

The relationship between red cell distribution width and cardiac autonomic function in heart failure

Shinya Yamada¹  | Akiomi Yoshihisa^{1,2} | Takashi Kaneshiro^{1,3} | Kazuaki Amami¹ | Naoko Hijioka¹ | Masayoshi Oikawa¹ | Yasuchika Takeishi¹

¹Department of Cardiovascular Medicine, Fukushima Medical University, Fukushima, Japan

²Department of Advanced Cardiac Therapeutics, Fukushima Medical University, Fukushima, Japan

³Department of Arrhythmia and Cardiac Pacing, Fukushima Medical University, Fukushima, Japan

Correspondence

Shinya Yamada, Department of Cardiovascular Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan.
Email: smyyamada0124@yahoo.co.jp

Abstract

Background: Both increases in red cell distribution width (RDW) levels and autonomic dysfunction are considered to be correlated with worsening heart failure. However, the relation of RDW levels to autonomic function remains uncertain. We aimed to investigate the association of RDW levels in heart failure with autonomic function, evaluated by heart rate variability (HRV) and heart rate turbulence (HRT), and prognosis.

Methods: We studied 222 hospitalized patients with stable heart failure before discharge, and Holter recordings (HRV and HRT) were performed. Additionally, RDW levels were measured, and high RDW was defined as over 14.5%. We then divided the patients into two groups based on RDW levels: high RDW group (>14.5%, n = 92) and low RDW group (\leq 14.5%, n = 130). The relation of RDW to autonomic function and prognosis was assessed.

Results: In the high RDW group, severely impaired HRV and HRT were found compared to the low RDW group. In the linear regression analysis after the adjustment of multiple confounders, RDW levels were correlated with a low-frequency (LF) to high-frequency (HF) ratio and very low-frequency (VLF) power (LF to HF ratio, $\beta = -0.146$, $P = .027$, and VLF power, $\beta = -0.137$, $P = .041$, respectively). During the observation period (median 1400 days), cardiac events (re-hospitalization of heart failure, cardiac death or sudden death) were found in 73 (32.8%) patients. The Kaplan-Meier analysis demonstrated that the high RDW group had a higher rate of cardiac events compared to the low RDW group (45.6% vs 23.8%, log-rank $P < .001$).

Conclusion: High RDW levels were correlated with autonomic dysfunction, resulting in poor clinical outcomes.

KEYWORDS

cardiac autonomic dysfunction, heart rate turbulence, heart rate variability, prognosis, red cell distribution width

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1 | INTRODUCTION

Heart failure is considered as one of the major causes of death in many countries. Abnormality of autonomic nervous system and systemic inflammation play important roles in worsening heart failure.^{1,2} Furthermore, both autonomic dysfunction and inflammation can alter bone marrow sensitivity to erythropoietin, which lead to the release of immature red cells.^{3,4} Therefore, circulating erythrocytes of variable size, evaluated by the red cell distribution width (RDW), could be observed in heart failure patients. Although high levels of RDW may be related to mortality in heart failure patients,³ the association of RDW levels with autonomic function has not yet been fully elucidated.

Noninvasive parameters on Holter recordings yield clinically beneficial information on the treatment of patients with heart failure⁵⁻⁹; cardiac autonomic function can be evaluated by heart rate variability (HRV) and heart rate turbulence (HRT). There is some convincing proof that the impairment of HRV and HRT is correlated with worsening heart failure and adverse outcomes⁵⁻¹⁰; however, the relation of these noninvasive parameters to RDW levels in patients with heart failure has not yet been fully investigated.

Thus, the purpose of the current study was to investigate the relation of RDW levels to cardiac autonomic function, evaluated by HRV and HRT, and prognosis in hospitalized patients with heart failure.

2 | METHODS

2.1 | Study population

The study subjects comprised of 222 patients with heart failure, who were hospitalized at our hospital for the medical management of heart failure between 2010 and 2017. The diagnosis of heart failure was made on the established heart failure criteria.¹¹ All patients underwent optimal medical management for heart failure, and they underwent electrocardiogram, echocardiography, and 24-hour Holter recordings in a clinically stable condition. In this study, patients with acute coronary syndrome were not included. In addition, patients who had atrial fibrillation, pacemaker rhythm (ie, pacemaker, implantable cardioverter-defibrillator, and cardiac resynchronization therapy), and absence of ventricular premature complex (VPC) were not included because of reliable data analysis. The calculation of RDW was performed based on [standard deviation of red cell volume/mean cell volume] \times 100.¹² We then divided the patients ($n = 222$) into two groups based on their RDW levels: high RDW group ($>14.5\%$, $n = 92$) and low RDW group ($\leq 14.5\%$, $n = 130$) as described in a previous study.¹² We investigated the relation of RDW levels to cardiac autonomic function, assessed using Holter recordings, and clinical outcomes. All patients gave written informed consent for the procedures.

2.2 | Prevalence and determinants of comorbidities

The determination of risk factors (ie, hypertension, diabetes, and dyslipidemia) was shown, as described previously.¹³ The prevalence and determinants of hypertension were receiving antihypertensive therapies and drugs, a systolic blood pressure of ≥ 140 mm Hg, and/or a diastolic blood pressure of >90 mm Hg. The prevalence and determinants of diabetes were receiving antidiabetic medications (antidiabetic drugs or insulin), a fasting blood glucose value of >126 mg/dL, and/or a hemoglobin A_{1c} value of $>6.5\%$. The prevalence and determinants of dyslipidemia were receiving cholesterol-lowering therapies, a triglyceride value of >150 mg/dL, a low-density lipoprotein cholesterol value of >140 mg/dL, and/or a high-density lipoprotein cholesterol value of <40 mg/dL.

2.3 | Data collection

Blood sampling test, electrocardiography, and echocardiography were performed in a clinically stable condition before discharge. Laboratory data included albumin, hemoglobin, RDW, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), using the Modification of Diet in Renal Disease formula,¹⁴ brain natriuretic peptide (BNP), and C-reactive protein (CRP). Standard 12-lead electrocardiogram tracing was endured as described in a previous study.¹³ The measurement of PR interval, QRS duration, and QTc interval, using Bazett's formula,¹⁵ was performed on the electrocardiogram recording. Echocardiographic parameters included left ventricular (LV) ejection fraction (LVEF), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), interventricular septum thickness, posterior wall thickness, tricuspid regurgitation pressure gradient (TRPG), and inferior vena cava (IVC) diameter.

2.4 | Holter recordings

We performed 24-hour Holter recordings in a clinically stable condition before hospital discharge.^{13,16} In the HRV analysis, very low-frequency (VLF) component, low-frequency (LF) component, high-frequency (HF) component, and LF to HF ratio were assessed based on the power spectral analysis. Spectral analyses were performed based on the fast-Fourier transform method and spectral powers were expressed in ms^2 , as described previously.¹⁶ A component in the frequency bands from 0.0033 to 0.04 Hz, 0.04 to 0.15 Hz, and 0.15 to 0.4 Hz was considered as VLF, LF, and HF powers, respectively. Additionally, on the time-domain analysis, the assessment of standard deviation of all R-R intervals (SDNN) and standard deviation of the 5-min mean R-R intervals (SDANN) was performed. In the HRT analysis, turbulence onset (TO) and turbulence slope (TS) were evaluated as described in a previous study.⁹ The definition of TO was the percentage of difference between the mean RR intervals of the two sinus beats preceding the VPC and the mean of the subsequent two sinus-rhythm RR intervals. The definition of TS (ms/RR) was the maximum positive regression slope over any sequence of five

subsequent sinus-rhythm RR intervals of the first 20 sinus beats after the VPC. The frequency of VPC was also assessed. The parameters derived from Holter recordings were evaluated by the use of the MARS PC Holter Monitoring and Review System (version 7; GE Healthcare).

2.5 | Definition of cardiac events

The overall end of follow-up for cardiac events was March 2019. In the current study, cardiac events were defined as re-hospitalization of heart failure, cardiac death, or sudden death, which were the clinical endpoints. Worsening heart failure was determined based on the established heart failure criteria.¹¹ Cardiac death and sudden death were identified by independent attending physicians and included death caused by life-threatening ventricular arrhythmia recorded by electrocardiogram and worsened heart failure on the basis of the Framingham criteria.¹¹ The status and/or dates of death of all patients were obtained from the patients' medical records or attending physicians at the patient's referring hospital. The calculation of observation period was performed from the date of Holter recordings until cardiac events or last follow-up.

2.6 | Statistical analysis

Data were expressed as the mean \pm standard deviation for parametric variables and numbers and percentages for categorical variables. Student's *t* test was performed to compare parametric variables, and the chi-square test was performed to compare categorical variables. The relation of RDW levels to clinical data was analyzed using Pearson's correlation analysis. In addition, linear regression analysis after the adjustment of possible confounders (age, LVEF, NYHA functional class, BNP, hemoglobin, and usage of β -blockers and amiodarone) was performed to investigate the relation of RDW levels to HRV and HRT parameters. The Cox proportional hazard regression analysis was performed to clarify the relationship between high RDW and the incidence of cardiac events. To prepare for potential confounding, we considered the following clinical factors, which are generally known to affect prognosis in patients with heart failure: age, sex, NYHA class III/IV, hemoglobin, BNP, and LVEF. Those variables were selected for testing in the multivariable analysis. The cumulative incidence curve of cardiac events was evaluated using the Kaplan-Meier method. All statistical significances were considered at a $P < .05$, and SPSS statistical software (version 26.0; SPSS Institute) was used to perform statistical analyses.

3 | RESULTS

3.1 | Patient characteristics

The baseline clinical characteristics of the patients are presented in Table 1. No significant differences between the high and low RDW groups were found in age, gender, prevalence of ischemic etiology,

TABLE 1 Comparisons of patient characteristics between the high and low RDW groups

	High RDW group (n = 92)	Low RDW group (n = 130)	P value
Age	63.4 \pm 14.8	59.7 \pm 16.3	.083
Male, n (%)	55 (59.7%)	93 (71.5%)	.067
NYHA class III/IV, n (%)	36 (39.1%)	41 (31.5%)	.258
Ischemic etiology, n (%)	35 (38.0%)	44 (33.8%)	.520
Co-morbidity, n (%)			
Hypertension	67 (72.8%)	99 (76.1%)	.574
Diabetes	42 (45.6%)	47 (36.1%)	.155
Dyslipidemia	74 (80.4%)	103 (79.2%)	.826
Medication, n (%)			
β blockers	79 (85.8%)	113 (86.9%)	.821
ACE-Inhibitors	50 (54.3%)	81 (62.3%)	.235
ARBs	23 (25.0%)	41 (31.5%)	.289
Amiodarone	20 (21.7%)	37 (28.4%)	.259
Diuretics	66 (71.7%)	82 (63.0%)	.177
Echocardiography			
LVEF (%)	44.1 \pm 15.4	45.5 \pm 16.1	.523
EDV (mL)	121.1 \pm 56.4	135.0 \pm 69.4	.125
ESV (mL)	73.0 \pm 47.0	79.3 \pm 56.4	.394
IVST (mm)	11.3 \pm 2.6	11.0 \pm 3.1	.477
PWT (mm)	11.4 \pm 2.6	11.6 \pm 3.7	.615
TRPG (mm Hg)	28.7 \pm 15.0	24.7 \pm 11.3	.019
IVC diameter (mm)	15.3 \pm 4.5	14.0 \pm 3.5	.026
Laboratory data			
Albumin (g/dL)	3.2 \pm 0.6	3.8 \pm 0.5	<.001
Hemoglobin (g/dL)	11.4 \pm 2.4	13.4 \pm 1.6	<.001
RDW (%)	16.4 \pm 1.8	13.3 \pm 0.6	<.001
BUN (mg/dL)	23.3 \pm 12.5	18.2 \pm 7.5	<.001
Creatinine (mg/dL)	1.60 \pm 1.75	1.00 \pm 0.72	.001
eGFR (mL/min/1.73 m ²)	52.2 \pm 25.2	66.1 \pm 24.5	<.001
BNP (pg/mL)	882.0 \pm 1618.7	249.6 \pm 273.7	<.001
CRP (mg/dL)	1.67 \pm 2.88	0.80 \pm 1.94	.013

Abbreviations: ACE-Inhibitors, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin II receptor blockers; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CRP, C-reactive protein; EDV, end-diastolic volume; eGFR, estimated glomerular filtration rate; ESV, end-systolic volume; IVC, inferior vena cava; IVST, interventricular septum thickness; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PWT, posterior wall thickness; RDW, red cell distribution width; TRPG, tricuspid regurgitation pressure gradient.

NYHA class III/IV, hypertension, diabetes, dyslipidemia, intake of amiodarone, or medications at baseline. In the echocardiographic findings, LV dimension and LVEF were not different between the two groups. However, TRPG and IVC were significantly higher in the high RDW

group compared to the low RDW group. In the correlation analyses with the RDW levels and other variables, RDW levels were positively related to TRPG and IVC ($R = .313, P < .001$ and $R = .241, P < .001$, respectively). In the laboratory findings, lower levels of albumin, hemoglobin, and eGFR, and higher levels of BUN, creatinine, BNP, and CRP were found in the high RDW group compared to the low RDW group. In the correlation analyses, RDW levels were negatively related to albumin, hemoglobin, and eGFR ($R = -.474, P < .001$; $R = -.443, P < .001$; and $R = -.258, P < .001$, respectively) and positively related to BUN, creatinine, BNP, and CRP ($R = .160, P = .017$; $R = .193, P = .004$; $R = .298, P < .001$; and $R = .192, P = .004$, respectively).

3.2 | Electrocardiogram and Holter recordings

The parameters derived from electrocardiogram and Holter recordings are presented in Table 2. In the 12-lead electrocardiogram, no significant differences between the high and low RDW groups were found in PR interval and QRS duration. However, the QTc interval was significantly longer in the high RDW group than in the low RDW group. In the correlation analysis, there was a positive correlation between RDW levels and QTc interval ($R = .140, P = .037$).

In the 24-hour Holter recordings, no significant differences were found in LF and HF powers, and the frequency of VPC between the

TABLE 2 Comparisons of parameters from 12-lead electrocardiogram and 24-h Holter recordings between the high and low RDW groups

	High RDW group (n = 92)	Low RDW group (n = 130)	P value
Electrocardiogram (ms)			
PR interval	175.7 ± 36.2	175.2 ± 32.3	.923
QRS duration	114.0 ± 25.0	114.4 ± 23.7	.882
QTc interval	456.7 ± 42.2	446.7 ± 31.7	.045
Holter recordings			
Average heart rate (bpm)	73.2 ± 13.2	69.7 ± 10.4	.030
VPC (beats/d)	780.1 ± 1335.6	996.1 ± 2384.3	.436
LF power (ms ²)	244.1 ± 564.7	271.6 ± 381.2	.665
HF power (ms ²)	162.4 ± 380.8	116.9 ± 143.4	.215
LF to HF ratio	1.5 ± 1.2	2.3 ± 1.6	<.001
VLF power (ms ²)	521.1 ± 610.6	1006.8 ± 983.5	<.001
SDNN (ms)	82.6 ± 33.8	100.1 ± 37.3	.001
SDANN (ms)	71.7 ± 30.3	86.0 ± 34.2	.002
Turbulence onset (%)	0.30 ± 1.62	-0.30 ± 2.46	.028
Turbulence slope (ms/RR)	3.14 ± 5.11	4.68 ± 4.58	.019

Abbreviations: HF, high-frequency; LF, low-frequency; SDANN, standard deviation of the 5-min mean R-R intervals; SDNN, standard deviation of all R-R intervals; VLF, very low-frequency; VPC, ventricular premature complex. The other abbreviations are as in Table 1.

two groups. However, average heart rate and TO were significantly higher in the high RDW group compared to the low RDW group. In addition, the LF to HF ratio, VLF power, SDNN, SDANN, and TS were significantly lower in the high RDW group compared to the low RDW group. In the correlation analyses, RDW levels were positively related to average heart rate and TO ($R = .132, P = .049$; and $R = .142, P = .034$, respectively) and negatively related to the LF to HF ratio, VLF power, SDNN, SDANN, and TS ($R = -.276, P < .001$; $R = -.271, P < .001$; $R = -.258, P < .001$; $R = -.251, P < .001$; and $R = -.205, P = .002$, respectively). These data indicate that the high RDW group was related to cardiac autonomic dysfunction assessed using HRV and HRT.

To evaluate the relation of RDW levels to the HRV and HRT parameters, we performed linear regression analysis (Table 3). In the linear regression analysis, the levels of RDW were significantly correlated with the LF to HF ratio ($\beta = -0.146, P = .027$) and VLF power ($\beta = -0.137, P = .041$) after the adjustment of age, LVEF, NYHA functional class, BNP, hemoglobin, and usage of β -blockers and amiodarone.

3.3 | RDW levels and cardiac events

During the observation period (median 1400 days), there were 73 (32.8%) cardiac events, which included cardiac death (n = 26) caused by heart failure (n = 23) and ventricular arrhythmia (n = 3); sudden death (n = 11); and re-hospitalization of heart failure (n = 36). The incidence of cardiac events was 45.6% in the high RDW group and

TABLE 3 Linear regression models on the relationship between RDW levels and cardiac autonomic function

	RDW levels (%)	β	P value
LF power (ms ²)	Unadjusted	-0.034	.618
	Adjusted ^a	0.016	.788
HF power (ms ²)	Unadjusted	0.085	.209
	Adjusted ^a	0.064	.293
LF to HF ratio	Unadjusted	-0.276	<.001
	Adjusted ^a	-0.146	.027
VLF power (ms ²)	Unadjusted	-0.271	<.001
	Adjusted ^a	-0.137	.041
SDNN (ms)	Unadjusted	-0.258	<.001
	Adjusted ^a	-0.105	.117
SDANN (ms)	Unadjusted	-0.251	<.001
	Adjusted ^a	-0.108	.099
Turbulence onset (%)	Unadjusted	0.142	.034
	Adjusted ^a	0.071	.247
Turbulence slope (ms/RR)	Unadjusted	-0.205	.002
	Adjusted ^a	-0.118	.097

Note: The abbreviations are as in Tables 1 and 2.

^aAdjusted for age, LVEF, NYHA functional class III/IV, BNP, hemoglobin, and usage of β blockers and amiodarone.

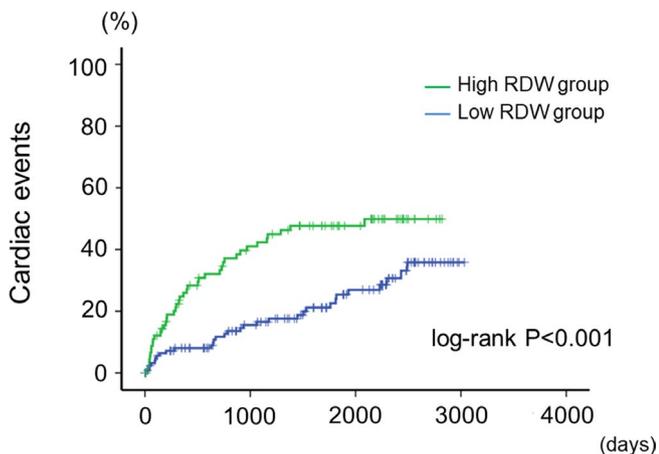


FIGURE 1 The risk of cardiac events in the high and low red cell distribution width (RDW) groups. The cumulative incidence curves with log-rank test showed that the high RDW group had a higher rate of cardiac events compared with the low RDW group

23.8% in the low RDW group. In the Kaplan-Meier analysis, the high RDW group had a higher rate of cardiac events compared with the low RDW group during the observation period (log-rank $P < .001$), as shown in Figure 1. In the present study, the univariable and multivariable Cox proportional hazard analyses were performed to investigate the relationship between high RDW level and the incidence of cardiac events. The univariable analysis revealed significant associations of high RDW level with cardiac events with a hazard ratio of 2.327 (95% confidence interval: 1.461-3.707, $P < .001$). In a multivariable model after adjusting for possible confounders (ie, age, sex, NYHA class III/IV, hemoglobin, BNP, and LVEF), high RDW level was significantly associated with cardiac events, with a hazard ratio of 2.182 (95% confidence interval: 1.263-3.771, $P = .005$).

4 | DISCUSSION

The present study demonstrated several important findings. First, RDW levels in heart failure were correlated with autonomic nervous system assessed by HRV and HRT. The levels of RDW were especially related to the decreased LF to HF ratio and VLF power after the adjustment of multiple confounders. Second, the high RDW group ($>14.5\%$) had a higher rate of cardiac events compared with the low RDW group ($\leq 14.5\%$) in the Kaplan-Meier analysis. These results indicate that RDW levels are correlated with autonomic nervous system and subsequent prognosis in hospitalized patients with heart failure.

4.1 | RDW and cardiac autonomic function

In the present study, RDW levels in heart failure were related to parameters obtained from HRV and HRT. Although it was previously reported that autonomic dysfunction was related to a

blunted erythropoietin response,⁴ the association of RDW levels with autonomic function has not been fully investigated. The impairment of HRV and HRT is considered as cardiac autonomic dysfunction and strong predictors of worsening heart failure and mortality.⁵⁻⁹ Although HRV can be analyzed using the frequency domain method (eg, LF, HF, LF to HF ratio, and VLF) or time domain method (eg, SDNN and SDANN) via Holter recordings, there is a complex interaction of sympathetic and parasympathetic influences.¹⁷ Generally, HF power purely reflects the regulation of vagal tone by measuring respiratory depth and frequency.¹⁸⁻²⁰ LF power reflects the regulation of sympathetic and vagal tone by baroreflex activity.¹⁸⁻²⁰ LF to HF ratio is generally useful for evaluation of the sympathovagal balance. A previous report showed that decreased LF to HF ratio was found in heart failure.⁶ VLF power reflects fluctuation in the renin-angiotensin system activity, thermoregulatory mechanisms, and the peripheral chemoreceptor function, and is recognized as the very slow mechanistic activity of sympathetic control.^{7,20,21} It has been reported that decreased VLF power has prognostic significance in heart failure.^{8,20} In the current study, lower LF to HF ratio and VLF power were found in the high RDW group than in the low RDW group. In the linear regression analysis, after the adjustment of multiple confounders, the levels of RDW were related to the LF to HF ratio and VLF power. Thus, our study findings indicate that higher levels of RDW are correlated with cardiac autonomic dysfunction.

In the current study, RDW levels were inversely related to hemoglobin concentration. Although anemia is a common feature of patients with heart failure, linear regression analysis showed that the levels of RDW were correlated with the LF to HF ratio and VLF power, irrespective of hemoglobin concentration. The causal relationship between RDW elevation and cardiac autonomic dysfunction remains unclear. However, previous studies demonstrated that stimulation of sympathetic nerves, acting through β_2 -adrenoreceptors, positively modulated erythropoiesis via increases in erythropoietin production.^{4,22} Therefore, autonomic dysfunction in heart failure may influence a blunted erythropoietin response, resulting in increased RDW levels.

4.2 | RDW and cardiac events in heart failure

RDW is a measurement of circulating erythrocytes of variable size, and its higher levels are related to a greater spread of circulating red cell sizes.³ High levels of RDW may be correlated with mortality in patients with heart failure.^{3,12} However, the exact roles of RDW in heart failure as a cause of cardiac events remain unclear. Nutritional deficiencies, renal dysfunction, inflammatory stress, and increased neurohormonal activity have been considered as possible mechanisms responsible for increased levels of RDW and their associations with worsening heart failure either alone or in combination with each other.^{3,23,24} In our study, RDW was positively related to TRPG and IVC, and it was negatively correlated with albumin. Malnutrition is associated with an increase in pulmonary

artery pressure and right-sided volume overload (eg, TRPG and IVC diameter) and a decrease in the rate of synthesis of albumin.^{25,26} In addition to malnutrition, chronic kidney disease is also considered a status of increased inflammation and neurohormonal dysregulation, which lead to ineffective erythropoiesis or augmented red cell destruction.^{24,27} In the current study, RDW levels were positively correlated with BUN, creatinine, BNP, and CRP, and it was negatively correlated with eGFR. Additionally, RDW levels were positively correlated with QTc interval. The causal relationship between RDW levels and QTc interval has not been elucidated in patients with heart failure. However, it has been reported that the QTc interval is affected by autonomic nervous system, and is a useful predictor of pump failure death.^{28,29} Autonomic dysfunction in heart failure might influence QTc interval and RDW elevation, which lead to adverse prognosis. Therefore, the Kaplan-Meier analysis demonstrated that the high RDW group had a higher incidence of cardiac events compared with the low RDW group during the observation period. Our study findings show that the assessment of RDW levels is useful for clinical management of hospitalized patients with heart failure.

4.3 | Limitations

Some limitations remain in the current study. First, the study was conducted in a single institution, and the number of patients was relatively small. Second, patients who had atrial fibrillation and/or pacemaker rhythm were not included because of reliable data analysis. Finally, in the present study, the association of changes in RDW with autonomic dysfunction and cardiac events was not evaluated. Therefore, it remains unclear whether RDW itself contributes to the pathophysiology of cardiac events or it functions merely as a marker of the incidence of cardiac events. We would consider performing a study on these issues in the future.

5 | CONCLUSION

Our study results indicate that RDW levels are related to cardiac autonomic function, evaluated by HRV and HRT. Higher levels of RDW in heart failure were especially correlated with the decreased LF to HF ratio and VLF power, which lead to poor prognosis.

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DISCLOSURES

None.

CONFLICT OF INTEREST

None. The ethical committee of Fukushima Medical University approved this study (approval number: 1656, approval date: 04/22/2013).

ORCID

Shinya Yamada  <https://orcid.org/0000-0001-5726-3926>

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