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ORIGINAL ARTICLE

Red cell distribution width as a prognosticator in patients with heart failure

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Abstract

Aims Increased red cell distribution width (RDW) is a poor prognostic factor in patients with heart failure (HF). However, only a few large-scale studies have identified the clinical utility of RDW after adjusting for covariates affecting RDW.

Methods and results From January 2010 to April 2021, we retrospectively enrolled patients diagnosed with HF from three referral hospitals with available RDW data (taken within 3 months of HF diagnosis) using an integrated clinical data system. Patients with an ejection fraction (EF) $<$ 50% or HFA-PEFF (Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology) score $\geq$ 2 without severe valvular heart disease or coronary revascularization were enrolled. The primary endpoint was all-cause mortality, and cardiovascular mortality was also collected. Multivariable Cox regression analysis and stabilized inverse probability of treatment weighting (IPTW) were used to identify any association between RDW and all-cause death by balancing covariates or compounding factors. The global χ^2 score was calculated and discrimination analysis was performed to evaluate the incremental value of RDW in predicting prognosis. Among the 6599 participants enrolled in this study, 1256 (19.0%) cases of all-cause death occurred, and the median duration of follow-up was 887 (interquartile range 351–1589) days. Elevated RDW at the initial diagnosis was associated with poor prognosis [cumulative incidence: 819 (30.2%) vs. 437 (11.2%), relative risk 1.58, 95% confidence interval (CI) 1.51–1.67, log-rank $P < 0.001$]. Multivariable Cox analysis showed that elevated RDW was a poor prognostic factor for the primary endpoint [hazard ratio (HR) 1.11, 95% CI 1.06–1.16, $P < 0.001$], independent of clinical risk factors, N-terminal pro-brain natriuretic peptide (NT-proBNP), and EF, which was concordant with the stabilized IPTW (HR 1.29, 95% CI 1.10–1.49, $P < 0.001$). Adding RDW to model composed of traditional risk factors, NT-proBNP, and echocardiographic parameters showed incremental prognostic value for predicting poor prognosis (area under the receiver operating characteristic curve, 0.799–0.826; $P < 0.001$).

Conclusions Increased RDW at the time of diagnosis is associated with poor prognosis in patients with HF, independent of clinical risk factors, such as NT-proBNP, and echocardiographic parameters. Therefore, RDW may aid in the management of these patients beyond traditional risk factors.

Keywords Red cell distribution width; Heart failure; Prognosis; Mortality

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Introduction

There are 26 million patients with heart failure (HF) worldwide. HF has an overall prevalence of 0.1–6.7%, a number that is gradually increasing due to the rise of ageing society.[1] HF is a major cause of hospitalization and is associated with significant medical expenses. In recent years, several treatments for HF patients have been studied, and their beneficial effects have been demonstrated. However, the prognosis of patients with HF is poor despite the availability of such interventions, with in-hospital and 1 year follow-up mortality rates of 4.8% and 18.2%, respectively.[2] Therefore, the early prediction of poor prognosis and identification of relevant clinical indicators is vital to avoid any delay in intensive treatment initiation in these patients. Parameters of transthoracic echocardiography, such as ejection fraction (EF), N-terminal pro-brain natriuretic peptide (NT-proBNP), and cardiac troponin, have already been studied as biomarkers to evaluate treatment response and to predict prognosis and are currently used in real-life clinical settings.[3–5] However, these tests are expensive and difficult to assess frequently; thus, there is a need for more accessible indicators as predictors of prognosis in patients with HF.

Red cell distribution width (RDW), often performed as part of complete blood cell counts, has been used to measure the variability in red blood cell volumes. The clinical utility of RDW as a prognosticator of cardiovascular and respiratory diseases has been well studied,[6–11] along with its in patients with HF. However, interactions with covariates affecting elevated RDW may not be sufficiently adjusted owing to the small number of studies or a select group of patients being evaluated.[12–14] Therefore, this study aimed to identify the clinical utility of RDW, an inexpensive and easily assessable parameter, as a prognosticator in patients with HF in a large study population, which allowed adjustments for compounding factors affecting RDW.

Methods

Study population

From January 2010 to April 2020, we retrospectively enrolled patients diagnosed with HF who underwent an RDW test within a 3 month period from HF diagnosis at three referral hospitals affiliated with the Yonsei University Health System. Patients with the I50 ICD-10 code recorded more than two times in the outpatient or once during admission, as the main diagnosis, were initially screened. Patients with the following conditions were excluded: (i) no available transthoracic echocardiography report; (ii) severe valvular heart disease; (iii) severe coronary artery disease leading to previous coronary revascularization with percutaneous or cardiac bypass surgery; (iv) pulmonary artery hypertension; (v) constrictive pericarditis; (vi) ischaemic, hypertrophic, and restrictive cardiomyopathies; (vii) pulmonary embolism; (viii) congenital heart diseases; and (ix) no follow-up data. Among the patients with ICD-10 code I50 indicating HF and with an EF $\geq$ 50%, we calculated the Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology (HFA-PEFF) score, which is a diagnostic algorithm for HF with preserved EF (HFpEF). Accordingly, we excluded patients with a low probability of HF, as indicated by a score of 0 or 1.[15] The investigation conforms with the principles outlined in the Declaration of Helsinki revised in 2013. The study protocol was approved by the Institutional Review Board of our hospital, and the requirement for informed consent was waived owing to the retrospective design of the study.

Data collection and outcomes

We used an integrated clinical data server analysis system incorporating data from three referral hospitals affiliated with our university health system, named the Severance Clinical Research Analysis Portal (SCRAP), to enrol potential participants and collect anonymized clinical data, including prescription history. Detailed definitions of covariates, including hypertension, diabetes mellitus, dyslipidaemia, non-obstructive coronary artery disease, previous history of cerebrovascular accident, peripheral artery disease, atrial fibrillation, and chronic kidney disease (CKD), are summarized in Supporting Information, *Table S1*. Medication history was identified, which included renin-angiotensin system inhibitors, beta-blockers, calcium channel blockers, statins, loop diuretics, mineralocorticoid receptor antagonist, and sodium-glucose cotransporter-2 inhibitors. The following laboratory parameters, besides RDW, were obtained: white blood cell count and platelet counts, haemoglobin level, albumin concentration, estimated glomerular filtration rate using creatinine, C-reactive protein level, and NT-proBNP level. Medication history and laboratory parameters were collected within 3 months from the day of HF diagnosis. The following echocardiographic parameters, if available, were retrieved: EF, left ventricular (LV) mass index, relative wall thickness, left atrial volume index, E/e', and LV global longitudinal strain. The HFA-PEFF score was calculated based on a consensus recommendation of the Heart Failure Association of the European Society of Cardiology.[15] The primary endpoint of the present study was all-cause death. Additionally, cardiac deaths were also recorded. Mortality events were collected from both the integrated clinical data server analysis system and the National Statistical Office of Korea. Patients were followed up until all-cause death occurred, or last visit to the hospital, or 31 December 2020, whichever was earlier, as the latter

was the date the patient was last recorded as being alive by the National Statistical Office of Korea.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation. Categorical variables are expressed as numbers and percentages. Continuous data were compared using Student's *t*-test, whereas categorical data were compared using the χ^2 test. We performed multivariable Cox regression analysis with two different models, clinical variables only and clinical, laboratory, and echocardiographic covariates with a *P*-value of <0.10 as the primary endpoint. The incremental values of RDW for predicting poor prognosis were evaluated by exploring changes in the global χ^2 values in the sequentially constructed multivariable models: age and sex (Model 1), clinical risk factors and HF medication (Model 2), NT-proBNP (Model 3), and echocardiographic parameters (Model 4). Kaplan–Meier survival curve analysis was used to evaluate the cumulative incidence according to the RDW and the difference was compared using the log-rank test. We calculated the cut-off value for predicting the primary endpoint using the Youden index with receiver operating characteristic curve analysis.[16] Missing data imputation was performed with the missForest algorithm.[17] Inverse probability of treatment weighting (IPTW) analysis using the calculated propensity score (PS) was performed to adjust covariates between participants with higher and lower RDW according to the cut-off value. Weighting for participants with the primary event was the inverse of the PS, and for participants without events weighting was the inverse of (1 − PS); the weights were stabilized using the trimming technique.[18] A standardized mean difference of covariates was used to show the balance in the matched cohort between the groups and a value < 0.10 indicated adequate adjustment. The incremental values of RDW over traditional risk factors, laboratory findings, and echocardiographic parameters for estimating the primary endpoint were assessed using sequential Cox regression analysis. Discrimination analyses, including C-statistics, net reclassification index (NRI), and integrated discrimination improvement (IDI), were also performed. Statistical significance was set at a two-sided *P*-value < 0.05. All statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria) Version 4.0.3.

Results

Baseline characteristics

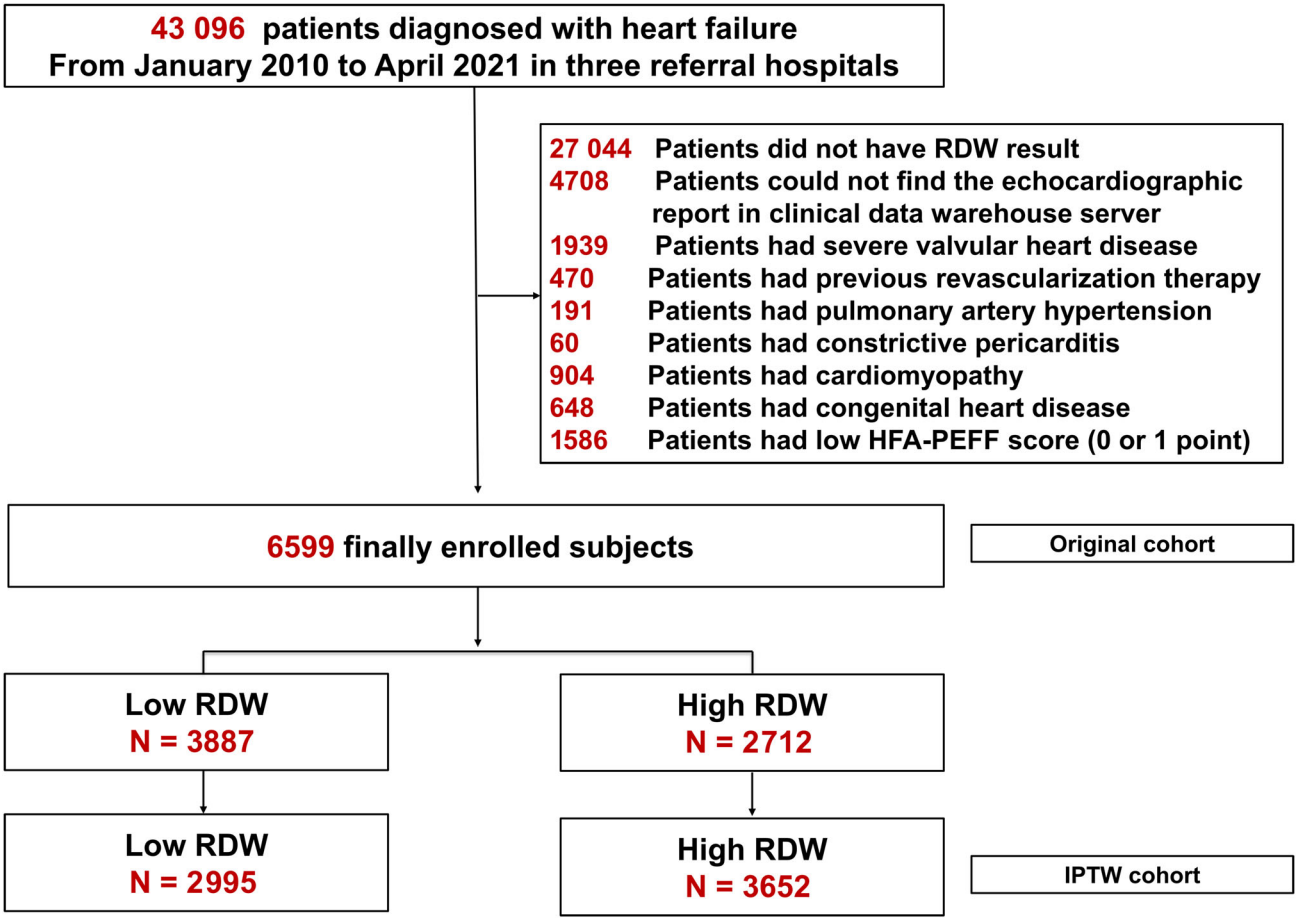
Among 43 096 participants from the three hospitals who satisfied the initial criteria of both HF diagnosis and undergoing an RDW test within 3 months from HF diagnosis, 6599 patients were finally enrolled in this study (*Figure 1*). The median follow-up duration was 887 days [interquartile range (IQR) 351–1589]. The mean age of participants was 65.0 ± 15.2 years and 3119 (47.3%) were female. The median value of NT-proBNP was 1103.0 pg/mL (IQR 242.0–3596.5) and there was a mild correlation between NT-proBNP and RDW (r = 0.301, P < 0.001) (Supporting Information, *Figure S1*). Patients with a higher RDW were older and more likely to have comorbidities such as diabetes mellitus, peripheral artery disease, atrial fibrillation, CKD, or use of loop diuretics and mineralocorticoid receptor antagonist but were less likely to be male and to have a lower body mass index. They were also less likely to have dyslipidaemia, coronary artery disease, or use of beta-blockers (*Table 1*). Patients with a higher RDW had lower levels of haemoglobin, platelet, albumin, and estimated glomerular filtration rate and a higher white blood cell count, C-reactive protein level, and NT-proBNP level. Regarding echocardiographic parameters, participants with a higher RDW had lower EF and higher HFA-PEFF scores.

Clinical outcome and prognostic impact of red cell distribution width

A total of 1256 mortality events (19.0%) occurred in the study population during the follow-up period. In the original cohort, the cumulative incidence of the primary event was significantly higher in the elevated RDW group according to both tertiles (*Figure 2A*) and 13.5% of the cut-off value [30.2% vs. 11.2%, relative risk (RR) 1.58, 95% confidence interval (CI) 1.51–1.67; log-rank P < 0.001] than those with lower RDW group (*Table 2* and *Figure 2B*). Spline regression curves showed that the cut-off value was associated with an increased risk of the primary event (Supporting Information, *Figure S2*). The cumulative incidence of cardiac death showed a similar trend to that of the primary event (12.8% vs. 4.6%, RR 1.61, 95% CI 1.50–1.72; log-rank P < 0.001) (*Table 2* and Supporting Information, *Figure S3*). These results were also observed according to the subtypes of HF with reduced EF (*Figure 3A,B*), HF with mildly reduced EF (*Figure 3C,D*), and HFpEF (*Figure 3E,F*).

We performed multivariate Cox regression analyses with the variables that showed significant differences in the univariable Cox analysis in the two different models of the original cohort (*Table 3* and Supporting Information, *Table S2*). RDW was an independent predictor of poor prognosis after traditional risk factors and medication history were adjusted for, including age, body mass index, diabetes mellitus, dyslipidaemia, coronary artery disease, CKD, and use of beta-blockers and loop diuretics [adjusted hazard ratio (HR) 1.15, 95% CI 1.11–1.19, P < 0.001]. After additional adjustment with laboratory and echocardiographic parameters,

Figure 1 Flow chart of the study. Among 43 096 patients diagnosed with heart failure from the three referral hospitals, 6599 subjects having available RDW data and an echocardiographic report with no other compounding comorbidities such as severe valvular heart disease, previous revascularization therapy, pulmonary artery hypertension, constrictive pericarditis, cardiomyopathy, or congenital heart disease were included in this analysis. Patients who had an ejection fraction of ≥50% and a low HFA-PEFF score of <2 were also excluded. Patients were classified into two groups according to an RDW level of 13.5%, which was the cut-off value for both all-cause and cardiac death calculated using the Youden index. The IPTW cohort was generated to balance different baseline characteristics according to RDW. HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology; IPTW, inverse probability of treatment weighting; RDW, red cell distribution width.



RDW remained a significant factor for estimating the primary endpoint (HR 1.07, 95% CI 1.02–1.13, $P = 0.010$).

We performed stabilized IPTW to identify the prognostic value of RDW after adjusting for different baseline characteristics affecting elevated RDW. The mean standardized differences of covariates that differed between the higher and lower RDW groups were all <0.1 in the stabilized IPTW cohort (Supporting Information, *Table S3* and *Figure S4*). Kaplan–Meier curves for the cumulative incidence of the primary endpoint showed concordant differences between the groups after IPTW adjustment (log-rank $P = 0.011$ in the stabilized IPTW cohort) (*Figure 1B*). RDW was an independent factor for estimating the primary endpoint in the stabilized IPTW cohort (HR 1.28, 95% CI 1.03–1.58, $P = 0.028$) (*Table 2*).

Incremental value of red cell distribution width for predicting prognosis

The incremental value of RDW in predicting poor prognosis over traditional clinical risk factors was assessed by sequential Cox analysis (*Figure 4*). Compared with the models of demographic parameters including age and sex ($\chi^2 = 807.2$, Model 1), clinical risk factors and HF medications ($\chi^2 = 963.5$, Model 2), NT-proBNP ($\chi^2 = 1181$, Model 3), and echocardiographic parameters including EF and the HFA-PEFF score ($\chi^2 = 1263$, Model 4), RDW showed a significant incremental predictive value for poor prognosis ($\chi^2 = 1383$, $P < 0.001$). RDW also showed an incremental value for predicting the primary endpoint with a significant increase in NRI of 0.381 (95% CI 0.322–0.442, $P < 0.001$)

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Table 1 Baseline characteristics of study participants: high versus low RDW

	Low RDW (N = 3887)	High RDW (N = 2712)	P-value
Age, years	62.9 ± 15.0	68.0 ± 14.9	<0.001
Female sex, *n* (%)	1791 (46.1)	1328 (49.0)	0.022
Systolic blood pressure, mmHg	131.0 ± 24.7	130.9 ± 27.9	0.819
Diastolic blood pressure, mmHg	78.4 ± 15.6	78.0 ± 17.6	0.409
Body mass index, kg/m^2	24.7 ± 4.0	23.8 ± 4.5	<0.001
Underlying disease, *n* (%)			
Hypertension	1474 (37.9)	1003 (37.0)	0.454
Diabetes mellitus	603 (15.5)	544 (20.1)	<0.001
Dyslipidaemia	581 (14.9)	284 (10.5)	<0.001
Coronary atherosclerosis	1108 (28.5)	605 (22.3)	<0.001
Previous CVA	33 (0.8)	28 (1.0)	0.525
Peripheral artery disease	45 (1.2)	49 (1.8)	0.037
Atrial fibrillation	893 (23.0)	823 (30.3)	<0.001
Chronic kidney disease	165 (4.2)	337 (12.4)	<0.001
Current medication, *n* (%)			
RAS inhibitor	1453 (37.4)	1036 (38.2)	0.516
Beta-blocker	1621 (41.7)	986 (36.4)	<0.001
Calcium channel blocker	488 (12.6)	429 (15.8)	<0.001
Statins	1020 (26.2)	707 (26.1)	0.898
Loop diuretics	2330 (59.9)	2294 (84.6)	<0.001
MRA	452 (11.6)	498 (18.4)	<0.001
Laboratory findings			
White blood cell, $\times 10^3/\mu L$	7824 ± 3308	8378 ± 4555	<0.001
Haemoglobin, g/dL	13.9 ± 1.8	12.3 ± 2.5	<0.001
Platelet, $\times 10^6/\mu L$	238.0 ± 70.2	227.7 ± 96.7	<0.001
Albumin, mg/dL	4.2 ± 0.5	3.8 ± 0.6	<0.001
eGFR, mL/min/1.73 m^2	88.2 ± 62.0	73.5 ± 67.3	<0.001
C-reactive protein, mg/L	21.5 ± 47.9	31.9 ± 54.6	<0.001
NT-proBNP, pg/mL	1954 ± 4774	7650 ± 12 922	<0.001
Red cell distribution width, %	12.7 ± 0.5	15.0 ± 1.9	<0.001
Echocardiographic parameters			
Ejection fraction, %	51.9 ± 17.4	46.3 ± 18.5	<0.001
Ejection fraction below 40%, *n* (%)	1072 (27.6)	1117 (41.2)	<0.001
LV mass index, g/m^2	125.6 ± 37.3	128.4 ± 37.1	0.323
Relative wall thickness	0.44 ± 0.10	0.43 ± 0.10	0.016
Relative wall thickness > 0.42	276 (7.1%)	182 (6.7%)	0.573
LA volume index, mL/m^2	50.7 ± 25.1	50.8 ± 19.2	0.979
E/e' (septal)	15.3 ± 7.4	15.6 ± 8.1	0.188
HFA-PEFF score	3.4 ± 1.5	3.8 ± 1.6	<0.001

Continuous variables were presented mean ± standard deviation or median [interquartile range], as appropriate. CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate (by CKD-EPI equation); HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology; LA, left atrial; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; RAS, renin-angiotensin system; RDW, red cell distribution width.

and positive integrated discrimination index of 0.165 (95% CI 0.118–0.212, $P < 0.001$) compared with the above-mentioned models composed of traditional risk factors, NT-proBNP, and echocardiographic parameters (*Table 4*).

Sensitivity analysis

We conducted a sensitivity analysis to demonstrate the clinical utility of RDW in the subgroup, which excluded participants who had NT-proBNP below 125 pg/mL. The results of the subgroup were similar to those of the original cohort. After 792 (12.0%) patients were excluded, the incidence rates and the RR for the primary endpoint were slightly increased (1.58 to 1.69 in RR) (Supporting Information, *Table S4*). Several Cox regression models showed an independent association between RDW and the primary endpoint (Supporting Information, *Table S5*). In addition, RDW had incremental value to predict the primary outcome in sequential Cox regression analysis, NRI, and IDI (Supporting Information, *Figure S5* and *Table S6*).

Discussion

The present study showed that elevated RDW was associated with poor prognosis in patients with non-ischaemic HF, with both reduced and preserved EF. In patients with HF, a 1% increase in RDW was associated with a 7% increase in the primary endpoint after adjustment. In contrast to previous studies, we adjusted the different baseline characteristics associated with RDW using multiple covariate analysis and

Figure 2 Kaplan–Meier survival curves for the primary endpoint according to the RDW tertile groups (A) and RDW level of 13.5% in original and inverse probability of treatment weighting cohort (B). The lowest tertile, 11.0–12.8%; the middle tertile, 12.8–13.7%; and the highest tertile, 13.7–31.7%. RDW, red cell distribution width.

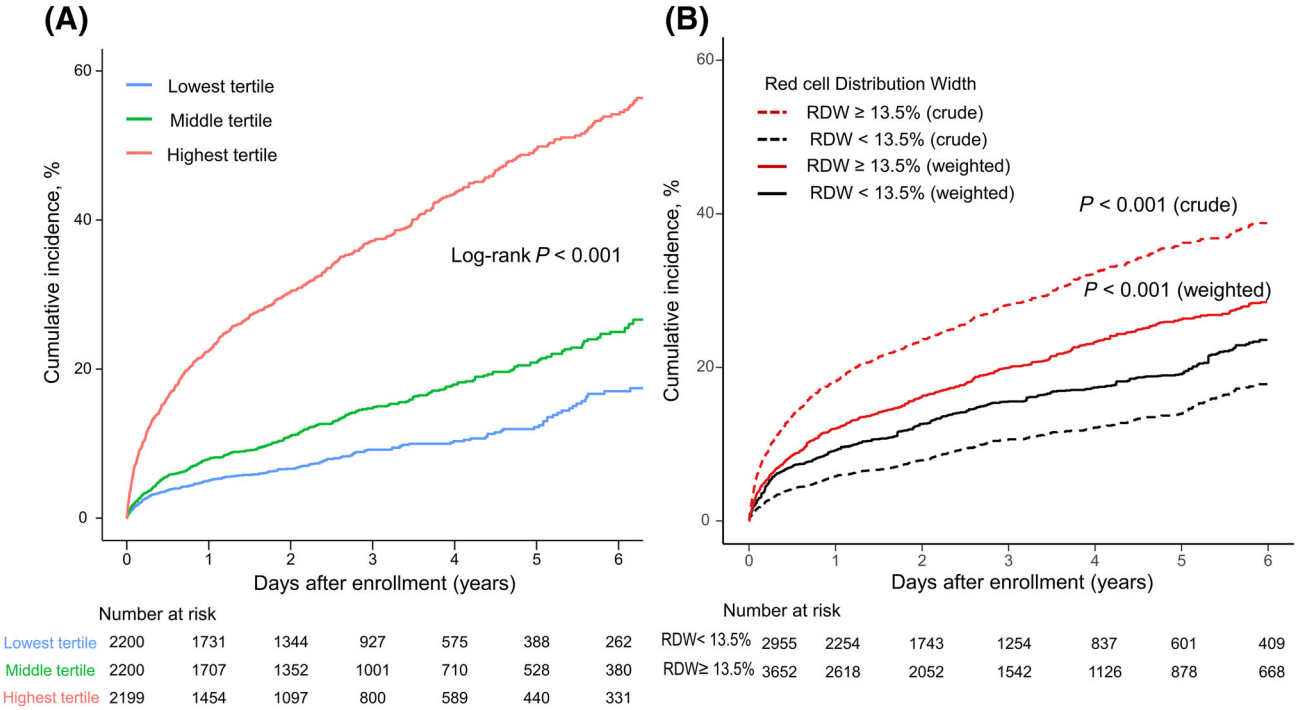


Table 2 Clinical outcomes between high and low RDW

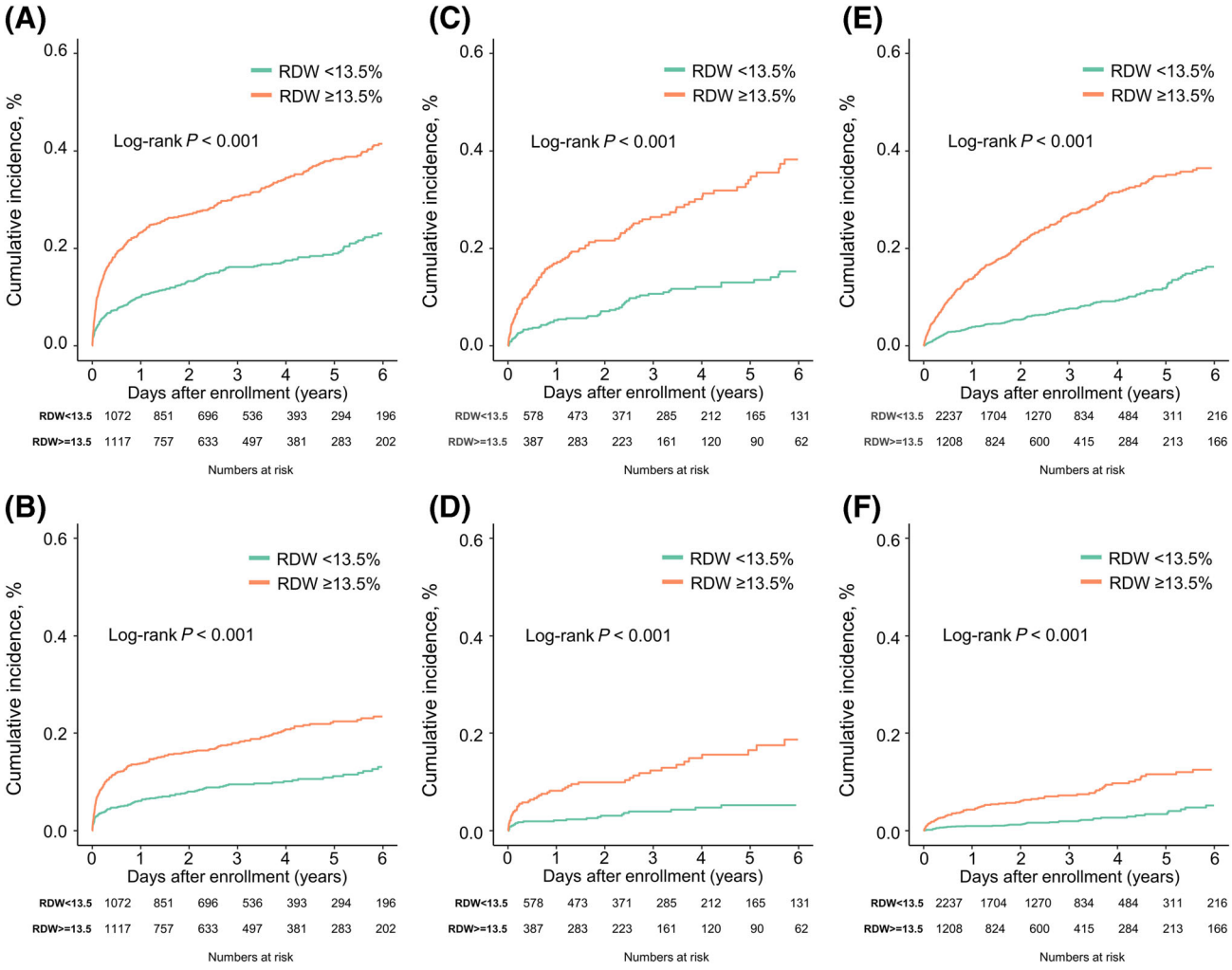
	Low RDW	High RDW	Relative risk	Log-rank *P*-value
Original cohort	*N* = 3887	*N* = 2712		
All-cause death, *n* (%)	437 (11.2)	819 (30.2)	1.58 (1.51–1.67)	<0.001
Cardiac death, *n* (%)	178 (4.6)	347 (12.8)	1.61 (1.50–1.72)	<0.001
IPTW cohort	*N* = 2955	*N* = 3652		
All-cause death, *n* (%)	482 (16.3)	770 (21.1)	1.11 (1.06–1.17)	<0.001
Cardiac death, *n* (%)	204 (6.9)	314 (8.6)	1.10 (1.02–1.18)	0.042

IPTW, inverse probability of treatment weighting; RDW, red cell distribution width.

stabilized IPTW in a large population to demonstrate the clinical usefulness of RDW, as an inexpensive and easily accessible parameter, for estimating poor prognosis in patients with HF.

Elevated RDW has been proven to be a predictor of poor prognosis in several cardiovascular diseases, including pulmonary embolism, ischaemic stroke, and haemorrhagic stroke.[7,8,10] With regard to patients with HF, in a large study aimed at identifying biomarkers to predict the prognosis of chronic HF that included 2679 patients, RDW showed the greatest association with mortality among 36 laboratory values.[19] In a prospective study of 614 patients with acute HF, RDW was also a strong independent predictor of hospitalization and mortality from recurrent HF, and an increase in RDW during hospitalization also showed adverse clinical outcomes.[13] However, because these studies were not randomized control studies, the difference in baseline characteristics according to RDW level was not sufficiently corrected. In the previously mentioned large cohort study, several covariates that are known to affect RDW, including sex, haemoglobin level, coronary artery disease, the Charlson comorbidity index, systolic function, and history of hypertension, were reported as independent prognostic factors with RDW, and age showed a higher HR than RDW.[19] Furthermore, there has been no additional analysis aimed at reducing the interaction of these variables. The tendency for patients in the group with higher RDW to be of older age was also observed in another large HF registry with 1012 participants.[20] A recent study conducted on patients with acute HF suggested that the prognostic power of RDW was consistent even after adjustment for covariates that may affect RDW such as anaemia, inflammation, nutritional status, and underlying diseases presenting the Charlson comorbidity

Figure 3 Kaplan–Meier survival curves for the primary endpoint and cardiac death according to the RDW level of 13.5% and HF subtypes in the original cohort: HF with reduced EF (EF ≤ 40%) (A and B), HF with mildly reduced EF (EF 41–49%) (C and D), and HF with preserved EF (EF ≥ 50%) (E and F). EF, ejection fraction; HF, heart failure; RDW, red cell distribution width.



index.[21] Our study demonstrated that RDW was a prognosticator in patients with HF after adjusting for several variables, including age, at baseline by including data from a large sample of patients extracted from three institutions over 10 years, thus enabling us to perform advanced statistical methods such as IPTW analysis. In addition, the strength of this study was that it showed concordant, independent, and incremental predictive power, even though NT-proBNP, which is known as a prognostic factor for HF and widely used in real clinical practice,[3–5] was included in the analysis.

Our cohort had 792 (12.0%) participants with a low level of NT-proBNP < 125 pg/mL, and there was only a modest correlation between RDW and NT-proBNP. Previous studies reported that the proportion of patients diagnosed with HFpEF proven by invasive measurement but low NT-proBNP did not meet the diagnostic criteria was up to 20%.[22–25] This means NT-proBNP and RDW have some limitations and may not always be the most accurate indicator to diagnose HF. In the HFA-PEFF diagnostic algorithm for HFpEF, NT-proBNP is not weighted but treated equally with other components such as structural and functional markers.[15] We expect that using RDW along with existing HF diagnostic tools will help improve the diagnosis and treatment of patients with HF.

Anaemia is common in patients with HF and contributes to reduced exercise capacity, hospitalization for HF, and high mortality.[26,27] Patients with both acute and chronic HF, accompanied by iron deficiency anaemia, showed good prognosis when intravenous iron supplementation was administered.[28,29] Based on previous studies, the guideline also recommended iron replacement therapy for patients with HF accompanied by iron deficiency.[30] In the early stages of iron deficiency anaemia, an increase in reticulocytes can lead to an elevation of RDW; thus, RDW elevation in patients with HF can be considered a secondary finding in anaemic

Table 3 Independent association between RDW and primary events in several Cox regression models

Models	HR (95% CI)	*P*-value
Univariate Cox regression[a]	1.23 (1.21–1.26)	<0.001
Multivariable Cox Model 1[b]	1.15 (1.12–1.18)	<0.001
Multivariable Cox Model 2[c]	1.11 (1.06–1.16)	<0.001
Stabilized IPTW model[d]	1.29 (1.10–1.49)	<0.001

CI, confidence interval; HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology; HR, hazard ratio; IPTW, inverse probability of treatment weighting; NT-proBNP, N-terminal pro-brain natriuretic peptide; RDW, red cell distribution width.

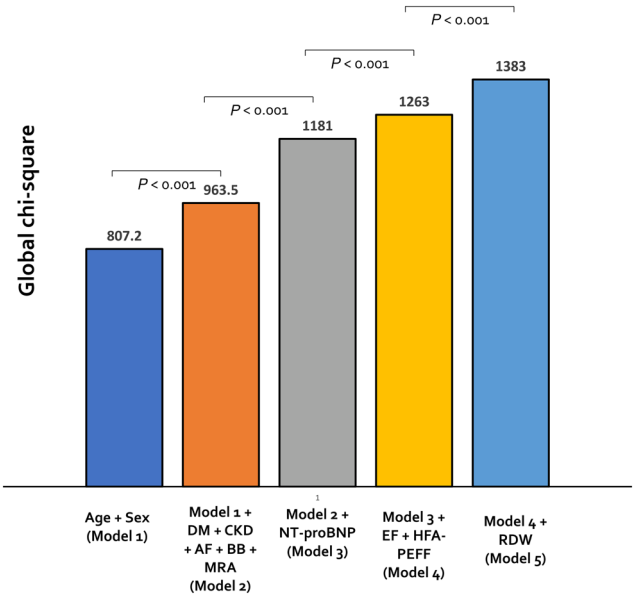
[a]Per 1% increase.

[b]Multivariable Cox Model 1: Multivariable model including significant clinical variables on univariate analysis with RDW: age, body mass index, history of diabetes mellitus, dyslipidaemia, coronary artery atherosclerosis, peripheral artery disease, atrial fibrillation, chronic kidney disease, beta-blockers, loop diuretics, and mineralocorticoid receptor antagonist.

[c]Multivariable Cox Model 2: Multivariable model including significant clinical, laboratory, and echocardiographic variables on univariate analysis with RDW: component of Model 1, white blood cell, haemoglobin, platelet, albumin, glomerular filtration rate, NT-proBNP, C-reactive protein, ejection fraction, and HFA-PEFF score.

[d]Stabilized IPTW model including variables with significantly higher mean standardized differences according to RDW: age, body mass index, history of diabetes mellitus, dyslipidaemia, coronary artery atherosclerosis, atrial fibrillation, chronic kidney disease, beta-blocker, loop diuretics, mineralocorticoid receptor antagonist, white blood cell, haemoglobin, platelet, albumin, glomerular filtration rate, NT-proBNP, C-reactive protein, ejection fraction, and HFA-PEFF score.

Figure 4 Incremental value of the RDW on clinical variables for predicting the primary endpoint by global χ^2 changes in sequential Cox analysis. Model 1: age and sex. Model 2: clinical risk factors and heart failure (HF) medications including diabetes mellitus (DM), chronic kidney disease (CKD), atrial fibrillation (AF), or medication history of beta-blocker (BB) and mineralocorticoid receptor antagonist (MRA) in Model 1. Model 3: NT-proBNP, a biomarker for estimating prognosis in patients with HF in Model 2. Model 4: echocardiographic parameters including ejection fraction (EF) and HFA-PEFF score in Model 3. Model 5: RDW in Model 4. HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology; NT-proBNP, N-terminal pro-brain natriuretic peptide; RDW, red cell distribution width.



patients.[31,32] However, anaemia in these is not always due to iron deficiency. There are also cases of pseudo anaemia due to increased plasma volume (haemodilution), which might be observed in patients with advanced HF, and the prognosis in these cases was observed to be worse than that in patients with true anaemia.[33] Several studies have suggested that elevated RDW was observed owing to increased inefficiency of iron utilization in the body due to increased inflammatory responses identified by elevated C-reactive protein and cytokine levels.[34,35] Inflammation has also been shown to delay red blood cell maturation, resulting in increased peripheral reticulocyte count, which in turn increases RDW.[36] In our study, the proportion of patients with CKD and the level of C-reactive protein was high in the elevated RDW group; thus, it is possible that the increase in RDW occurred through the above-mentioned mechanisms. Nonetheless, the present study showed consistent results even after sequential Cox regression and IPTW analysis, adjusted for kidney function and

Table 4 Incremental value of RDW compared with traditional variables for predicting the primary endpoint in patients with HF

	C-statistic		Net reclassification index		Integrated discrimination improvement	
	95% CI	*P*-value for difference	95% CI	*P*-value for difference	95% CI	*P*-value for difference
Model 1 (age, sex)	0.736 (0.721–0.751)					
Model 2 (Model 1 + clinical variables[a])	0.759 (0.744–0.774)	<0.001	0.187 (0.127–0.248)	<0.001	0.284 (0.227–0.340)	<0.001
Model 3 (Model 2 + NT-proBNP)	0.793 (0.779–0.807)	<0.001	0.593 (0.535–0.652)	<0.001	0.458 (0.382–0.534)	<0.001
Model 4 (Model 3 + echocardiographic parameters[b])	0.799 (0.786–0.813)	0.009	0.292 (0.231–0.352)	<0.001	0.181 (0.139–0.223)	<0.001
Model 5 (Model 4 + RDW)	0.812 (0.799–0.826)	<0.001	0.381 (0.322–0.442)	<0.001	0.165 (0.118–0.212)	<0.001

CI, confidence interval; HFA-PEFF, Heart Failure Association Pre-test assessment, Echocardiography and natriuretic peptide, Functional testing, Final aetiology; NT-proBNP, N-terminal pro-brain natriuretic peptide; RDW, red cell distribution width.
[a]Clinical variables included diabetes mellitus, chronic kidney disease, atrial fibrillation, beta-blockers, and mineralocorticoid receptor antagonist.
[b]Echocardiographic parameters included ejection fraction and HFA-PEFF score.

inflammatory markers, suggesting that elevated RDW is an independent prognostic factor. In a previous study, elevated RDW was observed in several diseases other than HF, including chronic obstructive pulmonary disease, pulmonary hypertension, and interstitial lung disease, which cause hypoxia and may cause an increase in erythropoietin secretion and the rate of red blood cell formation.[37] Patients with decompensated HF may have increased RDW owing to decreased organ perfusion, which is similar to hypoxia in peripheral tissue. Thus, RDW can be used as an inexpensive and easily assessable biomarker to screen patients who require intensive management in real-life clinical practice.

Our study had several limitations. First, because the present study was designed retrospectively, the power of the evidence may be weaker than that of a prospective or randomized control study. However, we tried to overcome this shortcoming by establishing some exclusion criteria, including congenital or genetic factors and diseases for which a treatment modality with a known mechanism exists. In addition, we enrolled participants over an extended period from three institutions using an integrated clinical data server analysis system. Advanced statistical methods were used to eliminate differences in the baseline characteristics to overcome the inherent limitations of this type of analysis. Second, serial measurements of RDW and the clinical utility of their changes were not shown. Nevertheless, one of the main hypotheses of our study was whether RDW could be used as a prognostic factor in patients with HF, excluding the interaction of several confounding factors, and this was sufficiently substantiated statistically. Third, because the definition of HF in the participants was based on the EF and ICD-10 codes, the diagnosis of HF in patients with an EF $\geq$ 50% may be ambiguous. However, we tried to overcome this shortcoming by excluding the low-probability group having an HFA-PEFF score of 1 or lower. Fourth, the enrolled participants were from a single Korean population. However, in previous studies, the usefulness of RDW as a parameter in patients with HF was shown to be common among various ethnicities.[14,19,21] Based on the findings of this study, further research is needed to evaluate the changes in RDW according to the approaches used to manage HF and their respective predictive power of prognosis.

Conclusions

Increased RDW at the time of diagnosis was associated with poor prognosis in patients with HF. In addition to traditional risk factors, RDW may serve as a prognostic indicator and aid in the management of non-ischaemic HF.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Definitions of covariates.
Table S2. Baseline clinical characteristics in original and IPTW cohort.
Table S3. Univariate analysis for the prediction of the primary event.
Table S4. Clinical outcomes between high and low RDW in the sensitivity analysis excluding participants with NT-proBNP <125 pg/mL.
Table S5. Independent association between RDW and the primary event in several Cox regression models as the sensitivity analysis excluding participants with NT-proBNP <125 pg/mL.
Table S6. Incremental value of RDW compared to traditional variables for predicting the primary endpoint in patients with HF in the sensitivity analysis excluding participants with NT-proBNP <125 pg/mL.
Figure S1. The association between NT-proBNP and RDW. RDW, red blood cell distribution width.
Figure S2. Spline regression curve for the estimated risk of the all-cause death according to the RDW.
The Ln (hazard ratio) is represented by a solid line and enclosed by a 50% confidence interval colored in gray, with RDW 13.5% as the reference. Risk of the all-cause death was significantly increased with RDW higher than 13.5%. RDW, red cell distribution width.
Figure S3. Kaplan–Meier survival curves for the cardiac death according to the RDW tertile groups. The lowest tertile, 11.0–12.8%; middle tertile, 12.8–13.7%; and highest tertile, 13.7–31.7%.
Figure S4. Mean standardized differences before and after adjusted or weighted in stabilized IPTW cohort. IPTW, inverse probability of treatment weighting; GFR, glomerular filtration rate.
Figure S5. Incremental value of the RDW on clinical variables for predicting the primary endpoint by global chi-squared changes in sequential Cox analysis in subgroup excluding participants with NT-proBNP level below 125 pg/mL.
Model 1: age and sex. Model 2: clinical risk factors and HF medications including diabetes mellitus, chronic kidney disease, atrial fibrillation, medication history of beta-blocker and mineralocorticoid receptor antagonist in model 1. Model 3: NT-proBNP, a biomarker for estimating prognosis in patients with heart failure in model 2. Model 4: echocardiographic parameters including ejection fraction and HFA-PEFF score in model 3. Model 5: RDW in model 4.

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