Predictive Value of Red Blood Cell Distribution Width on All-Cause Mortality in ESRD Patients on Peritoneal Dialysis

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Predictive Value of Red Blood Cell Distribution Width on All-Cause Mortality in ESRD Patients on Peritoneal Dialysis

Directed by Professor Tae-Hyun Yoo

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ABSTRACT

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Background

Red blood cell distribution width (RDW), which expresses variation in size of circulating erythrocytes, is routinely reported as a part of complete blood cell count test. Recent studies have demonstrated a strong independent association between increased RDW and the risk of adverse outcomes in patients with heart failure and coronary heart disease. In addition, RDW has been found to be predictive of all-cause mortality in two community-based cohorts irrespective of hemoglobin levels. Increased RDW levels are frequently observed in patients with end-stage renal disease (ESRD), however, little is known on the relationship between RDW and outcomes in this population. In this study, I sought to determine whether RDW value is associated with mortality in ESRD patients treated with continuous ambulatory peritoneal dialysis (CAPD).

Methods

A retrospective analysis was undertaken in 197 incident CAPD patients, who started CAPD between January 2005 and December 2010 at Yonsei University Health System and maintained CAPD for more than 3 months. Demographic, biochemical and echocardiographic data of the patients were collected based on their medical records. Patients were divided into 2 groups

according to the RDW levels at 3-month, and all-cause and cardiovascular mortalities were compared between groups.

Results

The mean age was 55.1 years and 115 patients (58.4%) were male. The main cause of ESRD was diabetic nephropathy (43.1%), followed by hypertensive nephropathy (34.0%) and chronic glomerulonephritis (16.8%). RDW at 3-month ranged from 11.3 to 16.8% (mean 13.6±1.1%), and 51 patients (25.8%) had RDW above the upper limit of normal value (>14.5%). There were significant positive correlations between RDW levels and age ($r=0.22$, $p<0.01$), Charlson comorbidity index (CCI) score ($r=0.27$, $p<0.01$), left ventricular mass index ($r=0.28$, $p<0.05$), left atrial volume index (LAVI) ($r=0.26$, $p<0.01$), the ratio of early mitral inflow velocity to peak mitral annulus velocity (E/E') ($r=0.16$, $p<0.05$) and left ventricular end diastolic dimension ($r=0.271$, $p<0.01$). In contrast, RDW values were negatively correlated with hemoglobin ($r=-0.16$, $p<0.05$) and albumin levels ($r=-0.28$, $p<0.01$). The all-cause mortality rates were significantly higher in the high RDW group compared to the normal RDW group ($p<0.05$). Cox regression analysis revealed that RDW was a significant independent predictor of all-cause mortality even after multivariate adjustment for age, gender, CCI score, hemoglobin, albumin, total cholesterol, LAVI, left ventricular ejection fraction (LVEF), and E/E' (HR 1.20, $p<0.05$).

Conclusion

This study demonstrates that RDW provide a meaningful prognostic value on all-cause mortality in incident CAPD patients.

Keywords: Red blood cell distribution width, Peritoneal dialysis, Mortality

Short summary: RDW predicts all-cause mortality in CAPD patients.

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I. Introduction

Even though the dialysis technology has rapidly improved during the last 20 years, the mortality rates are still very high in patients with end-stage renal disease (ESRD). The main cause of death in ESRD patients is cardiovascular disease (CVD) with annual mortality rates of approximately 9%, which is 10- to 20-folds higher than those in the general population, even after adjusting for age, gender, race, and the presence of diabetes mellitus[1].

Red blood cell (RBC) distribution width (RDW), which expresses variation in size of circulating erythrocytes, is routinely reported as a part of complete blood cell count test. Recent studies have demonstrated a strong independent association between increased RDW and the risk of adverse outcomes in patients with heart failure and coronary heart disease[2-5]. In addition, RDW has been found to be predictive of all-cause mortality in two community-based cohorts irrespective of hemoglobin levels[6,7]. Based on these findings, the prognostic significance of RDW could also be valuable for risk stratification in ESRD patients; however, little is known on the relationship between RDW and outcomes in this population. Therefore, in this study, I sought to determine whether RDW value is associated with mortality in ESRD patients. Since RDW is closely related with hemoglobin levels and the variability of hemoglobin is narrow in continuous ambulatory peritoneal dialysis (CAPD) patients compared

to hemodialysis patients, I elucidated the prognostic value of RDW levels only in CAPD patients.

II. Method

1. Patients

Five hundred and fifty ESRD patients, who started CAPD between January 2005 and December 2010 at the Yonsei University Health System, Seoul, Korea, were recruited. Among them, patients who had underlying malignancy or previous history of kidney transplantation or hemodialysis before CAPD were excluded. I also excluded patients who did not undergo baseline echocardiography nor maintain CAPD more than 3 months. Thus, a total of 197 patients were included for final analysis.

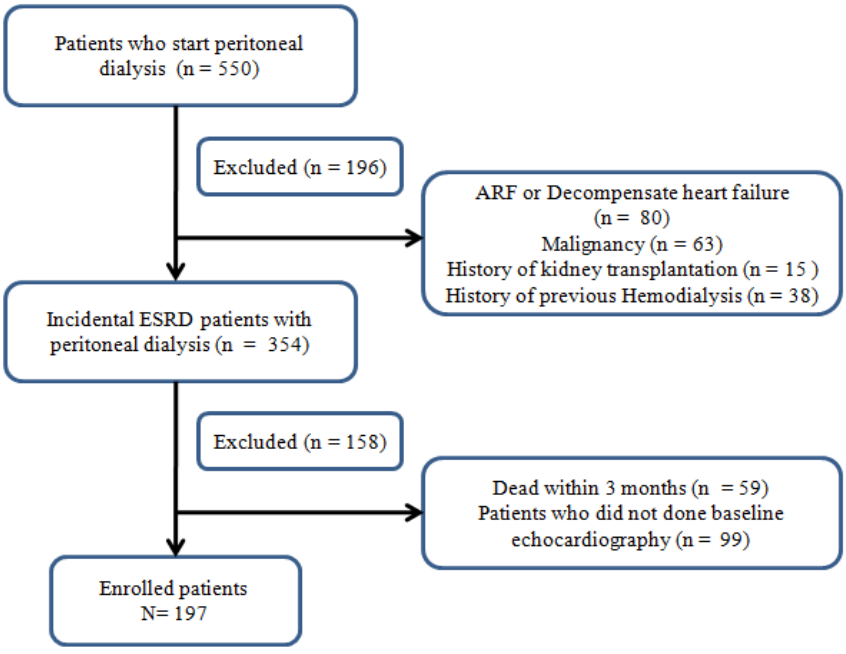

Figure 1. Flow diagram for patient selection

2. Data collection

Demographic and clinical data at the time of CAPD initiation, such as age, gender and comorbid conditions, were recorded. Comorbid conditions included hypertension, diabetes mellitus, coronary artery disease (CAD) and cerebrovascular accident (CVA), and the comorbidities was quantified by using age-unadjusted Charlson Comorbidity Index (CCI)[8]. Coronary artery disease was defined as a history of angioplasty, coronary artery bypass grafts, myocardial infarction, or angina. Cerebrovascular disease was defined as a previous transient ischemic attack, stroke, or carotid endarterectomy. Primary causes of ESRD, transfusion history, technical failure event and death were also checked. The following laboratory data were measured from blood samples at the start of CAPD and at-3-month after CAPD; hemoglobin (Hb), white blood cell count, blood urea nitrogen, creatinine, calcium, phosphorus, albumin, total cholesterol, high-sensitivity C-reactive protein (hsCRP) and intact parathyroid hormone. hsCRP concentration was measured by laser nephelometry (IMMAGE, Beckman Coulter, Brea, CA, USA). Hb levels and RDW were determined using the Advia 2120 Hematology Analyzer (Siemens Healthcare Diagnostics, Deerfield, IL, USA). RDW was reported as a coefficient of variation (percentage) of RBC volume and the reference range for RDW was 11.5%-14.5%. Residual GFR was calculated as the average clearance of urea and creatinine from a 24-hour urine collection. Kt/V urea was determined from the total loss of urea nitrogen in the spent dialysate using the Watson equation. The modified peritoneal equilibration test was performed with 4.25% glucose dialysis solution as described previously and the dialysate to plasma creatinine concentration ratios (D/P Cr) at 4-hours of dwell were used to describe the peritoneal small solute transport rate[9].

3. Echocardiography assessment

All patients underwent echocardiography with an empty abdomen based on the imaging protocol recommended by the American Society of Echocardiography[10] using a SONOS 7500 (Philips Ultrasound, Bothell, WA, USA). Left ventricular (LV) systolic function was defined by left ventricular ejection fraction (LVEF) using a modified biplane Simpson's method from the apical 2- and 4-chamber views[11]. LV mass (LVM) was determined by the method described by Devereux and Reichek and the LVM index (LVMI) was calculated by dividing LVM by body surface area (BSA)[12]. Left atrial volume (LAV) was assessed by the biplane area-length method from the apical 2- and 4-chamber views and was indexed for BSA (LAVI)[13]. Measurements were obtained in end systole from the frame preceding mitral valve opening. According to population-based studies, a value of 32 ml/m^2 was considered as the upper limit of a normal LAVI[14]. Mitral inflow was assessed with pulse-wave Doppler echocardiography from the apical 4-chamber view, and the mitral inflow profile was used to measure the peak E-wave velocity and its deceleration time, the peak A-wave velocity, and the isovolumetric relaxation time[15]. Doppler tissue imaging of the mitral annulus was also obtained from the apical 4-chamber view. Systolic right ventricular pressure (RVP) was calculated using the modified Bernoulli equation [4 X $(\text{tricuspid systolic jet})^2$ + 10mmHg][16].

4. Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± SD, and categorical variables as a number (percentage). Based on RDW levels, the patients were divided into 2 groups; a high RDW group (>14.5%) and a normal RDW group (≤14.5%). To compare differences between the two groups, Student's t-test or the chi-square test were used. Univariate and multivariate

Cox proportional hazard analysis was performed to determine the independent prognostic power for all-cause mortality of RDW. In univariate analysis, I included a series of traditional risk factors (age, gender, hypertension, diabetes mellitus, previous history of CV events and cholesterol), factors that are peculiar to ESRD (Hb, calcium, phosphate, albumin, and hsCRP), and emerging risk factors (LAVI, LVMI). To reduce the risk of confounding, I determined a set of parameters significantly associated with all-cause mortality ($p<0.10$), and then adjusted for these factors in multivariate analysis. These Cox proportional hazard analyses were performed in 2 different ways; by using RDW as a categorical or continuous variable. The results of univariate and multivariate Cox proportional hazard analysis were presented as hazard ratios (HRs) and the 95% confidence interval (CI). Kaplan-Meier curves were constructed to compare the difference in all-cause mortality between the two groups. I also conducted receiver operating characteristic (ROC) analysis to compare the predictive accuracy of RDW and, Hb levels on mortality and the area under the curve (AUC) was calculated. A p-value of less than 0.05 was considered significant.

III. Results

1. Patient characteristics

The baseline demographic and clinical characteristics of the patients are shown in Table 1. The mean age was 55.1 years, 115 patients (58.4%) were male and the most common cause of ESRD was diabetic nephropathy (43.1%). Sixty nine patients had a previous history of transfusion, and the majority of them (65 patients, 94.2%) received transfusion within 3 months before the initiation of CAPD. The mean CCI score was 4.0 ± 1.9.

Table 1. Baseline patient characteristics

Parameters	N=197
Demographic data	
Age (years)	55.1 ± 12.9
Male (%)	115 (58.4%)
Cause of ESRD	
Diabetic nephropathy	85 (43.1%)
Hypertensive nephropathy	67 (34.0%)
Chronic glomerulonephritis	33 (16.8%)
Others	12 (6.1%)
Comorbidity	
Charlson comorbidity index	4.0 ± 1.9

Data are shown as n (%) or mean ±SD.
ESRD; end stage renal disease.

2. Comparison between patients with high RDW and normal RDW

The mean RDW at 3-month was 13.6±1.1% (range: 11.3 to 16.8%). The patients were divided into 2 groups based on the upper normal limit of normal RDW value (14.5%); normal RDW group (RDW≤14.5%) (N=146) and high RDW group (RDW>14.5%) (N=51), and the baseline clinical, laboratory and echocardiographic data were compared between the two groups. Patients with

Table 2. Comparisons of demographic, laboratory and echocardiographic data between patients with normal and high RDW

Parameters	RDW≤14.5 (n=146)	RDW>14.5 (n=51)	p-value
Demographic data			
Age (years)	53.1 ± 12.6	58.3 ± 12.7	<0.01
Male, n (%)	79 (54.0%)	33 (64.7%)	0.014
CCI score	3.75 ± 1.7	4.36 ± 2.0	0.032
Biochemical data			
RDW (%)	13.2 ± 0.7	15.3 ± 0.6	<0.01
Hb (g/dL)	10.9 ± 1.5	10.5 ± 1.5	0.113
BUN (mg/ dL)	50.8 ± 20.9	54.7 ± 16.7	0.302
Cr (mg/dL)	8.1 ± 3.2	8.1 ± 4.0	0.926
hsCRP (mg/dL)	1.18 ± 3.0	1.76 ± 2.3	0.633
Albumin (g/dL)	3.7 ± 0.6	3.5 ± 0.5	0.041
T. chol (mg/dL)	179.7 ± 40.9	163.6 ± 37.8	0.042
Calcium (mg/ dL)	8.9 ± 0.7	8.9 ± 0.8	0.949
Phosphorus (mg/dL)	4.5 ± 1.2	4.6 ± 1.2	0.692
Intact PTH (pg/mL)	150.7 ± 161.1	134.5 ± 166.9	0.686
Iron (ug/dL)	76.5 ± 35.5	76.7 ± 50.5	0.982
TIBC (ug/dL)	242.4 ± 49.8	237.1 ± 37.1	0.594
Ferritin (ng/mL)	294.1 ± 330.2	307.8 ± 381.1	0.847
Echocardiographic data			
LVEDD (mm)	51.2 ± 6.2	54.7 ± 7.4	<0.01
LVMI (g/m^2)	127.1 ± 34.5	145.9 ± 46.5	<0.01
LVEF (%)	60.4 ± 13.2	57.2 ± 14.1	0.102
LAVI (ml/m^2)	31.5 ± 12.6	40.0 ± 19.1	<0.01
RVP (mmHg)	30.1 ± 9.7	34.5 ± 12.4	<0.01
E/E’	14.0 ± 5.9	17.5 ± 8.9	<0.01
Kt/V			
RRF	4.01 ± 3.13	3.2 ± 2.85	0.619
D/P Cr 4hr	0.70 ± 0.14	0.76 ± 0.14	0.062
Total Kt/V	2.37 ± 0.62	2.13 ± 0.52	0.086
Transfusion History, n (%)	42 (29.0 %)	27 (53.4 %)	0.011

Data are shown as n (%), mean (±SD).

CCI, Charlson comorbidity index; RDW, red blood cell distribution width; Hb, hemoglobin; BUN, blood urea nitrogen; Cr, creatinine; hsCRP, high-sensitivity C-reactive protein; T. chol, total cholesterol; PTH, parathyroid hormone; TIBC, total iron binding capacity; LVEDD, left ventricular end

diastolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; RVP, Right ventricular pressure; E/E', early mitral inflow velocity to peak mitral annulus velocity ratio; RRF, residual renal function; D/P Cr, dialysate to plasma creatinine ratio; Kt/V, K is the rate of clearance, t is the amount of time of the session, and V is the urea distribution volume.

high RDW were significantly older and had significantly more comorbidities than patients with normal RDW. The proportion of male patients was significantly higher, and the concentrations of serum albumin and total cholesterol were significantly lower in high RDW group. In addition, LVMI, LAVI, RVP and E/E' were significantly higher in patients with high RDW compared to patients with normal RDW. In contrast, there were no significant differences in Hb levels, iron profile (serum iron and TIBC concentration, and transferrin saturation) and Kt/V between the two groups (Table 2).

3. Factors associated with RDW values

To identify factors associated with RDW levels, correlation analysis was performed. There were significant positive correlations between RDW values and age ($r=0.22$, $p<0.01$), CCI score ($r=0.27$, $p<0.01$), LVEDD ($r=0.271$, $p<0.01$), LVMI ($r=0.24$, $p<0.01$), LAVI ($r=0.26$, $p<0.01$) and E/E' ($r=0.16$, $p<0.01$). In contrast, RDW values were negatively correlated with Hb ($r=-0.16$, $p<0.05$) and albumin levels ($r=-0.28$, $p<0.01$), and LVEF($r=-0.182$, $p=0.01$). On the other hand, there were no significant correlations between RDW values and white blood cell count, and hsCRP and total cholesterol levels (Table 3).

Table 3. Correlations between RDW values and selected clinical parameters

Variable	RDW (%)	
	r	p-value
Age (years)	0.224	< 0.01
CCI score	0.271	< 0.01
WBC (10^3/mm^3)	-0.014	0.85
Hb (g/dL)	-0.159	0.04
hsCRP (mg/dL)	0.154	0.40
Albumin (g/dL)	-0.276	< 0.01
T.chol (mg/dL)	-0.073	0.39
LVEDD (mm)	0.271	< 0.01
LVMI (g/m^2)	0.243	< 0.01
LVEF (%)	-0.182	0.01
LAVI (ml/m^2)	0.261	< 0.01
E/E'	0.239	< 0.01

CCI, Charlson comorbidity index; WBC, white blood cell count; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; T. chol, total cholesterol; LVEDD, left ventricular end diastolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E/E', early mitral inflow velocity to peak mitral annulus velocity ratio.

4. Comparisons between survivor and non-survivor groups

During the median duration of follow-up of 26 months, 20 patients (10.1%) died. When the patients were divided into survivor and non-survivor groups, the mean RDW (15.0±1.2 vs. 14.0±1.4%, $p<0.01$) and hsCRP levels (2.62±2.7 vs. 1.21±2.1 mg/dL, $p<0.05$) were significantly higher, whereas serum albumin concentrations were significantly lower in non-survivor (3.3±0.6 vs. 3.7±0.6 g/dL, $p<0.01$) compared to survivor group. In addition, patients who died during the follow-up period were significantly older ($p<0.01$), and had significantly more comorbidities and worse cardiac function (lower LVEF and higher LAVI and E/E') at baseline ($p<0.05$). However, there was no difference in Hb levels between the two groups (Table 4).

Table 4. Comparisons of demographic, biochemical and echocardiographic data between survivor and non-survivor groups

Parameters	Survivor (N=177)	Non-survivor (N=20)	p-value
Demographic data			
Age (years)	53.1 ± 12.6	58.3 ± 12.7	<0.01
Male, n (%)	105 (59.3 %)	10 (50.0 %)	0.423
CCI score	3.75 ± 1.7	4.36 ± 2.0	0.032
Biochemical data (3 month's)			
RDW (%)	14.0 ± 1.4	15.0 ± 1.2	<0.01
Hb (g/dL)	10.9 ± 1.4	10.5 ± 1.9	0.320
hsCRP (mg/dL)	1.21 ± 2.1	2.62 ± 2.7	0.045
Albumin (g/dL)	3.7 ± 0.6	3.3 ± 0.6	0.005
Echocardiographic data			
LVEDD (mm)	52.1 ± 6.7	55.9 ± 7.7	0.017
LVMI (g/m^2)	132.9 ± 39.9	144.4 ± 43.6	0.270
LVEF (%)	60.3 ± 12.6	50.0 ± 18.3	0.023
LAVI (ml/m^2)	33.7 ± 15.3	43.2 ± 17.8	0.011
E/E'	14.9 ± 6.9	18.8 ± 10.8	0.032

Data are shown as n (%), mean (±SD).
CCI, Charlson comorbidity index; RDW, red blood cell distribution width; Hb, hemoglobin; hsCRP, high-sensitivity C-reactive protein; LVEDD, left ventricular end diastolic dimension; LVMI, left ventricular mass index; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; E/E', early mitral inflow velocity to peak mitral annulus velocity ratio.

5. Comparison of mortality between patients with normal and high RDW

The most common cause of death was cardiovascular disease (13 patients, 65.0%), followed by infection (6, 30.0%) and gastrointestinal bleeding (1, 5.0%). The all-cause mortality rates were significantly higher in patients with high RDW (13/51, 25.5%) compared to the normal RDW group (7/146, 4.8%) ($p<0.01$). The cardiovascular mortality rates were also significantly higher in patients with high RDW ($p<0.01$) compared to the normal RDW group (Figure 2).

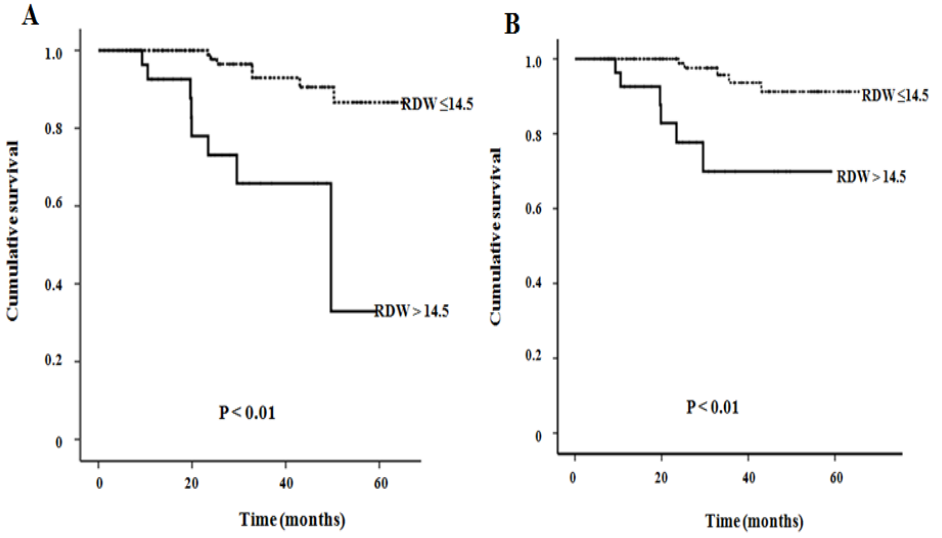

Figure 2. Kaplan-Meier survival curves for (A) all-cause mortality and (B) cardiovascular mortality according to the baseline RDW values. Both all-cause and cardiovascular mortalities were significantly higher in patients with high RDW compared to the normal RDW group.

6. RDW as an independent predictor of all-cause mortality

Univariate Cox regression analysis revealed that high RDW values, high CCI score and low albumin concentrations were associated with increased all-cause mortality. The association between RDW levels and mortality remained significant even after adjusting for age, gender, CCI score, Hb, albumin, total cholesterol, LVEDD, LVEF, LAVI and E/E' (HR: 1.29, 95% CI: 1.07 to 2.45, p=0.049) (Table 5). When analysis was performed with RDW values as a categorical variable, the adjusted HR was also significantly high in the high RDW group (HR: 3.69, 95% CI: 1.91 to 7.12, p<0.01).

ROC curves examining the power of RDW and Hb to predict all-cause and cardiovascular mortality are shown in Figure 3. The AUCs of RDW and 1-Hb for all-cause mortality were 77.5% and 57.5% (p<0.05), respectively, and those for cardiovascular mortality were 73.6% and 48.9% (p<0.05), respectively.

RDW provided a higher predictability of all-cause and cardiovascular mortality than Hb. The cutoff value of RDW greater than 14.35% provided a sensitivity of 60.0% and specificity of 81.6% for predicting all-cause mortality.

Table 5. Cox proportional hazard analysis for all-cause mortality according to RDW values

	RDW as continuous variable		
	HR	95% CI	p-value
Model 1	2.26	1.54-3.92	<0.01
Model 2	1.69	1.31-3.12	0.024
Model 3	1.29	1.07-2.45	0.049

HR, hazard ratio; CI, confidence interval.
Model 1: unadjusted relative risk
Model 2: adjusted for age, gender, Charlson comorbidity index score, hemoglobin, albumin and total cholesterol.
Model 3: adjusted for Model 2 plus LVEDD, LVEF, LAVI and E/E'.

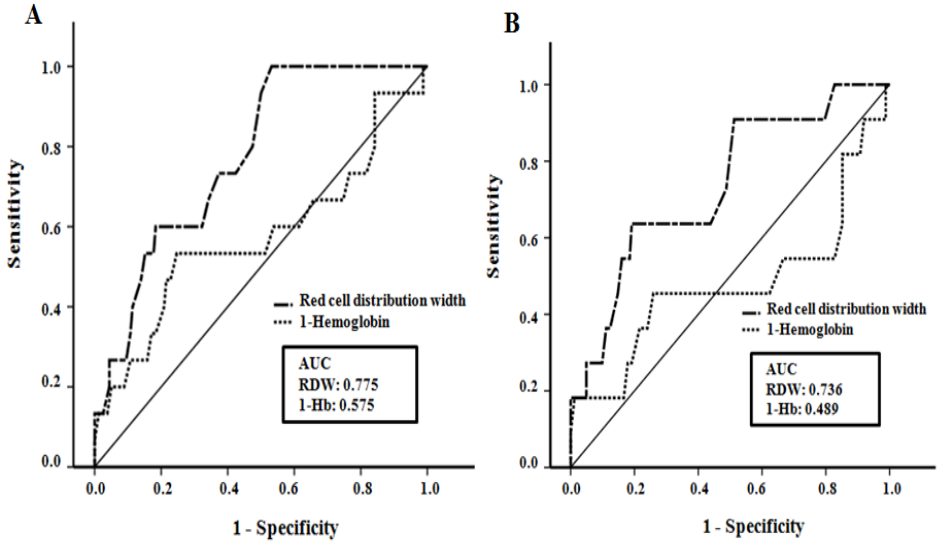

Figure 3. ROC curves for (A) all-cause mortality and (B) cardiovascular mortality with calculated AUCs.

7. Consistency of RDW values

The tendency of high RDW did not change during the 6-month follow-up. There was a positive and statistically significant correlation between baseline and 6-month RDW levels ($r=0.176$, $p<0.001$). This tendency may in part conquer the shortcoming of this study, using a single measurement of RDW for the analysis.

IV. Discussion

The results of the present study indicate that RDW levels are an independent predictor of all-cause mortality in ESRD patients on CAPD. As RDW levels increased by 1%, the risk of all-cause mortality rose by 29% (HR: 1.29) even after adjusting for other risk factors. In addition, the survival rates were significantly lower in patients with high RDW compared to the normal RDW patients.

RDW reflects the variability in size of circulating erythrocytes and is defined as the SD of erythrocyte size divided by the mean corpuscular volume (MCV). Traditionally, along with the MCV, RDW played a role in the differential diagnosis of anemia[17]. High RDW represents the state of anisocytosis and is typically observed in conditions of ineffective RBC production, including iron deficiency, vitamin B12 deficiency, folate deficiency and hemoglobinopathies, increased RBC destruction and following blood transfusion[17-20]. However, previous studies have demonstrated that high RDW levels are not uncommonly accompanied in patients with liver disease, malnutrition, occult colon cancer, and neoplastic metastases to marrow[21-23]. In addition, RDW has often been found to be increased in patients with renal failure. Moreover, Lippi et al. observed that high RDW values were associated with reduced residual renal functions independent of age, gender, MCV and hemoglobin levels[24]. On the other hand, numerous studies have shown a strong

association between high RDW and adverse clinical outcomes in patients with various conditions. In patients with chronic heart failure or ischemic heart disease, RDW is regarded as a potential predictor of mortality[2-5,25]. Epidemiologic cohort studies have also demonstrated that high RDW levels are associated with increased risk of mortality from CVD, cancer, and any other causes [6]. Moreover, a recent study carried out in patients with acute heart failure suggests that RDW has a prognostic significance in acute conditions as well [26]. Even though the subjects of my study were incident CAPD patients, the results of this study provide new evidence on the prognostic significance of RDW on mortality.

What is the mechanism underlying the strong association between RDW and patients' outcome? Several plausible explanations have been suggested in prior studies. Some studies speculated that underlying inflammatory state, which is associated with adverse clinical outcomes[27], could impair RBC maturation[28], resulting in high levels of RDW. In addition, systemic inflammatory response impacts bone marrow function and iron metabolism[29,30]. Moreover, proinflammatory cytokines are known to inhibit erythropoietin-induced RBC maturation and proliferation, and to down-regulate erythropoietin receptor expression, which may lead to an increase in RDW values[31]. Furthermore, a recent study has demonstrated that RDW levels significantly correlate with CRP concentrations, a well-known acute phase reactant, and are significantly associated with worse outcomes in patients with heart failure[32]. In the present study, unfortunately, I failed to find any correlation between RDW levels and hsCRP. In addition, there was no difference in hsCRP levels between patients with normal and high RDW. Since accumulating evidence has revealed that ESRD is a state of chronic low grade inflammation, I surmise that the influence of inflammation on RDW levels may be weakened in these subjects.

Another possibility is that high RDW values may be attributed to malnutrition. Previous studies have demonostrated a significant correlation

between malnutrition and RDW levels. In addition, a recent study showed that low cholesterol concentrations were associated with high mortality rates and were strongly correlated with high RDW levels in patients heart failure[33,34]. Moreover, since ESRD patients are under an increased catabolic state[35], malnutrition is frequently observed and is considered an independent predictor of poor clinical outcomes in patients with ESRD[36]. The results of this study revealed that there was a significant inverse correation between RDW and serum albumin levels. In addition, serum albumin concentrations were significantly lower in the high RDW group. Taken together, malnutrition may be associated with adverse outcomes in critically ill patients and RDW can be a simple integrative marker of malnutrition-inflammation syndrome[34] in this population.

In complete accordance with previous studies, I found that heart failure had an adverse effect on clinical outcomes in CAPD patients[37,38] LAVI and E/E' were higher and LVEF was lower in non-survivor group. In addition, univariate Cox proportional hazard analysis revealed that high LVMI, LAVI and E/E' and low LVEF were associated with mortality. Meanwhile, RDW was positively correlated with LVMI, LAVI and E/E'. Moreover, although RDW remained as a significant independent predictor of mortality even after adjusting for other risk factors, the significance decreased after adjustment for echocardiographic parameters. Based on these findings, it is speculated that heart failure may in part contribute to the prognostic power of RDW on mortality in ESRD patients on CAPD.

Current study has several limitations that should be considered. First, the present study was a retrospective study based on the medical records of a relatively small number of patients from a single centre, and therefore it can not rule out the possibility of residual confounding. Second, the results of a single measurement of RDW levels were used for the analysis. Even though there was a strong correlation between baseline and 6-month RDW levels, the possibility

of variation in RDW values over time still exists. In addition, there was a wide range of Hb concentrations (3.6 to 14.0%) at the time of CAPD initiation and some patients received transfusion at that time. For analysis, therefore, the data of RDW levels at 3-month, when the Hb concetrations were stabilized and the patients were sufficiently adapted to CAPD, was used as baseline. Lastly, the use of erythropoietin and reticulocyte count, that might affect RDW levels, was not considered.

V. Conclusion

In conclusion, I found that RDW levels were an independent predictor of all-cause mortality in incident CAPD patients. In addition, the survival rates were significantly lower in patients with high RDW compared to the normal RDW patients. Since RDW is a simple, inexpensive, and widely available test, these findings may have significant clinical implications for determining prognosis in ESRD patients who start CAPD. Further studies are needed to clarify the exact mechanisms underlying the impact of RDW values on clinical outcomes in these patients.

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Abstract (In Korean)

복막투석을 시작하는 말기 신부전 환자에서 RDW의 예후인자로서의 의의

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도 화 미

배 경

만성신부전환자의 약 70%가 심혈관 질환을 가지고 있으며 약 40%의 환자가 심혈관질환으로 사망하는 것으로 알려져 있다. 적혈구 분포폭 (Red blood cell distribution width)는 순환 적혈구 크기의 다양성을 나타내는 지표이며 전통적으로 빈혈의 원인 감별에 이용되었으나 최근 심질환 환자의 불량한 예후와 밀접한 관련이 있는 것으로 밝혀지고 있다. 또한 코호트 연구에서 헤모글로빈 수치와 상관없이 사망률을 예측할 수 있는 임자임이 밝혀졌다. 상승된 RDW 수치가 말기신부전 환자에서 흔하게 관찰되지만 말기신부전환자에서의 RDW의 예후인자로서의 의의에 대한 연구는 전무한 실정으로 본 연구에서는 복막투석을 시작하는 말기신부전 환자에서 RDW의 예후인자로서의 의의에 대하여 알아보고자 한다.

방 법

2005년 1월부터 2010년 12월까지 연세대학교 세브란스병원에서 복막투석을 시작하여 3개월 이상 안정적으로 유지 중인 197명의 말기신부전환자들을 대상으로 투석시작 시와 투석 시작 후 3개월 뒤의 임상 요소, 혈액학 검사, 심초음파 소견 및 RDW를 확인하고 RDW와

사망률과의 관계를 분석하였다.

결 과

환자들의 평균 나이는 55.1 ± 12.9세 이었고 남자가 115명 (58.4%) 이었다. 3개월의 RDW는 평균 13.6 ± 1.1이었으며 51명 (25.8%) 의 환자들이 상승된 RDW값을 보였다. RDW와 연령 (r=0.22, p<0.01), CCI 점수 (r=0.27, p<0.01), LAVI (r=0.26, p<0.01), LVMI (r=0.28, p<0.05), E/E' (r=0.16, p<0.05), LVEDD (r=0.271, p<0.01) 간에 유의한 양의 상관관계가 있었으며 헤모글로빈 (r=-0.16, p<0.05), 알부민 (r=-0.28, p<0.01) 과는 음의 상관관계가 있었다. 단순회귀분석에서 RDW와 사망률은 통계적으로 의미 있는 상관관계를 보였다 (HR=2.26, 95% CI 1.54 to 3.92, p<0.01). RDW에 따라 나이, 성별, CCI, 헤모글로빈, 알부민, 총 콜레스테롤, 초음파상 관찰된 LAVI, EF, E/E', LVEDD를 보정하여 다중회귀분석을 실시하였을 때 RDW가 1% 증가할 수록 사망 위험도가 1.29배로 증가함을 확인할 수 있었으며 (95% CI 1.07 to 2.45, p=0.049), RDW에 따라 두 군으로 나누었을 때 RDW가 정상 이상으로 상승된 환자들이 3.69배의 사망 위험도를 보였다 (95% CI 1.91 to 7.12, p<0.01).

결 론

임상요소와 헤모글로빈과 심초음파 소견을 보정하여도 다중회귀분석에서 RDW가 CAPD환자에서 통계적으로 유의하게 높은 사망률을 예측할 수 있는 인자임이 밝혀졌다.

핵심되는 말: 말기신부전, 적혈구분포폭, 예후인자