The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 491-497

Red Blood Cell Distribution Width Association with Resistance to Erythropoietin Stimulating Agents in Hemodialysis Patients

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ABSTRACT

Background: Red blood cell distribution width (RDW) is a quantitative marker of heterogeneity of circulating erythrocytes size and a marker of malnutrition, inflammation and mortality. Erythropoietin resistance index (ERI) is considered as an effective way to check erythropoietin resistance. ERI is related to all-causes of morbidity & mortality in hemodialysis patients. Association with aging and gender have also confirmed progressive increase in RDW with aging and in female gender.

Objective: this study aimed to check the relation between RDW & ERI in iron replete hemodialysis patients.

Patients and methods: 89 patients matched inclusion criteria followed up for 12 months and data analyzed including age, gender, diabetic status, serum iron, serum ferritin, red blood cell width, Erythropoietin dose per week per kg body weight.

Results: Patients included were 36 (40.5%) females and 53(59.5%) males with mean age of 42.7 ± 15.2 years old. Diabetic patients were 51 (57.3%) and non-diabetic were 38 (42.7%). All patients were iron replete as per inclusion criteria with serum ferritin 200-800 ug/dl and transferrin saturation 20-40%. Hemoglobin, RDW & ERI were repeated at 4 checkpoints during the 12-months follow-up period. The average of all (4) readings then processed for Pearson correlation logistic regression to identify the relation between RDW and ERI and we found linear correlation between RDW and ERI. R-square 0.158, P-value < 0.001, this relation was independent of age, gender, hemoglobin level, erythropoietin dose and diabetic status.

Conclusion: Our results confirmed the independent relation between RDW and resistance to erythropoietin in iron replete hemodialysis patients.

Keywords: Red blood cell distribution width, Erythropoietin resistance index, Anemia, Hemodialysis.

INTRODUCTION

RDW is a quantitative marker of heterogeneity of circulating erythrocytes size. It is routinely reported in a complete blood count and does not require an additional cost. It is measured by dividing the volume of red blood cell to mean corpuscular volume (MCV) and the result given as a percentage. It was used to narrow the differential diagnosis of nutritional anemia (iron, vitamin B12 and folate) in combination with MCV [(1-3)].

RDW has been implicated as a marker of malnutrition and inflammation. It has also been found to be an important marker for mortality independent of anemia across general population and in several conditions as heart failure, pulmonary embolism, pancreatitis, sepsis, acute kidney injury and renal transplantation but the association remains unexplained [(4-8)]. Association with aging and gender have also confirmed progressive increase in RDW with aging and in female gender [(9)].

Anemia is a common complication in patients on maintenance hemodialysis and usually it is managed by erythropoietin (EPO) injection with good response in most of the patients. Some do not respond well to EPO or need higher than average doses and this is defined as EPO resistance. ERI has been considered as an effective way to check EPO resistance [(10)]. ERI is related to all-causes of morbidity & mortality in maintenance hemodialysis patients [(11)].

Although RDW has been shown to closely correlate with kidney function [(12-13)]. There is a limited data about RDW and other lab parameters in maintenance hemodialysis patients. In this study we hypothesized a relation between RDW and ERI in maintenance hemodialysis patients. Aim of the study was to determine relation between RDW and ERI in iron replete hemodialysis patients.

PATIENTS AND METHODS

Inclusion criteria:

Patients undergoing hemodialysis in Ain Shams University Hospitals Outpatient dialysis facility for at least 3 months prior to study starting and having iron profile within target as per KDIGO anemia management guidelines serum Ferritin 200-800 ng/dl and transferrin saturation 25-50% .

Exclusion criteria: Patient not matching eligibility criteria.

Study design:

89 patients were included as per inclusion criteria, data collected including gender, age, duration on dialysis, dialysis modality, iron profile (serum ferritin,

Received: 16/09/2022
Accepted: 18/11/2022

serum iron, transferrin saturation, total iron binding capacity), HB level, diabetic status.
We checked RDW width coefficient percentage (RDW %) and Resistance to EPO defined as ERI (calculated as weekly dose of Erythropoietin per Kilogram of body weight divided by Hemoglobin level gm/dl).

Ethical consent:

An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. After explaining our research objectives, written informed consents were obtained from all study participants. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical tests:

Data were tabulated and analyzed using SPSS-26 version. Student T-test was used for comparison of mean of categorical variables with (Mean ± SD). Pearson Correlation and regression analysis where RDW is the dependent factor and ERI, serum ferritin, transferrin saturation, hemoglobin, age, gender, diabetes as independent factors. Linear regression analysis for relation between continuous variables and multivariate analysis was used to assess the independence of effect of each variable. Power test (85%) and significance ≤ 0.05 (5%) for significant relations and < 0.001 for highly significant relations.

RESULTS

Our study included 36 (40.5%) females and 53 (59.5%) males with mean age of 42.7±15.2 years old, diabetic patients were 51 (57.3%) and non-diabetic were 38 (42.7%). All patients were iron replete as per inclusion criteria with serum ferritin 200-800 ug/dl and transferrin saturation 20-40%. Hemoglobin, RDW % & ERI were repeated at 4 check points during 12 month follow up period for all patients and measurement was tabulated in table (1). The average of all (4) readings then processed for linear logistic regression to identify the relation between RDW and ERI.

Table (1): Baseline characteristics of the study group

Gender	**Male**	53(59.5)
	Female	36(40.5)
DIABETES	**DIABETIC**	38(42.7)
	NON-DIABETIC	51(57.3)
	AGE	42.7±15.2
	Dialysis Duration	37(265)
	Reading 1- Erythrocyte Distribution Width Coefficient Variation-B result [%]	15.8±3.91
	Reading 2- Erythrocyte Distribution Width Coefficient Variation-B result [%]	15.56±3.66
	Reading 3- Erythrocyte Distribution Width Coefficient Variation-B result [%	15.28±3.76
	Reading 4- Erythrocyte Distribution Width Coefficient Variation-B result [%]	15.38±2.14
	Erythrocyte Distribution Width Coefficient Variation-B result [%] AVERAGE	15.52±3.46
	Reading 1- EPO resistance index result [(U/Week/kg)/(g/dL)]	10.79±2.43
	Reading 2- EPO resistance index result [(U/Week/kg)/(g/dL)]	7.84±1.74
	Reading 3- EPO resistance index result [(U/Week/kg)/(g/dL)]	8.33±2.01
	Reading 4- EPO resistance index result [(U/Week/kg)/(g/dL)]	8.40±2.03
	EPO resistance index result [(U/Week/kg)/(g/dL)] AVERAGE	8.81±1.94

data presented as Mean ± SD , n (%) , or median (range) where appropriate

Among our findings we found RDW significantly higher in females (16.86 ± 3.84) than in males (15.1 ± 2.0) p value < 0.001 as shown in table (2) & figure (1). Also, there was a significant RDW higher in diabetic patient (17.2 ± 3.78) than in non-diabetic patients (14.6 ± 3.1) with p value < 0.001 as shown in table (3) & figure (2). There was a significant linear correlation between RDW and age as shown in figure (3) R-square 0.375, P-value < 0.001.

Table (2): RDW & ERI variation with gender

/	Gender	n (%)	Mean ± SD	t-test	P-VALUE
EPO resistance index result [(U/Week/kg)/(g/dL)] AVERAGE	F	36(40.5)	12.68±3.11	3.723	< 0.001
	M	53(59.5)	8.5±2.09		
Erythrocyte Distribution Width Coefficient Variation-B result [%] AVERAGE	F	36(40.5)	16.86±3.84	2.678	< 0.001
	M	53(59.5)	15.1±2.0		

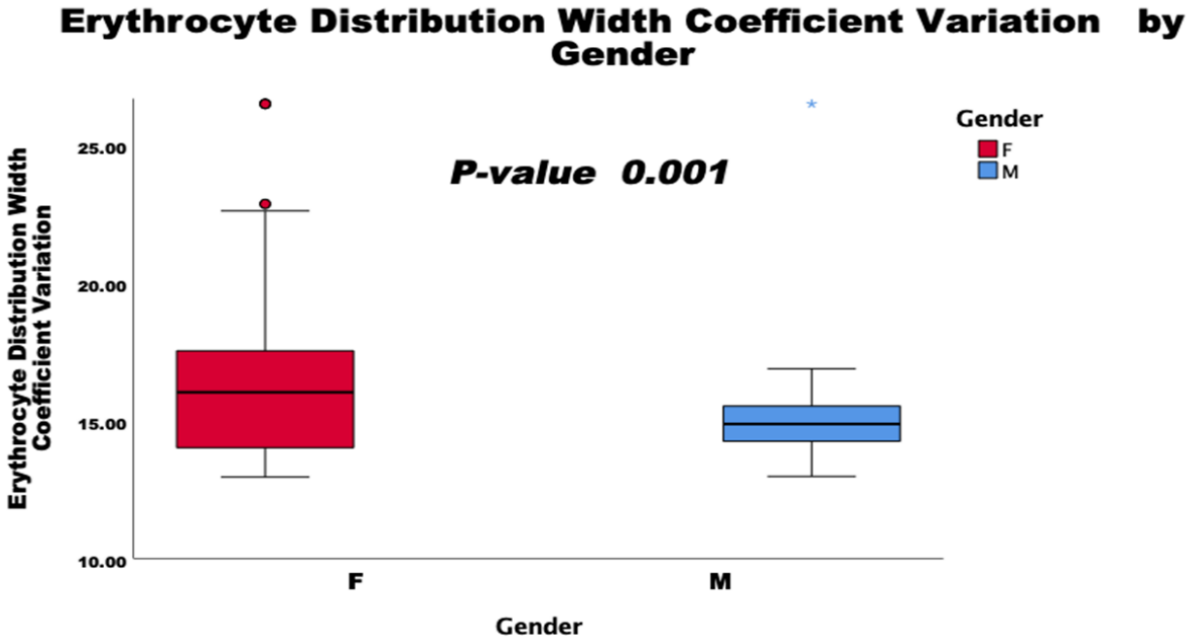


Figure (1): RDW & ERI variation with gender with RDW significantly higher in females than males with p value < 0.001.

Table (3): RDW & ERI variation with diabetes

	DM	n (%)	Mean±SD	t-test	P-VALUE
EPO resistance index result [(U/Week/kg)/(g/dL)] AVERAGE	Diabetic	38(42.7)	12.8±3.02	4.568	< 0.001
	Non-diabetic	51(57.3)	7.8±1.81		
Erythrocyte Distribution Width Coefficient Variation-B result [%] AVERAGE	Diabetic	38(42.7)	17.2±3.78	4.189	< 0.001
	Non-diabetic	51(57.3)	14.6±3.1		

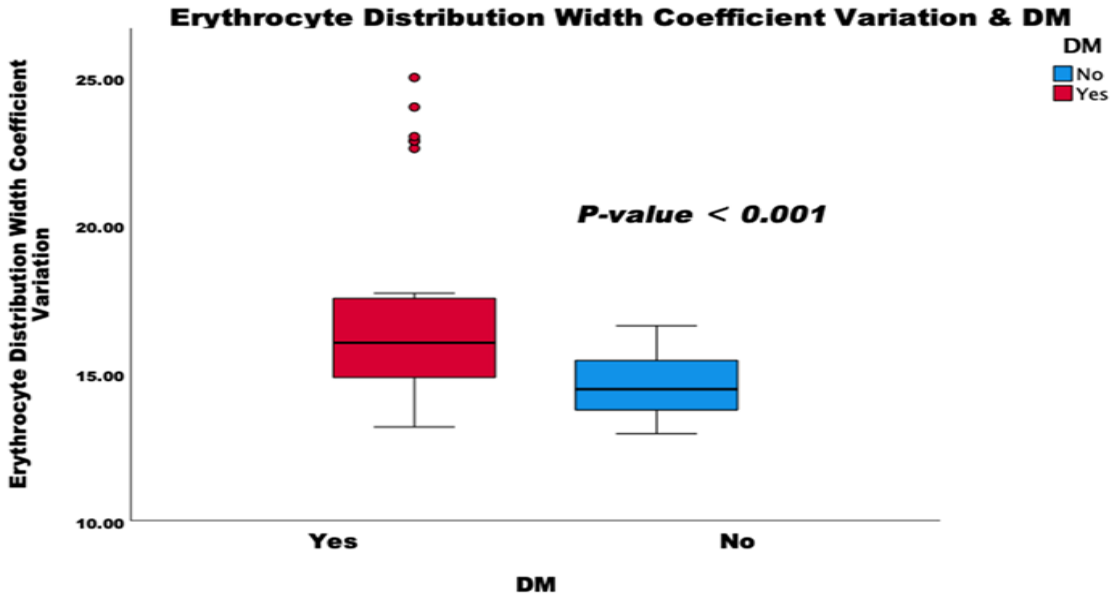


Figure (2): RDW & ERI variation with diabetic status with RDW significantly higher in diabetic than non-diabetic with p value < 0.001.

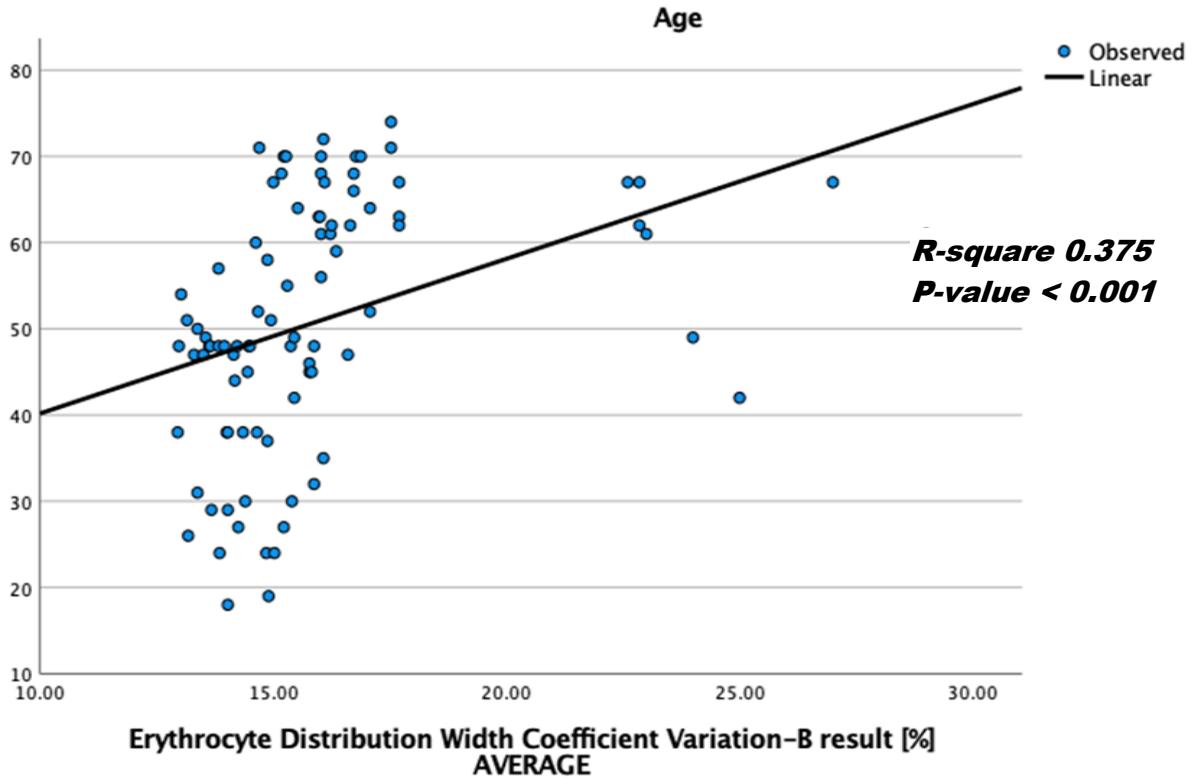


Figure (3): A significant linear correlation between RDW and age.

Multivariate analysis included covariates age gender diabetic status, we found a significant linear correlation between red blood cell width distribution coefficient variation % and resistance to erythropoietin (ERI), R-square 0.158 P-value< 0.001. This relation is independent of age, gender and diabetic status (Figures 4 & 5), which confirms the previous relations; found in literature that red blood cell width distribution coefficient is a predictor of erythropoietin resistance in iron replete hemodialysis patients independent of age, gender, iron profile, hemoglobin level and diabetic status.

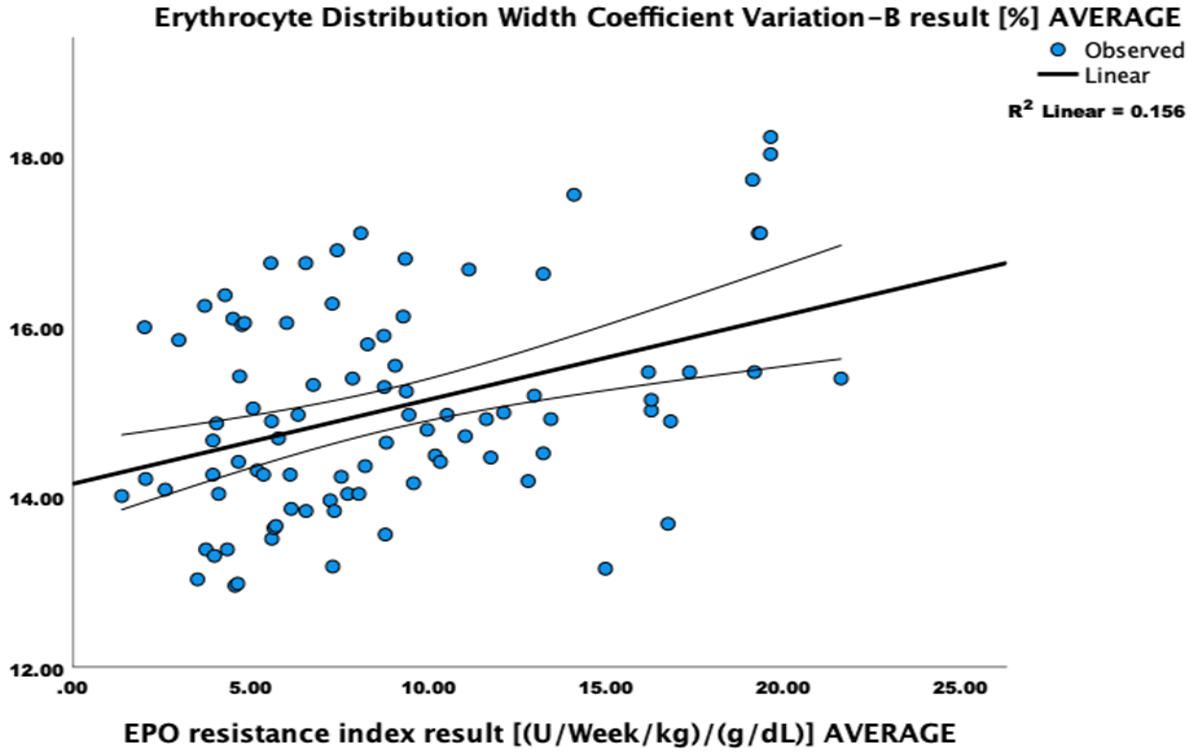
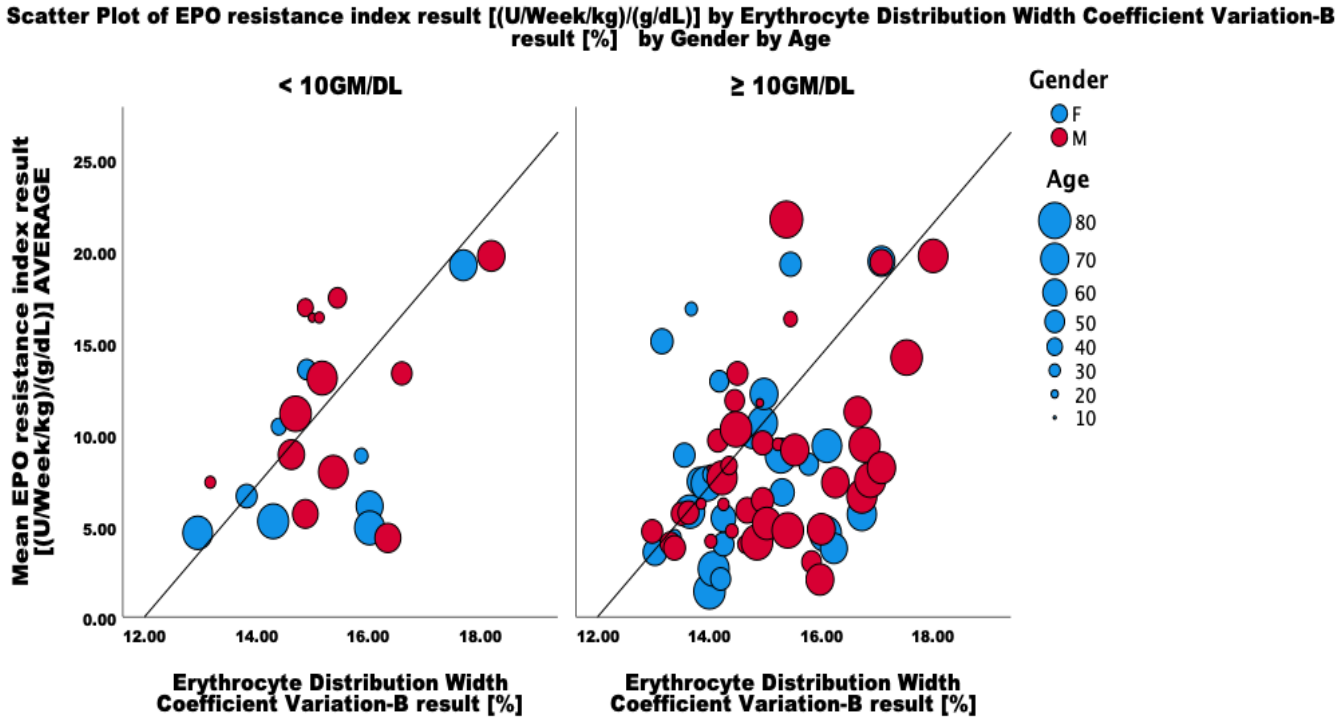


Figure (4): Linear Logistic Regression showing significant relation between RDW & ERI R^2 0.158 P-value < 0.001



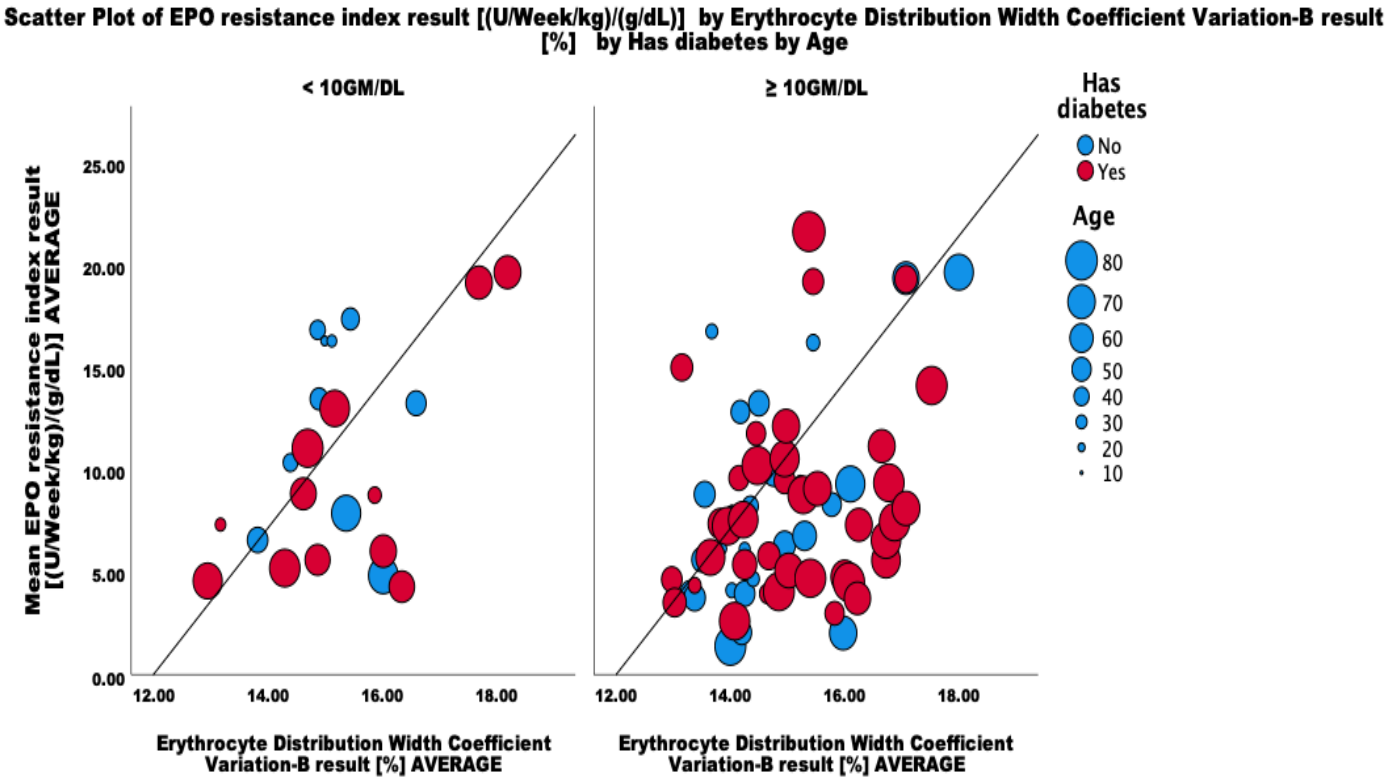


Figure (5A): The relation between RDW and ERI at different HB level and diabetic status

Figure (5B): The relation between (RDW) and (ERI) at different HB level and gender.

DISCUSSION

The pathogenesis of high RDW in hemodialysis patients is complex, RDW reflects red blood cells (RBCs) size heterogenicity. In hemodialysis patients there are RBCs destruction and ineffective production, which leads to increase RDW. RDW is an important marker of ineffective erythropoiesis [(14)]. There are multiple factors affects EPO resistance including iron deficiency, chronic blood loss, chronic inflammation, infection, drugs and malignancy [(15)].

In this cross-sectional study we evaluated the association between RDW and EPO resistance calculated by ERI in iron replete hemodialysis patients. We found a consistent and a linear relationship between RDW& ERI. In addition this relation was independent of age, gender, iron profile, hemoglobin level and diabetic status. The correlation between RDW & ERI may be due to that anemia of chronic disease regardless of iron status increase RDW [(16)]. Also, chronic inflammation impair RBCs synthesis and decrease RBCs survival with deformity of RBCs membrane, which leads to increase RDW [(17)].

Hemodialysis patients had high levels of inflammation & oxidative stress due to multiple factors including blood contact to dialysis membrane, reduced level of vitamin C & E, reduced activity of the glutathione system and malnutrition. Inflammation & pro-inflammatory cytokines inhibit erythropoietin-induced RBC maturation and down regulate erythropoietin receptor expression, which is associated with increased RDW [(18, 19)], and requires higher erythropoietin doses to overcome erythropoietin resistance [(20)].

In our study there was a significant increase in ERI in female gender in comparison to male gender & this matches with **López-Gómez *et al.*** [(21)] and **Afsar *et al.*** [(22)] and with older age than with younger, which matches with **Vashistha *et al.*** [(19)].The long-term hyperglycemia will leads to red blood cell deformity and this will get worse in diabetic and renal failure with an increase ERI [(23)]. There was a significant increase in ERI in diabetic patients in comparison with non-diabetic patients & this is also detected by **Afsar *et al.*** [(22)], **Tangdhanakanond *et al.*** [(24)] and **Abe *et al.*** [(25)].

CONCLUSION

RDW coefficient is a predictor of erythropoietin resistance in iron replete hemodialysis patients independent of age, gender, iron profile, hemoglobin level and diabetic status. It is still of debate whether RDW is a marker or mediator to ERI in iron replete hemodialysis patients and this is in need for further studies.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

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