

Age-Related Associations Between Red Blood Cell Indices and Hemoglobin A1c in Pediatric and Adult Patients: A Retrospective Study

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Objective: Hemoglobin A1c (HbA1c) is the primary laboratory marker for assessing long-term glycemic status, but its interpretation may be influenced by erythrocyte physiology. This study evaluated the association between routinely reported red blood cell (RBC) indices and HbA1c in pediatric and adult diabetic and non-diabetic patients.

Methods: A retrospective observational study was conducted using electronic medical record and laboratory information system data from the University of Texas Medical Branch between 2010 and 2025. The pediatric cohort included 565 encounters, and the adult cohort included 14,790 encounters. Hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW) were evaluated using correlation, group comparison, and multivariable regression analyses.

Results: Significant associations between HbA1c and multiple RBC indices were identified in both pediatric and adult populations, although the pattern of associations differed by age. Pediatric patients demonstrated predominantly hemoglobin-related associations, whereas adult patients showed stronger relationships involving erythrocyte morphology. Adult diabetic patients also demonstrated significant differences in several RBC indices compared with matched non-diabetic controls. However, glycemic control was not independently associated with the overall presence of abnormal RBC indices after multivariable adjustment.

Conclusion: Routine CBC-derived RBC indices demonstrated age-related associations with HbA1c across pediatric and adult populations. Although these indices should not be considered independent markers of diabetes or glycemic control, they may provide additional laboratory context when interpreting HbA1c results.

Keywords: Glycated Hemoglobin; Erythrocyte Indices; Diabetes Mellitus; Age Factors; Retrospective Studies.

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Introduction

Hemoglobin A1c (HbA1c) is the primary laboratory marker for assessing long-term glycemic status and plays a central role in the diagnosis and management of diabetes mellitus. Because HbA1c reflects the nonenzymatic glycation of hemoglobin throughout the lifespan of circulating erythrocytes, its interpretation depends not only on glucose exposure but also on red blood cell (RBC) physiology, lifespan, and turnover.¹⁻⁴

Conditions that alter erythrocyte survival or morphology may therefore influence HbA1c independent of true glycemic status, potentially affecting clinical interpretation.²⁻⁴ Growing evidence suggests that chronic hyperglycemia is associated with oxidative stress, membrane glycation, altered erythrocyte deformability, and inflammatory changes that may affect routinely reported CBC-derived RBC indices, including hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW).⁵⁻⁹ Because these parameters are generated as part of routine complete blood count testing, they have attracted increasing interest as potential adjunctive markers that may provide additional context for HbA1c interpretation without requiring additional laboratory testing.^{5,6}

Previous studies have reported associations between individual RBC indices and diabetes or HbA1c, particularly involving RDW, MCV, and MCH.^{5,7-9} However, published findings remain inconsistent with respect to the magnitude and direction of these relationships, likely reflecting differences in study populations, diabetes subtype, disease duration, and underlying hematologic variability. In addition, many investigations have focused exclusively on either pediatric or adult populations or evaluated isolated RBC parameters rather than broader hematologic patterns, limiting direct comparison across age groups.^{5,8,10} Because erythrocyte physiology differs throughout the lifespan, the relationship between HbA1c and

RBC indices may also differ between pediatric and adult patients. Clarifying these age-related patterns may improve understanding of the biologic factors influencing HbA1c interpretation and provide additional insight into routinely available hematologic parameters encountered in clinical laboratory practice. The objective of this study was to evaluate the association between routinely reported RBC indices and HbA1c in pediatric and adult diabetic and non-diabetic patients using a large retrospective cohort from an academic health system. We further sought to determine whether these associations differed between age groups and to assess the potential interpretive value of CBC-derived RBC indices in the evaluation of HbA1c.

Materials and Methods

Study Design and Setting

A retrospective observational study was conducted using electronic medical record (Epic) and laboratory information system (LIS) data from the University of Texas Medical Branch (UTMB), an academic health system serving Southeast Texas. Clinical encounters between January 1, 2010, and December 31, 2025, were eligible for inclusion if a complete blood count (CBC) and hemoglobin A1c (HbA1c) were performed on the same day. The unit of analysis was the clinical encounter to preserve temporal alignment between hematologic and glycemic measurements. Pediatric (≤ 18 years) and adult (>18 years) cohorts were analyzed separately because of known physiologic differences in erythrocyte parameters.

Data Collection

Following Institutional Review Board (IRB) approval (26-0066.002), clinical and laboratory data were collected from the Epic electronic medical record and laboratory information system (LIS). Laboratory variables included complete blood count (CBC) parameters consisting of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and hemoglobin A1c

(HbA1c). Demographic and clinical variables, including age, biological sex, body mass index (BMI), and diabetes status, were also collected. CBC and HbA1c results obtained during the same clinical encounter were paired to ensure temporal alignment between hematologic and glycemic parameters.

Study Population

Diabetic encounters were identified using ICD-10 codes for type 1 diabetes (E10.x), type 2 diabetes (E11.x), and other specified diabetes mellitus (E13.x). Encounters without diabetes-related ICD-10 codes served as non-diabetic controls. Adult diabetic and non-diabetic encounters were age- and sex-matched using a randomly selected sample, whereas all eligible pediatric encounters were included because of the smaller available cohort. Among pediatric diabetic encounters, 206 (72.0%) were classified as type 1 diabetes, whereas among adult diabetic encounters, 5,698 (77.0%) were classified as type 2 diabetes. Encounters associated with conditions known to affect erythrocyte physiology or HbA1c interpretation were excluded, including hemoglobinopathies, iron deficiency, vitamin B12 deficiency, folate deficiency, hemolytic anemia, bone marrow disorders, hematologic malignancies, chronic kidney disease, chronic liver disease, pregnancy or the postpartum period, blood transfusion within the preceding 3 months, active infection or inflammation, ICU encounters, and hemolyzed, incomplete, or otherwise invalid laboratory results.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 28 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables are presented as frequencies and percentages.

Among pediatric diabetic encounters, Spearman rank correlation was used to evaluate associations between HbA1c and individual RBC indices. Separate multivariable linear regression models were then performed to evaluate the association of each RBC index

with HbA1c after adjustment for age, biological sex, and BMI. Regression analyses were performed using complete-case analysis; encounters with missing values for variables included in a given model were excluded from that analysis.

Differences between pediatric diabetic and non-diabetic groups were evaluated using independent-samples *t*-tests.

Adult diabetic encounters were stratified according to HbA1c <7% or $\geq$ 7%. Differences in the prevalence of abnormal RBC indices between glycemic control groups were assessed using χ^2 tests, and multivariable logistic regression was performed to evaluate factors associated with the presence of at least one abnormal RBC index after adjustment for age, BMI, biological sex, and race. Abnormal RBC indices were classified using the institutional adult reference intervals in effect at the University of Texas Medical Branch during the study period. Hemoglobin and hematocrit abnormalities were determined using sex-specific reference intervals. An encounter was classified as having an abnormal RBC index if at least one evaluated RBC parameter fell below or above its corresponding reference interval. Adult reference intervals were as follows: hemoglobin, 14.0-17.5 g/dL (male) and 12.3-15.3 g/dL (female); hematocrit, 41.5-50.4% (male) and 35.9-44.6% (female); MCV, 80.0-96.1 fL; MCH, 27.5-33.2 pg; MCHC, 33.4-35.5 g/dL; and RDW, 11.6-14.6%.

Adult diabetic and non-diabetic groups were compared using independent-samples *t* tests for continuous variables and χ^2 tests for categorical variables. Additional Spearman correlation analyses evaluated associations between HbA1c and RBC indices within each group. Statistical significance was defined as a two-sided $p < .05$.

Ethics

The study was approved by the University of Texas Medical Branch Institutional Review Board (IRB No. 26-0066.002), which granted a waiver of informed consent because of the retrospective design and minimal risk to

participants. All data were de-identified before analysis. The study was conducted in accordance with applicable institutional and federal requirements for human-subject research and the Health Insurance Portability and Accountability Act (HIPAA).

Results

Study Population

A total of 15,355 clinical encounters met the study eligibility criteria, including 565 pediatric encounters (286 diabetic and 279 non-diabetic) and 14,790 adult encounters (7,399 diabetic and 7,391 non-diabetic). All encounters included same-day complete blood count (CBC) and hemoglobin A1c (HbA1c) measurements following application of the predefined inclusion and exclusion criteria (Figure 1).

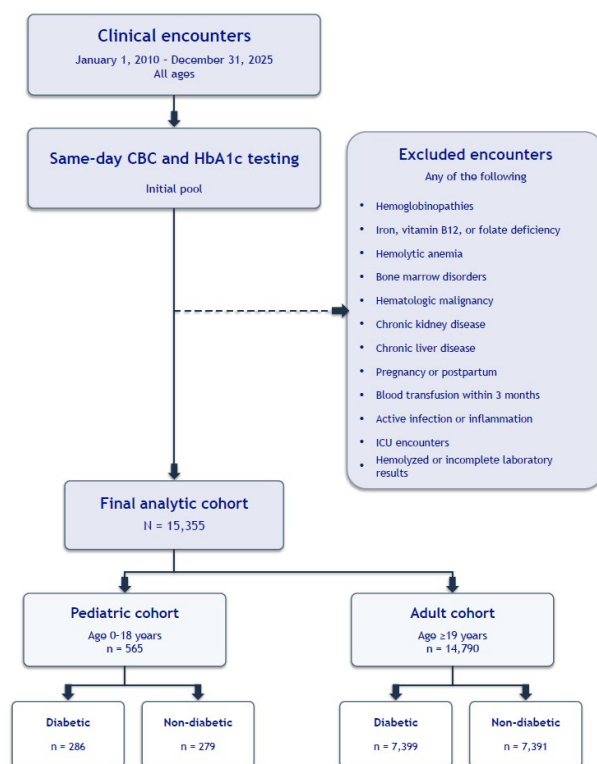


Figure 1. Study selection flow diagram.

Abbreviations: CBC, complete blood count; HbA1c, hemoglobin A1c; ICU, intensive care unit.

Baseline demographic and clinical characteristics are presented in Table 1. Pediatric diabetic and non-diabetic groups were matched on age and sex, with no significant differences in mean age, sex distribution,

race, or body mass index (BMI). In contrast, while adult diabetic and non-diabetic groups were also matched on age and sex, diabetic adults had a significantly higher mean BMI and differed in racial distribution compared with non-diabetic adults ($p < .001$ for both). As expected, mean HbA1c was significantly higher in diabetic than non-diabetic patients in both pediatric and adult cohorts (Table 1).

Pediatric diabetes consisted predominantly of type 1 diabetes (206/286, 72.0%), whereas the adult diabetic cohort was primarily composed of patients with type 2 diabetes (5,698/7,399, 77.0%).

Compared with non-diabetic pediatric patients, diabetic pediatric patients demonstrated significantly higher Hgb, Hct, and MCHC values and significantly lower MCV, whereas MCH and RDW did not differ significantly (Table 2).

Among diabetic pediatric patients, HbA1c demonstrated the strongest positive correlation with Hgb ($p = 0.379$, $p < .001$), followed by Hct ($p = 0.295$, $p < .001$) and MCHC ($p = 0.267$, $p < .001$). MCH showed a weak positive correlation with HbA1c ($p = 0.138$, $p = .020$), whereas no significant correlations were observed for MCV or RDW (Table 2).

In multivariable linear regression adjusting for age, sex, and BMI, Hgb remained the strongest independently associated parameter with HbA1c (standardized $B = 0.375$, $p < .001$), followed by Hct ($B = 0.307$, $p < .001$) and MCHC ($B = 0.184$, $p = .002$). RDW demonstrated a small positive independent association with HbA1c ($B = 0.175$, $p = .003$), whereas MCV and MCH were not independently associated with HbA1c.

Compared with non-diabetic adults, diabetic patients demonstrated significantly lower Hgb, Hct, MCV, and MCH values and significantly higher RDW, whereas MCHC did not differ significantly between groups (Table 3).

Among diabetic adults, HbA1c demonstrated the strongest inverse correlation with MCV ($p = -0.250$, $p < .001$), followed by MCH ($p = -0.186$, $p < .001$). Weak positive correlations were observed for Hgb ($p = 0.121$, $p < .001$),

Table 1. Baseline Characteristics of the Study Population.

Pediatric Cohort			
Characteristic	Diabetic (n = 286)	Non-Diabetic (n = 279)	p -Value
Age, years	13.17 ± 4.00	13.24 ± 3.96	0.846
Male, n (%)	139 (48.6)	134 (48.0)	-
Female, n (%)	147 (51.4)	145 (52.0)	
White, n (%)	202 (70.6)	220 (78.9)	
Black, n (%)	75 (26.2)	53 (19.0)	0.078
Other race, n (%)†	9 (3.2)	6 (2.2)	
BMI, kg/m ²	27.40 ± 10.54	27.68 ± 7.44	0.725
HbA1c, %	9.26 ± 2.40	5.42 ± 0.43	<.001
Adult Cohort			
Characteristic	Diabetic (n = 7,399)	Non-Diabetic (n = 7,391)	p -Value
Age, years	58.48 ± 14.59	58.55 ± 14.55	0.785
Male, n (%)	3,757 (50.8)	3,746 (50.7)	-
Female, n (%)	3,642 (49.2)	3,645 (49.3)	
White, n (%)	5,891 (79.6)	6,092 (82.4)	
Black, n (%)	1,192 (16.1)	883 (11.9)	<.001
Other race, n (%)†	316 (4.3)	416 (5.6)	
BMI, kg/m ²	33.89 ± 8.45	31.06 ± 7.67	<.001
HbA1c, %	8.43 ± 2.17	5.52 ± 0.39	<.001

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

†Other race includes Asian, American Indian/Alaska Native, Native Hawaiian/Other Pacific Islander (adults only), multiracial/unknown, and other infrequently represented racial categories.

Table 2. Comparison of Red Blood Cell Indices Between Pediatric Diabetic and Non-Diabetic Patients and Their Association with HbA1c.

RBC Index	Diabetic (n = 286) Mean ± SD	Non-Diabetic (n = 279) Mean ± SD	p -Value†	Spearman's ρ‡	p -Value
Hemoglobin (g/dL)	14.30 ± 1.80	13.57 ± 1.46	<.001	0.379	<.001
Hematocrit (%)	42.37 ± 5.05	41.01 ± 3.86	<.001	0.295	<.001
Mean corpuscular volume (fL)	83.29 ± 5.03	84.43 ± 5.48	0.010	-0.020	0.732
Mean corpuscular hemoglobin (pg)	28.07 ± 2.20	27.94 ± 2.19	0.472	0.138	0.020
Mean corpuscular hemoglobin concentration (g/dL)	33.70 ± 1.60	33.07 ± 1.23	<.001	0.267	<.001
Red cell distribution width (%)	13.06 ± 1.16	13.03 ± 1.15	0.768	0.060	0.309

Abbreviations: HbA1c, hemoglobin A1c. SD, standard deviation.

† p-values comparing diabetic and non-diabetic pediatric patients were calculated using the independent-samples t-test.

‡ Spearman rank correlation coefficients represent the association between HbA1c and RBC indices among pediatric diabetic patients.

Table 3. Comparison of Red Blood Cell Indices Between Adult Diabetic and Non-Diabetic Patients and Their Association with HbA1c.

RBC Index	Diabetic (n = 7,399) Mean ± SD	Non- Diabetic (n = 7,391) Mean ± SD	p- Value†	Spearman's ρ (Diabetic)‡	p- Value	Spearman's ρ (Non- Diabetic) ‡	p- Value
Hemoglobin (g/dL)	13.59 ± 1.92	13.66 ± 1.86	0.026	0.121	<.001	-0.052	<.001
Hematocrit (%)	41.09 ± 5.32	41.26 ± 5.18	0.039	0.105	<.001	-0.017	0.148
Mean corpuscular volume (fL)	88.58 ± 5.73	90.22 ± 5.49	<.001	-0.250	<.001	-0.178	<.001
Mean corpuscular hemoglobin (pg)	29.30 ± 2.33	29.86 ± 2.26	<.001	-0.186	<.001	-0.213	<.001
Mean corpuscular hemoglobin concentration (g/dL)	33.06 ± 1.40	33.08 ± 1.28	0.343	0.106	<.001	-0.112	<.001
Red cell distribution width (%)	13.51 ± 1.51	13.45 ± 1.50	<.001	-0.115	<.001	0.229	<.001

Abbreviations: HbA1c, hemoglobin A1c; SD, standard deviation.

† p-values comparing diabetic and non-diabetic adult patients were calculated using the independent-samples t-test.

‡ Spearman's rank correlation coefficients (ρ) represent the association between HbA1c and each RBC index within diabetic and non-diabetic adult cohorts separately.

Hct ($p = 0.105$, $p < .001$), and MCHC ($p = 0.106$, $p < .001$), whereas RDW demonstrated a weak inverse correlation with HbA1c ($p = -0.115$, $p < .001$). Among non-diabetic adults, HbA1c demonstrated weak inverse correlations with MCV ($p = -0.178$, $p < .001$), MCH ($p = -0.213$, $p < .001$), and MCHC ($p = -0.112$, $p < .001$), whereas RDW demonstrated a weak positive correlation ($p = 0.229$, $p < .001$). No significant correlation was observed between HbA1c and Hct ($p = -0.017$, $p = .148$), while the inverse correlation with Hgb was statistically significant but very weak ($p = -0.052$, $p < .001$). These findings suggest that the relationships between HbA1c and RBC indices differ according to diabetic status (Table 3). Among adult diabetic patients, the prevalence of at least one abnormal RBC index did not

differ significantly between those with controlled and uncontrolled glycemia (51.1% versus 50.6%, respectively; $p = .650$). Patients with uncontrolled glycemia had a higher prevalence of abnormal Hct than those with controlled glycemia (29.2% versus 27.1%, $p = .040$). In contrast, abnormal MCHC (22.5% versus 18.8%, $p < .001$) and RDW (20.7% versus 14.8%, $p < .001$) were more prevalent among patients with controlled glycemia. No significant differences were observed for abnormal Hgb, MCH, or MCV.

In multivariable logistic regression adjusting for age, BMI, sex, and race, glycemic control was not independently associated with the presence of at least one abnormal RBC index (OR 1.07, 95% CI 0.97-1.18, $p = .161$). Increasing age, higher BMI, male sex, and Black

race remained independently associated with abnormal RBC indices.

Discussion

Principal Findings

Significant associations were identified between HbA1c and multiple routinely reported RBC indices across both pediatric and adult populations. However, the pattern of these associations differed by age. Pediatric patients demonstrated predominantly hemoglobin-related associations, with Hgb, Hct, and MCHC showing the strongest relationships with HbA1c, whereas adult patients demonstrated stronger associations involving erythrocyte morphology, particularly MCV, MCH, and RDW. These findings extend previous evidence that erythrocyte characteristics influence HbA1c interpretation and support the concept that the relationship between HbA1c and erythrocyte physiology varies across different stages of life.¹⁻⁴

Although many of the observed differences were statistically significant, most were modest in magnitude and remained within their respective reference intervals. Accordingly, these RBC indices should not be interpreted as independent diagnostic markers of diabetes or glycemic control. Rather, they may serve as complementary laboratory parameters that provide additional context when interpreting HbA1c, particularly when HbA1c appears discordant with the clinical presentation or other measures of glycemia.^{1-3,6} Furthermore, these findings reinforce the importance of integrating routinely available hematologic parameters into the broader interpretation of laboratory results rather than evaluating HbA1c in isolation.⁶

Pediatric Findings

The pediatric cohort demonstrated a distinct pattern in which HbA1c was most strongly associated with hemoglobin-related parameters. Hgb, Hct, and MCHC were significantly higher in diabetic than non-diabetic patients and remained independently associated with HbA1c after adjustment for age, sex, and BMI.

In contrast, MCV and RDW were not independently associated with HbA1c. This pattern differs from that observed in many adult studies, in which alterations in erythrocyte morphology, particularly MCV and RDW, have shown stronger associations with glycemic status.^{5,8,14}

One plausible explanation is the predominance of type 1 diabetes within the pediatric cohort. Children with newly diagnosed or poorly controlled type 1 diabetes frequently present with marked hyperglycemia accompanied by osmotic diuresis, resulting in relative intravascular volume depletion before treatment. This physiologic response may contribute to the higher Hgb and Hct values observed in our study. However, hydration status, timing relative to diabetes diagnosis, and disease duration were not available in this retrospective dataset, so this proposed mechanism could not be directly evaluated. Tihic-Kapidzic et al. likewise reported significant differences in hematologic indices between children with type 1 diabetes and healthy controls, supporting the concept that diabetes-related hematologic alterations are detectable early in the disease course.¹⁰ In addition, Herance et al. demonstrated that type 1 diabetes is associated with metabolic and lipidomic alterations in erythrocytes, providing further evidence that hyperglycemia may influence erythrocyte physiology beyond glucose metabolism alone.¹²

Interestingly, MCV and RDW were not independently associated with HbA1c after adjustment, suggesting that structural alterations in erythrocytes may be less pronounced during pediatric diabetes than in adulthood. This may reflect shorter disease duration and reduced cumulative exposure to chronic hyperglycemia compared with adult populations. Similar observations have been reported by Salami et al., who demonstrated associations between RBC-related parameters and declining β -cell function in children at risk for type 1 diabetes, suggesting that hematologic alterations occur early but may differ from those observed in established adult

diabetes.¹³ Collectively, these findings suggest that the hematologic response to diabetes evolves over time and emphasize the importance of considering patient age when interpreting relationships between HbA1c and routine RBC indices.

Adult Findings

In contrast to the pediatric cohort, adult patients demonstrated a pattern characterized predominantly by alterations in erythrocyte morphology. Diabetic adults had significantly lower MCV and MCH values and higher RDW compared with non-diabetic adults, with MCV demonstrating the strongest inverse association with HbA1c. These findings are consistent with those reported by Alamri et al., who observed significantly lower MCV and MCH among adults with diabetes, and by Asmamaw et al., who demonstrated significant associations between multiple RBC indices and long-term glycemic control.^{5,8} More recently, Meshesha et al. further reported that several RBC indices were associated with glycemic control and diabetes-related complications, supporting the growing evidence that chronic hyperglycemia is accompanied by measurable alterations in erythrocyte morphology.¹³

Several biologic mechanisms may explain these findings. Chronic hyperglycemia promotes nonenzymatic glycation of erythrocyte membrane proteins, increases oxidative stress, and contributes to chronic low-grade inflammation, all of which impair membrane stability, reduce erythrocyte deformability, and alter erythrocyte survival.^{3,9,14,15} Alterations in erythrocyte lifespan may further influence both RBC indices and HbA1c interpretation, as demonstrated by Cohen et al. and Xu et al., who highlighted the importance of erythrocyte turnover in determining HbA1c values independent of glucose concentration.^{2,4} The persistence of the observed associations following multivariable adjustment in the present study further supports the relationship between chronic glycemic exposure and erythrocyte morphology.

An additional finding of interest was the differing relationship between RDW and HbA1c

according to diabetic status. Although RDW was significantly higher in diabetic than non-diabetic adults overall, HbA1c demonstrated a weak inverse correlation with RDW within the diabetic cohort, whereas a positive correlation was observed among non-diabetic adults. This finding differs from several previous studies reporting positive associations between RDW and glycemic measures.^{7,9} One possible explanation is the rigorous exclusion criteria applied in the present study. By excluding patients with iron deficiency, chronic kidney disease, active inflammation, malignancy, hemoglobinopathies, and other conditions known to independently influence RDW, the present analysis may have reduced important sources of confounding that contributed to the positive associations reported previously. Nevertheless, the underlying mechanisms remain uncertain and warrant prospective investigation incorporating biomarkers of iron metabolism, inflammation, reticulocyte production, and erythrocyte lifespan.

Age-Related Differences in RBC-HbA1c Associations

A major finding of this study was the identification of distinct age-related patterns in the relationship between HbA1c and routinely reported RBC indices. In pediatric patients, HbA1c was most strongly associated with hemoglobin-related parameters, whereas in adults, the strongest associations involved erythrocyte morphology, particularly MCV, MCH, and RDW. Previous studies have largely evaluated pediatric or adult populations independently, making direct comparisons across age groups difficult.^{5,8,10,11,13} By evaluating both cohorts using the same study design, laboratory parameters, and analytical approach, the present study provides a more comprehensive assessment of how the relationship between HbA1c and RBC indices differs across the lifespan.

Several factors may contribute to these age-related differences. The predominance of type 1 diabetes in the pediatric cohort and type 2 diabetes in the adult cohort likely

reflects differences in disease pathophysiology, duration of hyperglycemia, and cumulative metabolic exposure. Adults generally experience longer exposure to chronic hyperglycemia, oxidative stress, and inflammation, all of which contribute to progressive erythrocyte membrane damage and altered cell survival.^{3,4,14,15} In contrast, pediatric patients may exhibit earlier physiologic responses to hyperglycemia before substantial structural remodeling of erythrocytes has occurred. These age-related differences may explain why hemoglobin-related parameters predominated in the pediatric cohort, whereas morphology-related indices were more strongly associated with HbA1c in adults.

Our findings also provide a possible explanation for the variability reported across previous studies evaluating RBC indices in diabetes. Differences in patient age, diabetes type, disease duration, study populations, and exclusion criteria may contribute to the inconsistent associations reported between HbA1c and individual RBC indices. By examining both pediatric and adult cohorts within a single analytical framework while applying rigorous exclusion criteria to minimize hematologic confounders, the present study demonstrates that the relationship between HbA1c and erythrocyte indices is not uniform but varies according to patient characteristics and disease context. These findings underscore the importance of considering age when interpreting the interaction between erythrocyte physiology and HbA1c.

Clinical Significance

The findings of this study should be interpreted within the context of routine clinical laboratory practice. Although several RBC indices differed significantly between diabetic and non-diabetic patients and demonstrated significant associations with HbA1c, most of these differences were modest in magnitude and remained within established reference intervals. Consequently, these parameters should not be considered independent diagnostic markers of diabetes or replacements for

HbA1c. Rather, they should be viewed as complementary laboratory findings that may provide additional context during interpretation of HbA1c results.^{1,3,6}

These findings are particularly relevant when HbA1c appears discordant with the clinical presentation or other measures of glycemia. Current laboratory guidelines emphasize that HbA1c reflects not only glycemic exposure but also erythrocyte biology, including factors affecting erythrocyte lifespan and turnover.¹⁻⁴ Routine CBC parameters are inexpensive, widely available, and already incorporated into standard clinical practice. While they should not be used in isolation to guide diabetes diagnosis or management, awareness of age-related hematologic patterns may assist laboratorians and clinicians in recognizing situations in which erythrocyte physiology could influence HbA1c interpretation.

Strengths and Limitations

This study has several strengths. It included a large cohort of more than 15,000 pediatric and adult clinical encounters evaluated over a 16-year period using standardized laboratory measurements performed within a single health system. The inclusion of both pediatric and adult populations allowed direct comparison of age-related patterns using a common analytical framework, an approach that has been infrequently reported in the literature. In addition, rigorous exclusion criteria were applied to minimize the influence of conditions known to affect RBC indices or HbA1c interpretation, thereby reducing potential confounding and strengthening the validity of the observed associations.

Several limitations should also be acknowledged. First, the retrospective observational design permits identification of associations but does not establish causality. Second, analyses were performed at the encounter level rather than the patient level; therefore, repeated encounters from the same individual may not have been fully accounted for. Third, important variables that may influence erythrocyte physiology, including

disease duration, diabetes treatment, iron status, reticulocyte count, and direct measures of erythrocyte lifespan, were unavailable. Although extensive exclusion criteria were implemented to reduce confounding, residual confounding from unmeasured factors remains possible. Finally, many of the observed associations, while statistically significant, were modest in magnitude, and most RBC indices remained within their respective reference intervals. Consequently, these findings should be interpreted as complementary to existing approaches for HbA1c interpretation rather than as evidence supporting the independent clinical use of RBC indices.

Conclusion

In conclusion, significant associations were observed between HbA1c and multiple routinely reported RBC indices in both pediatric and adult patients, although the pattern of these associations differed according to age. Pediatric diabetes was characterized predominantly by associations with hemoglobin-related parameters, whereas adult diabetes demonstrated stronger relationships involving erythrocyte morphology, particularly MCV, MCH, and RDW. These findings suggest that the interaction between glycemic control and erythrocyte physiology is age dependent and should be considered when interpreting HbA1c in clinical practice.

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Although the observed differences were generally modest and do not support the independent clinical use of RBC indices for diagnosing or monitoring diabetes, routinely available CBC parameters may provide valuable complementary information when HbA1c appears discordant with the clinical presentation or other measures of glycemia. Future prospective studies incorporating longitudinal follow-up and direct measures of erythrocyte lifespan are warranted to further clarify the mechanisms underlying these age-related differences and their potential implications for HbA1c interpretation.

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Data Availability Statement

The data that support the findings of this study are not publicly available because they contain protected health information. Data may be made available from the corresponding author upon reasonable request and with approval from the University of Texas Medical Branch.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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