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ORIGINAL RESEARCH

Distribution Width of Red Blood Cells and Related Factors Among Patients with End-Stage Renal Disease in Addis Ababa, Ethiopia

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Background: RDW is critical to the clinical diagnosis and progression of ESRD. There is currently little data on the relationship between RDW and ESRD in sub-Saharan Africa. Because of this, the present study evaluates RDW in patients with ESRD and associated factors in Addis Ababa, Ethiopia.

Methods: The hospital-based cross-sectional study design was conducted on a total of 83 patients. RDW, MCV, SCR, BUN, GFR, FBS and serum albumin were determined. Blood pressure (mmHg), weight (kg), height (m), MUAC (cm) and BMI (kg/m2) were also measured. Data entry was via Epi-data version 3.4 and analyzed with SPSS version 26.0. A multivariate logistic regression analysis with a p-value < 0.05 at a 95% confidence interval was used to identify the associated factors of RDW.

Results: A total of 83 ESRD patients participated, with a response rate of 95.4%. RDW ranged from 15.5% to 23.6% with a mean of 17.40% + 1.46%. Anisocytosis was present in 98.8% of patients. Of 83 patients, 66.3% were hypertensive, 20.5% had diabetes, and the remaining 13.3% had other conditions (glomerulonephritis and peripheral vascular disease). The mean GFR value was 5.20 mL/min/1.73 + 1.58. RDW showed a significant association with GFR (AOR: 4.6, 95% CI [1.27, 20.74], P = 0.047), alcohol consumption (AOR: 13.4, P = 0.012, 95% CI [1.97, 22.62]), recurrent kidney disease (AOR=25.6, P=0.016, 95% CI [1.85, 53.71]) and use of medication (AOR=00.2, P=0.044), 95% CI [0.03, 0.95]).

Conclusion: RDW showed a significant association with GFR, recurrent kidney disease, alcohol consumption, and medication use in hemodialysis-dependent ESRD patients. The mechanisms of RDW disruption in ESRD patients need further investigation.

Keywords: red cell distribution width, end stage renal disease, glomerular filtration rate, serum creatinine, mean corpuscular volume, body mass index, blood urea nitrogen, mid-upper arm circumference

Introduction

RDW is part of the complete blood count which is used to quantify the size variation of red blood cells. Mostly, it is used for the diagnosis of anemia and other cardiovascular disorders.[1] The lower and upper limits of the RDW values ranged from (11.5–14.5%), but for women they ranged up to (11.5%–15.5%).[2] The RDW value was calculated by dividing the standard deviation of the erythrocyte volume by the mean corpuscular volume and multiplying by 100.[3] The RDW value below the standard reference range is not clinically significant, while values above the normal range reflect the presence of anisocytosis (the presence of small and large erythrocytes or both).[4]

CKD is a structural or functional abnormality in the kidneys' ability to filter blood for at least 3 months. It is characterized by either kidney damage (protein urea (> 30 mg/24 h or > 1 on a specific dipstick) or decreased GFR < 60 mL/min/1.73 m2).[5] A previous study had shown that in patients with stage[3–5] chronic kidney disease, higher RDW was associated with high morbidity.[5] ESRD is becoming a public health concern worldwide.[6] In addition, high RDW was associated with type 2 diabetes mellitus, CKD, and albumin in the general population.[7]

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Hemodialysis, one of the alternative treatments in patients with ESRD, can decrease the average survival time of red blood cells due to compression and twisting of the cells.[8,9] Even today, RDW has been used to diagnose various types of anemia. Higher RDW values indicate a shortened red blood cell lifespan due to poor erythropoiesis or increased red blood cell destruction.[10] Over the past few decades, there has been increasing evidence that high RDW is a predictor of cardiovascular morbidity in the general population,[11] chronic heart failure,[12] coronary artery disease,[13] stroke,[14] and kidney transplant recipients[15] and acute kidney injury treated with hemodialysis.[16]

In addition, it has been reported that high RDW is associated with the presence of type 2 diabetes mellitus, the progression of chronic kidney disease in patients with varying degrees of renal dysfunction,[7] and albumin in the general population.[17] The underlying mechanisms linking high RDW to all of these serious diseases are still unclear, but chronic inflammation, endothelial dysfunction, oxidative stress, and malnutrition have been suggested as possible causes.[18] Type 2 diabetes and hypertensive diseases accelerate atherosclerosis, deterioration in renal function and increased morbidity.[19] A higher RDW was associated with morbidity and a stronger predictor of disease worsening than other laboratory markers of anemia, such as transferrin saturation and ferritin levels in hemodialysis patients.[5] Globally, it has been estimated that more than 500 million individuals have CKD, defined by either kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m2 for >3 months.[20] In Africa CKD imposes disproportionate human suffering and a catastrophic economic burden. Less than 2% of the patients with ESRD have access to renal replacement therapy, making ESRD a death sentence for most patients.[21] According to WHO report,[22] death due to kidney disease in Ethiopia reached 12,038 or 1.47% of total deaths. Patients with the end-stage renal disease usually have various comorbidities.[22] A study done by Lippi et al, confirmed that the estimated glomerular filtration rate (GFR) progressively decreased when the RDW level increased in adult outpatients.[23] Another study[24] showed that a lower estimated GFR is related to a higher RDW level. Some of the significant risk factors for poor prognosis of ESRD were anemia and RDW which provides an additional prognostic marker for the progression of CKD.[24] In addition, a previous study also had shown that RDW significantly increases among CKD patients and has a negative relationship with the estimated GFR.[25] Evidence suggests that RDW may serve as a prognostic indicator in healthy individuals as well as specific patient populations including malignancy, renal failure, and cardiovascular disease independent of anemia.[26] RDW was associated with diabetes-associated complications including diabetic nephropathy. It is known that inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-a, desensitize bone marrow erythroid progenitors to erythropoiesis, inhibiting red blood cell maturation and thereby promote anisocytosis.[26] A previous study also showed that RDW level was associated with early renal injury in hypertensive patients,[27] and with diabetes-associated complications like diabetic nephropathy.[28] A previous study involving 513 patients with essential hypertension reported a statistically significant association between RDW and systolic blood pressure or albumin-to-creatinine ratio after adjustment for potential confounders such as age, sex, and hemoglobin.[28] In the United States, about 28% of patients with clinically significant stage 3 or worse CKD are neither diabetic nor hypertensive, particularly those older than 65 years.[29] Because it is known that chronic complications induce inflammatory cytokines, such as interleukin (IL)-1, IL-6,[29] tumor necrosis factor (TNF)-a,[30] desensitize bone marrow erythroid progenitors to erythropoiesis, inhibiting red blood cell maturation and thereby promote anisocytosis. ESRD is a destructive problem that lies in the medical, social, and economic areas which contributes to significant morbidity and mortality, and economic, social, and fundamental health problems in the community.[31] CKD is common in developed and developing nations which is conventionally assessed in terms of both overall renal function (GFR) and the presence of kidney damage ascertained by either kidney biopsy or other markers of kidney damage such as abnormal urinary sediment, abnormalities on imaging studies, or the presence of a kidney transplant.[32] According to the 2010 US Renal Data System Annual Report, the leading causes of CKD leading to ESRD in the United States were diabetes (153 per million population), hypertension (99 per million population), and glomerulonephritis (23.7 per million population).[33] In Sub-Saharan Africa, CKD more commonly affects individuals aged between 20 and 50 years, and the age of onset of ESRD is 20 years earlier in populations of African compared with other ethnic groups in western countries.[33] In developing countries, diabetes and hypertension now appear to be the leading causes of ESRD with a prevalence of about 30% and 21%, respectively, but glomerulonephritis and CKD of unknown origin account for a larger fraction of the total. For example, in a recent study of people with CKD detected by the International Society of Nephrology-sponsored screening programs 43% of people with CKD did not have diabetes or hypertension.[34] The prevalence of CKD in the northwest part of Ethiopia, defined by the estimated glomerular filtration rate <60 mL/min/1.73 m2, was found to be 17.3% and 14.3% by MDRD and CKD-EPI

(chronic kidney disease epidemiology collaboration) equations, respectively. The proportion of stage 3 CKD by MDRD equation was 14.7%, whereas the proportions of stage 4 and stage 5 CKD were 2.2% and 0.4%, respectively.[34] In addition to this, a study done in public hospitals of Addis Ababa on the prevalence and associated factors among stage[3–5] CKD diabetic patients were 79.4%, 16.2%, and 4.4% respectively by the Cockcroft Gault equation, whereas, it was 73%, 21.6%, and 5.4% respectively by the MDRD equation.[35] Elevated RDW reflects increased variations of red blood cell size which indicate altered erythrocyte life span or dysfunctional erythrocytes.[36] On the other hand, greater RDW was associated with a greater risk of morbidity in men compared to women, whereas no effect was observed by ethnicity.[37] In addition, RDW has been found as a predictor of morbidity in the general population[37] and in several conditions including acute and chronic heart failure,[38] acute pulmonary embolism and myocardial infarction,[39] peripheral arterial disease,[40] acute renal failure which required hemodialysis,[40] and kidney transplant recipients.[41] RDW was increased above the normal reference range in ESRD patients, especially in the subgroup of patients with inflammation and malnutrition. It was positively correlated with hemodialysis duration and weight gain, whereas, negatively correlated with serum albumin. These findings may reflect the negative effects of inflammation and malnutrition on the association between mortality and elevated RDW in ESRD patients.[42] A positive correlation between a high RDW and increased incidence of both macro and microvascular complications was seen in diabetic patients without marked vascular complications.[43] Several mechanisms can be postulated to explain the association between rising RDW and adverse outcomes. The most important one is inflammatory stress. RDW correlated positively with the log of the CRP concentration in the total population, and the correlation was stronger in the RDW-increased group. Similarly, RDW was positively associated with CRP levels in a study based on a nationwide database of people with diabetes.[43] People undergoing hemodialysis treatment suffer from numerous pathological processes along with kidney disease.[44] Patients with sustained, higher RDW demonstrated a significantly higher risk than did those with lower RDW (adjusted OR: 1.65, 95% CI: 1.02–2.67).[45] Patients with hypertension have elevated RDW. The possible pathophysiological mechanism that increases RDW among hypertensive patients is that hypertension is associated with inflammation. However, whether inflammation is a cause or effect of hypertension is not well understood.[46] RDW increased with increased age, obesity, smoking, and alcohol consumption.[47] Researchers have shown that inflammatory markers, deficient vitamin B-12, and folic acid were more common in the elderly as compared to younger age.[48] Females were found to have a statistically significant higher RDW value as compared to males. The reason behind this is that women are more likely to have a folic acid deficiency and menorrhagia (which is one of the most common complaints of females of reproductive age) which might result in an increased RDW level.[49] Multiple mechanisms may play a role in the relationship between RDW and prognosis in critically ill alcoholic patients. The most accepted one is that alcohol metabolites like acetaldehyde, increase the generation of free radicals, such as reactive oxygen and nitrogen species. These free radicals affect the normal development of red blood cells, reduce their oxygen-carrying capacity, and shorten the life span of these cells.[50] RDW values were found to be higher among smokers. The pathophysiological mechanism explaining the association of RDW with smoking is that chronic subclinical inflammation appears to be the driving factor. Hs-CRP levels, a well-established surrogate marker of inflammation, as well as numerous other inflammatory markers such as interleukin-6 and soluble tumor necrosis factor-alpha, VCAM-1, ICAM-1, and E-selectin have been independently associated with smoking.[51] Chronic kidney disease affects young adults aged 20–50, in sub-Saharan Africa and is primarily due to hypertension and glomerular diseases. Unlike developed countries, where chronic kidney disease presents in middle-aged and elderly patients is predominantly due to diabetes mellitus and hypertension.[52] In a study done among renal patients that attend Dessie referral hospital, the prevalence of CKD, was 3.0% had stage I, 11.9% had stage II, 9.5% had stage III, 3.8% had stage IV and 1.6% had stage V CKD respectively.[53] High RDW group patients had significantly higher BMI, lower hemoglobin, higher urea, and creatinine, lower estimated glomerular filtration rate (eGFR), high albumin, and a longer period of T2DM diagnosis compared to a low value.[54] Increased RDW can be an appropriate indicator for various types of diseases like inflammatory bowel disease (IBD), cardiovascular disease (CVD), pulmonary disease (PD), Cancer, and cerebrovascular accident.[55] Inflammatory cytokines may directly inhibit erythropoietin-induced erythrocyte maturation, which leads to an increase in RDW. It is also known that inflammatory cytokines, such as interleukin 1 or interleukin 6, upregulated hepcidin, which regulates iron homeostasis by inhibiting iron absorption from the intestine and iron release from reticuloendothelial stores.[56] A study demonstrated no association existed between RDW and sex in either gender.[57] Several genetic risks were previously associated with different traits and diseases and found that most of these, especially those related to cholesterol (both LDL and HDL), triglycerides, systolic blood pressure, BMI, diabetes, and

some inflammatory diseases were significantly associated with RDW.[58] However, the importance of RDW scores in screening, diagnosis, and progression of ESRD has not been well researched. Therefore, the intention of this study was to assess RDW and associated factors in ESRD patients.

Methods and Materials

Study Area and Time Period

This study was conducted from February to September 2021 at St. Paulo's Hospital Millennium Medical College, Menelik II Referral Hospital and Zewditu Memorial Hospital.

Study Design and Population

A hospital-based, cross-sectional study design was used and study participants were all ESRD patients who were followed up for hemodialysis during the study period.

Determination of Sample Size and Sampling Technique

The sample size was calculated using the formula for individual population proportions, assuming the prevalence of ESRD in Addis Ababa to be 4.4% and 5.4% using the Cockcroft Gault and MDRD equations, respectively.[35] A prevalence of 5.4 and a marginal error of 0.05 were assumed to calculate the sample size.

$n= (Z\alpha/_2)^2\ p\ (q)\ /d^2 = (1.96)^2\ (0.054)\ (0.946)/0.0025=78.5=79$

n = minimum sample size required for the study

z = standard normal distribution (z = 1.96) with 95% confidence interval

p = sampling proportion of success (0.054),

q = sampling proportion of failure (0.946),

d = tolerable error margin = 5% (0.05).

Allowing for a 10% non-response rate, the final sample size was 87.

A systematic random sample was used to recruit study participants. A proportionate allocation was made for each hospital. From St. Paulo's= (500, 87)/988=44, from Minilik= (188, 87) /988=17, from Zewditu= (300, 87) /988=26.

Inclusion and Exclusion Criteria

All ESRD patients between the ages of 18 and 70 years who attended selected hospitals during the data collection period were included in this study. However, those suffering from congestive heart failure, anemia, blood cell cancer, chronic liver disease, and inflammatory bowel disease, recent infections including Covid-19 and refusing to participate were excluded.

Variables

RDW was the dependent variable in this study. However, socio-demographic characteristics, behavioral factors, chronic illnesses, medication, and blood cell parameters other than RDW were independent variables.

Data Collection Tools and Measurement

Socio-demographic characteristics and medical history were collected from the patients using a questionnaire. Blood pressure (mmHg); using mercury sphygmomanometer; weight (kg), height (m); using digital weighing scale; and mid-upper arm circumference (cm) using tape were measured. The body mass index (BMI) (kg/m2) was calculated from the weight and height of the study patients.

Laboratory Tests

Five milliliter blood samples were taken from each patient by the laboratory technician. Blood taken from each patient was separated into two test tubes: an EDTA tube for CBC by using MINDRAY BC-5130 Hematology Analyzer and RDW and mean corpuscular volume were determined according to the standard reference range of the machine. SST for

serum chemical analysis was used and blood in SST was centrifuged at 3400 RPM for 15 minutes for blood urea and albumin analysis.

Serum creatinine, blood urea level, and serum albumin were measured by Cobas C 311 (Roche, India). Fasting blood glucose level was also measured by a glucometer. GFR was calculated using the diet modification formula for kidney disease. Physical measurements and blood sample collection were conducted thirty minutes before they start dialysis.

Serum creatinine, blood urea level, fasting blood glucose level (glucometer) and serum albumin were also measured. GFR was determined using (the MDRD eGFR formula). Physical measurements and blood sample collection were conducted thirty minutes before they start dialysis.

Data Quality Control

Data were collected by trained health officials and nurses under the supervision of the principal investigators. All variables were filled daily in data extraction format. The laboratory producers were handled by laboratory technologists and all the tests were standardized.

Operational Definition

End-stage renal disease: GFR < 15 mL/min/1.73 m^2 using the MDRD-GFR formula.

Anisocytosis: erythrocyte distribution ≥ 16%.

Medium anisocytosis: red cell distribution width between (≥16% - ≤ 17.4%).

High anisocytosis: red cell distribution width > 17.4%.

Statistical Analysis

Data entry was done with Epi-data (version 3.4) and analyzed with SPSS (version 26.0). Associations between variables were determined using logistic regression. A p-value < 0.25 during bivariate logistic regression analysis was subjected to multiple logistic regression, and a p-value < 0.05 during multivariate analysis at a 95% confidence level was considered statistically significant.

Ethical Approval

Ethical approvals for the study were obtained from the Addis Ababa University, Department of Medical Physiology and the Addis Ababa Public Health Research and Emergency Management Directorate with ethical approval reference number (A/A/13173/227). Patients were informed about the aims and benefits of the study before we began data collection. Written consent was obtained from each participant. Patient privacy and confidentiality has been maintained as we assign code numbers. This study is in line with the Declaration of Helsinki.

Results

Socio-Demographic Characteristics

A total of 83 adult ESRD patients took part in this study with a response rate of 95.4%. The average age of patients were 42±11.27, with a range of 20–68 years. Among the study patients, 69.0% were males, 54.2% were married, 45.8% had college or university education, 77.1% were from urban areas and 56.6% had a monthly salary (ETB) of less than 5462 (Table 1).

Clinical and Anthropometric Characteristics

RDW was ranged between 15.5% and 23.6% with a mean value of 17.40% ±1.46. Almost all patients (98.8%) had anisocytosis. Out of 83 patients, 55 (66.3%) were hypertensive, 17 (20.5%) had diabetes, and the remaining 11 (13.3%) had other diseases (glomerulonephritis and peripheral vascular disease) (Table 2). The mean value of GFR and MUAC was (5.20 mL/min ± 1.58) and (28.32cm ± 2.99) (Table 3).

Table 1 Socio-Demographic Characteristics

Variable	Frequency N (%)
Age group	
18–42	40 (48.2)
43–70	43 (51.8)
Sex	
Male	57 (69)
Female	26 (31)
Marital status	
Single	24 (28.9)
Married	45 (54.2)
Widowed/ Divorced	14 (16.9)
Occupation	
Teacher	7 (8.4)
Soldier	2 (2.5)
Merchant	29 (34.9)
Others	45 (54.2)
Educational status	
No education	10 (12)
Primary school	10 (12)
Secondary school	25 (30.2)
College or University	38 (45.8)
Residency	
Urban	64 (77.1)
Rural	19 (22.9)
Monthly income	
<5462	47 (56.6)
≥5462	36 (43.4)

Behavioral Characteristics

In this study, 9.6% of patients were smokers, 53.0% were alcoholics, 15.3% had a history of using traditional medicine, 4.8% use traditional medicines currently and 31.3% habitually chew Khat (Table 4).

Association Factors of RDW

Of patients with moderate anisocytosis, 25 of them had GFR < 5.20 mL/min and 30 had GFR > 5.20 mL/min. whereas of those with high anisocytosis, 20 had GFR < 5.20 mL/min and 8 had GFR > 5.20 mL/min. GFR (AOR=4.6, P=0.047, 95% CI [1.27, 20.74]), alcohol consumption (AOR=13.4, P=0.012, 95% CI [1.97, 22.62]), recurrent kidney disease (AOR=25.6, P=0.016, 95% CI [1.85, 53.71]), and use of antihypertensive and antidiabetic medications (AOR=0.2, P=0.044, 95% CI [0.03, 0.95]) showed a significant association with RDW (Table 5).

Discussion

In this study, 66.3% of patients with ESRD had a prior diagnosis of hypertension and 20.5% had diabetes mellitus (Table 2), indicating that it may be hypertension that contributes to ESRD. In contrast to this study, a previously conducted study showed that 30% of patients with ESRD had diabetes mellitus, while only 21% of them had hypertension.[34] In this earlier study, glomerulonephritis and CKD of unknown cause are a major cause of ESRD. In the United States, approximately 28% of elderly (over 65 years old) patients with clinically significant stage[3–5] chronic kidney disease were neither diabetic nor hypertensive.[29] This discrepancy between studies could be because the

Table 2 Frequency Distribution of Clinical Parameters

Variables	Category	Frequency N (%)
Mid-upper arm circumference (cm)	High	68 (81.9)
	Normal	15 (18.1)
	Low	0 (0.0)
Body mass index (kg/m2)	High	23 (27.7)
	Normal	52 (62.7)
	Low	8 (9.6)
History of repeated kidney infection	Yes	59 (71.1)
	No	24 (28.9)
Blood urea nitrogen (mg/dl)	High	83 (100.0)
	Normal	0 (0.0)
	Low	0 (0.0)
Serum creatinine (mg/dl)	High	83 (100.0)
	Normal	0 (0.0)
	Low	0 (0.0)
Serum albumin (g/dl)	High	22 (26.5)
	Normal	58 (69.9)
	Low	3 (3.6)
Glomerular filtration rate(mL/min)	<5.2	45 (54.2)
	≥5.2	38 (45.8)
Mean corpuscular volume(fl)	High	0 (0.0)
	Normal	77 (92.8)
	Low	6 (7.2)
Red cell distribution width (%)	≥16%	82 (98.8)
	<16%	1 (1.2)
Family history of chronic kidney disease	Yes	22 (26.5)
	No	61 (73.5)
Chronic diseases	Diabetes Mellitus	17 (20.5)
	Hypertension	55 (66.3)
	Others*	11 (13.3)
Medications taken	Nifedipine	21 (25.3)
	Enalapril	19 (22.9)
	Metformin	9 (10.8)
	Insulin	6 (7.2)
	Other drugs**	28 (33.7)

Notes: *Glomerulonephrites and Peripheral vascular disease, **Ciprofloxacin, Lisinopril and Ramipril.

Table 3 Mean Values of Clinical Parameters

Clinical Parameters	Mean	SD
Glomerular filtration rate (mL/min)	5.20	1.58
Red cell distribution width (%)	17.40	1.46
Mean corpuscular volume(fl)	88.80	5.62
Fasting blood sugar (mg/dl)	109.92	36.72
Mid upper arm circumference (cm)	28.32	2.99
Serum albumin (g/dl)	5.02	1.22
Body mass index (kg/m^2)	22.90	3.39
Serum creatinine (mg/dl)	9.84	2.39
Blood urea nitrogen (mg/dl)	130.54	35.65

Table 4 Behavioral Characteristics

Variables	Categories	Frequency N (%)
Smoking habits	Yes	8 (9.6)
	No	75 (90.4)
Drinking alcohol	Yes	44 (53)
	No	39 (47)
Khat chewing	Yes	26 (31.3)
	No	57 (68.7)
Drinking coffee	Yes	79 (95.2)
	No	4 (4.8)
Previous use of traditional medication	Yes	13 (15.3)
	No	70 (84.7)
Current Use of traditional medications	Yes	4 (4.8)
	No	79 (95.2)

Table 5 Bivariate and Multivariate Logistic Regression Analysis of RDW and Other Variables

Variables		RDW		COR (95% CI)	AOR (95% CI)	P-value
		Moderate	High			
Glomerular filtration rate	≥5.2	30	8	1	1	
	<5.2	25	20	3.0 (1.13, 7.97)	4.56 (1.27, 20.74)	0.047*
Drinking alcohol	No	31	8	1	1	
	Yes	24	20	3. 23 (1.22,8.59)	13.39 (1.97,22.62)	0.012*
History of repeated kidney diseases	No	20	4	1	1	
	Yes	35	24	3.43 (1.04, 11.29)	25.6 (1.85, 53.71)	0.016*
Medication taken	No	16	12	1	1	
	Yes	39	16	0.55 (0.21, 1.41)	0.16 (0.03, 0.95)	0.044*
Smoking status	No	52	23	1	1	
	Yes	3	5	3.77 (0.83, 17.11)	3.13 (0.52, 18.67)	0.211
Khat chewing	No	41	16	1	1	
	Yes	14	12	2.19 (0.84, 5.76)	1.84 (0.54, 6.29)	0.332
Traditional medication	No	49	21	1	1	
	Yes	6	7	2.72 (0.82, 9.07)	2.99 (0.81, 11.11)	0.102
Age	<42	28	12	1	1	
	≥ 42	27	16	1.38 (0.55, 3.46)	0.68 (0.25, 1.86)	0.460
Sex	Male	37	20	1	1	
	Female	18	8	0.82 (0.30, 2.22)	0.74 (0.23, 2.37)	0.615

Note: *Significant association.
Abbreviations: RDW, red cell distribution width; COR, crude odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

prevalence of hypertension in Ethiopia was high compared to diabetes and other glomerular diseases. In this study, reduced GFR (AOR=4.6, P=0.047, 95% CI [1.27, 20.74]), repeated renal infection (AOR=25.6, P=0.016, 95% CI [1.85, 53.71]), medication use (AOR=0.2, P=0.044, 95% CI [0.03, 0.95]), and alcohol consumption (AOR=13.4, P=0.012, 95% CI [1,97, 22.62]) were significantly associated with a high RDW (Table 5). In this study, low GFR was four times more likely to develop high RDW compared to high GFR. This result is consistent with other studies.[5] A cross-sectional study was conducted in adult outpatients and showed an inverse association between RDW and renal function.[24] The increase in RDW in patients with ESRD could be attributed to inflammation, stress response, malnutrition, and other comorbidities.[49] According to a previous study,[49] Inflammation plays an important role in increasing RDW in patients with ESRD. In addition, inflammatory cytokines such as interleukin-1 and interleukin-6, unregulated hepcidin that regulates iron hemostasis, are involved in RDW increase (67).

The second mechanism contributing to the higher RDW in patients with ESRD may be due to chronic hypoxia, oxidative stress, and endothelial dysfunction. A previously conducted study showed that RDW was autonomously associated with endothelial dysfunction and oxidative stress, which increases in patients with CKD, and oxidative stress can reduce red blood cell survival, inducing the release of premature and heterogenic shaped red blood cells.[48]

The third mechanism could be due to the increase in blood pressure and hyperglycemia in patients with ESRD. One of the risk factors for elevated blood pressure is wall tension. Wall tension contributes to the loss of normal red blood cell shape, resulting in increased levels of RDW.[54] Long-term hyperglycemia contributes to loss of red blood cell size, which is worse in diabetics with kidney damage. The loss of the normal size of the RBCs further increases the fragility of the erythrocytes.[50]

In this study, there was a significant association between RDW and recurrent kidney disease in patients with ESRD. Repeat kidney infection was twenty-five times more likely to develop high RDW than a single non-repeated infection (Table 5). This is similar to a previous study that reported that patients with many different chronic diseases had a higher baseline RDW.[53] The other factor that showed a significant association with the increase in RDW levels in this study was alcohol consumption. In patients with ESRD who consumed alcohol, the RDW level was 13 times higher than in patients who did not consume alcohol (Table 5). Although there is limited study of the association between alcohol consumption and RDW, alcohol metabolites such as acetaldehyde, which increase free radical formation such as reactive oxygen and nitrogen species, could be the possible mechanism. These free radicals interfere with the normal development of red blood cells, reduce their oxygen-carrying capacity and shorten the lifespan of these cells.[50] In this study, taking antihypertensive and antidiabetic medication also had a significant association with decreased RDW. This study is similar to a study done in China that, insulin therapy, beta-blockers, and ACE-inhibitors were protective in decreasing the level of RDW.[51] A significant association between serum albumin and RDW was not seen in this study, but the previous study reported that RDW was negatively correlated with serum albumin.[42] In the other study, patients in the high RDW group had significantly more albumin and a longer period of T2DM diagnosis compared to a low RDW group.[54] Although this difference occurred between studies, albumin and pre albumin are very poor predictors of nutritional status. Possible explanations for this were, first, that serum proteins such as albumin and pre albumin have not been included as defining characteristics of malnutrition, since evidence shows that serum levels of these proteins do not change in response to changes in nutrient intake, which shows no sensitivity. Specificity and reliability. Second, since serum albumin levels were time-averaged values over the year of hemodialysis, values from just a single measurement may not be representative of long-term nutritional status in this study population. The discrepancy in results could be due to differences in sample size, sociodemographic factors, the presence of comorbidity, and frequency of measurement of laboratory parameters, only once in this study but more than twice consecutively in other studies to investigate the relationship between nutritional statuses and to see RDW. In contrast to the previous study,[55] RDW was not associated with age and gender (Table 5). In contrast, another study showed that there is a positive relationship between RDW and age. This is because older people are more likely to be deficient in nutrients than younger people who have comorbidities and those who have had inflammation.[22] The discrepancy between these results could be due to variations in sample size and socio-demographic characteristics. Not enough older people participated in this study. Although the frequency of males with high RDW was higher than females in this study, gender has no significant association with RDW. Similar to this finding, another study showed that there was no association between RDW in either sex.[57] Conversely to this finding, a larger RDW was associated with a higher risk of morbidity in males compared to females.[37] On the other hand, a study has shown that women have a statistically significantly higher RDW value compared to men.[49] Women are more likely to have folic acid deficiency and menorrhagia (one of the most common complaints in women of childbearing age), which can lead to increased levels of RDW.[49] This is because only twenty-six female patients with end-stage renal disease were involved during the study period. Blood pressure, body mass index, diabetes, and inflammatory diseases were significantly associated with RDW.[58] A previous study of 513 patients with essential hypertension reported that a statistically significant association was found between RDW and blood pressure and albumin after adjusting for potential confounders such as age and gender.[25] But in this study, no significant association was observed between RDW and hypertension, diabetes mellitus, and BMI. The differences between these studies, particularly those related to factors considered risky for this study, have been matched in other studies. The other reason could be that the sample size (83) was small in this

study compared to another study (513).[25] Smoking had no significant association with RDW in this study (Table 5). In contrast to this study, higher RDW values were found in smokers.[51] The mechanism that explains RDW's relationship to smoking is that chronic inflammation appears to be the driving factor. Hs-CRP levels, a well-established surrogate marker of inflammation, as well as numerous other inflammatory markers such as interleukin-6 and soluble tumor necrosis factor-alpha, VCAM-1, ICAM-1, and E-selectin have been independently associated with smoking.[51] Although this explanation was accepted, the differences between the studies could be due to the fact that the number of patients who smoked cigarettes was small compared to others. In conclusion, RDW showed a significant association with GFR, recurrent kidney disease, alcohol consumption, and use of antidiabetic and antihypertensive drugs. As shown by the adjusted odds ratio, reduced GFR, recurrent kidney disease, and alcohol consumption were more likely to result in a high RDW, while medication taken was the protective factor. The mechanisms of RDW disruption in patients with ESRD need further investigation.

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Author Contributions

All authors made significant contributions to the reported work, whether in conception, study design, implementation, data collection, analysis and interpretation, or all of these areas; were involved in drafting, revising, or critically reviewing the article; give final approval of the version to be published; agreed on the journal to which the article was submitted; and agreed to be responsible for all aspects of the work.

Disclosure

This paper was done for the fulfilment of Master's Degree in Medical Physiology from Addis Ababa University. Since it is a must to give a full thesis after successful defense for Addis Ababa University Library to put it online for the purpose of reading for students. So that it is available online in Addis Ababa University Library Circulation. But it is our original work paper which is not a published yet. The authors declare no conflicts of interest in relation to this, and all authors are responsible for the content and writing of this document.

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