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Original Article

Biochemistry Section

# Impact of Erythrocyte Indices on Glycated Haemoglobin and Plasma Glucose Discordance in Non-diabetics: A Retrospective Study

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## ABSTRACT

**Introduction:** Glycated Haemoglobin (HbA1c) has evolved into one of the most essential tools for the diagnosis and follow-up of Diabetes Mellitus (DM). Discordance between plasma glucose and HbA1c is being observed, especially in individuals diagnosed with prediabetes. Different types of anaemia, such as iron deficiency, haemolytic, and megaloblastic anaemia, can affect HbA1c results.

**Aim:** To study the effect of erythrocyte indices on the levels of HbA1c, particularly in situations where HbA1c levels are discordant with plasma glucose. Also, to derive the cut-off value of Red Blood Cells (RBC) indices below or above which the HbA1c results will be affected.

**Materials and Methods:** The present retrospective analytical study was conducted at Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. from March to August 2023. Out of 495 non-diabetic individuals recruited, those whose HbA1c value matched their plasma glucose value were categorised under the concordant group (n=285), and the rest under the discordant group (n=210). Retrospective data, including Fasting Plasma Glucose (FPG), HbA1c, Haemoglobin (Hb), Packed Cell Volume (PCV), Erythrocyte Sedimentation Rate (ESR), Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC) were collected and compared between the groups. Statistical analysis was performed using the Mann-Whitney U test and Spearman's rho correlation via Statistical Package for Social Sciences (SPSS) Version 20.

**Results:** The study population had a mean age of 43.2±11.3 years, comprising 319 males (64.4%) and 176 females (35.5%). For identical FPG ranges in both groups, the discordant group had higher median HbA1c values compared to the concordant group ($p<0.001$). Discordance was more frequently observed when HbA1c was in the range of 5.8-6.2%. RBC indices such as MCV and MCH were significantly lower in the female discordant group, whereas MCHC was considerably lower, especially in the male discordant group. ROC curve analysis showed that the cut-off value derived for the RBC indices had approximately 60% sensitivity and 60% specificity for all indices except MCHC.

**Conclusion:** In the present study, HbA1c showed significant discordance with FPG in the 5.8-6.2% range, increasing the risk of misclassification around the prediabetes threshold.

**Keywords:** Concordance, Diabetes mellitus, Iron deficiency anaemia, Red blood cell indices

## INTRODUCTION

The DM is one of the most common chronic diseases in humans, while its increasing incidence has become a significant public health concern worldwide [1]. Diabetes predisposes an individual to serious complications like cardiovascular disease, neuropathy, retinopathy, and nephropathy. Management and early diagnosis of the disease are critical in preventing such complications and ultimately improving the patient outcome. Prediabetes is a condition with a high glucose level above normal yet below the cut-off established for diabetes. It represents a critical window for intervention because, over ten years, most individuals with prediabetes will eventually develop type 2 diabetes if no intervention is done [2].

HbA1c, has evolved into one of the most essential tools in the diagnosis and follow-up process of DM. Diagnosing diabetes with HbA1c has advantages over plasma glucose and the Oral Glucose Tolerance Test (OGTT), such as random sample collection, reduced day-to-day variability, pre-analytical stability, and a value that is independent of the patient's recent nutritional status, stress, and acute illness [3]. According to the diagnostic criteria established by the American Diabetes Association (ADA), a person is considered diabetic if their HbA1c level is 6.5% or higher [4]. As per the recommendations of the International Expert Committee, those with HbA1c values >6.0% and below the diabetic threshold are at high risk of developing Diabetes, emphasising the need for effective preventive interventions at this stage [5].

Anaemia, particularly Iron Deficiency Anaemia (IDA), has been shown to influence HbA1c levels [6-9]. IDA increases the lifespan of RBCs. This, on one hand, subjects haemoglobin to glucose for a more extended period, which is falsely reflected as a higher HbA1c level [6]. In the National Health and Nutrition Examination Survey (NHANES), false HbA1c elevation in iron deficiency was predominantly observed in the HbA1c spectrum of 5.5% to 6.0% [7]. However, diseases that reduce the lifespan of RBCs, such as haemolytic anaemia, can lower HbA1c [8,9]. All these differences can confound HbA1c values and can be the route to inappropriate diagnosis or treatment of Diabetes.

The influence exerted by RBC indices, which include MCV, MCH, and MCHC, on HbA1c, would be of utmost importance. However, aside from anaemia, various factors, including the influence of drugs and assay interference, have been demonstrated to affect the accuracy of the test results [10]. National Institute for Health and Care Excellence (NICE) recommends investigating the unexpected discrepancies occurring between plasma glucose levels and HbA1c [11].

It has been demonstrated that HbA1c concentration readings can be affected by parameters such as haemoglobin level, MCV, and Red Cell Distribution Width (RDW), irrespective of the blood glucose

level [12]. Nevertheless, the threshold values of those RBC indices that can cause HbA1c misclassification have been rarely reported.

Hence, the present study was conducted to determine optimal RBC index thresholds for HbA1c interpretation. It also clusters patients based on the overlapping and non-overlapping status of their HbA1c and glucose values (concordant vs discordant), thus providing emergent thresholds that can help improve diabetes diagnosis in individuals with blood-related changes.

## MATERIALS AND METHODS

The present retrospective study was conducted at the Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India. The data were collected from March to May 2023 and analysed from June to August 2023. Ethical committee approval (CSP/23/APR/127/387) was obtained before the initiation of the study.

**Inclusion criteria:** Non-diabetic individuals of both genders, aged 18 years and above, attending the Master Health Checkup clinic were included in the study.

**Exclusion criteria:** Those with a history of DM, renal failure, recent blood transfusions, or treatment for anaemia were excluded.

**Sample size selection:** The sample size of 495 was determined based on the availability of complete medical records that met the inclusion and exclusion criteria during the three-month data collection period.

### Study Procedure

Retrospective data were collected from 495 patients, including FPG, HbA1c, RBC count, Haemoglobin concentration (Hb%), PCV, red cell indices such as MCV, MCH, MCHC. The FPG was estimated by Roche Cobas c702 (hexokinase method), HbA1c by HPLC (Tosoh G8), and RBC indices by electrical impedance (Sysmex XN-1000). The corresponding methodologies and reference ranges are shown in [Table/Fig-1] [12-16].

| Parameters | Method of estimation | Reference range (Cut-off) | References |
|---|---|---|---|
| Fasting Plasma Glucose (FPG) | Roche Cobas c702 analyser (Hexokinase method) | Normal: <100 mg/dL<br>IFG: 100-125 mg/dL<br>Diabetes: ≥126 mg/dL | [13] |
| HbA1c | High-Performance Liquid Chromatography (HPLC) - Tosoh G8 | Normal: <5.7%<br>Prediabetes: 5.7-6.4%<br>Diabetes: ≥6.5% | [13] |
| Haemoglobin (Hb) | Electrical impedance - Sysmex XN-1000 | 13-17 g/dL (males);<br>12-15 g/dL (females) | [12,14-16] |
| Packed Cell Volume (PCV) | Electrical impedance - Sysmex XN-1000 | 40-54% (males); 36-46% (females) | [12,14-16] |
| Mean Corpuscular Volume (MCV) | Electrical impedance - Sysmex XN-1000 | 80-100 fL | [12,14-16] |
| Mean Corpuscular Haemoglobin (MCH) | Electrical impedance - Sysmex XN-1000 | 27-33 pg | [12,14-16] |
| Mean Corpuscular Hb Concentration (MCHC) | Electrical impedance - Sysmex XN-1000 | 31-36 g/dL | [12,14-16] |
| Red Cell Distribution Width (RDW) | Electrical impedance - Sysmex XN-1000 | 11.5-14.5% | [12,14-16] |

**[Table/Fig-1]:** Methods of estimation of study parameters [12-16].

**Grouping of participants:** According to the American Diabetes Association, FPG levels of 70-100 mg/dL and an HbA1c value of less than 5.7% are considered normal. FPG levels of 101-125 mg/dL and an HbA1c range of 5.8-6.4% are considered pre-diabetic [17]. In the present study, subjects were divided into two groups based on their FPG-related HbA1c level. The concordance group included individuals with normal, pre-diabetic, and diabetic statuses (as determined by both FPG and HbA1c) at a specific time point. Patients who had discrepancies in their classifications were included in the discordant group. This cluster helped identify cases where HbA1c did not accurately reflect the status of blood glucose, potentially due to low MCV or MCH, which would prolong the lifespan of RBC and lead to falsely high HbA1c values [18].

## STATISTICAL ANALYSIS

Statistical analysis was done using IBM SPSS Statistics software, Version 20. Normality of the distribution was assessed by the Shapiro-Wilk test. Non-parametric variables were expressed as medians and interquartile ranges and were compared using the Mann-Whitney U test between concordant and discordant groups. The Spearman rho correlation test was used to assess the correlation between HbA1c and other variables. Statistical results with a p-value <0.05 were considered to be significant.

## RESULTS

The overall baseline study characteristics of concordant and discordant groups. Out of 495 patients, 285 were categorised in the concordant group and 210 in the discordant group. The discordant group had a higher median age than the concordant group. The study population had a mean age of 43.2±11.3 years. Hb levels were significantly lower in the discordant group [Table/Fig-2].

| Variables | Overall (n=495) | Concordant Group (n=285) | Discordant Group (n=210) | p-value |
|---|---|---|---|---|
| Age (in years) | 38 (29-46) | 40 (32-51) | 48 (40-57.5) | 0.001* |
| Male (%) | 319 (64.4%) | 196 (68.8%) | 123 (58.6%) | 0.023† |
| Female (%) | 176 (35.5%) | 89 (31.2%) | 87 (41.4%) | |
| Hb (g/dL) | 13.8 (12.3-15.1) | 13.6 (12.5-14.9) | 13.1 (11.6-14.3) | 0.001* |
| RBC Count ($10^6$/µL) | 4.8 (4.4-5.3) | 4.8 (4.4-5.2) | 4.7 (4.3-5.1) | 0.058 |
| PCV (%) | 42.9 (39.2-45.6) | 42.2 (39.3-45.7) | 40.5 (37.1-44.8) | 0.001* |
| HbA1c (%) | 5.5 (5.4-5.7) | 5.7 (5.4-5.9) | 6.0 (5.8-6.2) | 0.001* |
| Fasting Plasma Glucose (FPG) (mg/dL) | 93 (88-98) | 97 (90-105) | 97 (92-102) | 0.465 |
| MCV (fL) | 89 (85.6-90.9) | 88.9 (85.6-91.7) | 87.7 (83.5-91.2) | 0.011† |
| MCH (pg) | 28.7 (27.3-29.7) | 28.7 (27.4-29.8) | 28.1 (26.2-29.4) | 0.002* |
| MCHC (g/dL) | 32.1 (31.3-33.2) | 32.0 (31.3-33.1) | 31.8 (30.8-32.6) | 0.002* |
| ESR (mm/hr) | 10.5 (5.0-20.7) | 11 (5-21) | 15 (8-29) | 0.001* |
| RDW (CV%) | 13.5 (12.7-14.5) | 13.4 (12.7-14.3) | 13.7 (12.7-14.7) | 0.297 |

**[Table/Fig-2]:** Study characteristics of concordant and discordant groups.
*Significance at p-value <0.01; †Significance at p-value <0.05

[Table/Fig-3] shows RBC indices such as MCV and MCH were significantly lower in the female discordant group, whereas MCHC was considerably lower, especially in the male discordant group. These results highlight the importance of considering RBC indices in the interpretation of HbA1c. The discordant group also had higher ESR levels, and female participants generally had higher ESR values.

[Table/Fig-4] summarises the percentage of discordance observed among different $HbA_1C$ ranges. Here "high" represents higher $HbA_1C$ observed in the study participants yet their corresponding plasma glucose value is low and vice versa. Discordance was more frequently observed when HbA1c was in the range of 5.8-6.2% where HbA1c values were higher than expected for FPG. Discordance was also more prominent when HbA1c was between 5-5.7%, where HbA1c values were lower than expected for FPG.

[Table/Fig-5] describes a comparison of haemato-logical and biochemical parameters in two discordant groups: high HbA1c (5.8-6.2%) vs. low HbA1c (5-5.7%). Fasting glucose, HbA1c, HB, PCV, ESR, MCV, and MCH were significantly different, suggesting that red cell parameter disparities could play a role in the association between HbA1c and plasma glucose levels. Subjects with HbA1c

| Variables | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | Concordant (n=196) | Discordant (n=123) | p-value | Concordant (n=89) | Discordant (n=87) | p-value |
| Age (years) | 40 (32-50) | 48 (38 – 58) | 0.001* | 42 (29-53) | 48 (42-57) | 0.001* |
| Hb (g/dL) | 14.4 (13.6-15.4) | 14.1 (13.3-15.1) | 0.076 | 12.3 (11.3-12.8) | 11.6 (10.8-12.4) | 0.002* |
| RBC Count ($10^6$/µL) | 4.99 (4.6-5.4) | 4.99 (4.6-5.4) | 0.588 | 4.5 (4.2- 4.7) | 4.3 (4.0-4.7) | 0.359 |
| PCV (%) | 44.4 (41.4-47.1) | 44.0 (40.8-46.9) | 0.408 | 39.1 (36.6-40.8) | 37.2 (35.2-39.4) | 0.001* |
| HbA1c (%) | 5.7 (5.5-5.9) | 5.9 (5.8-6.2) | 0.001* | 5.6 (5.4-6.0) | 6.0 (5.9-6.2) | 0.001* |
| Fasting Plasma Glucose (FPG) (mg/dL) | 97 (91-105) | 99 (94-105) | 0.239 | 95 (88-105) | 95 (90-100) | 0.831 |
| MCV (fL) | 89 (86-92) | 89 (85-92) | 0.679 | 88 (84-91) | 86 (81-89) | 0.006* |
| MCH (pg) | 29.1 (28-30) | 28.9 (27.5-29.7) | 0.077 | 27.7 (26.3-28.7) | 26.8 (24.5-28.5) | 0.029† |
| MCHC (g/dL) | 32.5 (31.6-33.4) | 32.1 (31.5-33) | 0.015† | 31.4 (30.6-32.0) | 31.2 (30.1-32) | 0.240 |
| ESR (mm/hr) | 8 (4-15) | 10 (6-17) | 0.043† | 21 (12-31) | 27.5 (17-41) | 0.009* |
| RDW (CV%) | 13.2 (12.7-14.4) | 13.4 (12.6-14.5) | 0.465 | 13.9 (13.2-14.3) | 13.9 (12.8-15.3) | 0.560 |

**[Table/Fig-3]:** Comparison between concordant and discordant group in male and female participants.
Significance at p-value <0.01; †Significance at p-value <0.05

| HbA1c (%) | Discordant (High/Low, Total %) |
|---|---|
| <5 | 0/3 (3, 1.4%) |
| 5-5.7 | 4/28 (32, 15.2%) |
| 5.8-6.4 | 144/15 (159, 75.7%) |
| ≥6.5 | 14/2 (16, 7.6%) |

**[Table/Fig-4]:** Discordance % among different HbA1c ranges

| Variables | Discordant group | | p-value |
|---|---|---|---|
| | Showing high HbA1c (5.8-6.4%) n=144 | Showing low HbA1c (5-5.7%) n=28 | |
| Fasting Plasma Glucose (FPG) (mg/dL) | 94 | 105 | 0.001* |
| HbA1c (%) | 6.0 | 5.5 | 0.001* |
| Hb (g/dL) | 12.6 | 14.1 | 0.001* |
| RBC Count ($10^6$/µL) | 4.7 | 4.9 | 0.062 |
| PCV (%) | 40.3 | 44.9 | 0.001* |
| ESR (mm/hr) | 16 | 10 | 0.016† |
| MCV (fL) | 87 | 90 | 0.001* |
| MCH (pg) | 27.8 | 29.0 | 0.002* |
| MCHC (g/dL) | 31.7 | 32.0 | 0.050 |

**[Table/Fig-5]:** Comparison of discordant high and low HbA1c groups.
*Significance at p-value <0.01, †Significance at p-value <0.05

<5% (n=3) and ≥6.5% (n=16) were very few; hence, subgroup analysis was not performed for these categories.

[Table/Fig-6] shows correlation analysis revealed a significant negative relationship between Hb, PCV, MCV, MCH, MCHC, and HbA1c, indicating that abnormal RBC indices, which are suggestive of IDA, can cause spurious HbA1c results. Out of 210 participants, 96 had IDA.

| Parameters | r-value | p-value |
|---|---|---|
| Hb | -0.160 | 0.001* |
| RBC count | -0.037 | 0.414 |
| PCV | - 0.127 | 0.005* |
| MCV | -0.203 | 0.001* |
| MCH | -0.222 | 0.001* |
| MCHC | -0.161 | 0.001* |
| RDW | -0.049 | 0.548 |
| ESR | -0.167 | 0.016 |

**[Table/Fig-6]:** Correlation of RBC indices with HbA1c in the discordant group (n=210).
r- correlation coefficient, *Significance at p-value <0.01

Analysis of RBC indices in males for predicting HbA1c-glucose discordance is shown in [Table/Fig-7]. The majority of the parameters, including Hb, PCV, MCV, and MCH, had AUC values approaching 0.5 with non-significant p-values indicative of poor discriminatory performance. Among them, only MCHC was statistically significant, although with a weak predictive power (AUC 0.581, p=0.015), and moderate sensitivity (57%) and specificity (60%).

| Test variables | AUC | Confidence interval | p-value | Cut-off value‡ | Sensitivity % | Specificity % |
|---|---|---|---|---|---|---|
| Hb | 0.559 | 0.494-0.624 | 0.076 | 14.8 | 70 | 37 |
| PCV | 0.528 | 0.463-0.593 | 0.408 | 45 | 60 | 44 |
| MCV | 0.514 | 0.448-0.580 | 0.679 | 88.7 | 50 | 56 |
| MCH | 0.559 | 0.494-0.624 | 0.077 | 28.8 | 50 | 59 |
| MCHC | 0.581 | 0.517-0.644 | 0.015† | 32.1 | 57 | 60 |

**[Table/Fig-7]:** ROC analysis of the test variables (male).
(AUC: Area under the curve), †Significance at p-value <0.05, ‡cut-off value below which HbA1c values are not reliable

[Table/Fig-8] shows Hb, PCV and MCV had statistically significant discriminatory ability (AUC 0.62-0.64, p<0.01) with moderate sensitivity (63-64%)/specificity (60%). MCH was a weaker but significant predictor (AUC=0.595, P=0.029). MCHC was not significant (p=0.240) and therefore had small or no diagnostic value in this subgroup.

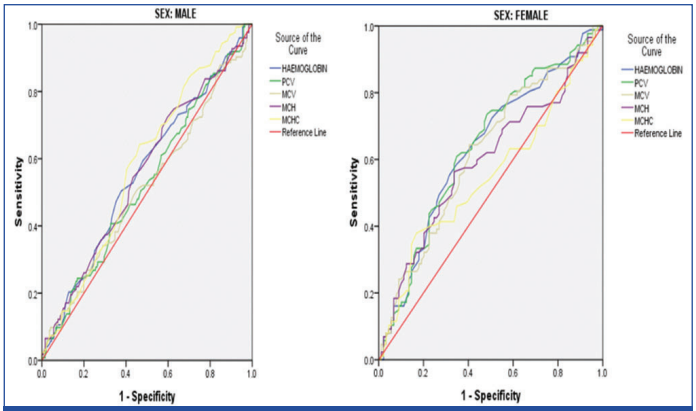
| Variables | AUC | Confidence interval | p-value | Cut-off value‡ | Sensitivity % | Specificity % |
|---|---|---|---|---|---|---|
| Hb | 0.633 | 0.550-0.715 | 0.002* | 12.05 | 63 | 60 |
| PCV | 0.639 | 0.557-0.722 | 0.001* | 38.0 | 63 | 60 |
| MCV | 0.620 | 0.537-0.702 | 0.006* | 87 | 64 | 60 |
| MCH | 0.595 | 0.511-0.680 | 0.029† | 27.2 | 58 | 62 |
| MCHC | 0.551 | 0.465-0.637 | 0.240 | 31.0 | 46 | 65 |

**[Table/Fig-8]:** ROC analysis of the test variables (Female).
(AUC: Area under the curve), *Significance at p-value <0.01, †Significance at p-value <0.05, ‡cut-off value below which HbA1c values are not reliable

[Table/Fig-9] shows ROC analysis, indicating that in males, AUC values of Hb, PCV, MCV, MCH, and MCHC were near and above the reference line and had low discriminatory capacity, while in females, Hb, PCV, and MCV showed reasonable discrimination (AUC ~0.62-0.64), MCH provided less but satisfactory discrimination, and MCHC was non-significant.

## DISCUSSION

The analysis of RBC indices and their impact on HbA1c levels in diabetic patients reveals critical insights into the complexities of glycaemic control metrics. This study focused on two distinct groups: concordant and discordant, to evaluate how varying RBC indices influence HbA1c levels. The findings underscore the importance of




**[Table/Fig-9]:** ROC analysis of test variables.

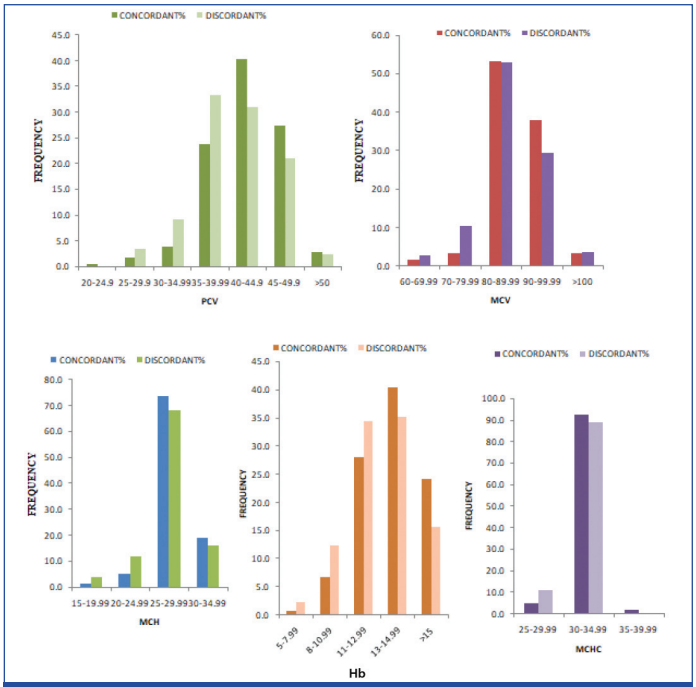
considering RBC parameters when interpreting HbA1c, particularly in populations with altered Hb levels.

In the concordance group, HbA1c and fasting glucose concentrations tended to agree across normal RBC indices, particularly in the range of 5.0-5.7%, with minimal effect on concordance in relation to RBC indices. Nevertheless, the association of HbA1c with fasting glucose was weak and without clinical value. Attention instead is focused on the discordant group in which differences in RBC indices are significantly related to HbA1c. The results indicate that the discordant group exhibited statistically significantly lower Hb% and PCV. The discordant group had a higher median HbA1c, suggesting that even with comparable FPG values between the two groups, more precise interpretations are needed for HbA1c when RBC indices are abnormal. Further examination of RBC indices revealed significant differences between groups. The discordant group demonstrated consistently lower MCV and MCH, particularly within female participants. All these laboratory findings with decreased Hb%, PCV, MCV, and MCH are classic indicators of microcytic hypochromic anaemia, which may lead to spurious elevations in HbA1c levels. These findings also align with the previous studies done in healthy controls and pre-diabetic patients with IDA [19-22].

In the present study, discordance was most notable in specific ranges, specifically between 5.8% and 6.4%, in which elevated HbA1c levels were unexpected based on the FPG results. This finding is supported by a similar study where the preponderance for this mismatch is higher in healthy controls and pre-diabetic patients [23]. This discordance suggests that the diagnostic threshold for HbA1c should consider the status of RBC indices, particularly for patients who exhibit features of anaemia [24]. Elevated HbA1c levels in such ranges may cause misdiagnosis or inappropriate initiation in therapy and potentially lead to suboptimal management of diabetes.

The correlation analysis reinforced this notion, revealing a significant negative relationship between HbA1c values and various RBC parameters [Table/Fig-10]. This inverse relationship is evidenced in a study done by Koga M et al., where a one-page decrease in MCH can increase HbA1c by 0.03% [25]. Although the exact mechanism is not precise, researchers hypothesise that the increased HbA1c levels, especially in IDA, are due to the prolonged survival time of erythrocytes. This delay in RBC turnover can expose the globin chains in RBCs to glycation for a longer period. Also, the changes in the quaternary structure of globin chains due to iron deficiency may increase the glycation rate [26,27].

Hence, anaemia with altered RBC indices can hinder the accuracy of HbA1c as a test for long-term glycemic control and can complicate diabetes management strategies. Specifically, the presence of microcytic anaemia, as commonly observed in iron deficiency states, can lead to a misinterpretation of glycaemic status, emphasising the need to generate cut-off values for these indices to guide clinicians in deciding on a treatment plan. Minimal studies have derived the cut-off value for RBC indices for the reliable interpretation of HbA1c [28].




**[Table/Fig-10]:** Distribution of concordance - discordance ratio at different ranges of the RBC indices.

The Receiver Operating Characteristic (ROC) curve analysis provided additional clarity on the diagnostic utility of lower RBC indices [Table/Fig-9]. The results for males indicated only moderate diagnostic ability, underscoring gender differences in RBC indices and their implications for the interpretation of HbA1c [Table/Fig-8]. Conversely, in females, the ROC outcomes showed promising sensitivity and specificity, indicating that clinicians could reliably utilise these values, which were within the lower limit of reference ranges for predictive purposes regarding HbA1c variability [Table/Fig-9]. This observation is critical as it suggests that therapeutic approaches could differ based on gender, necessitating personalised strategies for diabetes care.

## Limitation(s)

The participants in the present study were limited to normal and pre-diabetic patients and did not include patients already diagnosed with diabetes. Furthermore, study participants were categorized into concordant and discordant groups based on their FPG and glycated Hb values, without including postprandial glucose values. As the current study focuses only on RBC indices affected by different types of anaemia, other assay interferences in HbA1c measurement, such as those due to drugs, were not ruled out.

# CONCLUSION(S)

In conclusion, the present study validates the importance of considering RBC indices, along with their derived cut-offs, in interpreting HbA1c levels in pre-diabetic patients, especially in females. Clinicians should prioritise plasma glucose measurements when RBC indices exhibit abnormalities since relying solely on HbA1c could misguide treatment decisions. Adopting a comprehensive assessment approach, which includes HbA1c and RBC indices, is essential for optimising Diabetes management.

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