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Age and Red Blood Cell Parameters Mainly Explain the Differences Between HbA1c and Glycemic Management Indicator Among Patients With Type 1 Diabetes Using Intermittent Continuous Glucose Monitoring

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Abstract

Background: Glycated hemoglobin (HbA1c) is the gold standard to assess glycemic control in patients with diabetes. Glucose management indicator (GMI), a metric generated by continuous glucose monitoring (CGM), has been proposed as an alternative to HbA1c, but the two values may differ, complicating clinical decision-making. This study aimed to identify the factors that may explain the discrepancy between them.

Methods: Subjects were patients with type 1 diabetes, with one or more HbA1c measurements after starting the use of the Freestyle Libre 2 intermittent CGM, who shared their data with the center on the Libreview platform. The 14-day glucometric reports were retrieved, with the end date coinciding with the date of each HbA1c measurement, and those with sensor use $\geq$70% were selected. Clinical data prior to the start of CGM use, glucometric data from each report, and other simultaneous laboratory measurements with HbA1c were collected.

Results: A total of 646 HbA1c values and their corresponding glucometric reports were obtained from 339 patients. The absolute difference between HbA1c and GMI was $<$0.3% in only 38.7% of cases. Univariate analysis showed that the HbA1c-GMI value was associated with age, diabetes duration, estimated glomerular filtration rate, mean corpuscular volume (MCV), red cell distribution width (RDW), and time with glucose between 180 and 250 mg/dL. In a multilevel model, only age and RDW, positively, and MCV, negatively, were correlated to HbA1c-GMI.

Conclusion: The difference between HbA1c and GMI is clinically relevant in a high percentage of cases. Age and easily accessible hematological parameters (MCV and RDW) can help to interpret these differences.

Keywords

continuous glucose monitoring, glucose management indicator, HbA1c, mean corpuscular volume, red cell distribution width, type 1 diabetes mellitus

Introduction

The value of glycated hemoglobin (HbA1c) as a surrogate of glycemic control in patients with diabetes dates back to the mid-1970s.[1] However, its role as risk marker for the development of diabetes chronic complications was established with the publication of the two landmark diabetes intervention studies, the Diabetes Control and Complications Trial (DCCT),[2] in type 1 diabetes, and the United Kingdom Prospective Diabetes Study,[3] in type 2 diabetes. Since then,

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HbA1c has been unanimously recognized as the gold standard for monitoring glycemic control in patients with diabetes.

The DCCT confirmed the results of previous studies,[1,4] which had demonstrated the association between HbA1c and glycemia, but, in addition, by analyzing the capillary blood glucose readings of the study participants, it made it possible to create a regression equation to calculate average glucose levels from the HbA1c value.[5] However, both the DCCT and all previous studies were constrained by the limited number of glucose measurements. The advent of continuous glucose monitoring (CGM), which provides interstitial glucose measurements every few minutes, 24 hours a day, issued an opportunity to study the relationship between glucose levels and HbA1c more accurately. Soon after its incorporation into clinical practice, a new equation,[6] although initially created to calculate the average glucose from HbA1c, also began to be used to estimate HbA1c from the average glucose level measured by the CGM. In fact, the International Consensus on Use of CGM, launched in 2017,[7] recommended the inclusion of the estimated-HbA1c as one of the metrics that should be used for evaluation of glycemic control in patients using CGM. Although the consensus recognized that there could be discrepancies between estimated-HbA1c and laboratory-measured HbA1c, due to different non-glycemic factors affecting the value of the latter, the fact is some confusion was created among clinicians and patients when there was no coincidence between both measurements. This led a group of experts to rename estimated-HbA1c as "glucose management indicator" (GMI),[8] on the assumption that its value should not necessarily be matched with the laboratory HbA1c. The authors of the initiative proposed a new ameliorated formula to estimate GMI based on CGM data coming from devices from a single manufacturer (Dexcom G4 and Dexcom G5, San Diego, CA, USA), but the formula has been subsequently validated for other types of CGM systems.[9,10]

It has recently been emphasized that GMI and HbA1c are going to disagree in a considerable number of cases, and that the clinician must have the skill to interpret these discrepancies on an individual patient basis.[11] However, it seems clear that the deviation between GMI and HbA1c can complicate the interpretation of glycemic control data for a given patient, making it difficult to make therapeutic decisions. This study was carried out to identify, among a number of clinical variables widely available in clinical practice, those that best explain the discrepancies between HbA1c and GMI among patients with type 1 diabetes who wear the FreeSytle Libre 2, an intermittent CGM that has become the most popularly used glucose monitoring system all over the world, mainly because of its lower cost.

Methods

Subjects

The 660 subjects potentially eligible for study inclusion were all adult patients (age > 18 years) with type 1 diabetes seen at the Complejo Hospitalario Universitario Insular Materno-Infantil, who had been approved for public funding of FreeStyle Libre 2 until December 2021. Patients who had not yet received or ultimately refused to use this system of CGM were excluded. Next, the electronic medical records and the web-based data download platform Libreview (https://www.libreview.com/) were accessed to collect data from the remaining subjects. Patients who did not share their glucose records with the hospital, women who were pregnant during the study period, and all those for whom no HbA1c test was available between the start date of CGM use and December 31, 2021, were also excluded. This left a total of 364 valid patients for investigation. For each of them, through Libreview, glucose monitoring reports were retrieved for 14-day time periods, whose end date coincided with the date of each of the HbA1c determinations; however, only those reports in which the sensor use was ≥70% were accepted for analysis. This resulted in a total of 646 reports, obtained from 339 patients who constituted the definitive study population. The complete subject selection procedure is illustrated in Figure 1.

Research Variables

A series of demographic and clinical data were collected from each patient before the start of CGM use. This information was obtained by consulting the forms that had been sent to the Advisory Committee on New Diabetes Technologies of the Canary Islands Health Service to request public funding for the device. These data included age, sex, year of diagnosis of diabetes, height, weight, most recent HbA1c value at the time of application, insulin dose, and chronic complications of the disease. From patients' electronic records, when available, other laboratory results that had been measured concurrently with HbA1c were also collected, including

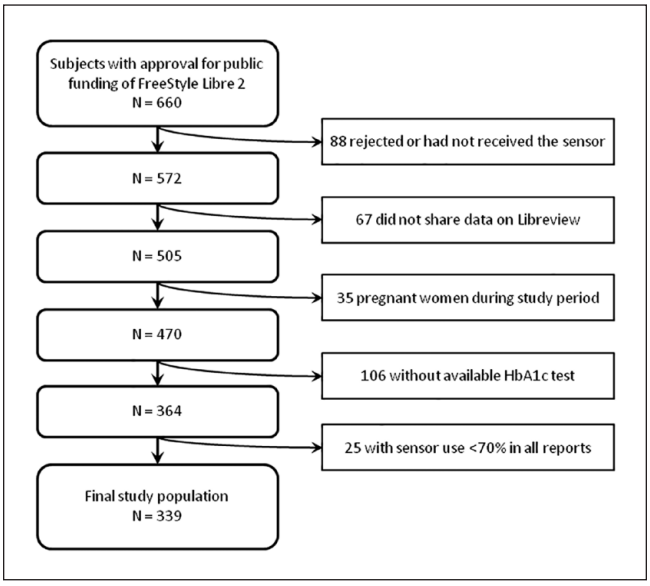

Figure 1. Flowchart of the study population.

hemoglobin, mean corpuscular volume (MCV), red cell distribution width (RDW), and serum creatinine. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. In addition, the following glucometric data were extracted from each report downloaded from Libreview: percentage of time CGM was active, average glucose, GMI, percentages of time in target range (glucose between 70 and 180 mg/dL, between 181 and 250 mg/dL, above range >250 mg/dL, between 54 and 69 mg/dL, and below <54 mg/dL), and glucose coefficient of variation.

Statistical Analyses

Categorical variables were expressed as frequencies and percentages, and continuous variables as mean ± standard deviation, when the data followed a normal distribution, or as median and interquartile range (25th, 75th percentiles), when the distribution deviated from normality. Percentages were compared, as appropriate, by the chi-square test (χ^2) or Fisher exact test, means by the *t* test, and medians by the Wilcoxon test for independent data.

The difference between each paired HbA1c and GMI value (HbA1c-GMI) was calculated. To explore which variables were associated with the discrepancy between HbA1c and GMI, subjects were divided into three groups, according to tertiles of HbA1c-GMI, and groups were compared for a wide set of clinical, biochemical, and glucometric variables. When a subject had more than one simultaneous HbA1c and GMI measurement, the HbA1c-GMI value where GMI had been estimated with a higher percentage of sensor usage time was chosen for analysis.

To identify variables independently associated with the discrepancy between HbA1c and GMI, a multivariate mixed model was constructed, in this case including all repeated measures for each subject in which the dependent variable was HbA1c-GMI. The patient effect was adjusted as a random effect, whereas the covariates analyzed were adjusted as fixed effects. Only covariates that had been associated with HbA1c-GMI with a *P* value of less than .2 in the univariate study were entered into the model. The goodness of fit of the model was assessed using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). The better the fit, the lower the two statistics. The model was summarized in the form of coefficients and standard errors, *P* values, as well as the AIC and BIC values that would result if each selected factor were removed. Data were analyzed with the R package, Version 3.6.1 (R Core Team[12]).

Ethical Issues

This study was conducted in accordance with the Helsinki Declaration and it was approved by the ethics committee of the province of Las Palmas, Spain.

Results

The final study population consisted of 185 women and 154 men who had one or more HbA1c laboratory measurements performed after the initiation of CGM systems (CGMS) use, with their paired glucometric reports downloaded from Libreview. Specifically, there were 142 subjects with a single measurement of HbA1c, 106 subjects with two measurements, 75 subjects with three, 14 subjects with four, one subject with five, and one subject with six measurements. Table 1 shows the demographic and clinical characteristics of the 339 subjects under study, prior to the initiation of CGM use. Table 2 shows the degree of discrepancy between

Table 1. Characteristics of Subjects, Overall and by Sex, Prior to Initiation of Use of the CGMS.

	Total (N = 339)	Women (N = 185)	Men (N = 154)	*P*
Age, y	41.9 ± 12.2	41.5 ± 12.3	42.4 ± 12.2	.517
Diabetes duration time, y	20 (11; 30)	22 (11; 31)	18 (11; 27)	.075
Body mass index, kg/m^2	26 (23; 29)	25 (23; 29)	26 (24; 29)	.246
Insulin dose (U/kg/day)	0.65 (0.50; 0.80)	0.62 (0.50; 0.78)	0.67 (0.51; 0.80)	.246
Smoking, n (%)	29 (8.6)	19 (10.3)	10 (6.5)	.216
Hypertension, n (%)	77 (22.7)	31 (16.8)	46 (29.9)	.004
HbA1c, %	7.4 (6.8; 8.1)	7.4 (6.9; 8.1)	7.4 (6.73; 8)	.49
Severe hypoglycemia in previous year, n (%)	6 (2.0)	2 (1.2)	4 (3.0)	.413
Unaware hypoglycemias, n (%)	58 (17.1)	26 (14.1)	32 (20.8)	.102
Diabetes chronic complications, n (%)				
Diabetic retinopathy	66 (22.3)	35 (22.1)	31 (22.5)	.949
Diabetic nephropathy, n (%)	34 (10.0)	21 (11.3)	13 (8.4)	.375
Diabetic polyneuropathy, n (%)	39 (11.5)	21 (11.3)	18 (11.7)	.923
Coronary heart disease, n (%)	6 (1.8)	5 (2.7)	1 (0.7)	.226
Stroke, n (%)	2 (0.6)	2 (1.1)	0	.502
Peripheral artery disease, n (%)	6 (1.8)	3 (1.6)	3 (1.9)	1

Abbreviation: CGMS, continuous glucose monitoring systems; HbA1c, glycated hemoglobin.

Table 2. Absolute Difference Between HbA1c and GMI in the 646 Recordings Obtained With Sensor Uptime ≥70%, According to HbA1c Levels.

|HbA1c-GMI| (%)	Total (N = 646)	HbA1c tertile 1 (N = 228)	HbA1c tertile 2 (N = 223)	HbA1c tertile 3 (N = 195)
<0.1	104 (16.1)	46 (20.3)	42 (18.8)	16 (8.2)
<0.2	180 (27.9)	83 (36.6)	67 (30.0)	30 (15.4)
<0.3	250 (38.7)	112 (49.3)	93 (41.7)	45 (23.1)
<0.4	330 (51.1)	139 (61.2)	128 (57.4)	63 (32.3)
<0.5	408 (63.2)	159 (70.0)	170 (76.2)	79 (40.5)

Abbreviation: HbA1c, glycated hemoglobin; GMI, glucose management indicator.

HbA1c and GMI, for the overall 646 pairs of data, according to HbA1c tertiles. The agreement between the two measures decreased as the HbA1c value increased.

Subsequently, for each individual, the report in which the sensor activity time was highest was selected. Considering the GMI value of this report and its corresponding HbA1c measurement, a single HbA1c-GMI value was assigned to each subject, and they were divided into three groups, according to HbA1c-GMI tertiles. Table 3 presents the baseline clinical characteristics of the three groups, as well as the results of the biochemical analyses and the glucose metrics obtained with the CGM in the selected report. Age, diabetes duration time, eGFR, hemoglobin, MCV, RDW and percentage of time with glucose between 181 and 250 mg/dL were significantly associated with the difference between HbA1c and GMI.

The multilevel mixed model analysis, performed with the 646 records, only selected age and RDW, positively, and MCV, negatively, as independent predictors of HbA1c-GMI. According to the AIC and BIC values, MCV was the variable that had the greatest influence on the dependent variable (Table 4).

Discussion

The results of this study confirm that, in real-life clinical practice, in this case specifically among patients with type 1 diabetes wearing FreeStyle Libre 2, there is a significant discrepancy between the HbA1c measured in the laboratory and the GMI value provided by the CGM in a great proportion of subjects. The difference between the two measures was less than 0.1% in only 16% of the cases and ≥0.3% in 61.3% of them, a difference that is considered to have a clinic impact when HbA1c levels are considered. The concordance between HbA1c and GMI in our population, therefore, was somewhat lower than that reported by Bergenstal et al[8] in the reference study that served to define the formula to calculate GMI, but lies within the range of results observed in other real-world studies.[13-15]

Glycated hemoglobin (HbA1c) is considered the gold standard for estimating the degree of glycemic control and the risk of chronic complications in subjects with diabetes and, at the population level, it performs well in reflecting average glucose levels.[6,8] However, it has important limitations for assessing glycemic control at the individual level. It does not take into account glycemic variability or time in hypoglycemia, and the range of average glucose values can differ markedly for the same HbA1c value.[16] The assessment of glucometry reports provided by CGM helps to better interpret all these variables, so it is now accepted that it should be evaluated together with HbA1c as part of the comprehensive assessment of the patient's glycemic control.[11] In addition, HbA1c can be modified by other factors not directly related to glycemia, some of which could also explain its discrepancies with the CGM-derived GMI.[17] For example, any condition that prolongs red cell half-life or reduces red cell turnover, such as iron deficiency or asplenia, can increase HbA1c levels. At the opposite side, situations in which red cell half-life is shorter, such as hemolytic anemia, chronic kidney disease, splenomegaly, or liver cirrhosis, can lower HbA1c values. In addition, it is also recognized that there may be an interindividual variation in the ability to glycate hemoglobin at equal blood glucose concentrations. This is known as the hemoglobin glycation index (HGI) and might also contribute to explain the discrepancies between the levels of HbA1c and GMI observed among individual subjects.[11,18] Certain genetic factors have been proposed to influence on the HGI,[19] which could account for the different correlation between GMI and HbA1c among ethnic groups. Some data suggest that GMI will be typically higher than HbA1c in white people but lower than HbA1c in black African Americans or in Chinese Asians.[20]

The aim of this work was to detect variables that could better explain the differences between HbA1c and GMI in an ethnically homogeneous cohort of people with type 1 diabetes, both in terms of those glucometric variables that could detect recent glucose fluctuations not captured by HbA1c, and those other non-glycemic variables that could modify hemoglobin glycation.

Age was a positive independent predictor of the difference between HbA1c and GMI, so that older adults trended to have a higher laboratory-measured HbA1c compared with GMI. This finding could be in line with general population-based studies that have shown that, when estimated solely on the basis of a single measure of HbA1c and fasting blood glucose, age is significantly associated with an increased HGI.[21] However, age has not been found to be a determinant of the difference between laboratory-measured HbA1c and

Table 3. Clinical Characteristics, Laboratory Results, and Glucometric Values of Study Population, According to HbA1c-GMI Tertiles.

	HbA1c-GMI			
	<–0.127 (N = 116)	–0.127-0.374 (N = 117)	>0.374 (N = 116)	*P*
HbA1c, %	6.8 (6.4; 7.2)	7.4 (6.9; 7.8)	8.1 (7.7; 8.57)	<.001
GMI, %	7.26 (6.87; 7.73)	7.27 (6.83; 7.67)	7.39 (6.97; 7.72)	.317
HbA1c-GMI	–0.44 (–0.64; –0.32)	0.09 (–0.01; 0.25)	0.64 (0.49; 0.93)	<.001
Age, y	38.4 ± 11.6	41.6 ± 12.5	46.1 ± 11.5	<.001
Male sex, n (%)	58 (50.0)	49 (41.9)	47 (44.3)	.444
Body mass index, kg/m^2	25 (23; 27)	26 (23; 30)	26 (23; 29)	.168
Insulin dose, U/kg/day	0.66 (0.50; 0.80)	0.61 (0.49; 0.80)	0.65 (0.50; 0.78)	.855
Smoking, n (%)	6 (5.2)	15 (12.8)	8 (7.5)	.103
Hypertension, n (%)	20 (17.2)	25 (21.4)	32 (30.2)	.065
Diabetes duration time, y	18 (9; 27)	18 (12; 29)	25 (16; 31)	.003
Serum creatinine, mg/dl	0.76 (0.67; 0.86)	0.76 (0.68; 0.90)	0.77 (0.66; 0.92)	.659
Estimated GFR, ml/min/1.73 m^2	110 (100; 119)	102 (92; 114)	102 (91; 110)	.001
Estimated GFR <60 ml/min/1.73 m^2, n (%)	2 (1.9)	4 (3.7)	5 (5.1)	.473
Hemoglobin, g/dL	14 (14; 15)	14 (13; 15)	14 (13; 15)	.061
Mean corpuscular volume, fL	91 (88; 94)	90 (87; 93)	89 (85; 92)	.031
Red blood cell distribution width (%)	13 (13; 13)	13 (13; 14)	14 (13; 15)	<.001
Time of sensor use, %	99 (94; 100)	98 (95; 100)	98 (93; 100)	.448
Mean glucose, mg/dL	166 (149; 186)	166 (147; 183)	171 (153; 185)	.317
Time in range, %	60 (49; 69)	58 (48; 69)	56 (48; 64)	.248
Time above range (181-250 mg/dL), %	25 (20; 30)	24 (18; 30)	27 (23; 32)	.044
Time above range (>250 mg/dL), %	10 (4; 17.2)	11 (5; 18)	12 (6; 18)	.473
Time below range (54-69 mg/dL), %	3 (1; 5)	3 (1; 6)	2 (1; 4.7)	.327
Time below range (<54 mg/dL), %	0 (0; 1)	0 (0; 1)	0 (0; 1)	.628
Glucose variation coefficient, %	38 (33; 43)	39 (34; 43)	37 (34; 42)	.523

Abbreviations: HbA1c, glycated hemoglobin; GMI, glucose management indicator; eGFR, estimated glomerular filtration rate.

Table 4. Mixed Model for the Difference Between HbA1c and GMI.

	Coefficient (SE)	*P*	AIC[a]	BIC[a]
Intercept	1.1100 (0.7882)	—	—	—
Age, y	0.0103 (0.0026)	<.001	665.4	685.9
Mean corpuscular volume, fL	–0.0255 (0.0063)	<.001	667.1	687.6
Red blood cell distribution width, %	0.0642 (0.0279)	.022	659.3	679.8

Estimation of fixed effects.
Abbreviations: HbA1c, glycated hemoglobin; GMI, glucose management indicator; AIC, Akaike information criterion; BIC, Bayesian information criterion.
[a]AIC and BIC values that would result if the corresponding variable were excluded from the model are shown. The AIC and BIC values for the overall model were 661.6 and 686.1, respectively.

CGM-derived GMI in other previous studies that have evaluated people with diabetes.[13-15,22]

Our results also demonstrate that MCV, negatively, and RDW, positively, are independent predictors of the difference between HbA1c and GMI. In other words, the lower the MCV and the higher the RDW, the higher the HbA1c value compared with the GMI. The MCV measures the average volume of erythrocytes and is calculated indirectly from hematocrit and red blood cell concentration. Several previous studies have shown a strong inverse correlation between MCV and HbA1c, both in subjects without and with diabetes.[23-25] Using cell separation techniques, it has been shown that there is also a negative correlation between HbA1c and MCV within individuals, and this has been interpreted as both variables reflecting the same underlying factor, that is, the life span of red blood cells.[26] In this regard, experimental studies have shown that senescent erythrocytes are smaller as they lose volume as a consequence of both vesicle shedding and loss of water.[27] In view of all this, our findings suggest that the association of MCV with the difference between HbA1c and GMI could be explained because subjects with a lower MCV are characterized by a longer half-life of their red blood cells, leading to spuriously elevated HbA1c values. This is consistent with a small study that, by measuring the life expectancy of red blood cells, showed that heterogeneity in erythrocyte survival can significantly modify HbA1c levels, even in subjects without any hematological abnormalities.[28]

As for RDW, it is a parameter that measures the variation in the volume of red blood cells and serves as a measure of anisocytosis. It is calculated as the coefficient of variation of

the MCV and, therefore, its measurement depends on MCV. However, the results of our multivariate study showed that the effects of RDW and MCV on the difference between HbA1c and GMI were independent. Unlike MCV, RDW has been classically associated with increased red blood cell destruction, ineffective erythropoiesis, and low red cell life span.[29] Therefore, the association between RDW and the difference between HbA1c and GMI should be due to causes other than increased red blood cell half-life. In this regard, several studies, both cross-sectional and prospective, have shown that HbA1c, but not glucose, is positively associated with RDW.[30-32] In fact, RDW (as well as MCV) was strongly associated with HGI in general US population without diabetes in the National Health and Nutrition Examination Survey.[33] In that same study, HGI was also shown to be associated with different markers of systemic inflammation, and the authors suggested that elevated RDW, inflammation, and increased propensity to glycation might be elements of a same cluster. This hypothesis would explain why RDW has been shown to be a marker of microvascular and macrovascular diabetes complications,[34] cardiovascular disease, and many other chronic conditions.[35]

In our study, glucometric variables provided by the CGM, including the periods of time in target range or in hyperglycemia or hypoglycemia and the coefficient of glucose variation, were not related to the difference between HbA1c and GMI, suggesting that recent fluctuations in glucose levels are not as much of a determining factor in the difference between HbA1c and GMI, as usually admitted. Two weeks of sensor glucose data are currently considered sufficient to calculate the GMI representatively. If six consecutive two-week GMIs had been combined and then compared with a single HbA1c concentration, which reflects mean glycemia over approximately 12 weeks, then the correlations might have been different from the correlations that were found in this study. However, clinicians almost always use GMI as a single stand-alone value rather than as part of a set of six recent measurements that become combined. Furthermore, there is no widely accepted formula for combining six recent GMI results to assess correlation with an every-12-week HbA1c where recent levels of glycemia are represented out of proportion to older levels of glycemia.

Finally, we also found no association with body mass index, which had been identified as a potential discrepancy factor in subjects with type 2 diabetes in a previous study.[22]

In conclusion, discrepancies between HbA1c and GMI measurements are not uncommon. Together with age, MCV and RDW, two very inexpensive and accessible laboratory parameters, could help to identify subjects in whom a greater deviation between the two measures might be expected. This can guide clinicians toward a more personalized approach to therapeutic decision-making.

Abbreviations

AIC, Akaike information criterion; BIC, Bayesian information criterion; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CGMS, continuous glucose monitoring systems; DCCT, Diabetes Control and Complications Trial; eGFR, estimated glomerular filtration rate; GMI, Glucose management indicator; HbA1c, glycated hemoglobin; HGI, hemoglobin glycation index; MCV, mean corpuscular volume; RDW, red cell distribution width.

Declaration of Conflicting Interests

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