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Correlation of red cell distribution width and left atrial enlargement in Maltese dogs with myxomatous mitral valve disease in Republic of Korea

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Abstract

Myxomatous mitral valve disease (MMVD) is a degenerative disease of the valve leaflets, causing left atrial dilatation and eccentric hypertrophy of the left ventricle by hemodynamic instability. Red cell distribution width (RDW) is a hematologic parameter that indicates the variation of red blood cell volume and size, reflecting anisocytosis. Human studies have found that anisocytosis is associated with poor prognosis in heart disease patients, and recent veterinary studies have also confirmed that the increase in RDW is associated with high mortality in MMVD patients. Medical records of 37 Maltese dogs with MMVD were retrospectively reviewed. When comparing RDW among the MMVD stage groups, there was a significant difference between stage B1, B2 and C. A significant and strong correlation between RDW and the left atrial-to-aortic ratio was identified. RDW was significantly correlated with the reticulocyte count independent of hematocrit, and the reticulocyte count exhibited a significant increase at stage C. This suggests that the congestive heart failure secondary to MMVD could be a contributory factor leading to an elevation in RDW. In conclusion, elevated RDW may associated with left atrial enlargement and progression of MMVD.

Keywords: dogs; myxomatous mitral valve disease; erythrocyte indices; reticulocytosis

Introduction

Myxomatous mitral valve disease (MMVD) is a significant and common heart disease in dogs, which is characterized by degeneration of the mitral valve leaflets. This degenerative change leads to hemodynamic instability between the left atrium and ventricle through mitral regurgitation, causing an increase in left atrial pressure and cardiac remodeling. Given the progressive nature of valve degeneration, structural alterations and functional impairment of the heart perpetuate, potentially leading to the manifestation of congestive heart failure [1]. Therefore, periodic monitoring is crucial to assess and manage MMVD.

To date, the diagnosis and monitoring of MMVD primarily rely on various radiographic and echocardiographic indices. Radiographic indices such as the vertebral heart score (VHS) are employed in the assessment of MMVD. Regarding echocardiographic indices, the left-atrial-to-aortic-root ratio (LA/Ao ratio) and the normalized left ventricular internal diameter in diastole (LVIDDn) are used in the grading of MMVD [2]. These radiographic and echocardiographic parameters

offer a comprehensive understanding of the morphological and functional deviations inherent to MMVD. However, despite the hemodynamic nature of MMVD pathophysiology, the contribution of hematological indices to the diagnosis, management, and prognosis of MMVD remains relatively under-investigated.

Red cell distribution width (RDW) is a hematologic parameter that indicates the variation of red blood cell volume and size, reflecting anisocytosis [3]. RDW is usually increased by reticulocytosis secondary to regenerative anemia, but can also increase in various systemic abnormalities such as inflammation, oxidative stress and kidney disease [3]. Human medical studies have suggested a correlation between elevated RDW values and poor prognosis in patients with heart diseases [4–6]. Additionally, a recent veterinary study involving dogs with MMVD has indicated a significant association between increased RDW and heightened mortality risk [7].

This study explored the feasibility of utilizing RDW as a hematological parameter for the diagnosis or monitoring of MMVD by investigating the correlation between left atrial enlargement and RDW in dogs with MMVD.

Materials and Methods

Animals

Medical records from 37 Maltese dogs diagnosed with MMVD that were presented to the Veterinary Medical Teaching Hospital of Chungnam National University from January 2013 to December 2022 were retrospectively reviewed. MMVD was diagnosed based on physical examination, thoracic radiography, and echocardiographic findings. According to the American College of Veterinary Internal Medicine (ACVIM) guidelines, patients were classified into MMVD stage B1 (n = 11), B2 (n = 15), or C (n = 11). Ten Maltese dogs with normal physical examination results and unremarkable thoracic radiography, echocardiography, complete blood count (CBC), and serum biochemical profiles were included as controls. All 47 dogs exhibited no laboratory evidence of anemia.

Thoracic radiography

The VHS was derived from the patients' thoracic radiographs. Radiographs were taken in the right lateral recumbency. The long axis spanned from the ventral aspect of the mainstem bronchi to the cardiac apex, while the short axis was measured at the heart's widest point perpendicular to the left atrium. The VHS was determined by summing these measurements and comparing them to the number of vertebral bodies, beginning from the anterior end of the fourth thoracic vertebra.

Echocardiography

Echocardiographic examinations assessed the mitral valve and mitral regurgitation, as well as the dimensions of the left ventricle and left atrium. Color Doppler images and two-dimensional echocardiography from the left parasternal long-axis four-chamber view were used to evaluate mitral valve and mitral regurgitation. The LA/Ao ratio was determined from the right parasternal short-axis view at the heart base. The left ventricular internal diameter at end-diastole (LVIDD) was obtained from the M-mode, and LVIDDn was evaluated using the formula = LVIDD [cm]/body weight [kg]$^{0.294}$

Blood analysis

Blood samples obtained from dogs that had fasted for a minimum of 12 hours were subjected to a CBC. Hematological parameters, including RDW, were measured using the commercial automated CBC analyzer (Advia 120 Hematology System; Siemens, Germany) with a reference range for RDW of 11.9% to 14.5%.

Statistical analysis

Statistical analyses were performed using commercially available computer software (IBM SPSS Statistics ver. 29.0; IBM Corp., USA). A normal distribution of radiographic, echocardiographic, and laboratory variables was assessed using the Shapiro-Wilk test. Mean comparisons among the four groups were conducted using analysis of covariance (ANOVA), with subsequent *post-hoc* testing applying the Bonferroni correction. The association between all variables and RDW was explored using the Spearman correlation analysis. A p-value of less than 0.05 was determined as the criterion for statistical significance for all analyses.

Results

A total of 47 Maltese dogs were evaluated and classified according to ACVIM stage criteria. Among these, 11 and 14 patients were diagnosed with stage B1 and B2, respectively. There were 12 patients classified as stage C. The age, sex and body weight showed no significant differences between the control, B1, B2 and C groups (Table 1).

While comparisons of diagnostic imaging indices among ACVIM stage groups were conducted, VHS, LA/Ao ratio and LVIDDn showed a significant difference between the B1, B2 and C groups (Table 2). In the control group, VHS, LA/Ao ratio, and LVIDDn showed significant differences when compared with the B2 and C groups, but not with the B1 group.

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Table 1. Demographic distribution according to American College of Veterinary Internal Medicine stage

Characteristic	Total (n = 47)	Group				*p*-value
		Control (n = 10)	B1 (n = 11)	B2 (n = 14)	C	
Sex						
Male	3 (6.4)	2 (20.0)	0 (0)	1 (7.1)	0 (0)	0.509
Female	4 (8.5)	1 (10.0)	1 (9.1)	1 (7.1)	1 (8.3)	
Castrated male	17 (36.2)	2 (20.0)	6 (54.5)	5 (35.7)	4 (33.3)	
Spayed female	23 (48.9)	5 (50.0)	4 (36.4)	7 (50.0)	7 (58.3)	
Age (y)	10.93 ± 3.33	10.60 ± 3.77	11.09 ± 3.12	11.46 ± 3.65	10.50 ± 2.60	0.894
Body weight (kg)	3.41 ± 1.12	3.21 ± 1.17	3.32 ± 1.12	3.74 ± 0.94	3.28 ± 1.17	0.663

Values are presented as number (%) or mean ± standard deviation. The age, sex and body weight did not exhibit significant differences between the control, B1, B2 and C groups.

Table 2. Diagnostic imaging indices and Red cell distribution width values of total study population according to American College of Veterinary Internal Medicine stage

Index	Control (n = 10)[a]	Stage B1 (n = 11)[b]	Stage B2 (n = 14)[c]	Stage C (n = 12)[d]	*p*-value	*Post-hoc*
VHS	9.75 ± 0.35	10.24 ± 0.74	10.55 ± 0.36	11.93 ± 0.76	< 0.001	A, B < C < D[a,b,d,e,g,i]
LA/Ao ratio	1.38 ± 0.13	1.43 ± 0.15	1.97 ± 0.21	2.50 ± 0.28	< 0.001	A, B < C < D[a,c,d,f,g,i]
LVIDDn	1.22 ± 0.22	1.36 ± 0.18	1.82 ± 0.13	1.94 ± 0.34	< 0.001	A, B < C < D[a,c,d,e,g,h]

Values are presented as mean ± standard deviation. Significant differences were identified in vertebral heart score (VHS), left atrial-to-aortic ratio (LA/Ao ratio), and left ventricular end-diastolic internal diameter corrected for body weight (LVIDDn) among the B1, B2, and C groups. Within the control group, all three indices exhibited significant variances relative to the B2 and C groups, but not with the B1 group.
[a]p >0.05 between A and B; [b]p <0.05 between A and C; [c]p <0.01 between A and C; [d]p <0.01 between A and D; [e]p <0.05 between B and C; [f]p <0.01 between B and C; [g]p <0.01 between B and D; [h]p <0.05 between C and D; [i]p <0.01 between C and D.

Differences in hematologic indices between groups were analyzed (Table 3). Hematocrit, hemoglobin, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) exhibited no significant differences between the control, B1, B2 and C groups. The reticulocyte count exhibited significant differences between the control, B1, B2 and C groups ($p < 0.05$), but not individually among the control, B1, and B2 groups. The RDW values were significantly different between B1 and B2 groups ($p < 0.01$), as well as between B2 and C groups ($p < 0.01$), but not between the control and B1 groups. The results are represented by a box plot in Fig. 1.

Results of the Spearman's correlation analysis between RDW and radiographic, echocardiographic, and hematologic variables are depicted in Table 4. All diagnostic imaging indices (VHS, LA/Ao ratio and LVIDDn) demonstrated a significant positive correlation with RDW. The LA/Ao ratio presented the most robust correlation with RDW, evidenced by a correlation coefficient of 0.751. Correlation graphs of RDW and diagnostic imaging indices are presented in Fig. 2. Hematologic indices including hematocrit, hemoglobin, MCV and MCHC did not exhibit a significant correlation with RDW. The reticulocyte count was the sole hematologic index to show a significant correlation with RDW, recording a correlation coefficient of 0.485.

Discussion

The objective of this research was to investigate the possibility of utilizing RDW as a hematological parameter for the diagnosis or monitoring of MMVD by examining variations in RDW across different stages of MMVD and correlation between RDW and radiographic and echocardiographic indices.

Reticulocytes, which are immature and larger red blood cells, can be elevated in response to increased hematopoietic stimulation, consequently affecting RDW due to their larger size [8,9]. In recent research about reticulocytosis in dogs and MMVD patients, cardiac diseases have been identified as the predominant cause of reticulocytosis in absence of anemia (RAA) in dogs and RAA was observed in 80.9% of cardiogenic pulmonary edema patients caused by MMVD [10,11]. In this study, despite the absence of anemia in subjects across all stages and control groups, the reticulocyte count of the stage C showed a statistically significant difference from the control and B1 and B2 stages. Since ACVIM stage C contains patients with clinical signs caused by MMVD, the result is similar to previous studies and it might be ascribed to RAA as a result of hypoxia secondary to congestive heart failure. Furthermore, the improvement of dyspnea and pulmonary infiltration following diuretic treatment had led to a significant resolution of RAA in these pa-

Table 3. Hematologic indices of total study population according to American College of Veterinary Internal Medicine stage

Index	Control (n = 10)[a]	Stage B1 (n = 11)[b]	Stage B2 (n = 14)[c]	Stage C (n = 12)[d]	*p*-value	*Post-hoc*
Hematocrit (%)	42.47 ± 5.59	44.28 ± 6.30	41.68 ± 6.48	41.23 ± 5.56	0.635	A, B, C, D[a,b,d,g,j,l]
Hemoglobin (g/dL)	14.40 ± 1.83	15.03 ± 1.65	14.54 ± 3.30	13.94 ± 1.86	0.584	A, B, C, D[a,b,d,g,j,l]
MCV (fL)	69.97 ± 3.26	70.62 ± 4.56	68.28 ± 4.27	68.44 ± 2.73	0.375	A, B, C, D[a,b,d,g,j,l]
MCHC (g/dL)	32.66 ± 3.43	34.13 ± 1.78	34.35 ± 5.94	33.62 ± 0.60	0.752	A, B, C, D[a,b,d,g,j,l]
Reticulocyte (10^3/μL)	47.83 ± 24.50	77.56 ± 30.92	81.56 ± 35.25	127.10 ± 28.10	< 0.001	A, B, C < D[a,b,e,g,j,m]
RDW (%)	13.16 ± 0.45	13.13 ± 0.43	14.27 ± 0.47	15.07 ± 0.75	< 0.001	A, B < C < D[a,c,f,h,k,n]

Values are presented as mean ± standard deviation. Hematocrit, hemoglobin, mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) showed no significant variances between the control, B1, B2 and C groups. Reticulocytes were found to be significantly elevated in the stage C group, while red cell distribution width (RDW) showed significant differences across the B1, B2, and C stages.
[a]p >0.05 between A and B; [b]p >0.05 between A and C; [c]p <0.01 between A and C; [d]p >0.05 between A and D; [e]p <0.05 between A and D; [f]p <0.01 between A and D; [g]p >0.05 between B and C; [h]p <0.01 between B and C; [i]p >0.05 between B and D; [j]p <0.05 between B and D; [k]p <0.01 between B and D; [l]p >0.05 between C and D; [m]p <0.05 between C and D; [n]p <0.01 between C and D.

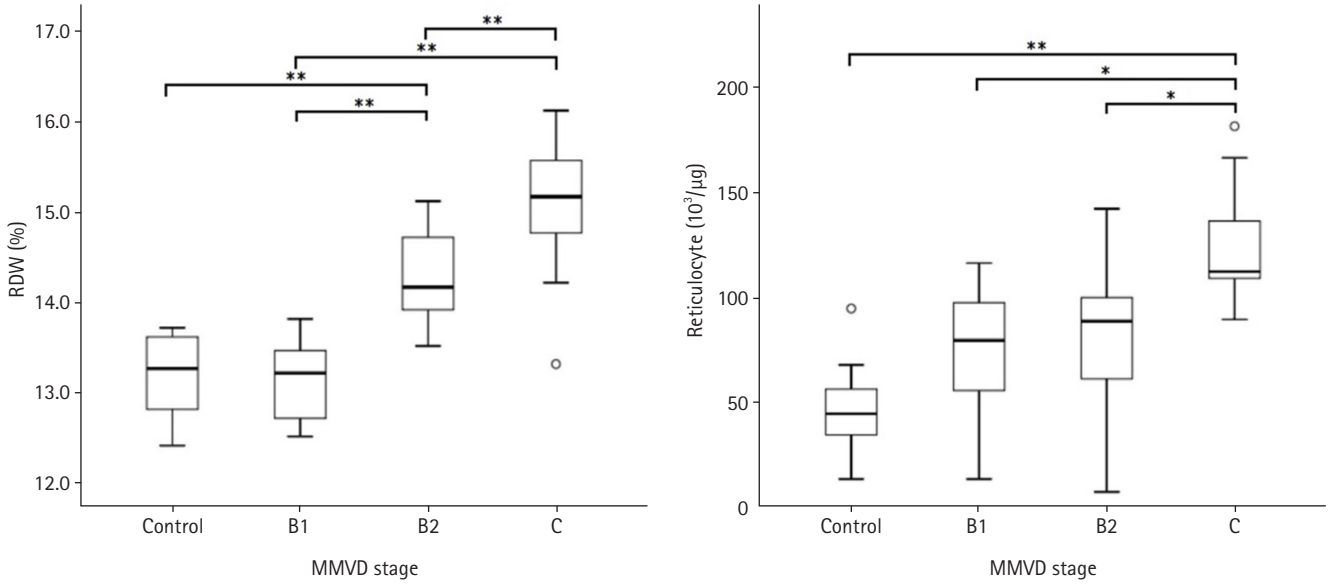

Fig. 1. Evaluation of the correlation of red cell distribution width (RDW) and the reticulocyte count with the American College of Veterinary Internal Medicine stage. RDW showed significant differences among B1, B2, and C groups, although B1 group did not demonstrate a significant difference compared to the control group. The reticulocyte count showed significant variances among the control, B1, B2, and C groups, but not individually among the control, B1, and B2 groups. MMVD, myxomatous mitral valve disease. *$p < 0.05$, **$p < 0.01$.

tients, allowing for the inference that the RAA was likely triggered by hypoxia [11].

In previous studies, however, RDW did not differentiate between compensated and decompensated heart failure in groups with MMVD or chronic degenerative valvular disease [7,12]. Additionally, it did not show a significant correlation with the LA/Ao ratio in dogs affected by MMVD, findings that contradict the results of this research [7,12]. It is important to recognize that RDW is influenced by several factors, including anemia status, age, and breed. Therefore, controlling for these variables is recommended to accurately explore the RDW-MMVD relationship.

Previous study has shown a significant negative correlation between hematocrit and RDW in dogs with MMVD [7]. Additionally, age was shown either to differ significantly from the control groups or to have a significant positive relationship with RDW [7,12]. Age is known to cause anisocytosis in humans, and an increasing tendency in RDW was observed in clinically healthy senior dogs [13–15]. Furthermore, these studies were conducted on various breeds rather than a single breed, and since there is a significant variation in average lifespan among different dog breeds, caution is required in the interpretation of age-related correlations [16]. Also, the size and morphology of red blood cells display a range of variations under healthy con-

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Table 4. Spearman's correlation coefficients for red blood cell distribution width and reticulocyte count with radiographic, echocardiographic and hematologic variables in 47 dogs

Variable	RDW	*p*-value
VHS	0.624	< 0.001
LA/Ao ratio	0.751	< 0.001
LVIDDn	0.738	< 0.001
Hematocrit (%)	-0.183	0.219
Hemoglobin (g/dL)	-0.188	0.206
MCV (fL)	-0.161	0.286
MCHC (g/dL)	0.040	0.792
Reticulocyte (10^3/μL)	0.485	0.002

Vertebral heart score (VHS), left-atrial-to-aortic-root ratio (LA/Ao ratio) and left ventricular end-diastolic internal diameter corrected for body weight (LVIDDn) exhibited a significant positive correlation with red cell distribution width (RDW), while the LA/Ao ratio presented the strongest correlation with RDW. Hematocrit, hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC) showed no correlation with RDW, but reticulocyte has significantly correlated with RDW.

ditions in various canine breeds, resulting in asymptomatic anisocytosis [17,18]. Similarly, radiographic indicators of heart size showed considerable differences between breeds, and differences in the LA/Ao ratio by breed were also identified [19,20].

In this study, RDW demonstrated significant differences across stages B1, B2, and C, which is a finding not previously reported in the literature. This result is noteworthy as it reflects outcomes from a state uninfluenced by age, breed, or hematocrit levels, which affect RDW. The investigation was confined to subjects within the Maltese breed, and no significant differences in age and hematocrit were observed across MMVD stages. Given that RDW was elevated with the increasing reticulocyte count [8], this outcome can be attributed to the significantly elevated reticulocyte count detected in stage C. Additionally, a significant elevation in RDW was observed in the B2 stage compared to both the control and B1 stages, representing a nov-

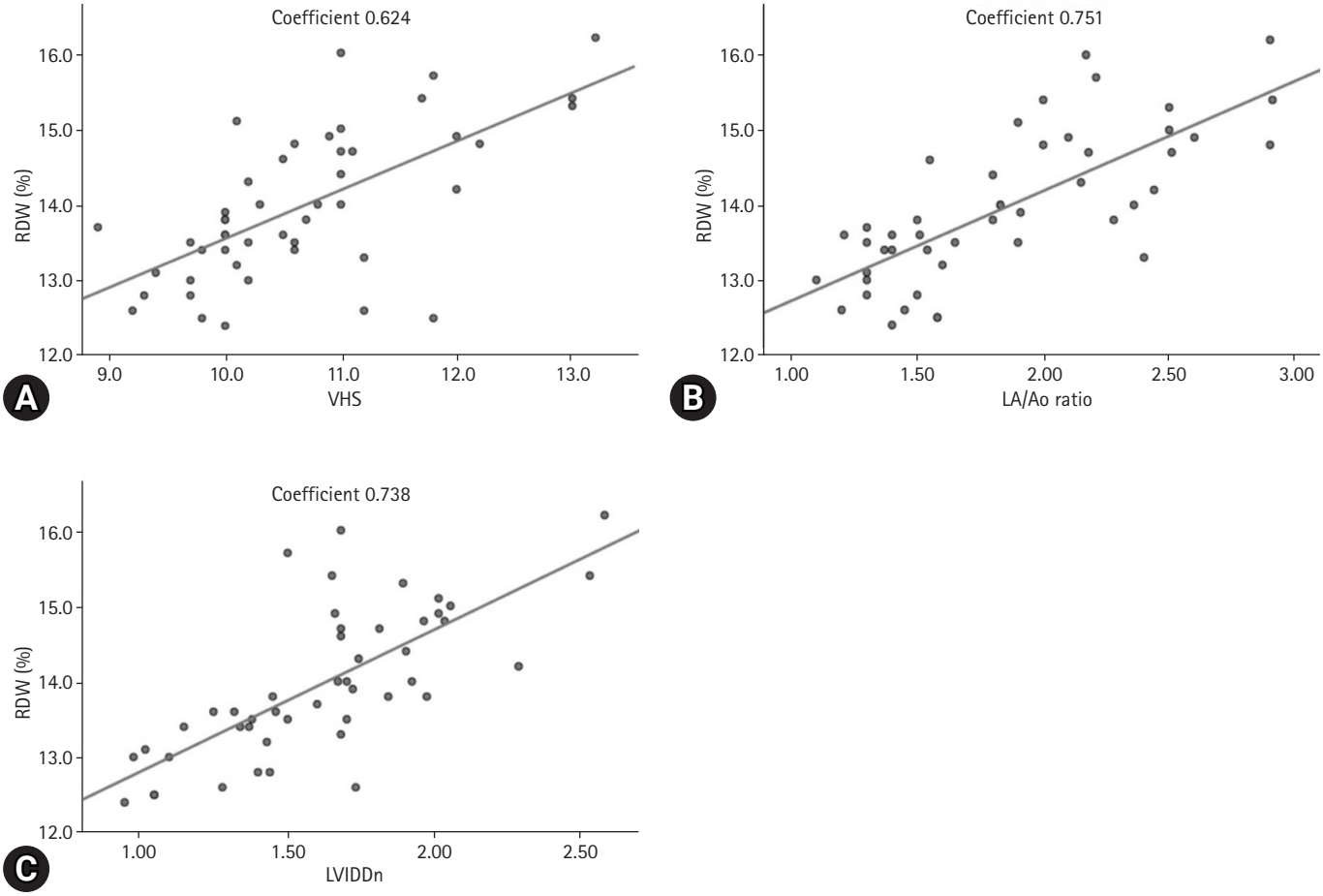

Fig. 2. Correlation graphs of red cell distribution width (RDW) between radiographic and echocardiographic indices. (A) Vertebral heart score (VHS); (B) left-atrial-to-aortic-root ratio (LA/Ao ratio); (C) left ventricular end-diastolic internal diameter corrected for body weight (LVIDDn). LA/Ao ratio and RDW exhibited a strong positive correlation, with a correlation efficient value of 0.751.

el discovery. Earlier research classified cases into compensated or non-compensated heart failure groups, lacking a distinction between the compensated stages (B1 and B2) [7,12]. The observed pattern may be influenced by the altered biochemical and serologic status due to cardiac remodeling, which can affect RDW, or by the small sample size of this study. Therefore, further research in hematology, biochemistry, and serology, particularly with a larger sample size and focusing on the Maltese breed, is necessary to validate these findings.

Furthermore, RDW showed a strong positive correlation with the LA/Ao ratio and demonstrated a higher correlation coefficient than both VHS and LVIDDn. Focusing exclusively on the Maltese breed enabled the derivation of reliable correlations by controlling for breed-specific variations in RDW as well as in the LA/Ao ratio. Two studies in human cardiology have identified a significant positive correlation between RDW and left atrial volume in patients with heart failure, which have been analogous to the findings of this study [21,22]. Additionally, both studies have demonstrated significant correlations between left ventricle ejection fraction, early mitral inflow velocity to early diastolic mitral annular velocity ratio (E/E' ratio) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) with RDW, suggesting a relationship between RDW and hemodynamic stress [21,22]. Therefore, future studies are needed to assess the correlation of RDW with further systolic and diastolic echocardiographic indices and NT-proBNP in MMVD dogs especially within the Maltese breed.

This study had several potential limitations. The sample size of affected animals in the research was relatively limited. Also, continuous tracking of changes in RDW as MMVD progressed was not conducted. RDW was measured only once at the time of MMVD diagnosis, and this single-point measurement constrains understanding of the dynamic alterations in RDW relative to the progression of MMVD.

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Author's Contributions

Conceptualization: Song KH, Choi HS; Data curation: Choi HS, Lee HJ; Formal analysis: Choi HS; Funding acquisition: Song KH; Investigation: Choi HS; Methodology: Song KH, Lee HJ; Project administration: Song KH, Lee HJ; Resources: Song KH; Soft ware: Choi HS, Lee HJ; Supervision: Song KH; Validation: Song JH; Visualization: Choi HS; Writing–original draft: Choi HS, Lee HJ; Writing–review & editing: Song KH, Song JH.

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