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Incremental predictive value of echocardiographic indices of right ventricular function in the assessment of long-term prognosis in dogs with myxomatous mitral valve disease

Short title: Prognostic value of RV function in MMVD dogs

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Abstract

Introduction: Few studies have evaluated the utility of echocardiographic indices of right ventricular (RV) function in predicting prognosis in dogs with myxomatous mitral valve disease (MMVD).

Animals: Sixty-seven client-owned dogs were diagnosed with MMVD.

Materials and Methods: Clinical cohort study. Dogs diagnosed with ACVIM stage B2, C, or D between April 2014 and March 2017 were enrolled. Long-term outcomes were assessed by telephone or from the medical record. The primary endpoint was defined as cardiac-related death. Echocardiographic indices of RV function, including the RV Tei index, free wall and septal RV longitudinal strain (RVLS), were obtained. Univariable and multivariable Cox proportional hazard analyses were used to identify variables predictive of cardiac-related death.

Results: Twenty-four dogs died during the follow-up period. The median follow-up time was 482 days, and the median survival time for dogs with cardiac-related death was 230 days. For cardiac-related death, peak early diastolic mitral inflow velocity, ACVIM stage C or D, tricuspid regurgitation velocity, RV Tei index, and RV end-diastolic area were predictors in univariable Cox proportional hazard analysis. In

multivariable Cox proportional analysis adjusted for the left atrial to aorta ratio, peak early diastolic mitral inflow velocity, and ACVIM stage, an increase in the Tei index by 0.1 increased the hazard ratio of cardiac-related death by 33% (95% CI, 16 to 70%; *p* = 0.002).

Conclusions: In dogs with MMVD, RV dysfunction assessed by the Tei index is an independent predictor of cardiac-related death.

Keywords: Canine, Mitral regurgitation, Tei index, Strain, Speckle tracking echocardiography

ABBREVIATIONS

DPD	dual pulsed-wave Doppler
Emax	peak early diastolic mitral inflow velocity
FAC	fractional area change
LA/Ao	left atrial to aorta root ratio
LVIDDN	left ventricular end-diastolic diameter normalized for body weight

MMVD	myxomatous mitral valve disease
MR	mitral regurgitation
PA	pulmonary artery
PH	pulmonary hypertension
RV	right ventricle
RVEDA	right ventricular end-diastolic area
RVESA	right ventricular end-systolic area
RVLS	right ventricular longitudinal strain
RV-SD4	standard deviation of the systolic shortening time of four mid-basal segments of right ventricular
STE	speckle tracking echocardiography
TAPSE	tricuspid annulus plane systolic excursion
TDI	tissue Doppler
TR	tricuspid regurgitation

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Introduction

Myxomatous mitral valve disease (MMVD) is the most common heart disease in dogs, and the natural history of these dogs is heterogeneous, with many dogs never developing heart failure or cardiac-related death [1,2]. Therefore, the ability to identify dogs at higher risk could be of clinical value. To date, several echocardiographic indices (i.e., left atrial to aorta root ratio (LA/Ao) [1–3], peak early diastolic mitral inflow velocity (Emax) [1,4], left ventricular (LV) end-diastolic diameter normalized for body weight (LVIDDN) [3,5,6], left atrial function [7]), age [2,5,6], cardiac biomarkers (i.e., N-terminal pro B-type natriuretic peptide [5,6] and cardiac troponin I [6]), and classification of MMVD [2,3,8], have been demonstrated to be good prognostic indicators for dogs with MMVD. In addition, pulmonary hypertension (PH) assessed by a peak tricuspid regurgitation (TR) pressure gradient >55 mm Hg was reported to be a predictor of worse outcome in dogs with MMVD [3].

Right ventricular (RV) dysfunction assessed by various modalities is an independent predictor of poor outcome in human patients with left heart disease, such as mitral regurgitation (MR) and dilated cardiomyopathy [9–13]. Several echocardiographic indices of RV function, including tricuspid annulus plane systolic excursion (TAPSE), fractional area change (FAC), and RV Tei index, have been

demonstrated to be independent prognostic factors in human patients with MR [11–13]. Furthermore, recently, a novel quantitative method for the assessment of myocardial deformation, speckle tracking echocardiography (STE), has been applied for assessing RV function, and free wall RV longitudinal strain (RVLS) derived from STE, which is an index of RV systolic function, has been reported to be related to poor outcomes in human patients with cardiomyopathy and advanced systolic heart failure [14–17]. However, the prognostic value of RVLS is unknown in human patients with MR.

On the other hand, little is available on the prognostic value of echocardiographic indices of RV function in dogs with MMVD [8]. We previously showed that the RV Tei index is an independent predictor of cardiac-related death within one year in dogs with MMVD [8]. However, in this previous study, the utility of other echocardiographic indices of RV function, including RVLS, for assessing prognosis was not assessed. Therefore, the objective of this study was to determine the prevalence of RV dysfunction assessed by echocardiography and to estimate the survival and prognostic value of echocardiographic indices of RV function, including RVLS, on cardiac-related death in dogs with stage B2, C, and D MMVD.

Animals, Materials and Methods

Animals

Sixty-seven client-owned dogs were enrolled in this study. The population included six dogs from our previous study [8]. Dogs were selected based on an echocardiographic diagnosis of MMVD at the Hokkaido University Veterinary Teaching Hospital between April 2014 and March 2017. Informed consent was obtained from all owners involved in this study.

Inclusion and exclusion criteria

Dogs with ACVIM stage B2, C, or D MMVD who underwent physical examination, thoracic radiography, and echocardiography were included in this study. Inclusion criteria were the presence of a left apical systolic murmur (murmur intensity ≥3/6) and the presence of MR on Doppler echocardiography in conjunction with mitral valvular lesions and LA/Ao ≥1.6; LVIDDN ≥1.7; vertebral heart score >10.5 [18]. Dogs were classified as ACVIM stage B2, C, or D based on a previous report [18]. Based on ACVIM consensus statement guidelines, the probability of PH was determined using echocardiography [19]. Dogs were excluded if they had congenital heart disease, dilated cardiomyopathy, or infective endocarditis from this study. Dogs with known

clinically important systemic or other organ-related diseases that were expected to limit the dog's life expectancy, such as tumours, pneumonia, and severe chronic kidney disease, were also excluded.

Echocardiographic measurements

Echocardiographic examinations were performed by one echocardiographer (KN) using two ultrasound machines[c, d] equipped with a 3–7 MHz sector probe[e] and a 3–6 MHz sector probe[f]. HI VISION Preirus[d] was used to measure the RV Tei index by dual pulsed-wave Doppler (DPD). An ECG trace (lead II) was recorded simultaneously with echocardiographic imaging and automatically measured heart rate.

Left ventricular end-diastolic diameter was measured from M-mode echocardiography with a right parasternal short-axis view. The normalized dimensions were calculated according to the following equations [20]: Left ventricular end-diastolic diameter normalized for body weight (LVIDDN) = Left ventricular end-diastolic diameter/(body weight)$^{0.294}$. Left atrium and aorta root diameters and pulmonary artery (PA) valve annulus diameter were obtained with a right parasternal short-axis view, and the LA/Ao and PA/Ao ratios were calculated. Measurements of transmitral Emax and peak late diastolic mitral inflow velocity were obtained with

pulsed-wave Doppler with a left apical four-chamber view, and then the E/A ratio was calculated. Pulmonary artery flow was measured with a left parasternal short-axis view. The acceleration time of PA flow was measured from the onset of the PA flow signal to peak velocity, the ejection time was measured from the onset to the end of the PA flow signal, and then the acceleration time/ ejection time ratio was calculated. The peak TR velocity was measured from the echocardiographic view that provided the highest velocity.

Peak systolic tricuspid annular velocity was determined by tissue Doppler (TDI) at the lateral tricuspid annulus with an apical four-chamber view. Tricuspid annulus plane systolic excursion was obtained by placing an M-mode cursor over the tricuspid annulus with an apical four-chamber view and measuring its amplitude of motion during systole, and then TAPSE was normalized by body weight as follows: normalized TAPSE = TAPSE/(body weight)$^{0.33}$[21]. RV end-diastolic area (RVEDA) and end-systolic area (RVESA) were obtained by tracing the RV endocardium in systole and diastole from the annulus to the apex in the modified apical four-chamber view, which included the RV apex, and then FAC was calculated as (RVEDA - RVESA)/RVEDA × 100%. Right ventricular end-diastolic area and RVESA were normalized according to the following equation: normalized RVEDA (nRVEDA) and

RVESA (nRVESA) = RVEDA/body surface area and RVESA/body surface area. To obtain a modified left apical four chamber view, the transducer was rotated until the maximal plane of the RV basal diameter was obtained. The RV should not be foreshortened, and visualization of the left ventricular outflow tract should be avoided. The RV Tei index was calculated using DPD and TDI as the sum of the isovolumic contraction time and isovolumic relaxation time divided by the ejection time. Tei index was calculated after image acquisition. Tricuspid inflow and PA flow were measured simultaneously using DPD with a left parasternal short-axis view, and the sum of the isovolumic contraction time and isovolumic relaxation time was derived by subtracting the ejection time from the time of cessation of the tricuspid valve peak late diastolic mitral inflow velocity to the onset of the tricuspid valve E-wave in one image (Figure 1A) [22]. The right ventricular Tei index derived from TDI was calculated as the sum of the isovolumic time derived by subtracting the peak systolic tricuspid annular velocity duration from the time from the end of the late diastolic tricuspid annulus velocity to the onset of the early diastolic tricuspid annulus velocity on the basis of TDI recordings (Figure 1B) [23].

Speckle tracking echocardiography was performed using conventional greyscale echocardiography with a modified apical four-chamber view. The frame rate was

optimized to >200 frames/s by narrowing the imaging sector and reducing the depth to focus on the RV. Three consecutive cardiac cycles were stored on a hard drive, and the images were analysed with offline software[i]. The value for STE indices was determined from the average of three cardiac cycles. Care was taken to obtain the best visualization of the RV endocardial border from the base to apex. The endocardial border was manually traced in an end-diastolic frame, and a region of interest was generated followed by adjustments to incorporate the entire RV wall myocardial thickness. The RV wall was divided into inner and outer layers, and the RV-free and septal walls were divided into three segments (basal, middle, and apical). Right ventricular longitudinal strain, which is a systolic index of RV, is defined as the percentage shortening of a region of interest relative to its original length and is expressed as a negative percentage [24]. Right ventricular longitudinal strain was obtained for each segment at the highest peak of the software-generated strain curves. Global RVLS was calculated by averaging values observed in four mid-basal segments of the RV, and free wall and septal RVLS were calculated by averaging values of two segments each along the entire RV (Figure 1C). Systolic shortening time was calculated from the QRS onset to peak longitudinal strain of each of the 4 segments of the RV. To quantify RV intraventricular dyssynchrony, the standard

deviation of the systolic shortening time of four mid-basal segments of the RV (RV-SD4) was calculated using online software[i] (Figure 1D), and RV-SD4 was corrected for the RR interval according to Bazett's formula: Corrected RV-SD4 = RV-SD4/√RR interval [25].

Follow-up

An investigator (TM) conducted telephone interviews with dog owners or referral veterinarians or reviewed medical records to determine the outcomes and the cause of death. The primary endpoint of this study was cardiac-related death. Cardiac-related death was defined as spontaneous death due to progression of clinical signs of heart failure or sudden death when no other cause was evident. Euthanasia due to cardiac reasons was also defined as cardiac-related death, but no dog was euthanized in this study. Death from any other cause was defined as noncardiac death. Survival time was calculated as the time from the day of diagnosis of MMVD to either the day of death or closing time of the study. Dogs were censored in the survival analysis if they were alive at the end of the study period (November 2017) or if they died due to noncardiac-related causes.

199 Statistical analysis

200 Statistical analysis program[h] was used. Power calculations for sample size
201 determination were made based on our previous report [8]. When a statistical power
202 is 80% and level of significance is 0.05, the necessary sample size is 62. The normal
203 distribution of the data was confirmed by the Shapiro Wilk test. All data was normality
204 distributed. Data are presented as the mean ± standard deviation for normally
205 distributed continuous variables. Two-group comparisons for characteristics and
206 echocardiographic indices were performed with unpaired *t*-tests for continuous
207 variables with Bonferroni correction for multiple comparisons and with Fisher's exact
208 test for categorical variables. The relationships between TR velocity, LVIDDN,
209 nRVEDA and echocardiographic indices of RV function were assessed by Pearson's
210 correlation coefficient test with Bonferroni correction for multiple comparisons.
211 Univariable Cox proportional hazard analysis was used in survival analysis to
212 evaluate the hazard ratio of cardiac-related death. Variables with a *p*-value <0.2 on
213 univariable analysis were entered into a multivariable Cox proportional hazard
214 analysis using a forward selection stepwise method and Akaike information criteria
215 adjusted for ACVIM stage, LA/Ao, and Emax. The results of multivariable analysis
216 were considered significant when $p < 0.05$.

The effects of the clinical and echocardiographic variables, such as ACVIM stage, LA/Ao, Emax, and RV Tei index by DPD, on survival were determined with the Kaplan-Meier method, and comparisons of cumulative event rates were performed with the log-rank test. Cut-off values were determined based on the median value (LA/Ao and Emax) or the cited veterinary literature (RV Tei index by DPD > 0.61 [8]). Six dogs included our previous study for establishing cut-off value [8] were not included in survival analysis with the Kaplan-Meier method using cut-off value of RV Tei index.

A *p*-value of less than 0.05 was considered significant.

Results

Characteristics

Sixty-seven dogs from 14 breeds, with Chihuahua being the most frequently represented (n = 15, 22.4%), followed by Shih Tzu (n = 10, 14.9%), Miniature Schnauzer (n = 7, 10.4%), mixed breeds (n =6, 9.0%), and Cavalier King Charles Spaniel (n = 6, 9.0%), were included in this study. Thirty-seven dogs (55.2%) were in ACVIM stage B2, 28 dogs (41.8%) were in ACVIM stage C, and 2 dogs (3.0%) were in ACVIM stage D of MMVD. Characteristics and echocardiographic variables in dogs

235 with MMVD at different stages are summarized in Table 1. Left atrial to aorta root ratio,
236 Emax, peak TR velocity, RV Tei index by DPD, RV Tei index by TDI, nRVEDA, and
237 nRVESA were significantly increased in dogs with ACVIM stage C or D MMVD. The
238 presence of ascites was significantly more common in dogs with ACVIM stage C or D
239 MMVD. At baseline, 35 dogs (52.2%, 15 stage B2; 18 stage C; 2 stage D) received
240 pimobendan, and 24 dogs (35.8%, 7 stage B2; 15 stage C; 2 stage D) received
241 diuretics.
242 Correlations between peak TR velocity, LVIDDN, and nRVEDA and
243 echocardiographic indices of RV function are summarized in Table 2. In contrast to
244 peak systolic tricuspid annular velocity and TAPSE, the FAC (r = -0.44, P <0.001), RV
245 Tei index by DPD (r = 0.57 p <0.001), and RV Tei index by TDI (r = 0.55, P <0.001)
246 were significantly correlated with peak TR velocity. Tricuspid annulus plane systolic
247 excursion (r = 0.48, p <0.001), and normalized TAPSE (r = 0.46, p <0.001) were
248 significantly correlated with LVIDDN. Right ventricular Tei index by TDI (r = 0.63, p
249 <0.001), RV Tei index by DPD (r = 0.61, p <0.001), and septal RVLS (r = 0.42, p
250 <0.001) were all significantly correlated with nRVEDA.
251
252 Survival analysis

253 The primary endpoint (cardiac-related death) occurred in 24 dogs (35.8%), with 19
254 deaths (28.4%) due to progression of clinical signs of heart failure and five sudden
255 deaths (7.5%). Eleven dogs (16.4%) were considered to have died of other causes,
256 and 32 dogs (47.8%) were still alive at the end of the study. The median survival time
257 for all-cause death was 616 days (95% CI, 364 to 730 days), and the median survival
258 time for cardiac-related death was 230 days (95% CI, 131 to 364 days). The median
259 follow-up time for dogs still alive was 482 days (95% CI, 444 to 652 days).

260 Characteristics and echocardiographic variables in dogs with cardiac-related death
261 and without cardiac-related death are summarized in Table 3. Dogs that experienced
262 cardiac-related death exhibited significantly increased Emax, peak TR velocity, RV
263 Tei index by DPD, RV Tei index by TDI, nRVEDA, and nRVESA compared to dogs
264 without cardiac-related death. In contrast, free wall RVLS was not different between
265 patients with and without cardiac-related death. Stage C or D MMVD was more
266 common in dogs with cardiac-related death.

267 Univariable Cox proportional hazard analysis of the predictive value of continuous
268 and categorical variables for cardiac-related death is shown in Table 4. In the
269 univariable analysis, descriptive statistics, including age, presence of ascites, and
270 ACVIM stage C or D, and echocardiographic indices, including LA/Ao, Emax, LVIDDN,

peak TR velocity, TAPSE, FAC, RV Tei index by DPD, RV Tei index by TDI, septal RVLS, nRVEDA, nRVESA, and presence of septal flattening, were significantly associated with cardiac-related death.

Exploratory Multivariable analysis demonstrated that the RV Tei index by DPD (hazard ratio per 0.1 unit increase, 3.30; 95% CI, 1.57 to 6.95; $p = 0.002$) and TAPSE (hazard ratio per 1 unit increase, 1.37; 95% CI, 1.05 to 1.781; $p = 0.019$) remained significant predictors of cardiac-related death after adjusting for ACVIM stage, LA/Ao, and Emax (Table 4).

Kaplan-Meier analysis

Figure 2 shows event-free survival in dogs with MMVD. The long-term outcomes were worse for dogs with ACVIM stage C or D MMVD than for those with ACVIM stage B2 MMVD (log-rank $p < 0.001$), as expected. Similarly, long-term outcomes for dogs with LA/Ao ≥ 2.15 or Emax ≥ 1.1 m/s were worse than those with LA/Ao < 2.15 or Emax < 1.1 m/s (log-rank $p = 0.001$ and $p < 0.001$). In addition, dogs with a Tei index of DPD ≥ 0.61 exhibited worse outcomes than those with a Tei index < 0.61 (log-rank $p < 0.001$).

Discussion

The present study demonstrates that the RV Tei index by DPD and TDI are impaired in dogs with ACVIM stage C or D compared to those with ACVIM stage B2 MMVD, and RV dysfunction as evaluated by the RV Tei index derived from DPD was associated with worse long-term outcomes for dogs with MMVD. In addition, the combined assessment of the RV Tei index and previously reported prognostic indices by echocardiography, such as LA/Ao and Emax, may further enhance the ability to predict worse long-term outcomes in MMVD dogs.

Mitral regurgitation due to MMVD causes volume overload in the left heart, and the onset of left heart failure depends on the severity of volume overload. Indeed, several echocardiographic variables assessing volume overload, such as LA/Ao, Emax, and LVIDDN, have been reported as good prognostic indices in dogs with MMVD [1–3,5,6]. Furthermore, PH was common in dogs with ACVIM stage C, and PH diagnosis assessed by a peak TR pressure gradient >55 mm Hg by echocardiography has been shown to be an independent predictor of worse outcomes in dogs with MMVD [3]. Similar to a previous study, our results showed that peak TR velocity was associated with cardiac-related death on univariate Cox proportional hazard analysis. On the other hand, multivariate Cox analysis revealed

307 that peak TR velocity was not an independent predictor of cardiac-related death. The
308 reason for this finding may be related to the limitation of peak TR velocity
309 measurement. The Doppler measurement of peak TR velocity has been reported to
310 be an inaccurate method for assessing the severity of PH due to several factors, such
311 as the effect of RV contractility, technical difficulties in obtaining an ideal alignment,
312 and the absence of TR [26].

313 In human patients with MR, RV systolic dysfunction is partially related to pulmonary
314 arterial pressure elevation and is an independent predictor of poor outcome [9].
315 Therefore, assessment of RV function may be needed to determine the prognosis in
316 dogs with MMVD. However, little is available on the effect of RV function on the
317 prognosis in dogs with MMVD.

318 The RV Tei index by DPD was impaired in dogs with cardiac-related death and was
319 associated with long-term outcome in dogs with MMVD in multivariate analysis. We
320 previously reported that the RV Tei index by DPD was an independent predictor of
321 cardiac-related mortality within one year in dogs with MMVD [8]. The present result
322 strengthens and expands our previous finding. The present study confirms the
323 prognostic significance of the RV Tei index by DPD in dogs with MMVD. In human
324 patients with PH, it was reported that not only RV systolic dysfunction but also

diastolic dysfunction occurred [27]. The RV Tei index has also been reported to assess both RV systolic and diastolic function in healthy dogs and dog models of mild RV pressure overload [28,29]. Given these findings, the RV Tei index by DPD may be superior to other echocardiographic indices of RV function for assessing prognosis in dogs with MMVD.

The RV Tei index by TDI was also impaired in dogs with cardiac-related death and was significantly correlated with TR velocity. In addition, the RV Tei index by TDI was related to long-term outcome in dogs with MMVD in univariate analysis. Therefore, the RV Tei index by TDI is also useful for predicting worse long-term outcomes in dogs with MMVD. However, in the multivariable analysis, there was no association between the RV Tei index by TDI and long-term outcomes. The reason for differences in echocardiographic methods may be related to differences in the measurement site. The RV Tei index by TDI is measured only at the right ventricular inlet portion, in contrast to that by DPD, which is measured at both the RV inlet and outlet portions; therefore, the RV Tei index by TDI may be unrelated to global RV function. In addition, we previously reported that values of the RV Tei index by TDI were higher than those measured by DPD [22]. Therefore, RV Tei indices derived from different methods should be interpreted with caution and not used interchangeably.

343 Free wall RVLS has been shown to be correlated with invasive haemodynamic
344 variables, and impaired RVLS has been strongly predicted to lead to a poor outcome
345 in human patients with left heart failure due to cardiomyopathy and advanced systolic
346 heart failure [14–16]. However, to date, the prognostic values of RVLS in human
347 patients with MR and dogs with MMVD have not been clarified. In the present study,
348 septal RVLS by STE was impaired, but free wall RVLS was not impaired in dogs with
349 cardiac-related death. In addition, only septal RVLS was related to long-term outcome
350 on univariate analysis. These results are consistent with some previous human
351 studies. Some groups have reported that global RVLS, including the septum and free
352 wall, was superior to free wall RVLS for assessing the prognosis in human patients
353 with left heart disease [15,17]. The superiority of septal RVLS can potentially be
354 explained by the fact that septal RVLS is not only related to RV function but also
355 reflects the influence of LV function. Therefore, septal RVLS can be considered a
356 marker of biventricular function. In addition, free wall RVLS may be affected by
357 hyperkinetic LV contraction due to LV volume overload via interventricular
358 interdependence. Our previous study demonstrated that free wall RVLS significantly
359 decreased in dogs with precapillary PH had the same degree of maximum TR velocity
360 compared to control dogs (median, -12.2%; interquartile range -16.1–-8.5%) [30]. On

361 the other hand, free wall RVLS was enhanced in dogs with ACVIM stage B2 MMVD
362 compared to those with ACVIM stage B1 MMVD [31]. Indeed, while both free wall and
363 septal RVLS were significantly correlated with TR velocity, only free wall RVLS was
364 significantly correlated with LVIDDN in the present study. Hyperkinetic LV contraction
365 can mask a possible free wall RVLS impairment.
366 In contrast to the RV Tei index, other echocardiographic indices of RV function
367 were not impaired in dogs with ACVIM stage C or D or in those with cardiac-related
368 death. The TAPSE increase, which represents enhanced RV contractility, was
369 correlated with worse outcomes in dogs with MMVD in univariate and multivariate
370 analyses. This finding conflicts with a previous human study [11] in which decreased
371 TAPSE was an independent predictor of worse outcomes in human patients with
372 secondary MR due to dilated cardiomyopathy [11]. This discrepancy might be due to
373 the difference between primary and secondary MR or differences between dogs and
374 humans. Tricuspid annulus plane systolic excursion has been reported to be no
375 different among dogs with MMVD, regardless of the ACVIM stage or the severity of
376 PH [21,31]. Tricuspid annulus plane systolic excursion is affected by hyperkinetic LV
377 contraction caused by LV volume overload via interventricular interdependence [32]
378 and RV volume overload due to TR [33]. Indeed, there was a significant positive

correlation between normalized TAPSE and LVIDDN (r = 0.46), similar to a previous study [21]. Therefore, the present result suggests that the increase in TAPSE reflects more severe LV volume overload. Further studies are needed to validate the effect of the severity of TR on echocardiographic indices of RV function.

There remain several limitations in the present study. The gold standard of haemodynamic measurement, cardiac catheterization, was not performed. Another limitation is the small number of dogs with cardiac-related death. Therefore, the statistical power for determination of prognosis is low and because the number of explanatory variables relative to deaths is high, the multivariable model might be unstable and not accurately predictive of outcome in a larger population of dogs with MMVD. In this study, instances of non-cardiac death were censored, and because non-cardiac death is a competing event, this might have led to informative censoring and over-estimation of cumulative incidence. Although stepwise forward selection was used for multivariable Cox proportional hazard analysis in this study, there are several limitations of stepwise selection such as bias in parameter estimation. In addition, this study was a retrospective design. Retrospective studies increase the risk of uncontrolled systematic errors, and some echocardiographic variables were not available at baseline. The dogs were administered many medications, and it is

possible that medications influenced the echocardiographic indices and survival time. Furthermore, it was difficult to standardize the treatment. In the present study RV strain was measured using software for LV strain. Finally, although the inter- and intra-observer repeatability of RV Tei index by DPD were higher than those by TD and pulsed-wave Doppler in our previous study [22], DPD is a novel application of ultrasonography that is available on only a few ultrasonographic systems. Therefore, the utility of the Tei index by DPD may be limited in clinical settings.

Conclusions

The RV Tei index measured by DPD is an independent predictor of cardiac-related death in dogs with ACVIM stage B2, C, or D MMVD. Therefore, assessment of the RV Tei index in combination with traditional left heart assessments such as LA/Ao and Emax will result in more accurate prediction of worse long-term outcomes and may have clinical implications for better management of dogs with MMVD.

Conflicts of interest

None of the authors have any financial or personal relationship that would inappropriately influence or bias the contents of this paper.

Footnotes

c. Artida, Toshiba Medical Systems Corp., Tochigi, Japan.

d. HI VISION Preirus, Hitachi Aloka Medical Ltd., Tokyo, Japan.

e. PST-50BT, Toshiba Medical Systems Corp., Tochigi, Japan.

f. EUP-S52, Hitachi Aloka Medical Ltd., Tokyo, Japan.

g. 2D Wall Motion Tracking, Toshiba Medical Systems Corp., Tochigi, Japan.

h. JMP, version 13.0, SAS Institute Inc., Cary, NC, USA.

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552

553 **Table 1. Comparison of clinical and echocardiographic variables in dogs with**

554 **ACVIM B2 and C or D of MMVD.**

Variables	Stage B2 (n = 37)	Stage C or D (n = 30)	*p* value
Number	B2 (37)	C (28), D (2)	
Age (year)	10.9 ± 2.4	12.6 ± 1.9	0.003
Body weight (kg)	5.1 ± 2.6	5.3 ± 2.0	0.806
Sex (male/female)	19 / 18	20 / 10	0.465
Heart rate (bpm)	138 ± 24	130 ± 24	0.169
Mean blood pressure (mmHg)	114 ± 11	115 ± 18	0.847
High probability of PH	12 (32%)	21 (70%)	0.005
Ascites (Yes/No) *	0 / 37 (0% / 100%)	5 / 25 (17% / 83%)	0.001
Pimobendan (Yes/No)	15 / 22 (41% / 59%)	20 / 10 (67% / 33%)	0.032
Diuretics (Yes/No) *	7 / 30 (19% / 81%)	17 / 13 (57% / 43%)	0.001
LA/Ao *	2.01 ± 0.30	2.43 ± 0.43	<0.001
Emax (m/s) *	1.01 ± 0.25	1.35 ± 0.37	<0.001
LVIDDN	1.88 ± 0.34	1.99 ± 0.28	0.168
TR velocity (m/s) *	3.1 ± 0.6	3.8 ± 0.7	<0.001
S'_{TV} (cm/s)	13.9 ± 3.9	14.1 ± 3.4	0.793
TAPSE (mm)	11.8 ± 2.6	12.2 ± 2.6	0.507
Normalized TAPSE	0.70 ± 0.15	0.74 ± 0.15	0.250
FAC (%)	41.1 ± 7.5	39.3 ± 10.3	0.431
Tei index by DPD *	0.38 ± 0.12	0.65 ± 0.23	<0.001
Tei index by TDI *	0.53 ± 0.09	0.73 ± 0.18	<0.001
Free wall RVLS (-1%)	24.1 ± 6.5	26.0 ± 5.3	0.175
Septal RVLS (-1%)	20.5 ± 5.2	18.8 ± 5.0	0.183
RV-SD4 (msec)	22.6 ± 10.2	27.1 ± 9.5	0.068
AT/ET	0.36 ± 0.10	0.30 ± 0.09	0.016
nRVEDA (cm^2/m^2) *	15.2 ± 2.9	19.3 ± 5.2	<0.001
nRVESA (cm^2/m^2) *	9.0 ± 2.2	11.9 ± 4.3	<0.001
Septal flattening (Yes/No)	2 / 32 (6% / 94%)	5 / 19 (21% / 79%)	0.086

555 AT/ET, acceration time to ejection time ratio; DPD, dual pulsed-wave Doppler; E,

peak early diastolic mitral inflow velocity; FAC, fractional area change; LA/Ao, left atrial to aorta root ratio; LVIDDN, normalized left ventricular end-diastolic diameter; nRVEDA, normalized right ventricular end-diastolic area; nRVESA, normalized right ventricular end-systolic area; PH, pulmonary hypertension; RVLS, right ventricular longitudinal strain; RV-SD4, standard deviation of the systolic shortening time of right ventricular 4segment corrected for RR interval according to Bazett's formula; S'$_{TV}$, peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler; TR, tricuspid regurgitation .

* $p < 0.002$ were statistically significant after Bonferroni correlation.

Table 2. Correlation between TR velocity, LVIDDN, and nRVEDA and echocardiographic indices of RV function.

Variables	TR velocity		LVIDDN		nRVEDA	
	r	*p* value	*r*	*p* value	*r*	*p* value
S'_{TV} (cm/s)	0.03	0.849	0.23	0.059	-0.14	0.238
TAPSE (mm)	0.09	0.540	0.48*	< 0.001	0.18	0.157
Normalized TAPSE	0.03	0.842	0.46*	< 0.001	0.22	0.073
FAC (%)	-0.45*	< 0.001	-0.13	0.292	-0.27	0.025
Tei index by DPD	0.57*	< 0.001	0.39	0.002	0.61*	< 0.001
Tei index by TDI	0.55*	< 0.001	0.20	0.102	0.63*	< 0.001
Free wall RVLS (%)	0.40	0.003	-0.26	0.034	0.15	0.232
Septal RVLS (%)	0.33	0.014	-0.07	0.583	0.42*	< 0.001

DPD, dual pulsed-wave Doppler; FAC, fractional area change; LVIDDN, normalized left ventricular end-diastolic diameter; nRVEDA, normalized right ventricular end-diastolic area; RVLS, right ventricular longitudinal strain; S'_{TV}, peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler; TR, tricuspid regurgitation.

* $p < 0.002$ were statistically significant after Bonferroni correlation.

575

576 **Table 3. Comparison of clinical and echocardiographic variables in dogs with**

577 **cardiac-related death and without cardiac-related death.**

Variables	Dogs with cardiac-related death (n = 24)	Dogs without cardiac-related death (n = 43)	*p* value
Age (year)	12.0 ± 2.0	11.4 ± 2.5	0.298
Body weight (kg)	5.3 ± 2.5	5.2 ± 2.1	0.841
Sex (male/female)	15 / 9	24 / 19	0.853
Heart rate (bpm)	139 ± 24	130 ± 24	0.158
Mean blood pressure (mmHg)	114 ± 14	115 ± 17	0.735
Ascites (Yes/No)	4 / 20 (17% / 83%)	2 / 41 (5% / 95%)	0.107
ACVIM stage (B/C or D) *	7 / 17 (29% / 71%)	30 / 13 (70% / 30%)	0.001
High probability of PH	18 (75%)	15 (35%)	0.002
Pimobendan (Yes/No)	15 / 9 (63% / 37%)	20 / 23 (47% / 53%)	0.207
Diuretics (Yes/No)	12 / 12 (50% / 50%)	12 / 31 (28% / 72%)	0.072
LA/Ao	2.39 ± 0.47	2.09 ± 0.34	0.004
Emax (m/s) *	1.38 ± 0.38	1.04 ± 0.27	<0.001
LVIDDN	2.07 ± 0.29	1.85 ± 0.30	0.004
TR velocity (m/s) *	3.8 ± 0.8	3.1 ± 0.5	<0.001
S'_{TV} (cm/s)	14.3 ± 3.5	13.8 ± 3.8	0.562
TAPSE (mm)	13.0 ± 2.8	11.4 ± 2.4	0.016
Normalized TAPSE	0.78 ± 0.16	0.68 ± 0.14	0.015
FAC (%)	38.2 ± 9.5	41.5 ± 8.3	0.155
Tei index by DPD *	0.68 ± 0.23	0.41 ± 0.15	<0.001
Tei index by TDI *	0.74 ± 0.18	0.55 ± 0.13	<0.001
Free wall RVLS (-1%)	24.1 ± 7.4	25.7 ± 4.9	0.291
Septal RVLS (-1%)	18.0 ± 5.7	20.8 ± 4.6	0.032
RV-SD4 (msec)	25.4 ± 10.6	24.2 ± 9.9	0.647
AT/ET	0.31 ± 0.10	0.35 ± 0.10	0.078
nRVEDA (cm^2/m^2) *	19.7 ± 5.6	15.6 ± 3.0	<0.001
nRVESA (cm^2/m^2) *	12.3 ± 4.2	9.2 ± 1.5	<0.001
Septal flattening (Yes/No)	5 / 14 (26% / 74%)	2 / 37 (5% / 95%)	0.025

AT/ET, acceration time to ejection time ratio; DPD, dual pulsed-wave Doppler; E, peak early diastolic mitral inflow velocity; FAC, fractional area change; LA/Ao, left atrial to aorta root ratio; LVIDDN, normalized left ventricular end-diastolic diameter; nRVEDA, normalized right ventricular end-diastolic area; nRVESA, normalized right ventricular end-systolic area; PH, pulmonary hypertension; RVLS, right ventricular longitudinal strain; RV-SD4, standard deviation of the systolic shortening time of right ventricular 4segment corrected for RR interval according to Bazett's formula; S'_{TV}, peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler; TR, tricuspid regurgitation.

* $p < 0.002$ were statistically significant after Bonferroni correlation.

590

591 **Table 4.** Univariate and multivariate Cox proportional hazard analysis of the

592 predictive value for cardiac-related death in dogs with MMVD.

Variables	Univariate Hazard ratio (95% CI)	*p*	† Multivariate Hazard ratio (95% CI)	*p*
Age (per 1 year increase) *	1.23 (1.01–1.52)	0.035		
Body weight (per 1kg increase)	1.01 (0.84–1.21)	0.886		
Sex (male)	1.18 (0.52–2.83)	0.691		
Heart rate (per 10 bpm increase)	5.33 (0.60–52.7)	0.136		
Mean blood pressure (per 10mmHg increase)	1.28 (0.78–1.35)	0.834		
Ascites (Yes) *	4.23 (1.19–11.87)	0.028		
ACVIM stage (C or D) *	4.66 (2.00–12.10)	<0.001	2.64 (0.30–23.25)	0.382
Pimobendan (Yes)	1.37 (0.61–3.27)	0.449		
Diuretics (Yes)	1.69 (0.75–3.82)	0.204		
LA/Ao (per 0.1 increase) *	1.19 (1.08–1.31)	<0.001	0.13 (0.01–1.88)	0.138
Emax (pre 0.1 m/s increase) *	1.30 (1.16–1.45)	<0.001	1.60 (0.21–12.07)	0.646
LVIDDN (per 0.1 increase) *	1.20 (1.06–1.36)	0.005		
TR velocity (per 0.1 m/s increase) *	1.10 (1.05–1.17)	<0.001		
S'_{TV} (per 1 cm/s increase)	1.04 (0.93–1.15)	0.532		
TAPSE (per 1 mm increase) *	**1.22 (1.05–1.42)**	0.012	**1.37 (1.05–1.78)**	**0.019**
Normalized TAPSE (per 0.1 increase) *	1.48 (1.11–1.98)	0.008		
FAC (per 1% increase) *	0.94 (0.88–0.99)	0.016		
Tei index by DPD (per 0.1 increase) *	**1.81 (1.47–2.26)**	**<0.001**	**3.30 (1.57–6.95)**	**0.002**
Tei index by TDI (per 0.1 increase) *	1.65 (1.34–2.00)	<0.001		
Free wall RVLS (per -1% increase)	0.95 (0.87–1.03)	0.194		
Septal RVLS (per -1% increase) *	0.91 (0.94–0.98)	0.017		
RV-SD4 (per 1 msec increase)	1.01 (0.97–1.05)	0.663		

AT/ET (per 0.1 increase)	0.66 (0.43–1.01)	0.057
nRVEDA (per 1 cm^2/m^2 increase) *	1.17 (1.09–1.26)	<0.001
nRVESA (per 1 cm^2/m^2 increase) *	1.22 (1.11–1.33)	<0.001
Septal flattening (Yes) *	5.78 (1.76–16.93)	0.006

† Adjusted for ACVIM stage, LA/Ao, and Emax.

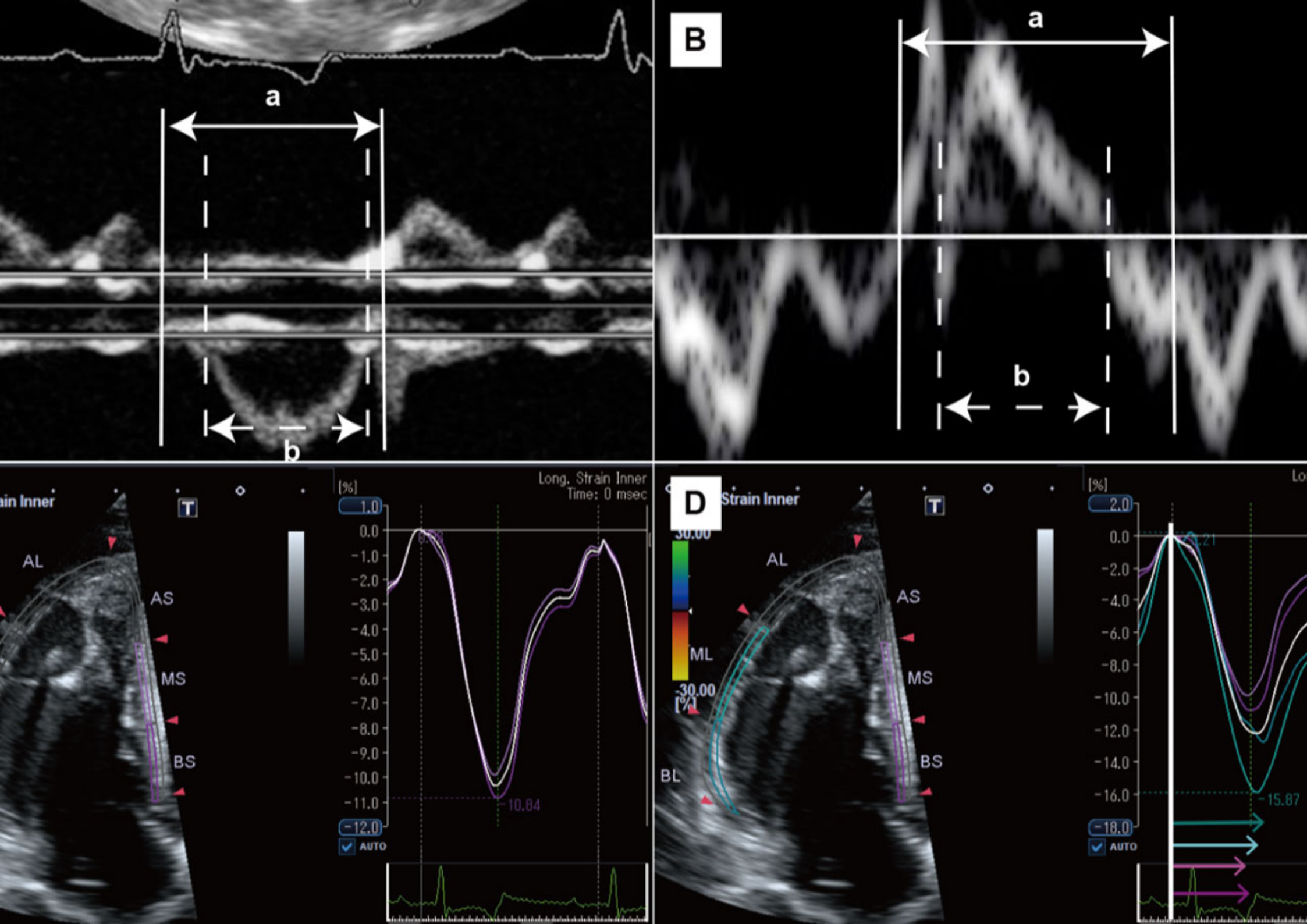
AT/ET, acceration time to ejection time ratio; DPD, dual pulsed-wave Doppler; E, peak early diastolic mitral inflow velocity; FAC, fractional area change; LA/Ao, left atrial to aorta root ratio; LVIDDN, normalized left ventricular end-diastolic diameter; nRVEDA, normalized right ventricular end-diastolic area; nRVESA, normalized right ventricular end-systolic area; PH, pulmonary hypertension; RVLS, right ventricular longitudinal strain; RV-SD4, standard deviation of the systolic shortening time of right ventricular 4segment corrected for RR interval according to Bazett's formula; S'_{TV}, peak systolic tricuspid annular velocity; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler; TR, tricuspid regurgitation.

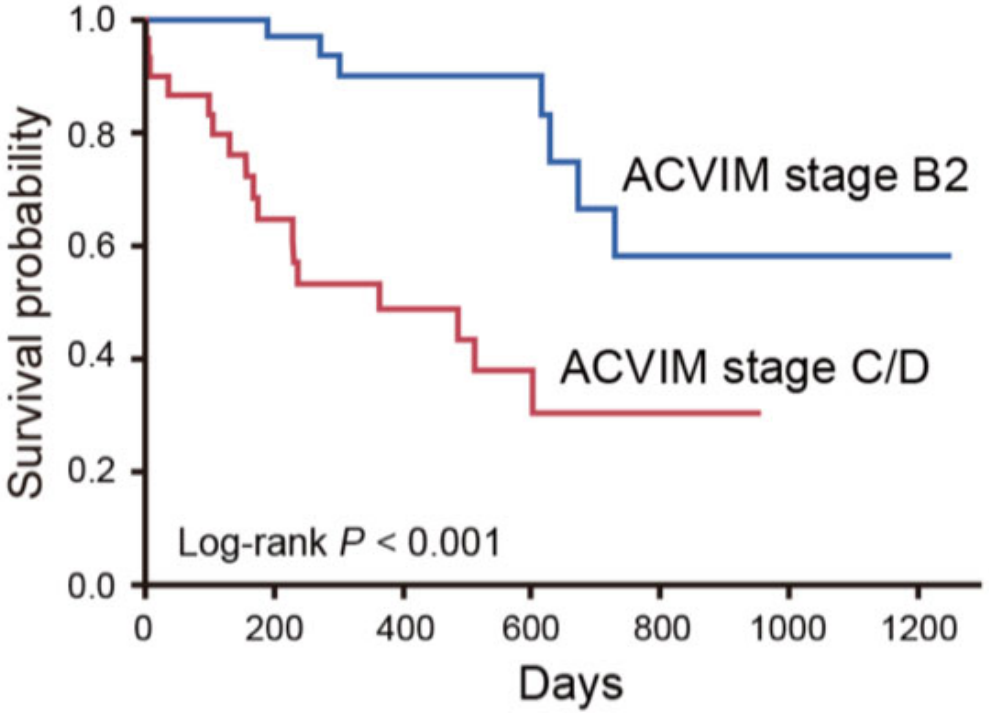
* $p < 0.05$.

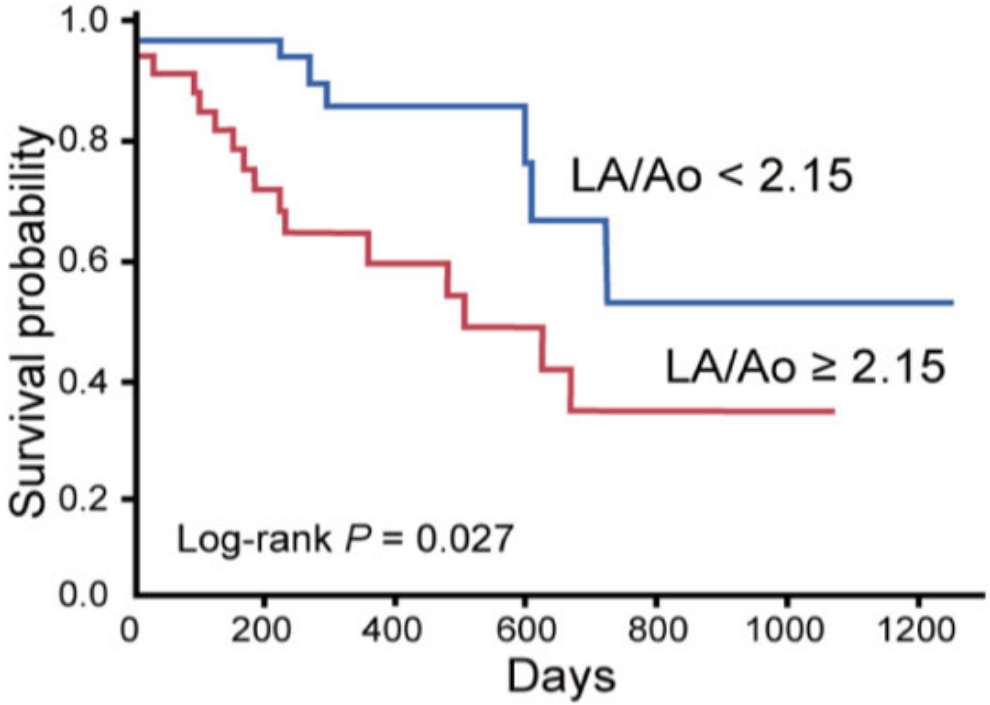
Figure Legends

Figure 1. Echocardiographic images illustrating the technique used to measure the right ventricular (RV) Tei index and speckle tracking echocardiographic indices. (A) The RV Tei index was calculated using dual-pulsed Doppler as follows: (a - b)/b. (B) The RV Tei index was calculated using tissue Doppler at the lateral tricuspid annulus with an apical four-chamber view as follows: (a - b)/b. (C) The RV free wall and septum were each automatically divided into three segments (apical, middle, and basal). The free wall and septal right ventricular longitudinal strain (RVLS) were calculated by averaging the peak longitudinal strain values in each two mid-basal segments of the RV with a modified apical four-chamber view. This image shows the septal RVLS. (D) RV-SD4 was calculated as the standard deviation of systolic shortening time of the four mid-basal segments of RV and corrected for the R-R interval (Bazett's formula). The coloured arrows indicate each segmental systolic shortening time. AL = apical lateral free wall; AS = apical septum; BL = basal lateral free wall; BS = basal septum, ML = middle lateral free wall; MS = middle lateral septum; RV-SD4 = standard deviation of the systolic shortening time of four mid-basal segments of right ventricle corrected for RR interval according to Bazett's formula.

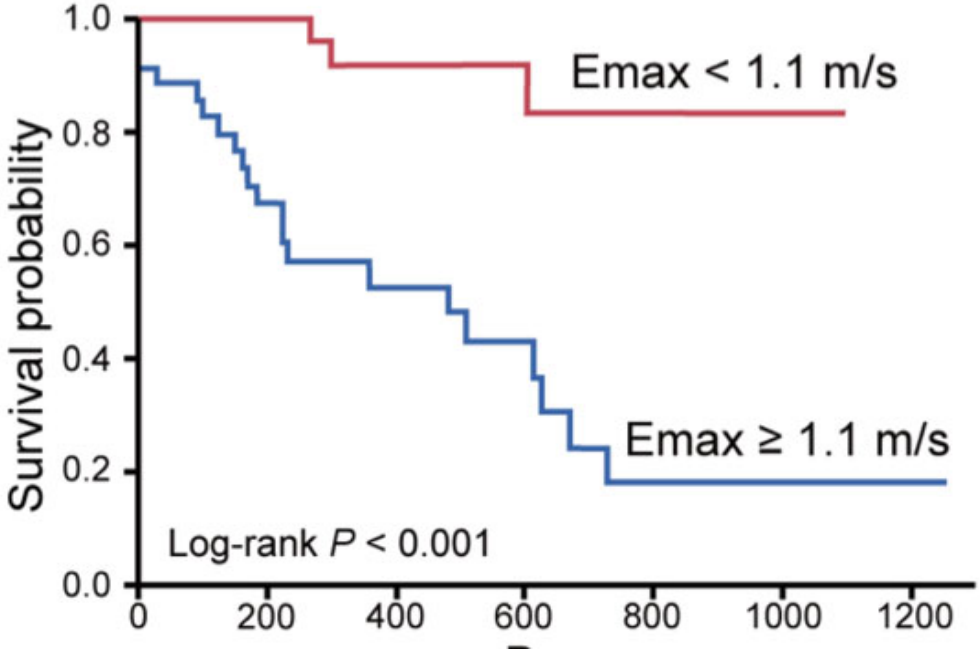
Figure 2. Kaplan-Meier curves for long-term survival in dogs with MMVD. (A) Kaplan-Meier analysis revealed that long-term outcomes for patients with ACVIM stage C or D (median survival time, 364 days; 95% CI, 168 days to not applicable) were worse than those for patients with ACVIM stage B2 MMVD (median survival time, not reached; 95% CI, 629 days to not applicable). (B) Dogs with LA/Ao ≥ 2.15 (median survival time, 486 days; 95% CI, 231 days to not applicable) exhibited worse outcomes than those with LA/Ao < 2.15 (median survival time, not reached; 95% CI, 616 days to not applicable). (C) Dogs with Emax ≥ 1.1 m/s (median survival time, 364 days; 95% CI, 168 to 616 days) showed worse outcomes than those with Emax < 1.1 m/s (median survival time, not reached; 95% CI, 730 days to not applicable). (D) The long-term outcome for patients with a right ventricular Tei index by DPD ≥ 0.61 (median survival time, 237 days; 95% CI, 131 to 486 days) was worse than for patients with a right ventricular Tei index by DPD < 0.61 (median survival time, not reached; 95% CI, 629 days to not applicable).


a
b
B
a
b
AL
AS
MS
BS
[%]
Long. Strain Inner
Time: 0 msec
1.0
0.0
-1.0
-2.0
-3.0
-4.0
-5.0
-6.0
-7.0
-8.0
-9.0
-10.0
-11.0
-12.0
AUTO
-10.84
D
Strain Inner
30.00
ML
-30.00
[%]
BL
AL
AS
MS
BS
[%]
2.0
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
-16.0
-18.0
AUTO
-15.87

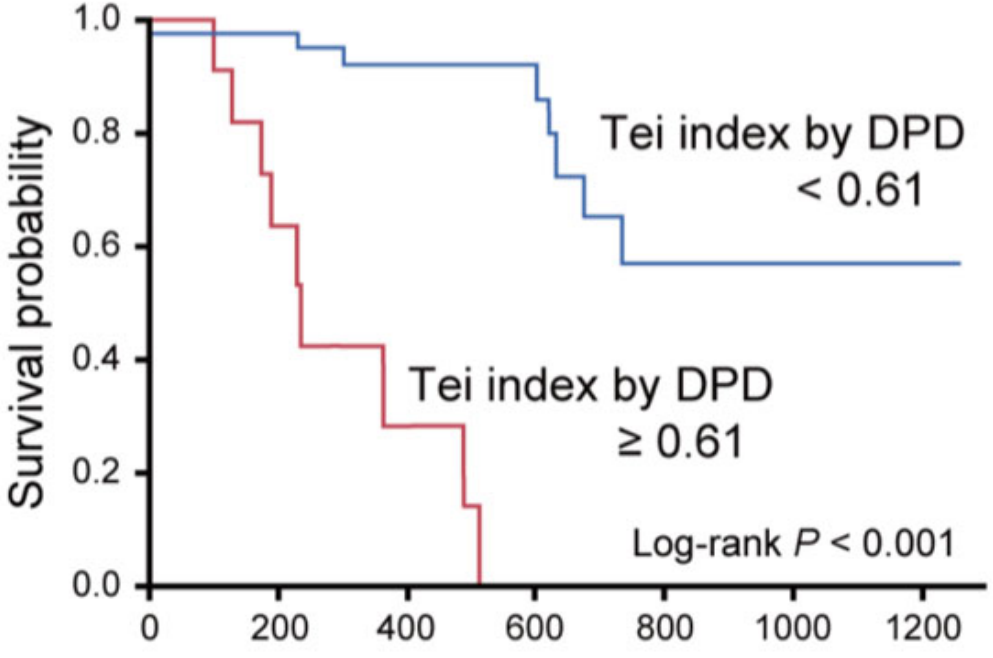

1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
ACVIM stage B2
ACVIM stage C/D
Log-rank P < 0.001
0
200
400
600
800
1000
1200
Days


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
LA/Ao < 2.15
LA/Ao ≥ 2.15
Log-rank P = 0.027
0
200
400
600
800
1000
1200
Days

C


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
Emax < 1.1 m/s
Emax ≥ 1.1 m/s
Log-rank P < 0.001
0
200
400
600
800
1000
1200

D


1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
Tei index by DPD
< 0.61
Tei index by DPD
≥ 0.61
Log-rank P < 0.001
0
200
400
600
800
1000
1200