Methods:** Retrospective study. Echocardiography was used to diagnose HCM (end-
26
27 diastolic LV wall thickness ≥ 6 mm) and to measure MAPSE and TAPSE. Survival
28
29 information was obtained.
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31
32 **Results:** No multivariable model including MAPSE or TAPSE could be generated in this
33
34 population. Cats with pleural effusion \pm pulmonary oedema had lower MAPSE IVS and
35
36 TAPSE, compared to cats with pulmonary oedema only. MAPSE IVS was the only factor
37
38 predicting pleural effusion on multivariable regression model.
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40
41 **Conclusions:** Lower MAPSE and TAPSE were not independently associated with outcome
42
43 on multivariable analysis. Cats with pleural effusion \pm pulmonary oedema had lower
44
45 TAPSE and MAPSE IVS than cats with pulmonary oedema and MAPSE IVS was the only
46
47 predictive factor associated with the development of pleural effusion in this population.
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50 **Key words:** survival, pleural effusion, pulmonary oedema, feline, echocardiography
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3 PROGNOSTIC VALUE OF MITRAL ANNULAR SYSTOLIC PLANE EXCURSION
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5 (MAPSE) AND TRICUSPID ANNULAR PLANE SYSTOLIC EXCURSION (TAPSE) IN
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7 CATS WITH HYPERTROPHIC CARDIOMYOPATHY.
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37 Short title: Prognostic value of MAPSE and TAPSE in HCM
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1 Abbreviation Table

ATE	arterial thromboembolism
CHF	congestive heart failure
HCM	hypertrophic cardiomyopathy
LVFS	left ventricular fractional shortening
MAPSE	mitral annular plane systolic excursion
MAPSE FW	MAPSE measured at the free wall
MAPSE IVS	MAPSE measured at the interventricular septum
TAPSE	tricuspid annular plane systolic excursion

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3

4 Introduction

5 Hypertrophic cardiomyopathy (HCM) is defined as a symmetrical or asymmetrical
6 increase in left ventricular wall thickness in the absence of other cardiovascular or
7 systemic causes that would result in similar changes. [1] Hypertrophic
8 cardiomyopathy is the most common cardiac disease in cats [2,3], it has a variable
9 clinical progression and several echocardiographic parameters have been shown to
10 be of prognostic value. [4-8] Furthermore, recent investigations have identified
11 involvement of the right ventricle in HCM with 29-50% of cats in different studies
12 having an increased thickness of the right ventricular wall [9, 10]. Mitral annular plane
13 systolic excursion (MAPSE) and the right-sided counterpart tricuspid annular plane
14 systolic excursion (TAPSE) are indices of systolic longitudinal displacement of the

60
61
62 15 atrioventricular annular plane [11, 12]. Mitral and tricuspid annular plane systolic
63
64 16 excursion can be obtained by M-mode from echocardiography [11-14], by magnetic
65
66 17 resonance imaging (MRI) [15] and TAPSE has also been measured from 2-D
67
68 18 cineloops [10]. Mitral and tricuspid annular plane systolic excursion were decreased
69
70
71 19 in cats with HCM compared to healthy control cats [13], and cats with congestive
72
73 20 heart failure (CHF) showed the lowest values. One study showed that MAPSE and
74
75 21 TAPSE may be of prognostic importance at the univariable level, but the end-point
76
77 22 included all-cause mortality due to low number of events and sample size; no
78
79 23 multivariable analysis was performed for similar reasons [13]. To the authors'
80
81 24 knowledge, the potential prognostic utility of MAPSE and TAPSE in cats with HCM
82
83 25 has not been fully evaluated.

84
85
86 26 Cats in CHF due to HCM can present with either pulmonary oedema and/or pleural
87
88 27 effusion [16]. The underlying mechanism(s) responsible for the development of
89
90 28 pleural effusion in cats with left-sided congestive heart failure is not fully understood.
91
92 29 One study showed that cats with pleural effusion secondary to cardiac disease had
93
94 30 poorer left atrial active emptying and increased right ventricular diameters measured
95
96 31 by M-mode echocardiography [17], compared to cats that presented with pulmonary
97
98 32 oedema. A more recent paper has also identified lower TAPSE values in a
99
100 33 subpopulation of cats with pleural effusion compared to cats with pulmonary oedema
101
102 34 [10]. Whether the presence of pleural effusion in cats with HCM is associated with a
103
104 35 lower value of both MAPSE and TAPSE indicating worse left and/or right heart
105
106 36 function has not yet been fully determined.

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110 37 The aim of the study was to evaluate the prognostic value of MAPSE and TAPSE in
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112 38 a larger population of cats with HCM, for which a longer follow up is available

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121 39 compared to our previously published study [13] and to determine whether cats
122
123 40 presenting with pleural effusion have a lower value of MAPSE and TAPSE compared
124
125 41 to cats with pulmonary oedema. Our first hypothesis was that MAPSE and TAPSE
126
127 42 would have prognostic value in a population of cats with HCM. Our second
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129 43 hypothesis was that in a subset of cats with HCM and CHF, those presenting with
130
131 44 pleural effusion would have lower MAPSE and TAPSE compared to those that
132
133 45 presented with only pulmonary oedema.
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137 46 Animals, materials and methods:

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139 47 Retrospective study. The study population comprised cats previously included in
140
141 48 studies investigating survival in cats with HCM. [7, 8] Inclusion criteria were cats
142
143 49 diagnosed with HCM by a board-certified cardiologist or a cardiology resident
144
145 50 supervised by a board-certified cardiologist at the Royal Veterinary College, Queen
146
147 51 Mother Hospital for Animals based on two-dimensional (2D) echocardiography [18]
148
149 52 between June 2004 and August 2009. In addition, cats were required to have a left
150
151 53 apical four-chamber cine loop of sufficient quality to enable accurate measurement of
152
153 54 MAPSE and TAPSE. Cats were excluded from the study if they had a concurrent
154
155 55 diagnosis of hyperthyroidism or hypertension or if no cine loop deemed to be of good
156
157 56 quality was available for MAPSE and TAPSE measurement.
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161 57 Cats were diagnosed with HCM when end-diastolic left ventricular wall thickness
162
163 58 measured in B-mode was equal or greater than 6 mm. In addition, left atrial size was
164
165 59 assessed on right parasternal short axis view by measuring left atrium to aorta ratio
166
167 60 at the onset of QRS [7,19, 20], whilst left atrial diameter in long axis [7,19] was
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169 61 measured from a right parasternal long-axis view, by drawing a line parallel with the
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171 62 mitral annulus bisecting the left atrium in the last frame before mitral valve opening.
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180 63 Left atrial function was evaluated by measuring left atrial fractional shortening [7] and
181
182 64 left atrial ejection fraction [7]. Left ventricular systolic function was assessed using
183
184 65 left ventricular fractional shortening (LVFS) on M-mode. [7] Where available, the S'
185
186 66 wave of the interventricular septum and left ventricular free wall were measured from
187
188 67 mitral annular septal and free wall Tissue Doppler Imaging respectively [19, 21].
189
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191 68 Off-line measurement of MAPSE and TAPSE were performed by anatomical M-mode
192
193 69 from the left apical four-chamber view as described [13]. Briefly, the anatomical M-
194
195 70 mode cursor was aligned parallel to the interventricular septum (IVS) in order to
196
197 71 obtain an M-mode tracing for the measurement of MAPSE IVS. Subsequently, the
198
199 72 anatomical M-mode cursor was aligned parallel to the free wall (FW) in order to
200
201 73 obtain an M-mode tracing for MAPSE FW and finally the cursor was aligned parallel
202
203 74 to the right ventricular free wall in order to obtain an M-mode tracing for TAPSE.
204
205 75 MAPSE and TAPSE were measured in mm between the most basilar position of the
206
207 76 annulus in end-diastole and its most apical displacement at end-systole using the
208
209 77 leading edge method. Three consecutive measurements were performed by a single
210
211 78 observer (IS) and the results were averaged. MAPSE and TAPSE measurements
212
213 79 were performed by a single observer blinded to the clinical status of the patient. All
214
215 80 other 2D and Doppler values formed part of the previous study and were measured
216
217 81 by a board-certified cardiologist or cardiology resident as described in the original
218
219 82 studies [7, 8]. Clinical status classification was no clinical signs, CHF, arterial
220
221 83 thromboembolism (ATE), syncope and open mouth breathing during activity based
222
223 84 on that described in the previous studies [7,8]. Cats with HCM were classified as not
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225 85 showing clinical signs if they were not receiving diuretic therapy and had no signs or
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227 86 history of increased respiratory rate, dyspnoea, syncope or ATE. To be included in
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239 87 the CHF group cats had to have documented increased respiratory rate responsive
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241 88 to furosemide and evidence of pulmonary oedema or pleural effusion by imaging
242
243 89 (either thoracic ultrasound or thoracic radiography) at the time of presentation or
244
245 90 immediately prior to referral. Cats were classified in the pulmonary oedema group if
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247
248 91 the thoracic radiographs showed an alveolar or interstitial infiltrate and no pleural
249
250 92 effusion, whereas cats with pleural effusion had to have at least thoracic ultrasound
251
252 93 performed, which confirmed the presence of pleural effusion. Due to the retrospective
253
254 94 nature of the study, it was not possible to exclude concurrent pulmonary oedema in
255
256 95 cats with pleural effusion and therefore it is possible that a proportion of cats with
257
258 96 pleural effusion had concurrent pulmonary oedema. The two groups were therefore
259
260 97 classified as pulmonary oedema and pleural effusion \pm pulmonary oedema. Aortic
261
262 98 thromboembolism was defined based on the location of the thrombus. A limb ATE
263
264 99 was defined as a sudden onset painful lower motor neuron deficits in one or more
265
266 100 limbs with concurrent pallor and pulselessness. A cerebral ATE was defined based
267
268 101 on MRI findings of a well-demarcated lesion that was hyperintense on T2-weighted
269
270 102 images. Syncope was defined as a transient episode of loss of consciousness
271
272 103 characterised by absence of pre- or postictal signs and rapid recovery. Open mouth
273
274 104 breathing during activity was defined as the presence of open mouth breathing
275
276 105 noticed by the owners at home only during physical activity (playing or running). [7]
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280 106 Survival information was obtained by reviewing the electronic clinical archive of the
281
282 107 institution and by contacting referring veterinarians or owners. For cats that died,
283
284 108 date of death and cause of death (non cardiac, cardiac) were recorded. Cardiac
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286 109 death was defined as euthanasia or natural death following CHF refractory to medical
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288 110 treatment, euthanasia or natural death following ATE or sudden death.

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111 Statistical analysis:

112 Statistical analysis was performed by a commercially available statistical software ^a.

113 The Shapiro Wilk test was used to verify normal distribution of variables. Normally

114 distributed data are reported as mean (standard deviation, SD) and non-normally

115 distributed data are reported as median (interquartile range, IQR1-3, 25th percentile

116 to 75th percentile).

117 ANOVA with Tukey post-hoc comparisons, Kruskal Wallis with Dunn post-hoc

118 comparisons or chi-squared tests as appropriate were performed to assess

119 differences based on clinical status at presentation. For analysis of clinical status,

120 cats with open mouth breathing during activity were grouped with cats with syncope

121 due to small group sizes.

122 Cardiac mortality was the end-point in the survival analysis. Cardiac survival was

123 calculated as the days between diagnosis and death or last visit/contact. Cats still

124 alive at the last point of follow up were right-censored as were cats that died of non-

125 cardiac disease. The Kaplan Meier method was used to estimate survival function

126 and plot time to event curves in the different groups. Continuous variables were

127 explored by division into groups based on quartiles. A log-rank test was used to

128 determine whether a significant difference existed between groups at univariable

129 level. If one or more groups had a disproportionately different hazard (i.e., the

130 quartile curve diverging markedly from the others), a threshold effect was identified

131 and the variable was included in the Cox model as a categorical variable using the

132 cut-off established by the exceptional quartile. Multivariable survival analysis was

133 explored by Cox's proportional hazard analysis.

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357 134 Student's t test, Mann-Whitney U test or Fisher's exact were performed as
358
359 135 appropriate to assess differences within CHF groups (pulmonary oedema and pleural
360
361 136 effusion). Multivariable binary logistic regression models were generated to explore
362
363 137 factors independently associated with the development of pleural effusion in cats with
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365
366 138 CHF. Variables significant at $p < 0.2$ were taken forward in a manual forwards
367
368 139 stepwise construction. Odds ratios (OR) and 95% confidence intervals (CIs) were
369
370 140 calculated and overall model assessment was performed looking at the Hosmer-
371
372 141 Lemeshow goodness-of-fit test statistic and the percentage of cases the model
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375 142 correctly classified.

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378 143 Statistical significance was set at $p < 0.05$. The statistical significance for post-hoc
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380 144 tests with multiple comparisons was set using a Bonferroni correction for 6
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382 145 comparisons ($p < 0.0083$).

383 384 146 Results:

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387 147 The study population comprised 184 cats. Median age at presentation was 6.5 years
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389 148 (IQ 1-3 2.8-10.0 years), with a mean body weight of 4.7 kg (SD 1.1kg). Male cats
390
391 149 were overrepresented ($n=140$) compared to female cats ($n=44$). The majority of cats
392
393 150 were Domestic Shorthairs ($n=137$), followed by British Shorthairs ($n=13$), Persians
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395 151 ($n=10$), Domestic Longhair ($n=9$), Ragdoll ($n=5$), Sphynx ($n=2$), and one each of
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397 152 Bengal, Devon Rex, European Shorthair, Exotic Shorthair, Maine Coon, Manx,
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400 153 Oriental Shorthair and Selkirk Rex. One hundred sixty nine cats presented at least
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402 154 one auscultatory abnormality (heart murmur, gallop rhythm or arrhythmia) and the
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404 155 remaining 15 cats had no auscultatory abnormalities. Overall, a heart murmur was
405
406 156 auscultated in the majority of cats ($n=139$), and only a minority presented with a
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416 157 gallop sound (n=44) or an arrhythmia (n=33). A heart murmur was the only
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418 158 auscultatory abnormality in 102 cats, a gallop was the only auscultatory abnormality
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420 159 in 13 cats and an arrhythmia was the only abnormality in 13 cats. ECGs were
421
422 performed in 174 cats and an arrhythmia was documented in 54 of them, 26 of which
423 160
424
425 161 had not been reported on auscultation. A total of 76 cats had clinical signs, including
426
427 162 52 cats with CHF alone, 12 with ATE (including 3 with concurrent CHF), 9 with
428
429 163 syncopal episodes and 3 with open mouth breathing during activity at home. Of the 9
430
431 164 cats with syncopal events, 5 were suspected to be secondary to dynamic left
432
433 165 ventricular outflow tract obstruction and 4 were suspected to be related to arrhythmic
434
435 166 events (two intermittent supraventricular tachycardia, one intermittent ventricular
436
437 167 tachycardia and one intermittent third degree AV Block). The three cats that had
438
439 168 open mouth breathing during activity at home all had dynamic outflow tract
440
441 169 obstruction. The remaining 108 cats did not show clinical signs.

442
443
444 170 One hundred twenty eight cats (69%) received at least 1 medication. Furosemide
445
446 171 (n=61), angiotensin converting enzyme inhibitor (n=65), beta blockers (n=53) and
447
448 172 antithrombotic treatments (aspirin n= 33, heparin n= 3, clopidogrel n= 2) were the
449
450 173 most common medications. Other medications included spironolactone (n= 14),
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452 174 pimobendan (n=14), positive inotropes during the hospitalisation (one each on
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454 175 dopamine, dobutamine), diltiazem (n=1). Potassium was supplemented in 5 cats,
455
456 176 rutin was administered in 2 cats and taurine was administered in 1 cat. All cats with
457
458 177 congestive heart failure were receiving furosemide. In addition, cats with pleural
459
460 178 effusion± pulmonary oedema were receiving angiotensin converting enzyme
461
462 179 inhibitors (n=22), pimobendan (n=12), spironolactone (n= 6), antithrombotic agents
463
464 180 (aspirin n=9, heparin n=1, clopidogrel n=1) and potassium supplementation (n=4).

473
474
475 181 Positive inotropes were administered during hospitalisation (dobutamine n=1,
476
477 182 dopamine n=1) and taurine was supplemented in one cat. Cats with pulmonary
478
479 183 oedema were receiving angiotensin converting enzyme inhibitors (n=18),
480
481 184 pimobendan (n=1), spironolactone (n= 2), antithrombotic agents (aspirin n=9,
482
483 185 clopidogrel n=1), beta blockers (n=1) and potassium supplementation (n=1).
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485
486 186 Compared to cats not showing clinical signs, cats with congestive heart failure were
487
488 187 more likely to have a gallop sound (p<0.001), arrhythmia on auscultation (p=0.002) or
489
490 188 on ECG (p<0.001) and were less likely to have a heart murmur (p< 0.001) (Table 1).
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492
493 189 Cats with congestive heart failure also had more severe maximal left ventricular wall
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495 190 thickness (p<0.001), enlarged left atrium on both short- (p<0.001) and long-axis
496
497 191 (p<0.001), lower left ventricular fractional shortening (p<0.001), poorer left atrial
498
499 192 function as assessed by left atrial fractional shortening (p<0.001) and ejection
500
501 193 fraction (p<0.001). A higher prevalence of spontaneous echo-contrast was observed
502
503 194 in cats with CHF and ATE (p<0.001) (Table 2).
504
505
506 195 In the overall population MAPSE FW was 4.28 ± 1.15 mm, MAPSE IVS was 3.86
507
508 196 ± 1.02 mm and TAPSE 7.65 ± 1.99 mm. Cats with CHF had significantly lower MAPSE
509
510 197 FW, MAPSE IVS and TAPSE compared to cats not showing clinical signs (Table 2).
511
512
513 198 At last follow up, 74 cats were alive, a cardiac cause of death was identified in 71
514
515 199 cats (35 due to CHF, 24 due to ATE and 12 due to sudden death) and 38 cats died of
516
517 200 non-cardiac disease. One cat was lost to follow up. When exploring the association
518
519 201 between survival and MAPSE FW, MAPSE IVS and TAPSE in the overall HCM
520
521 202 population by univariable analysis, Kaplan Meier curves showed that cats in the
522
523 203 lowest quartile (MAPSE FW < 3.58 mm, MAPSE IVS < 3.20 mm, TAPSE < 6.33 mm)
524
525 204 were more likely to reach the final endpoint (cardiac death) earlier than cats in the
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527

532
533
534 205 remaining quartiles. Kaplan Meier curves and survival data were therefore presented
535
536 206 using these cut-off values (supplement data, figures 1-3). It was not possible to
537
538 207 generate a multivariable Cox proportional hazards model that included MAPSE at the
539
540 208 left ventricular free wall, MAPSE at the interventricular septum or TAPSE because
541
542 209 these parameters were not statistically significant in the final multivariable model,
543
544 210 which was similar to a previously published multivariable model [7]. Neither MAPSE
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546 211 FW, MAPSE IVS or TAPSE had prognostic value at the univariable level in the
547
548 212 subgroup of cats without clinical signs or in the subgroup of cats with CHF.
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552 213 Of the 55 cats that presented with CHF (including 3 cats with both CHF and ATE), 32
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554 214 cats were included in the pleural effusion \pm pulmonary oedema group (16 of which
555
556 215 had confirmed concurrent pulmonary oedema) and 21 in the pulmonary oedema only
557
558 216 group. The remaining 2 cats presented with mild pericardial effusion not causing
559
560 217 tamponade. In the CHF group, cats with pleural effusion \pm pulmonary oedema had
561
562 218 significantly lower MAPSE IVS and TAPSE than cats with pulmonary oedema
563
564 219 ($p=0.041$ and $p= 0.020$ respectively). Cats with pleural effusion \pm pulmonary oedema
565
566 220 had lower LAEF ($p=0.010$) than cats with pulmonary oedema. No statistically
567
568 221 significant difference was observed between the groups for MAPSE FW ($p= 0.609$),
569
570 222 left atrium to aorta ratio ($p=0.237$), left atrial diameter in long axis ($p= 0.082$), left
571
572 223 atrial fractional shortening ($p=0.091$), LVFS ($p=0.071$), peak velocity of systolic mitral
573
574 224 annular motion as determined by pulsed wave Doppler measured at the free wall
575
576 225 ($p=0.841$) or at the interventricular septum ($p=0.441$) (Table 2). For the remaining
577
578 226 groups of cats with clinical signs (aortic thromboembolism, syncope, exertional
579
580 227 dyspnoea), no sub-analyses were performed due to small sample sizes. In the
581
582 228 multivariable binary logistic regression model, only MAPSE IVS was independently
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591
592
593 229 associated with development of pleural effusion. The model correctly predicted
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595 230 62.3% of cases and the Hosmer-Lemeshow test statistic suggested good model fit
596
597 231 (p=0.924).
598
599

600 232 Discussion:
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602

603 233 This study has demonstrated that neither MAPSE at the free wall, interventricular
604
605 234 septum or TAPSE are independently associated with outcome in cats with HCM. On
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607 235 univariable analysis, MAPSE IVS and TAPSE, but not MAPSE FW, were lower in
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609 236 cats with pleural effusion ± pulmonary oedema than pulmonary oedema only.
610

611 237 Multivariable analysis of the above parameters in cats with CHF demonstrated that
612
613 238 cats with higher MAPSE IVS were less likely to have pleural effusion.
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615

616 239 Mitral and tricuspid annular plane systolic excursions are M-mode derived
617
618 240 parameters that assess the longitudinal displacement of the atrio-ventricular annulus
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620 241 during systole, as the heart base moves toward the apex. These parameters can
621
622 242 therefore be considered as markers of systolic longitudinal function. Subclinical
623
624 243 longitudinal dysfunction is recognised in people with HCM when assessed by
625
626 244 deformation imaging [22] and also in cats with HCM when assessed by MAPSE [13].
627
628 245 TAPSE is considered a robust parameter of right ventricular systolic function in
629
630 246 people and dogs [12, 23-25]. There is increasing interest in assessing right
631
632 247 ventricular size and function in people and cats with HCM [9, 10, 13, 26-29], given
633
634 248 that one third of people and cats with HCM have concomitant left and right ventricular
635
636 249 wall thickening [9, 27]. In a previous study involving a smaller population of cats,
637
638 250 MAPSE and TAPSE were both found to be decreased in cats with HCM compared to
639
640 251 healthy cats [13], with cats in CHF having the lowest MAPSE and TAPSE values.
641
642 252 Another study found similar results for TAPSE [10].
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651
652 253 The present study has confirmed the decrease in MAPSE and TAPSE in cats with
653
654 254 CHF compared to cats not showing clinical signs of congestion in a greater number
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656 255 of cats than previously published. Univariable survival analysis of all cats showed
657
658 256 that those in the lowest quartile for MAPSE FW, MAPSE IVS and TAPSE had a
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660
661 257 poorer outcome than cats in the other quartiles. However, neither MAPSE FW,
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663 258 MAPSE IVS or TAPSE were independently associated with outcome at the
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665 259 multivariable level. Furthermore, MAPSE FW, MAPSE IVS and TAPSE did not show
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667 260 prognostic value at univariable level when cats without clinical signs or cats with CHF
668
669 261 were assessed separately.

671
672 262 These findings confirm that longitudinal function is impaired in cats with HCM, as also
673
674 263 shown in people [15, 22]. This may be compensated by alterations in other cardiac
675
676 264 mechanics such as increased torsion [30,31], or circumferential function [22] so that
677
678 265 longitudinal function is not itself a major prognostic factor for survival as long as other
679
680 266 compensating mechanism are in place. This may explain why a decrease in LVFS
681
682 267 had a prognostic impact in cats with HCM in a previous study [7]. LVFS can be
683
684 268 considered a marker of short axis function, indicating that as long as circumferential
685
686 269 function is maintained, longitudinal function may not impact survival. Once overall
687
688 270 systolic function is decreased, as could be the case when both longitudinal and
689
690 271 circumferential function decrease, survival may be impaired. Circumferential function
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692 272 assessed by advanced imaging are variable in people affected by HCM [22], but
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694 273 some authors have suggested that it may play a role in preserving overall systolic
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696 274 function.

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700 275 Cats with pleural effusion \pm pulmonary oedema had lower MAPSE IVS and TAPSE,
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702 276 but no difference in MAPSE FW, compared to cats with pulmonary oedema.
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711 277 Multivariable analysis in this subgroup identified that lower MAPSE IVS was
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713 278 significantly associated with an increased risk of development of pleural effusion.
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715 279 Pleural effusion is a major clinical presentation in cats with CHF and HCM, and the
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717 280 influence of both right ventricular and left atrial function on the development of pleural
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719 281 effusion has been previously studied [10,17]. Our data complements previously
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721 282 published findings, which show that cats with pleural effusion have decreased right
722
723 283 and interventricular longitudinal function compared to cats with pulmonary oedema
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725 284 as well as decreased left atrial ejection fraction. These findings would be expected
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727 285 since longitudinal deformation is the dominant component of myocardial deformation
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729 286 of the right ventricle [32] and right ventricular wall thickness and right atrial size are
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731 287 shown to be increased in cats with pleural effusion [10]. Furthermore, the decrease
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733 288 in left atrial ejection fraction in cats with pleural effusion \pm pulmonary oedema in this
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735 289 study complements previous data showing a decrease in active atrial emptying in
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737 290 cats with pleural effusion [17]. Mitral annular plane systolic excursion at the
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739 291 interventricular septum was the only factor associated with the development of
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741 292 pleural effusion on multivariable regression analysis, which may indicate a role of the
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743 293 interventricular septum. Based on the available literature and the results of the
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745 294 present study, it is likely that worsening atrial function, decreased right ventricular
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747 295 longitudinal function and possibly more pronounced ventricular interdependence in
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749 296 hypertrophic cardiomyopathy [36] are potentially responsible for the development of
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751 297 pleural effusion. Systolic S' waves measured at the mitral annulus by pulsed wave
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753 298 Doppler results did not correlate with the MAPSE results in cats with CHF in this
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755 299 study. This is likely to reflect the reduced number of cases where the S' wave was
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757 300 available rather than being a true discrepancy between the two techniques,
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770 301 particularly since these two parameters align closely in human patients [29]. When
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772 302 comparing outcome in cats with pulmonary oedema and pleural effusion ± pulmonary
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774 303 oedema, no difference in survival was found. These findings may suggest that once
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776 304 congestive heart failure develops, the prognosis is poor regardless of the clinical
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779 305 presentation (pleural effusion vs pulmonary oedema).
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781 306 The authors are aware that the study has limitations. First of all, being a retrospective
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783 307 study, it may contain limitations related with data collection, survival information and
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785 308 classification. This study included clinical patients, which received tailored treatment
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788 309 based on clinician's judgement and personal preference. The timing from stabilisation
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790 310 to echocardiographic assessment was also variable, as well as the treatment
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792 311 protocol, thus we cannot exclude that the effect of treatment may have influenced the
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794 312 results. Fourteen cats received oral pimobendan, which in the vast majority of the
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796 313 cases would have been administered on the basis of, and therefore following, the
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798 314 echocardiographic examination, but we cannot rule out the possibility that some cats
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800 315 received pimobendan prior to echocardiographic assessment. It is not known how
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802 316 much influence this may have had on the reported MAPSE and TAPSE values.
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805 317 Survival information was based on the information provided by the referring vets and
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807 318 only if insufficient information was provided, a questionnaire was sent to the owners.
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809 319 It is possible that some of the cases may have been incorrectly classified into cardiac
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811 320 or non-cardiac cause of death due to a bias in the information provided. Due to the
812
813 321 retrospective nature of the study, it was not possible to dichotomise the CHF
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815 322 population into pulmonary oedema versus pleural effusion only. The authors elected
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817 323 not to exclude cats with concurrent pulmonary oedema from the pleural effusion
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820 324 group as the focus was on right ventricular function and the development of pleural
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325 effusion. Mitral and tricuspid annular plane systolic excursion were derived from an
326 M-mode technique, and this can be associated with angle-dependency, however the
327 ability to position the M-mode cursor over the 2D image in the anatomical M-mode
328 limits the weakness of the technique. In addition, in a previous study the coefficient of
329 variation and the interobserver bias was deemed to be acceptable for this technique
330 [13]. Mitral and tricuspid annular plane systolic excursions were not normalised to
331 body length, however most cats have body weights that only cover a small range and
332 therefore the lack of normalisation is unlikely to be an important source of error. The
333 presence of pulmonary hypertension was not assessed with echocardiography or
334 invasively. It was beyond the scope of the study to assess correlations with other
335 echocardiographic parameters of right or left ventricular size or function.

336 Conclusion:

337 The present study showed that MAPSE and TAPSE were not independently
338 associated with outcome in cats with HCM. Cats with pleural effusion± pulmonary
339 oedema had lower TAPSE and MAPSE IVS at the univariable level and lower
340 MAPSE IVS in the multivariable model than cats with pulmonary oedema, suggesting
341 a potential role of right ventricular function and of the interventricular septum in the
342 development of pleural effusion.

343 Footnotes:

344 a. IBM® SPSS® Statistics version 22, IBM (UK) Ltd, Portsmouth, UK

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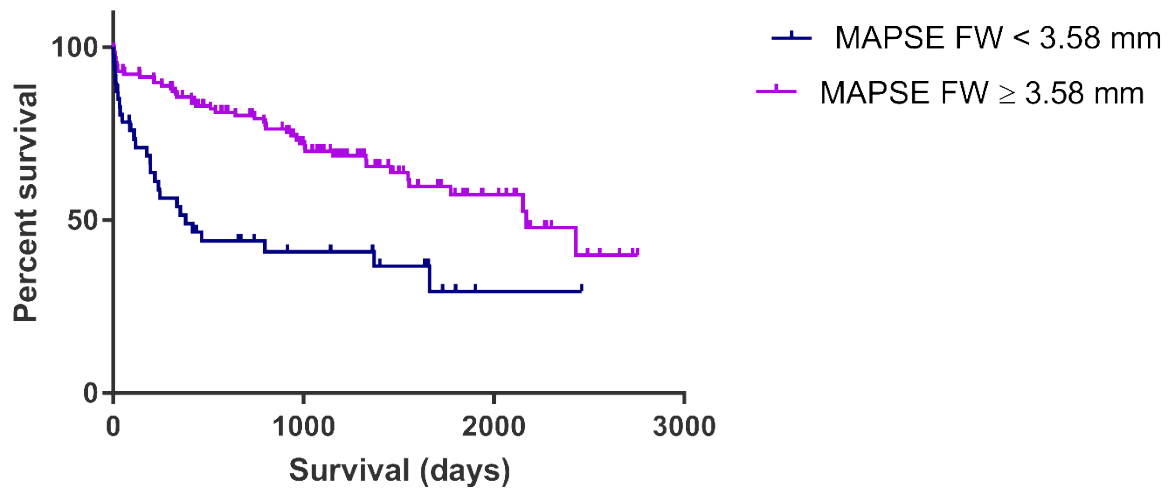
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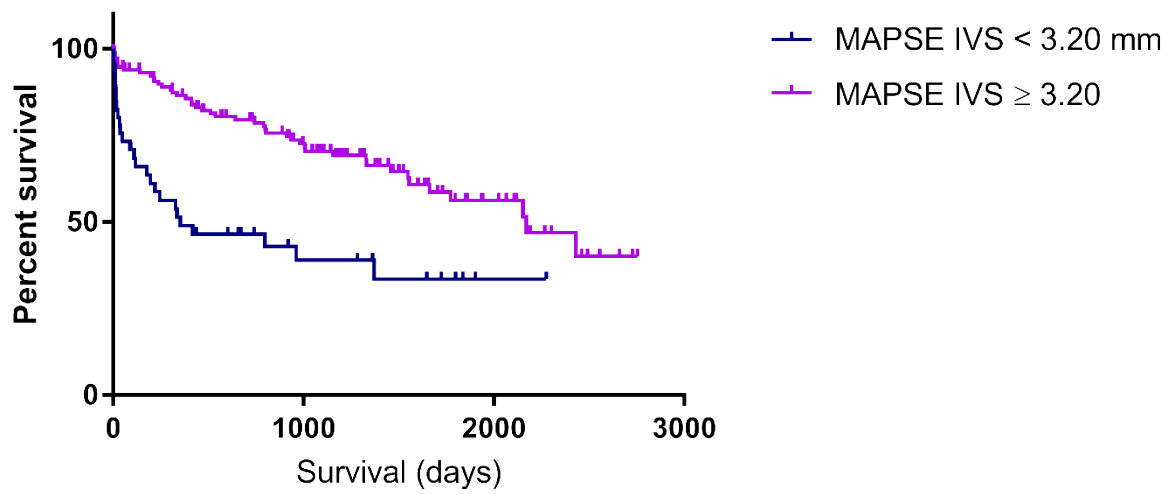
MAPSE FW



Supplemental material

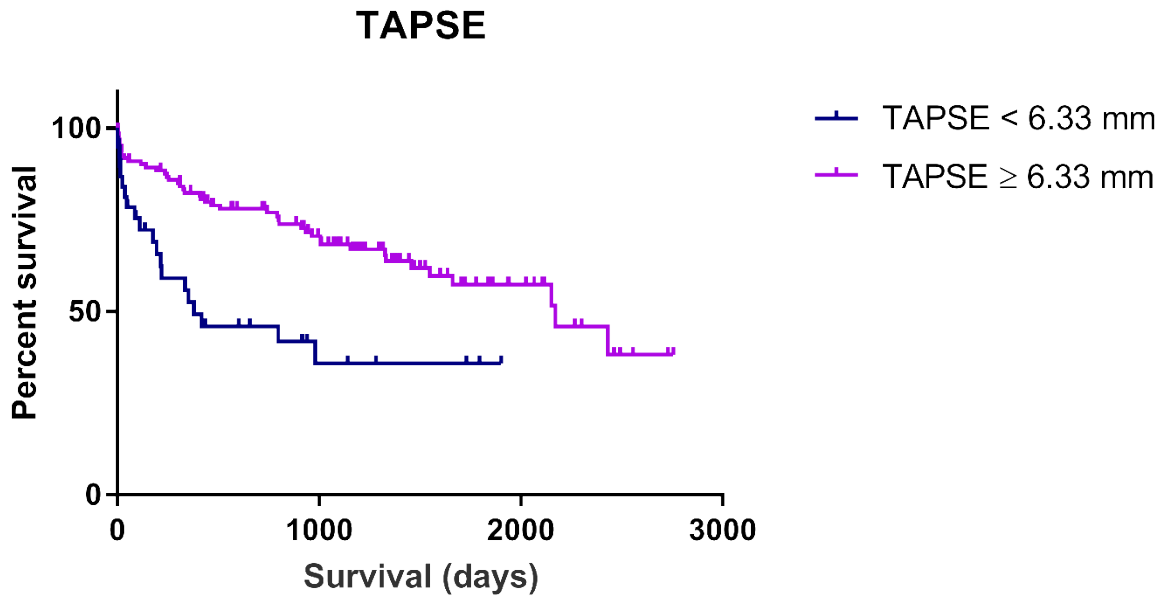
Fig 1: Univariate Kaplan Meyer survival curve for mitral annular plane systolic excursion measured at the left ventricular free wall (MAPSE FW). Log rank test, $p < 0.001$. Median survival time for MAPSE FW < 3.58 mm is 352 (1-1902) days, for MAPSE FW ≥ 3.58 mm median survival time is 2171 (0-2755) days. MAPSE FW – mitral annular plane systolic excursion measured at the free wall,

MAPSE IVS



Supplemental material

Fig 2: Univariate Kaplan Meyer survival curve for mitral annular plane systolic excursion measured at the interventricular septum (MAPSE IVS). Log rank test, $p < 0.001$. Median survival time for MAPSE IVS < 3.20 mm is 352 (0-2276) days, for MAPSE IVS \geq 3.20 mm median survival time is 2171 (2-2755) days. MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum



Supplemental material

Fig 3: Univariate Kaplan Meyer survival curve for tricuspid annular plane systolic excursion (TAPSE). Log rank test, $p < 0.001$

Median survival time for TAPSE < 6.33 mm is 380 (0-1902) days, for TAPSE ≥ 6.33 mm median survival time is 2171 (2-2755) days. TAPSE – tricuspid annular plane systolic excursion

Table 1: Clinical data in 184 cats with HCM

	No clinical signs n=108	Congestive heart failure n=52	Aortic thromboembolism n=12	Syncope/ open mouth breathing n=12	P value
Age (years)	6.52 (2.72-10.02) n=108	6.95 (2.98-10.21) n=52	6.29 (3.52-10.59) n=12	6.38 (2.80-10.61) n=12	0.963
Sex (% male)	78.7% (85/108)	75.0% (39/52)	75.0% (9/12)	58.3% (7/12)	0.470
Breed (% non-pedigree)	77.8% (84/108)	76.9% (40/52)	100.0% (12/12)	83.3% (10/12)	0.309
Weight (kg)	4.81 ± 1.08 n=96	4.64 ± 1.18 n=50	4.44 ± 0.61 n=12	4.69 ± 1.01 n=11	0.623
Murmur (%)	87.0% ^{a, b} (94/108)	55.8% ^b (29/52)	50.0% ^a (6/12)	83.3% (10/12)	<0.001
Gallop (%)	13.0% ^a (14/108)	42.3% ^a (32/52)	33.3% (4/12)	33.3% (4/12)	<0.001
Arrhythmia (%)	10.2% ^a (11/108)	34.6% ^a (18/52)	8.3% (1/12)	25.0% (3/12)	0.002
Arrhythmia on ECG (%)	20.0% ^{a, b} (21/105)	47.8% ^a (22/46)	18.2% (2/11)	75.0% ^b (9/12)	<0.001
Heart rate (bpm)	180 (160-200) n=103	190 (164-200) n=49	180 (148-206) n=12	178 (138-200) n=12	0.755
Respiratory rate (breaths/min)	40 (32-60) n=97	51 (41-60) n=48	48 (40-56) n=11	48 (36-52) n=11	0.063

Table 1: Clinical data in the study population grouped by the absence/ presence and type of clinical signs. Within a line, different superscript letters indicate statistical differences ($p < 0.0083$) between groups. CHF – congestive heart failure, ATE – arterial thromboembolism. Normally distributed data are presented as mean \pm standard deviation, non-normally distributed data are presented as median (IQR1-3) and proportions are presented as percentage (nr of cats with clinical sign/total number of cats).

Table 2 Echocardiographic data in 184 cats with HCM

	No clinical signs n=108	Congestive heart failure n=52	Aortic thromboembolism n=12	Syncope/ open mouth breathing n=12	P value
Max 2D LVWd thickness	7.6 (6.8-8.1) ^a n=108	8.5 (7.7-9.7) ^a n=52	8.6 (6.6-9.9) n=12	8.2 (7.3-8.8) n=12	<0.001
LVFS (%)	53.8 ± 11.2 ^a n=105	43.1 ± 18.0 ^a n=48	45.3 ± 4.0 n=12	51.5 ± 10.8 n=12	<0.001
Infarct (%)	1.9% (2/108)	11.5% (6/52)	0.0% (0/12)	0.0% (0/12)	0.027
LVOTO (%)	74.1% ^a (80/108)	52.4% (22/42)	27.3% ^a (3/11)	72.7% (8/11)	0.003
RVOTO (%)	35.9% (37/103)	32.5% (13/40)	10.0% (1/10)	41.7% (5/12)	0.377
Restrictive filling (%)	8.5% ^{a,b} (4/47)	70.8% ^a (17/24)	55.6% ^b (5/9)	0.0% (0/4)	<0.001
LAD (mm)	15.5 (14.2-16.8) ^a n=100	22.3 (17.5-5.7) ^{a,b} n=44	20.1 (14.8-23.9) n=11	15.9 (15.2 -17.3) ^b n=12	<0.001
LA:Ao	1.27 (1.16-1.44) ^{a,b} n=102	2.17 (1.75-.61) ^{a, c} n=46	2.15 (1.29-2.60) ^b n=11	1.35 (1.24-1.69) ^c n=12	<0.001
LAFS (%)	22.7 ± 6.7 n=97	9.6 ± 4.9 n=43	14.1 ± 9.1 n=11	19.8 ± 6.3 n=10	<0.001
LAEF (%)	60.1 (50.8-66.0) ^{a, b} n=97	22.3 (12.3-9.8) ^{a, c} n=43	27.5 (22.6-46.5) ^b n=11	57.3 (33.6-63.0) ^c n=10	<0.001
SEC/Thrombus (%)	0.0% ^{a,b} (0/108)	49.0% ^a (25/51)	50.0% ^b (6/12)	8.3% (1/12)	<0.001
MAPSE FW (mm)	4.75 ± 0.88 ^a n=105	3.35 ± 1.06 ^{a, b} n=51	3.94 ± 1.31 n=12	4.43 ± 1.12 ^b n=12	<0.001
MAPSE IVS (mm)	4.16 ± 0.78 ^a n=108	3.08 ± 0.97 ^{a, b} n=52	3.61 ± 1.34 n=12	4.14 ± 1.15 ^b n=12	<0.001
TAPSE (mm)	8.41 ± 1.65 ^a n=99	6.10 ± 1.89 ^a n=48	7.50 ± 1.61 n=12	7.77 ± 1.90 n=10	<0.001
S' FW (cm/s)	7.0 (6.0-9.0) ^a n=73	5.0 (3.2-7.0) ^a n=19	6.4 (3.7-10.1) n=6	9.0 (6.5-10.5) n=6	0.001
S' IVS (cm/s)	9.0 (8.0-11.0) ^a n=99	6.0 (5.0-7.0) ^{a, b} n=41	7.3 (6.3-9.1) n=10	9.3 (7.5-14.9) ^b n=9	<0.001

Table 2: Echocardiographic data in the study population grouped by the absence/presence and type of clinical signs. Within a line, different superscript letters indicate statistical differences ($p < 0.0083$) between groups. Normally distributed data are presented as mean \pm standard deviation, non-normally distributed data are presented as median (IQR1-3) and proportions are presented as percentage (nr of cats with echocardiographic finding/total number of cats). CHF – congestive heart failure, ATE – arterial thromboembolism, 2D LVWd – two dimensional end-diastolic left ventricular wall thickness, LVFS – left ventricular fractional shortening, LVOTO – left ventricular outflow tract obstruction, RVOTO – right ventricular outflow tract obstruction, LAD – left atrial diameter in long axis, LA:Ao – left atrium to aorta ratio, LAFS – left atrial fractional shortening, LAEF – left atrial ejection fraction, SEC – spontaneous echo contrast, MAPSE FW – mitral annular plane systolic excursion measured at the free wall, MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum, TAPSE – tricuspid annular plane systolic excursion, S' FW – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the left ventricular free wall, S' IVS – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the interventricular septum

Table 3: Clinical data in 53 cats with hypertrophic cardiomyopathy and congestive heart failure

	Pleural effusion n=32	Pulmonary oedema n=21	P value
Age (years)	9.02 (3.08-11.78) n=32	4.76 (2.58 – 8.38) n=21	0.079
Sex (% male)	71.9% (23/32)	76.2% (16/21)	>0.999
Breed (% non- pedigree)	71.9% (23/32)	90.5% (19/21)	0.167
Weight (kg)	4.52 ± 1.16 n=31	4.72 ± 1.20 n=20	0.561
Murmur (%)	40.6% (13/32)	71.4% (15/21)	0.048
Gallop (%)	53.1% (17/32)	28.6% (6/21)	0.096
Arrhythmia (%)	34.4% (11/32)	23.8% (5/21)	0.544
Arrhythmia on ECG (%)	51.9% (14/27)	30.0% (6/20)	0.152
Heart rate (bpm)	200 (168-200) n=31	180 (160-200) n=19	0.559
Resp rate (breaths/min)	50 (36-60) n=31	60 (48-83) n=18	0.033

Table 3: Clinical data in cats with hypertrophic cardiomyopathy and congestive heart failure . Cats were grouped in the pulmonary oedema group if thoracic radiographs showed alveolar/ interstitial pattern, whereas to be include in the pleural effusion group at radiographic or thoracic ultrasound had to confirm the presence of pleural effusion. A t-test or Mann-Whitney U test (for normally and non- normally distributed data, respectively) to test for significant difference between cats with pleural effusion vs pulmonary oedema.

Table 4: Echocardiographic data in 53 cats with hypertrophic cardiomyopathy and congestive heart failure

	Pleural effusion n=32	Pulmonary oedema n=21	P value
Max 2D LVWd thickness	8.3 (7.6-9.3) n=32	8.5 (7.7-9.8) n=21	0.682
LVFS (%)	39.6 ± 19.0 n=29	48.7 ± 13.4 n=20	0.071
Infarct	19.4% (6/32)	0.0% (0/21)	0.070
LVOTO	34.8% (8/23)	65.0% (13/20)	0.069
RVOTO	14.3% (3/21)	52.6% (10/19)	0.017
Restrictive filling (%)	78.6% (11/14)	66.7% (8/12)	0.665
LAD (mm)	23.3 (19.0-26.8) n=27	20.3 (17.4-22.6) n=18	0.082
LA:Ao	2.44 (1.85-2.61) n=27	2.06 (1.70-2.48) n=20	0.237
LAFS (%)	8.6 ± 4.7 n=24	11.1 ± 4.9 n=20	0.091
LAEF (%)	17.4 (8.6-32.5) n=24	29.1 (20.2-44.1) n=20	0.010
SEC/Thro mbus (%)	54.8% (17/31)	42.9% (9/21)	0.572
MAPSE FW (mm)	3.29 ± 1.17 n=32	3.43 ± 0.91 n=21	0.609
MAPSE IVS (mm)	2.87 ± 1.01 n=32	3.42 ± 0.80 n=21	0.041
TAPSE (mm)	5.68 ± 1.95 n=30	6.86 ± 1.47 n=19	0.020
S' FW (cm/s)	4.5 (3.0-7.0) n=14	4.9 (4.0-5.5) n=6	0.841
S' IVS (cm/s)	6.0 (4.1-7.0) n=24	6.5 (5.0-7.1) n=17	0.441

Table 4. Echocardiographic data in cats with hypertrophic cardiomyopathy and congestive heart failure. Cats were grouped in the pulmonary oedema group if thoracic radiographs showed alveolar/ interstitial pattern, whereas to be include in the pleural effusion group at radiographic or thoracic ultrasound had to confirm the presence of pleural effusion. A t-test or Mann-Whitney U test (for normally and non- normally distributed data, respectively) to test for significant difference between cats with pleural effusion vs pulmonary oedema. 2D LVWd – two dimensional end-diastolic left ventricular wall thickness, LVFS – left ventricular fractional shortening, LVOTO – left ventricular outflow tract obstruction, RVOTO

– right ventricular outflow tract obstruction, LAD – left atrial diameter in long axis, LA:Ao – left atrium to aorta ratio, LAFS – left atrial fractional shortening, LAEF – left atrial ejection fraction, SEC – spontaneous echo contrast, MAPSE FW – mitral annular plane systolic excursion measured at the free wall, MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum, TAPSE – tricuspid annular plane systolic excursion, S' FW – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the left ventricular free wall, S' IVS – peak velocity of systolic mitral annular motion as determined by pulsed wave Doppler measured at the level of the interventricular septum

Table 5: multivariable regression model in cats with pleural effusion ± pulmonary oedema vs pulmonary oedema only

	Odds ratio (95% CI)	p value
MAPSE IVS	0.528 (0.281-0.992)	0.047
Constant	11.390	0.023

Table 5. Multivariable binary logistic regression model of factors associated with development of pleural effusion± pulmonary oedema rather than pulmonary oedema alone. MAPSE IVS – mitral annular plane systolic excursion measured at the interventricular septum