Analysis Of Differences In Erythrocyte Index As An Indicator Of Early Hematological Changes In Prediabetes And Normoglycemic Individuals

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ABSTRACT

Background: Prediabetes is a transitional state characterized by impaired glucose regulation that triggers oxidative stress and metabolic changes, potentially altering erythrocyte morphology before the onset of type 2 diabetes. **Objective:** This study aimed to analyze the differences in erythrocyte indices between individuals with prediabetes and normoglycemia to identify early hematological changes. **Methods:** A quantitative observational analytic study with a cross-sectional design was conducted using secondary medical record data from eighty subjects, equally divided into prediabetes and normoglycemia groups through consecutive sampling. Data analysis utilized independent t-tests and Mann-Whitney U tests. **Results:** The results demonstrated a significantly higher mean corpuscular volume in the prediabetes group compared to the normoglycemia group. Additionally, the mean corpuscular hemoglobin concentration was significantly lower in prediabetic individuals. However, the mean corpuscular hemoglobin showed no significant difference between the two groups. In conclusion, significant structural erythrocyte changes, specifically increased volume and decreased hemoglobin concentration, occur during the prediabetic phase. **Conclusion:** These findings suggest that specific erythrocyte indices could serve as potential early hematological biomarkers for detecting metabolic deterioration associated with glucose regulation disorders.

Keywords Biomarkers; Blood Glucose; Erythrocyte Indices; Erythrocytes; Prediabetic State.

INTRODUCTION

Diabetes mellitus (DM) is a major global public health challenge, with a rapidly increasing prevalence worldwide. According to the International Diabetes Federation (IDF), approximately 588.7 million adults were living with diabetes in 2024, and this number is projected to increase to 852.5 million by 2050. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases and is associated with serious microvascular and macrovascular complications, including nephropathy, cardiovascular disease, and stroke, which contribute substantially to morbidity and mortality worldwide (1,2). Prediabetes is an intermediate metabolic state characterized by blood glucose levels above normal but below the diagnostic threshold for diabetes. According to the American Diabetes Association (ADA), prediabetes is defined by fasting plasma glucose of 100–125 mg/dL, 2-hour plasma glucose of 140–199 mg/dL during an oral glucose tolerance test, or glycated hemoglobin (HbA1c) levels of 5.7–6.4%. Although individuals with prediabetes are often asymptomatic, this stage is characterized by insulin resistance, compensatory hyperinsulinemia, chronic low-grade inflammation, and oxidative stress, all of which contribute to progressive pancreatic β-cell dysfunction and increase the risk of developing T2DM (3,4).

Chronic hyperglycemia induces biochemical and structural alterations in erythrocytes through several mechanisms, including protein glycation, oxidative stress, activation of the polyol pathway, and the formation of advanced glycation end products (AGEs). These

processes impair erythrocyte membrane integrity, decrease cellular deformability, increase blood viscosity, and shorten erythrocyte lifespan. Consequently, alterations in erythrocyte morphology and function may be reflected in erythrocyte indices obtained from routine complete blood count examinations (5,6). Erythrocyte indices—including Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC)—are commonly used to evaluate erythrocyte morphology and hemoglobin content. In recent years, these parameters have attracted increasing attention as potential biomarkers of metabolic disorders because they may reflect hematological alterations associated with chronic hyperglycemia and oxidative stress. Previous studies have reported significant changes in erythrocyte parameters among patients with T2DM, including reductions in hemoglobin concentration, erythrocyte count, MCV, MCH, and MCHC, particularly in individuals with long-standing disease or diabetic complications (7-11).

However, evidence regarding erythrocyte indices during the prediabetic stage remains limited and inconsistent. Some studies have reported alterations in erythrocyte indices among individuals with prediabetes, whereas others found no significant associations between HbA1c and erythrocyte parameters (12-13). Furthermore, most previous studies compared individuals with prediabetes and patients with T2DM rather than comparing prediabetic individuals with normoglycemic controls. Consequently, hematological alterations occurring during the early stages of glucose dysregulation remain poorly understood. Identifying early hematological changes in prediabetes may improve the understanding of disease progression and provide inexpensive, widely available biomarkers for early detection. Since erythrocyte indices are routinely measured as part of complete blood count examinations, they may represent practical adjunctive indicators of metabolic abnormalities before the onset of overt diabetes. Therefore, this study aimed to analyze the differences in erythrocyte indices, including MCV, MCH, and MCHC, between individuals with prediabetes and those with normoglycemia.

METHODS

This quantitative study employed an observational analytical design with a cross-sectional approach using secondary data. The study aimed to compare erythrocyte indices between individuals with prediabetes and normoglycemia. Data were obtained from the medical records database of Redy Clinical Laboratory, Surakarta, Indonesia, covering the period from October 2025 to March 2026. Data collection was conducted between April and May 2026. The study population consisted of all patients who underwent fasting blood glucose (FBG) and complete blood count (CBC) examinations at Redy Clinical Laboratory. A total of 80 eligible subjects were included using a consecutive sampling technique, comprising 40 individuals with prediabetes and 40 individuals with normoglycemia. Inclusion criteria were patients aged 19–61 years with complete fasting blood glucose and erythrocyte index (MCV, MCH, and MCHC) results obtained on the same examination date. Prediabetes was defined as fasting blood glucose levels between 100 and 125 mg/dL, whereas normoglycemia was defined as fasting blood glucose levels below 100 mg/dL according to the American Diabetes Association criteria. Patients with clinical anemia, iron deficiency anemia, thalassemia or other hemoglobinopathies, chronic kidney disease, chronic liver disease, pregnancy, acute infection, severe inflammation, or incomplete laboratory records were excluded to minimize potential confounding factors affecting erythrocyte indices. The independent variable was glycemic status (prediabetes and normoglycemia). The dependent variables were erythrocyte indices, including Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC). Secondary laboratory data were retrieved from the laboratory database. Erythrocyte indices were obtained from complete blood count examinations performed using an automated hematology analyzer (Mindray BC-30, Mindray Bio-Medical Electronics Co., Shenzhen, China). The analyzer operates based on the

electrical impedance principle for cell counting and volume measurement, photometric determination of hemoglobin concentration, and automatic calculation of erythrocyte indices. Data extracted from the database included age, sex, fasting blood glucose, MCV, MCH, and MCHC. Prior to statistical analysis, all records underwent data editing, coding, entry, and cleaning procedures to ensure completeness and accuracy. Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies, percentages, mean ± standard deviation, and minimum–maximum values.

Data normality was assessed using the Shapiro–Wilk test, followed by Levene's test to evaluate homogeneity of variance. Normally distributed variables with homogeneous variance were analyzed using the independent-samples t-test. Variables that did not satisfy the assumptions of parametric analysis were compared using the Mann–Whitney U test. Statistical significance was established at a p-value of <0.05.

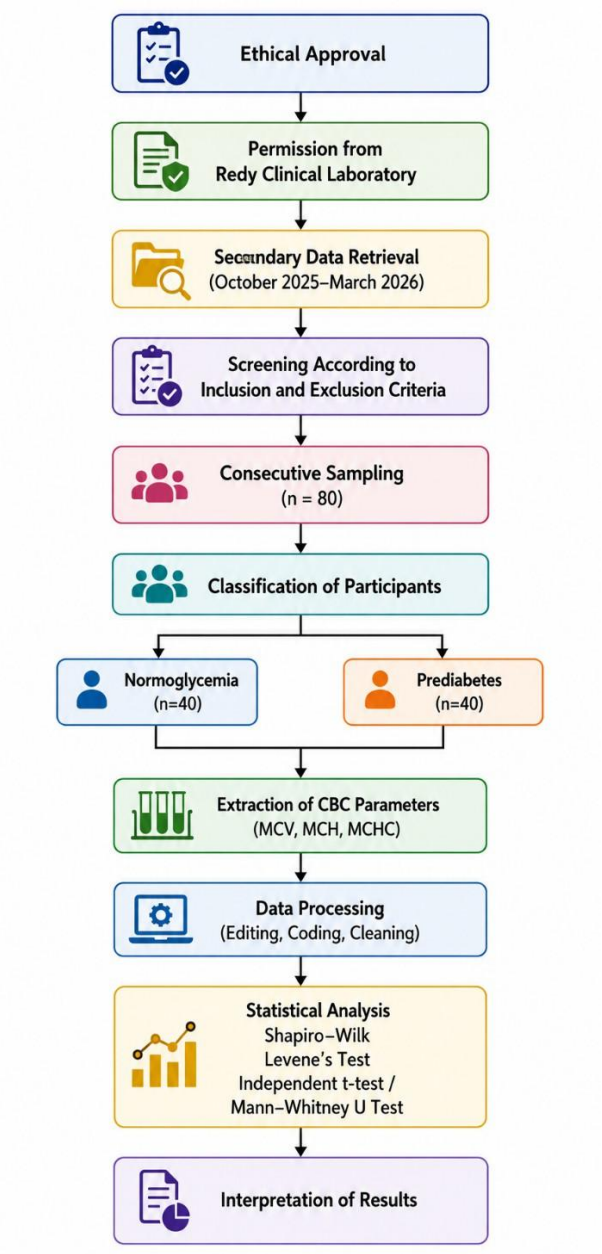

Figure 1. Research Stages Flowchart

RESULTS

This study involved 80 respondents divided equally into two groups: 40 individuals with normoglycemia and 40 individuals with prediabetes.

Table 1 Characteristics of Research Subjects

Characteristic	Normoglycemia (n=40)	Prediabetes (n=40)
Age (years, Mean ± SD)	23.98 ± 3.28	37.60 ± 14.17
Gender:		
- Male, n (%)	28 (70.0)	29 (72.5)
- Female, n (%)	12 (30.0)	11 (27.5)
BMI (kg/m², Mean ± SD)	24.18 ± 5.59	24.46 ± 5.01

Source: Processed primary data, 2026

Both groups were predominantly composed of male respondents. The mean age of the prediabetes group was significantly higher compared to the normoglycemia group. Meanwhile, the average Body Mass Index (BMI) values were relatively similar between the two groups.

Descriptive analysis was conducted to describe the quantitative profile of erythrocyte indices in both groups, including minimum, maximum, mean, and standard deviation values.

Table 2 Distribution of Erythrocyte Index Values

Variable	Group	Mean ± SD	Min	Max
MCV (fL)	Normoglycemia	84.83 ± 4.33	70.60	90.40
	Prediabetes	89.20 ± 5.59	78.10	99.60
MCH (pg)	Normoglycemia	27.61 ± 1.70	22.60	30.30
	Prediabetes	28.17 ± 1.65	23.80	31.20
MCHC (g/dL)	Normoglycemia	32.54 ± 0.70	31.00	33.70
	Prediabetes	31.63 ± 1.40	28.30	34.30

Source: Processed primary data, 2026

The mean value of MCV was higher in the prediabetes group compared to the normoglycemia group. Similarly, the mean MCH value was slightly higher in the prediabetes group. In contrast, the mean MCHC value was lower in the prediabetes group than in the normoglycemia group. The range of values for each parameter is presented in the table above.

Before conducting difference tests, a normality test was performed to check the distribution of erythrocyte index data. The **Shapiro-Wilk test** was used since the sample size in each group was fewer than 50 respondents. The significance level was set at $\alpha = 0.05$.

Table 3 Results of Normality Test

Variable	Shapiro-Wilk Statistic	p-value	Conclusion
Mean Corpuscular Volume (MCV)	0.975	0.114	Normally distributed
Mean Corpuscular Hemoglobin (MCH)	0.971	0.062	Normally distributed
Mean Corpuscular Hemoglobin Concentration (MCHC)	0.944	0.002	Not normally distributed

Source: Processed primary data, 2026

MCV showed a significance value of 0.114 ($p > 0.05$), indicating normal distribution. MCH had a significance value of 0.062 ($p > 0.05$), also indicating normal distribution. Conversely, MCHC had a significance value of 0.002 ($p < 0.05$), meaning the data was not normally distributed.

This test was conducted as a prerequisite for parametric analysis using **Levene's Test**. The decision rule: $p > 0.05$ = variances are homogeneous; $p < 0.05$ = variances are not homogeneous.

Table 4 Results of Homogeneity of Variance Test

Variable	F-value	p-value	Conclusion
Mean Corpuscular Volume (MCV)	4.545	0.036	Not homogeneous
Mean Corpuscular Hemoglobin (MCH)	0.032	0.859	Homogeneous
Mean Corpuscular Hemoglobin Concentration (MCHC)	12.753	0.001	Not homogeneous

Source: Processed primary data, 2026

Only MCH met the homogeneity assumption. MCV was normally distributed but had unequal variance, while MCHC was neither normally distributed nor homogeneous. Therefore, the appropriate statistical tests were selected as follows:

MCH: Independent Sample *t*-test

MCV and MCHC: Mann-Whitney U Test (non-parametric alternative)

This test aimed to identify significant differences in erythrocyte indices between the prediabetes and normoglycemia groups.

Table 5 Comparison of Erythrocyte Indices Between Groups

Variable	Normoglycemia (n=40) Mean ± SD	Prediabetes (n=40) Mean ± SD	Statistical Test	p-value	Conclusion
MCV (fL)	84.83 ± 4.33	89.20 ± 5.59	Mann-Whitney U	0.01	Significant difference
MCH (pg)	27.61 ± 1.70	28.17 ± 1.65	Independent *t*-test	0.138	No significant difference
MCHC (g/dL)	32.54 ± 0.70	31.63 ± 1.40	Mann-Whitney U	0.02	Significant difference

Source: Processed primary data, 2026

There was a statistically significant difference in MCV (p = 0.001) and MCHC (p = 0.002) values between the two groups. Meanwhile, MCH values did not show a statistically significant difference (p = 0.138).

DISCUSSION

The present study demonstrated a significant difference in Mean Corpuscular Volume (MCV) between individuals with prediabetes and normoglycemia (p = 0.001). Participants with prediabetes exhibited a higher mean MCV (89.20 ± 5.59 fL) than normoglycemic individuals (84.83 ± 4.33 fL), suggesting that alterations in erythrocyte morphology may occur during the early stage of glucose dysregulation.Several biological mechanisms may explain the observed increase in MCV. Chronic exposure to elevated glucose concentrations promotes the formation of advanced glycation end products (AGEs), which alter erythrocyte membrane proteins and reduce membrane stability. Hyperglycemia also enhances oxidative stress through excessive production of reactive oxygen species (ROS), resulting in lipid peroxidation and membrane damage that may increase erythrocyte volume and reduce cellular deformability. These structural alterations may be detectable before the clinical onset of type 2 diabetes mellitus (14-15).

The present findings are consistent with those reported by Sirdah et al., who demonstrated that chronic hyperglycemia was associated with alterations in erythrocyte morphology, including increased MCV, due to membrane protein glycation and impaired erythrocyte biomechanics (16). Similar observations were reported by Alsalhen and Mahmood, who found that individuals with impaired glucose metabolism exhibited significant changes in erythrocyte indices compared with healthy controls (17). Collectively, these findings suggest that MCV may serve as an early hematological marker of metabolic disturbance during the prediabetic stage.

Unlike MCV, Mean Corpuscular Hemoglobin (MCH) did not differ significantly between the two groups (p = 0.138), although the mean value was slightly higher in individuals with

prediabetes. MCH reflects the average amount of hemoglobin contained within a single erythrocyte. The absence of a significant difference indicates that hemoglobin synthesis and erythropoiesis remain relatively preserved during the prediabetic stage. Although insulin resistance and mild hyperglycemia are already present, these metabolic disturbances may not yet be sufficiently severe to alter intracellular hemoglobin content. This finding agrees with Rafat et al., who reported no significant difference in MCH between individuals with impaired glucose metabolism and healthy controls (18).

Likewise, Akinsegun et al. observed that MCH was less responsive to chronic hyperglycemia than other erythrocyte indices, particularly MCV, indicating that erythrocyte volume may change earlier than hemoglobin content during disease progression (19). Therefore, MCH appears to have limited value as an isolated biomarker for detecting early hematological alterations associated with prediabetes.

A significant difference was also observed in Mean Corpuscular Hemoglobin Concentration (MCHC) ($p = 0.002$), with lower values in the prediabetes group than in the normoglycemia group. MCHC reflects the average concentration of hemoglobin within erythrocytes. Reduced MCHC may result from structural changes in erythrocytes caused by oxidative stress and non-enzymatic glycation of membrane proteins. Hyperglycemia-induced oxidative damage compromises membrane integrity, alters intracellular water balance, and affects hemoglobin distribution within erythrocytes. These changes may contribute to reduced erythrocyte deformability and shortened erythrocyte survival (20,21).

Our findings are supported by Nada et al., who reported significant alterations in hematological parameters among individuals with elevated blood glucose levels, particularly those associated with oxidative stress and chronic inflammation (22). Sherif et al. also demonstrated that increasing glucose concentrations impair erythrocyte quality and deformability, thereby influencing erythrocyte indices, including MCHC (23). The observed reduction in MCHC indicates that erythrocyte structural abnormalities may already be present during prediabetes and could represent an early manifestation of metabolic dysfunction.

Overall, the present study demonstrated significant alterations in MCV and MCHC, whereas MCH remained unchanged. These findings indicate that erythrocyte morphological changes may precede overt diabetes mellitus and become detectable during the prediabetic stage. Prediabetes is characterized by insulin resistance, persistent low-grade inflammation, oxidative stress, and increased protein glycation, all of which contribute to erythrocyte membrane remodeling and impaired cellular function (24). Consequently, routine erythrocyte indices obtained from complete blood count examinations may provide valuable information regarding early hematological changes associated with metabolic disorders. Because complete blood count analysis is inexpensive, rapid, and widely available, MCV and MCHC may serve as practical adjunctive biomarkers for identifying individuals at increased risk of progression to type 2 diabetes mellitus. However, these parameters should not be considered standalone diagnostic markers but rather complementary indicators alongside established glycemic measurements such as fasting plasma glucose and glycated hemoglobin (25).

This study has several limitations that should be considered when interpreting the findings. First, the mean age differed substantially between the normoglycemia and prediabetes groups. Because aging is known to influence erythrocyte morphology and hematological parameters, age may have acted as a confounding factor affecting the observed differences in erythrocyte indices.Second, age matching was not performed during sample selection, and multivariable analyses such as analysis of covariance (ANCOVA) or multiple regression were not conducted to adjust for potential confounding effects. Consequently, the observed associations between glycemic status and erythrocyte indices should be interpreted with caution. Future studies should include age-matched participants or apply multivariable statistical models to control for confounding variables. Prospective cohort studies with larger sample sizes are also warranted

to clarify whether alterations in erythrocyte indices can predict progression from prediabetes to type 2 diabetes mellitus.

CONCLUSION

This study demonstrated significant differences in erythrocyte indices between individuals with prediabetes and normoglycemia. Mean Corpuscular Volume (MCV) was significantly higher, whereas Mean Corpuscular Hemoglobin Concentration (MCHC) was significantly lower in the prediabetes group. In contrast, Mean Corpuscular Hemoglobin (MCH) did not differ significantly between the two groups. Among the evaluated erythrocyte indices, MCV showed the strongest association with prediabetes, indicating that changes in erythrocyte morphology may occur during the early stage of glucose dysregulation before the onset of overt type 2 diabetes mellitus.

These findings suggest that MCV and MCHC may serve as complementary hematological markers for the early identification of individuals with impaired glucose metabolism. Given that erythrocyte indices are routinely obtained from complete blood count examinations, they may provide a simple, inexpensive, and widely accessible adjunctive tool for the early detection of hematological alterations associated with prediabetes. Future studies with larger sample sizes, age-matched participants, longitudinal designs, and multivariable analyses are recommended to validate these findings and further clarify the clinical utility of erythrocyte indices as early biomarkers of diabetes progression.

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