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Correlation between Red Cell Distribution Width (RDW) and Mean Corpuscular Volume (MCV) as a Prognostic Biomarker for Diabetic Nephropathy Patients in a South Indian Hospital

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Context: Diabetic nephropathy is one of the microvascular complications of diabetes mellitus, capable of leading to end-stage renal disease. Diabetic nephropathy could only be identified through renal biopsy testing, which is expensive and can impose a financial burden on patients.

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Therefore, there is a necessity to develop a cost-effective method for identifying diabetic nephropathy.
Aim: To evaluate the correlation between RBC parameters, such as RDW and MCV values, as prognostic biomarkers for patients with diabetic nephropathy.
Methods and Material:
Study Design: Prospective comparative study.
Study Site: Sudha Institute of Medical Science, Erode.
Study Duration: Study was carried out over six-months.
Sample Size: 101 diabetic nephropathy patients and 101 type 2 diabetes mellitus patients.
Statistical Analysis: Pearson correlation**.**
Results: The majority of diabetic nephropathy patients were 40 years old or older, and most of them were males. Among the study participants, a significant number of male participants had habits of smoking and alcohol consumption. The duration of diabetes and BMI exhibited a strong correlation with the occurrence of diabetic nephropathy. Furthermore, there were notable increases in urea, creatinine, FBS, RBS, PPBS, and HbA1C, alongside a decrease in MCV and eGFR as diabetic nephropathy progressed.
Conclusions: Our research indicates a positive correlation between RDW and HbA1c, FBS, RBS, PPBS, urea, and creatinine. In contrast, negative correlation of RDW with MCV and eGFR. MCV is negatively correlated with HbA1c, FBS, RBS, PPBS, urea, creatinine. In contrast, positive correlation between MCV and eGFR.

Keywords: Diabetes mellitus; diabetic nephropathy; RDW; MCV.

1. INTRODUCTION

The world's capital of diabetes is India, and diabetes mellitus is a non-communicable illness that is spreading around the globe [1]. In addition to macrovascular consequences like stroke and cardiovascular disease, diabetes is a systemic metabolic illness that may cause a number of long-term microvascular complications, including diabetic retinopathy and diabetic nephropathy (DN). End-stage renal failure might result from DN [2]. A persistent and irreversible decline in eGFR is a characteristic of diabetic nephropathy, which is diabetes characterized by albuminuria and has been proven at least twice at intervals of 3 to 6 months [3]. Asian Indians had an overt prevalence of diabetic nephropathy of 2.2% [4]. Podocyte death, extracellular matrix protein deposition, and mesangial growth and hypertrophy are pathological features of the illness. These features may result in glomerulosclerosis and tubulointerstitial fibrosis, which can eventually induce diabetic nephropathy [5]. Identification of the renal damage brought on by DN requires a renal biopsy. In diabetic individuals with an unusual appearance of renal illness that might be related to various renal entities other than diabetic nephropathy, a renal biopsy is recommended [6]. In addition to the generation of Glycated hemoglobin, hyperglycemia affects RBCs in a number of ways, including by reducing their deformability, altering their mechanical properties, which in turn affect how they are structured and how they function hemodynamically, and raising their RDW level [7]. Despite the fact that RDW has traditionally been used to investigate anemia, there is mounting evidence that links elevated RDW to poor outcomes in patients with metabolic syndrome, including diabetes mellitus and its complications [8]. Due to the high degree of vascularity in the kidney, hematomas and gross hematuria are the most frequent consequences after kidney biopsies. Because renal biopsies are so expensive, patients bear a heavy financial burden. It is necessary to develop a cost-effective method to look into the nephrological effects. Consequently, a test that can detect a biomarker for diabetic nephropathy and is both affordable and accessible is required. Therefore, the goal of this study was to determine whether RDW and MCV in patients with diabetes and diabetic nephropathy are related to renal function parameters like urea, creatinine, and eGFR in comparison to blood sugar parameters like RBS, FBS, PPBS, and HbA1C.

1.1 Aim

To evaluate the correlation between RBC parameters, such as RDW and MCV values, as prognostic biomarkers for patients with diabetic nephropathy.

1.2 Objectives

- To examine the RDW and MCV as a prognostic biomarker in patients with diabetic nephropathy.
- Comparison and correlation of hematologic, renal and blood glucose parameters between Diabetes Mellitus and Diabetic nephropathy patients.
- To find out the percentage cost difference between renal biopsy and complete blood count

2. MATERIALS AND METHODS

2.1 Study Design

Prospective comparative study

2.2 Study Site

Sudha Institute of Medical Science, Erode, Tamilnadu.

2.3 Study Duration

Study was carried out over a six-month period, from April 2023 to September 2023.

2.4 Study Criteria

2.4.1 Inclusion criteria

- Patients undergoing treatment for type 2 Diabetes Mellitus for atleast 2 years.
- Patients diagnosed with diabetic nephropathy (newly during the study period)

2.4.2 Exclusion criteria

- Type 2 diabetes mellitus patient who doesn't have CBC report
- Patient with known case of any malignancy and myelo-proliferative disorder, CKD, End stage renal disease, Gestational diabetes mellitus, and Type 1 diabetic mellitus.
- Patient who had kidney disease before diabetes was diagnosed

2.5 Study Procedure

The data collection was done by visiting the hospital on a regular basis. The patient's previous CBC reports were collected from DM participants, and they are taken into note as "DM Group 1". Then the latest CBC reports of the same participants were collected, and they are taken into notes as "DM Group 2 ". The data was then collected from the "Diabetes nephropathy" patients from their recent CBC and blood glucose reports, and it is mentioned as "DN" patients, and it is taken for comparison with DM 1 and DM 2 participants for the study.

2.6 Sample Size

We included 101 diabetic nephropathy patients and 101 type 2 diabetes mellitus patients in this study.

2.7 Data Collection

All data for the research was gathered from patient profiles and laboratory investigation using specially prepared forms, which included demographic information like age, sex, height, weight and Laboratory investigation includes Complete Blood Count, Renal Function Test, and Blood glucose test. Complete blood count includes Mean corpuscular volume, Red cell distribution width. Renal function test includes Serum creatinine, Urea. Blood glucose test includes RBS, FBS, PPBS and HbA1C. The GFR was calculated according to CKD EPI creatinine equation.

2.8 Statistical Analysis

The data obtained was entered into MS Excel and data was analysed using SPSS. Descriptive statistics like mean, standard deviation were applied. Correlations were assessed using Pearson's test. Receiver Operating Characteristic (ROC) curve analysis was used to determine the optimum cut-off values of RDW and MCV to predict Diabetic nephropathy.

3. RESULTS

Majority of the patients (48.51% diabetes mellitus patients and 49.5% diabetic nephropathy patients) were in the age category of 41 to 60 years, followed by the age group of 61 to 80 years with 37.62% diabetes mellitus patients and 45.54% diabetic nephropathy patients. There were only 13.87% diabetes mellitus patients and 4.96% diabetic nephropathy patients in the 20–40 year age category. In our study, the average age of diabetes mellitus patients was 56.16 years, while that of diabetic nephropathy patients was 60.08 years.

The diabetes mellitus group had 59 males and 42 females, and the diabetic nephropathy group had 75 males and 26 females. There were a total of 134 male patients and 68 female patients.

In our study, females were neither smoker nor alcoholism habits. Among 134 male participants, 29 with diabetes and 36 with diabetic nephropathy had both smoking and alcohol habits. Additionally, 8 patients from each group (DM and DN) had alcohol habits but did not smoke, while 5 DM patients and 13 DN patients were smokers but did not consume alcohol. Notably, 17 DM patients and 18 DN patients were neither alcoholics nor smokers.

In the DM 1st report group, there were 1 underweight patient, 94 normal weight patients, and 6 overweight patients. In the DM latest report group, there were 1 underweight patient, 56 normal weight patients, 19 overweight patients, and 25 obese patients. Among DN patients, there were 9 normal weight patients, 46 overweight patients, and 46 obese patients. BMI increased as diabetic nephropathy progressed, with average BMIs of 22.13 Kg/m² for DM 1st report group patients, 27.11 Kg/m² for DM latest report group patients, and 31.24 Kg/m² for DN group patients.

The progression of DN was purely correlated with the duration of diabetes (in months). The mean duration of diabetes was 6.78 years for DM 1st report group patients, 10.16 years for DM latest report group patients, and 13.19 years for DN group patients.

The hematological, renal, and blood glucose level parameters among the study participants are listed in Table 1.

The results of this study showed an increase in RDW, Urea, Creatinine, FBS, RBS, PPBS, HbA1C levels, and a decrease in MCV and eGFR among patients with alcohol and smoking habits, as well as in either alcoholic or smoker groups in both DM and DN groups.

The results of this study showed an increase in RDW, Urea, Creatinine, FBS, RBS, PPBS, HbA1C levels, and a decrease in MCV among patients with abnormal weight in both the DM and DN groups. Interestingly, our study also highlighted an increase in eGFR levels among abnormal weight DN patients.

Our study found that patients with prolonged diabetes had elevated RDW, Urea, Creatinine, FBS, RBS, PPBS, HbA1C, and reduced MCV and eGFR.

Table 2 showed the correlation between MCV and renal parameters.

Table 3 demonstrated the correlation between MCV and blood glucose parameters.

Table 4 illustrated the correlation between RDW, MCV, and renal parameters.

Lastly, Table 5 revealed the correlation between RDW and blood glucose parameters.

Our study found a 96% cost difference between renal biopsy tests and complete blood counts.

In Fig. 1, the ROC curves depicted MCV cut-off values among study participants, showing a decrease in MCV levels with the progression from DM to DN.

In Fig. 2, the ROC curves depicted RDW cut-off values among study participants, indicating an increase in RDW levels with the progression from DM to DN.

Table 1. Hematological, renal and blood glucose parameters among study populations

Parameters	Mean ± S.D			P Value (between DM 1st and latest report)	P Value (between DM latest report and DN)
	DM 1st report	DM latest report	DN		
RDW	14 ± 2.5	14.82 ± 2.26	19.49 ± 10.63	0.0153*	<0.0001*
MCV	86.08 ± 6.97	83.22 ± 9.17	82.16 ± 9.31	0.0134*	0.416
Urea	28.86 ± 13.88	32.11 ± 11.69	75.8 ± 32.13	0.0734*	<0.0001*
Creatinine	0.9 ± 0.41	1.1 ± 0.53	3.32 ± 2.38	0.003*	<0.0001*
eGFR	91.65 ± 24.29	78.13 ± 25.03	31.56 ± 22.25	<0.0001*	<0.0001*
RBS	173.35 ± 8.16	201.58 ± 8.17	267.73 ± 78.72	<0.0001*	<0.0001*
FBS	136.94 ± 13.17	156.31 ± 7.05	174.54 ± 62.16	<0.0001*	<0.0001*
PPBS	173.32 ± 7.83	203.74 ± 9.15	256.04 ± 62.63	<0.0001*	<0.0001*
HbA1C	7.29 ± 0.51	9.65 ± 1.02	11.26 ± 1.87	<0.0001*	0.004*

** - Significant difference*

Table 2. Correlation of MCV with renal parameters among study populations

Variable		MCV		
Test		**Pearson correlation**	**Sig. (2-tailed)**	**N**
Urea	DM - 1	-0.023	0.822	101
	DM -2	-0.102	0.309	101
	DN	-0.152	0.129	101
Creatinine	DM - 1	-0.13	0.124	101
	DM -2	-0.04	0.692	101
	DN	-0.272*	0.006	101
eGFR	DM - 1	0.058	0.564	101
	DM -2	0.136	0.174	101
	DN	0.104	0.303	101

Table 3. Correlation of MCV with blood glucose parameters among study populations

Variable		MCV		
Test		**Pearson correlation**	**Sig. (2-tailed)**	**N**
RBS	DM - 1	-0.024	0.814	101
	DM -2	-0.034	0.735	101
	DN	-0.126	0.211	101
FBS	DM - 1	-0.113	0.259	101
	DM -2	-0.078	0.439	101
	DN	-0.086	0.393	101
PPBS	DM - 1	-0.026	0.795	101
	DM -2	-0.216*	0.030	101
	DN	-0.038	0.705	101
HbA1C	DM - 1	-0.074	0.461	101
	DM -2	-0.035	0.73	101
	DN	-0.074	0.464	101

Table 4. Correlation of RDW with MCV and renal parameters among study populations

Variable		RDW		
Test		**Pearson correlation**	**Sig. (2-tailed)**	**N**
MCV	DM - 1	-0.311*	0.002	101
	DM -2	-0.389*	<0.001	101
	DN	-0.068	0.502	101
Urea	DM - 1	0.029	0.771	101
	DM -2	0.149	0.136	101
	DN	0.08	0.428	101
Creatinine	DM - 1	0.366*	<0.001	101
	DM -2	0.153	0.126	101
	DN	0.124	0.218	101
eGFR	DM - 1	-0.200*	0.045	101
	DM -2	-0.08	0.174	101
	DN	-0.05	0.62	101

4. DISCUSSION

In this study, the majority of diabetic nephropathy patients were aged above 40 years old. An earlier study conducted by Nombwende et al. in 2019 focusing on diabetic nephropathy found that those aged 35 years and more exhibited an elevated susceptibility to cause diabetic nephropathy [9]. Male were significantly affected with diabetes and diabetic nephropathy in this study. This distribution of gender could potentially be linked to risk factors like smoking and alcohol consumption. Similar research conducted by Arkew et al. in 2021 concluded that males were more commonly affected with diabetes mellitus [10].

Table 5. Correlation of RDW with blood glucose parameters among study populations

Variable		MCV		
Test		**Pearson correlation**	**Sig. (2-tailed)**	**N**
RBS	DM - 1	0.037	0.711	101
	DM -2	0.002	0.985	101
	DN	0.027	0.789	101
FBS	DM - 1	0.009	0.926	101
	DM -2	0.119	0.235	101
	DN	0.193	0.054	101
PPBS	DM - 1	0.015	0.885	101
	DM -2	0.102	0.312	101
	DN	0.062	0.536	101
HbA1C	DM - 1	0.074	0.463	101
	DM -2	0.036	0.722	101
	DN	0.407*	< 0.001	101

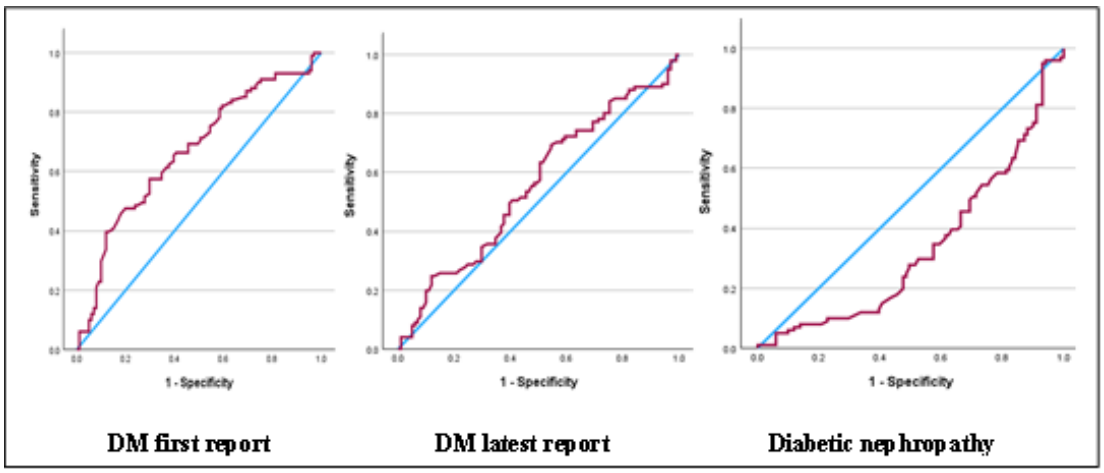

Fig. 1. ROC curves portray MCV cut-off values across distinct study groups

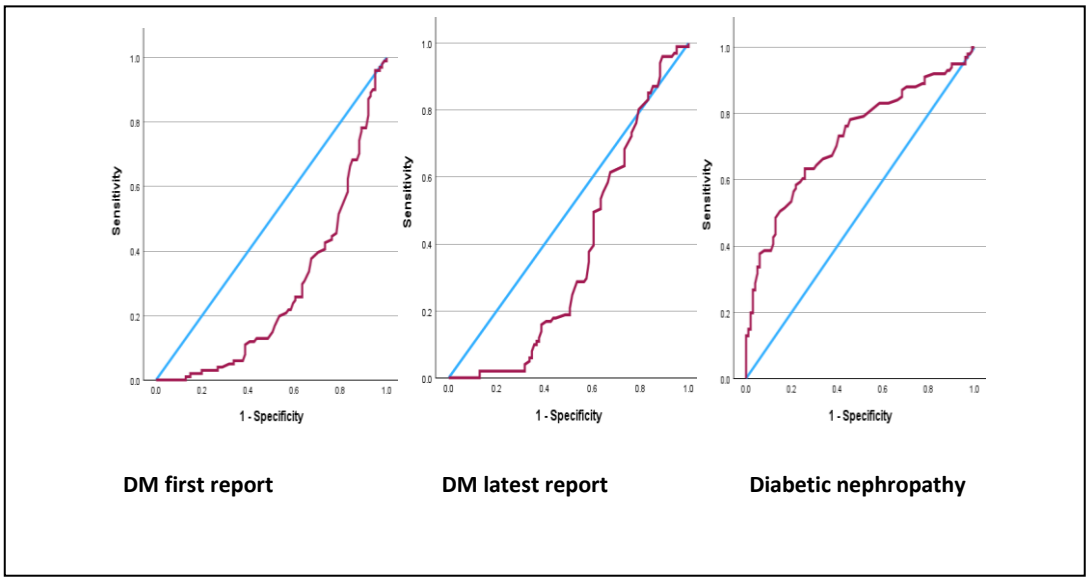

Fig. 2. ROC curves portray RDW cut-off values across distinct study groups

According to the findings of our study, diabetic nephropathy male patients were more prone to smoking and alcohol consumption habits. A similar investigation conducted by Yin Y et al. in 2018 concluded that smoking and alcohol consumption habits were more prevalent in patients with poorly controlled diabetes mellitus [11]. This connection could be attributed to the oxidative stress induced by smoking. Increased oxidative stress has the potential to impede the production of red blood cells, shorten their lifespan, and contribute to irregularities in their shape. These factors may consequently result in an increase in RDW and a reduction in MCV [12]. Acetaldehyde, a by-product of alcohol metabolism, disrupts the natural development of red blood cells, diminishing their capacity to transport oxygen and decreasing their lifespan, ultimately leading to a higher RDW [13].

Our study significantly difference in elevation in RDW, Urea, creatinine, RBS, FBS, PPBS, and HbA1C levels among patients with both smoking and alcohol consumption habits. A similar study conducted by Eid HA et al. in 2022 concluded that increase in urea and creatinine levels, accompanied by a decline in eGFR values among patients with smoking and alcohol consumption habits [14]. Smoking can potentially inflict damage on the kidneys through diverse mechanisms, encompassing immediate effects such as sympathetic stimulation leading to reduced GFR, as well as on-going consequences, notably compromised endothelial cell functionality [15]. Elevated levels of ethanol metabolism, combined with hyperglycemia, can contribute to endothelial dysfunction and widespread inflammation by generating an oxidative environment. Ultimately, this cascade could potentially culminate in glomerulosclerosis [16].

This result revealed a connection between the progression of diabetic nephropathy and an increase in BMI. Among diabetes mellitus patients in our study, the average BMI was 22.13. Similar research conducted by Yin Y et al. in 2018 indicated that patients with poorly controlled diabetes mellitus had a higher BMI (26.7 kg/m^2) compared to those with well-controlled diabetes mellitus (25.6 kg/m^2) [11]. Nada et al. in 2015 observed that diabetic patients with higher BMI exhibited an elevation in RDW and a reduction in MCV level [17]. Ray SA et al. in 2020 found that obese patients had higher levels of urea and creatinine, as well as lower estimated eGFR compared to normal-weight diabetic patients [18]. Another study by Okabayashi et al. in 2020 concluded that obesity-related glomerulonephropathy was associated with larger glomerular volume, lower glomerular density, and increased glomerulosclerosis, even with similar total nephrons. Notably, glomeruli enlarged with increasing obesity, accompanied by a rise in eGFR [19]. Mohan V et al. in 1997 concluded that elevated levels of FBS, PPBS, and HbA1C among underweight diabetes mellitus patients [20]. Roy Mousomi et al. in 2020 noted higher PPBS, FBS, and HbA1C levels among obese diabetes patients compared to those with normal weight [21]. Obesity-associated diabetic nephropathy is linked to elevated blood glucose levels, increased glucose production in the liver and reduced glucose uptake by muscles [22].

In 2014, Al-Rubeaan and colleagues conducted a study involving a significant cohort of 54,670 individuals diagnosed with Type 2 Diabetes Mellitus (T2 DM). Their findings suggested a correlation between the duration of the disease and diabetic nephropathy [23]. In our study, we observed that the average duration of diabetes was 6.78 years among diabetes mellitus patients, while for those with diabetes nephropathy; it was notably extended at 12.49 years. Arkew et al. in 2021 similarly ascertained that the mean duration of diabetes was 7.65 years among diabetes mellitus patients [10]. Over time, the prolonged exposure of renal cells to a high-glucose environment accentuates the severity of harm to renal blood vessels, stimulates the formation of Advanced Glycation End-products (AGEs), and contributes to the progression of diabetic nephropathy [24]. Our study results revealed a clear relationship between increased RDW and decreased MCV as the duration of diabetes increased among patients with diabetic nephropathy. Bilir B et al. in 2016 study demonstrated that RDW increases with the prolonged duration of diabetes [25]. KIYKIM et al. in 2014 established a link between an extended duration of diabetes and high levels of creatinine, FBS, HbA1C, along with a decrease in the eGFR [26]. Notably, Al-Rubeaan K et al. in 2014 reached analogous conclusions to our study, extended periods of diabetes could amplify the susceptibility to suboptimal glycemic control and associated comorbidities, both of which could influence renal functionality through vascular impairment [23].

Our study findings reveal that there was an increase in urea, creatinine, RDW, FBS, RBS,

PPBS, and HbA1C levels and a decrease in MCV and eGFR levels with the progression from diabetes mellitus to diabetic nephropathy. Alamri BN et al. in 2019 concluded that reduction in MCV levels among diabetic patients when compared to healthy individuals [27]. However, a study conducted by Nombwende G et al. in 2019 contradicts our findings, suggesting an increase in MCV levels in diabetic nephropathy patients [9]. Similarly, the study by Arkew M et al. in 2022 supports our results, indicating an elevation in RDW levels among diabetic patients when compared to healthy subjects [10]. Conversely, Yin Y et al. in 2018 reported discordant outcomes, noting that poorly controlled diabetes patients exhibited lower RDW levels compared to well-controlled diabetes patients [11]. The presence of chronic inflammation and oxidative stress in diabetes is well-established, contributing to reduced red blood cell survival, leading to fluctuations in erythrocyte size and elevated RDW values [12]. Nombwende et al. in 2019 concluded that creatinine and urea levels were higher, while eGFR was lower in type 2 diabetes mellitus patients with diabetic nephropathy compared to those without nephropathy [9]. Elevated blood sugar levels damage a significant number of nephrons, impairing the kidney's function [28]. A similar study by KIYKIM et al. in 2014 concluded that FBS and HbA1C levels were higher among diabetic nephropathy patients in comparison to diabetic patients without nephropathy [26].

Our study showed a positive correlation between MCV and eGFR, as well as a negative correlation between MCV and urea, creatinine, RBS, FBS, PPBS, and HbA1C. Additionally, our study revealed a negative correlation between RDW and MCV and eGFR, and a positive correlation between RDW and urea, creatinine, RBS, FBS, PPBS, and HbA1C. A study conducted by Renuka et al. 2020 among diabetes mellitus patients concluded that positive correlation of RDW with Urea, creatinine, FBS, HbA1C and negative correlation of RDW with Urea, creatinine, FBS, HbA1C [29].

5. CONCLUSION

Our study concludes that RDW, Urea, Creatinine, FBS, RBS, HbA1C, PPBS are increases and MCV, eGFR level decreases in the progression of DN from DN. RDW is positively correlated HbA1c, FBS, RBS, PPBS, urea, creatinine and negatively correlated with eGFR, MCV. Conversely, MCV is negatively correlated with HbA1c, FBS, RBS, PPBS, urea, creatinine, and positively correlated with eGFR. The study highlights a significant association between RDW and MCV with diabetic nephropathy, indicating their potential as sensitive and non-invasive prognostic biomarkers for early DN diagnosis. RDW and MCV are cost-effective tools in the early detection of vascular complications in diabetes and hence prove to be prognostic indicators in preventing diabetic-related vascular complications. Complete blood count tests are 96% less costly than renal biopsy tests. Regular evaluation of red blood cell metrics like RDW and MCV is recommended for individuals with type 2 diabetes. These assessments can offer valuable insights beyond glycemic control, potentially aiding in more effective management and even the prevention of diabetic nephropathy and cost savings.

Note: As diabetic nephropathy advances from Type-2 diabetes mellitus, there is an elevation in RDW levels and a reduction in MCV levels. Consequently, RDW and MCV serve as economical and efficient prognostic biomarkers in diabetic nephropathy diagnosis.

ETHICAL APPROVAL

The study was approved by the Institutional Ethical Committee (IEC) for ethical approval.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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