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RESEARCH ARTICLE

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Analytical performance evaluation of the Norudia HbA_{1c} assay

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Abstract

Background: Hemoglobin A_{1c} (HbA_{1c}) is arguably the most important biomarker used in the diagnosis and treatment monitoring of diabetes mellitus. We evaluated the analytical performance of the Norudia HbA_{1c} assay (Sekisui Medical Co., LTD), which uses an enzymatic method incorporated into a fully automated, high-throughput system.

Methods: The precision, linearity, and carryover of the Norudia HbA_{1c} assay were evaluated. Using 60 patient samples, comparative analysis of HbA_{1c} measurements with two commonly used HbA_{1c} assays, the D100 (Bio-Rad Laboratories, Inc) and HLC-723 G11 (Tosoh), was undergone. Thirteen commutable samples with known HbA_{1c} concentrations measured using an IFCC reference measurement procedure were used to compare accuracy between methods. Interference of HbA_{1c} measurement by Hb variants was evaluated using 16 known Hb variant samples.

Results: Repeatability (% CV) for low and high concentrations ranged from 1.12%-1.50% and 0.66%-0.75%, respectively, and within-laboratory precision for low and high concentrations ranged from 1.73%-2.89% and 0.98%-1.64%, respectively. For linearity, the coefficient of determination was 0.9987. No significant carryover was observed. When compared to the D100 and HLC-723 G11 assays, the Norudia HbA_{1c} assay showed the best accuracy with the lowest mean bias (−1.72%). Furthermore, the Norudia was least affected by Hb variants and gave the most reliable HbA_{1c} measurements.

Conclusion: The Norudia HbA_{1c} showed excellent analytical performance with good precision and linearity, and minimal carryover. When compared to other routine HbA_{1c} methods, the Norudia HbA_{1c} assay showed the highest accuracy and was least affected by Hb variants.

KEYWORDS

accuracy, analytical performance, Hb variant, linearity, Norudia HbA_{1c} assay, precision

1 | INTRODUCTION

Diabetes mellitus (DM) continues to increase in global prevalence and has taken its toll with over 1.5 million deaths due to DM in 2012 and an additional 2.2 million deaths associated with a high blood glucose level.[1] Hemoglobin A_{1c} (HbA_{1c}) is by far the most popular and widely used biomarker for the diagnosis and monitoring of DM. HbA_{1c} levels are directly related to blood glucose levels,[2] but have the advantage

of less diurnal variation (<2% for HbA_{1c} vs 12%-15% for fasting blood glucose levels),[3] and have been proven in prospective studies to be directly associated with the risk of diabetic complications.[4]

Introduced by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the current reference measurement procedure (RMP) for HbA_{1c} analysis utilizes either high-performance liquid chromatography-electrospray mass spectrometry (HPLC-ESI/MS) or HPLC/capillary electrophoresis (HPLC-CE).[5] Various routine methods to measure HbA1c including, but not limited to, ion-exchange HPLC, capillary electrophoresis, isoelectric focusing, affinity chromatography, immunoassay, and enzymatic assays are used in clinical laboratories. Each method has its own advantages and disadvantages, but the heterogeneity resulting from the diversity of surrogate methods has further emphasized the importance of standardization.

According to the recent College of American Pathologists (CAP) proficiency testing survey results for HbA_{1c}, the HPLC method is one of the most common methods used for HbA_{1c} testing worldwide,[6] with the ability to detect common hemoglobin variants, one of its main advantages. However, rarer variants which coelute with the peaks of interest can still cause interference, in addition to issues with regard to negative intermethod differences at higher HbA_{1c} (>74.9 mmol/mol or >9% in NGSP units) concentrations [7,8] being pointed out as its limitations. Thus, continuous efforts to develop a HbA_{1c} assay with diagnostic accuracy near-equivalent to the IFCC-RMP, while being robust enough for routine use in the clinical laboratory, remain ongoing.

The Norudia HbA_{1c} assay (Sekisui Medical Co., LTD) is a fully automated, high-throughput HbA_{1c} analyzer based on an enzymatic method. Enzymatic assays are known to not receive analytical interference from Hb variants, thus giving reliable HbA_{1c} values.[9] The aim of this study was to evaluate the analytical performance of the Norudia HbA_{1c} assay and compare its results with reference target values obtained via IFCC-RMP, and with other routine HbA_{1c} assays.

2 | MATERIALS AND METHODS

2.1 | Instruments, reagents, and study samples

The performance of the Norudia HbA_{1c} assay (Sekisui Medical Co., LTD), on a LABOSPECT 008 (Hitachi High-Tech Co) analyzer, was evaluated. The assay principle is as follows. In the first reaction, glycosylated dipeptide derived from the N-terminal of the β-chain of HbA_{1c} is cut out by a protease. In the second reaction, hydrogen peroxide is produced by the action of fructosyl peptide oxidase on glycosylated dipeptide and then causes color development by 10-(carboxymethylaminocarbonyl)-3,7-bis(dimethylamino) phenothiazine sodium (coloring agent) in the presence of peroxidase. The HbA_{1c} concentration is determined by measuring the absorbance of this complex. The percentage of total Hb existing as HbA_{1c} is calculated from the concentrations of HbA_{1c} and Hb. All measurements with the Norudia HbA_{1c} assay were executed in accordance with the manufacturer's instructions.

Fresh EDTA blood samples referred for HbA_{1c} measurement at Seoul National University Bundang Hospital, commutable frozen whole blood specimens with HbA_{1c} reference target values obtained with RMP [5] from the Korea Centers for Disease Control and Prevention (KCDC) which is one of the approved IFCC network reference laboratories, and frozen whole blood samples previously confirmed for commonly found Hb variants in the Korean population [10] were used in the evaluation process. This research was approved by the Seoul National University Hospital Institutional Review Board (IRB number B-1711/430-302).

2.2 | Precision

The repeatability and within-laboratory precision of the Norudia HbA_{1c} assay were evaluated according to the Clinical and Laboratory Standards Institute (CLSI) guideline EP05-A3.[11] Two different commercial quality control (QC) material (manufactured by Sekisui and Bio-Rad) were measured in duplicate, twice per day over a total period of 20 days. The corresponding low and high HbA_{1c} concentrations were 34.8 and 83.6 mmol/mol for the Sekisui QC material, and 24.8 and 72.0 mmol/mol for the Bio-Rad QC control. Coefficients of variation (CV) were calculated and denoted for repeatability and within-laboratory precision.

2.3 | Linearity

The linearity was evaluated according to the 2003 CLSI guideline EP06-A[12] using duplicate measurements of five specimens of different HbA_{1c} levels, prepared from mixed ratios (100:0, 25:75, 50:50, 25:75, 0:100) of two patient samples with known low (21.3 mmol/mol) and high (143.7 mmol/mol) HbA_{1c} concentrations.

2.4 | Carryover

The presence/absence of sample carryover was evaluated by four consecutive measurements of high (143.7 mmol/mol) HbA_{1c} concentrations (H1-4), followed by four consecutive measurements of low (21.3 mmol/mol) HbA_{1c} concentrations (L1-4). A % carryover was calculated according to the following equation: (L1-(L3 + L4)/2 × 100)/((H2 + H3)/2-(L3 + L4)/2), and a value of 1.0% was used as the reference value.[13]

2.5 | Comparative analysis with routine HbA1c diagnostic assays

Sixty patient samples were measured for comparison of Norudia HbA_{1c} results with the D100 (Bio-Rad Laboratories, Inc) and HLC-723 G11, referred to as G11 (Tosoh), HbA_{1c} assays. Passing-Bablok regression and Bland-Altman plots of the compared methods were obtained according to the 2018 CLSI Guideline EP09c.[14]

TABLE 1 Imprecision with 95% confidence intervals (95% CI) for the Norudia HbA_{1c} assay based on EP05-A3

	Sekisui QC control				Bio-Rad QC control			
	Low	34.8 mmol/mol	High	83.6 mmol/mol	Low	24.8 mmol/mol	High	72.0 mmol/mol
	CV	95%CI	CV	95%CI	CV	95%CI	CV	95%CI
Repeatability	1.12%	0.92%-1.43%	0.66%	0.54%-0.85%	1.50%	1.23%-1.92%	0.75%	0.61%-0.95%
Within-Laboratory	1.73%	1.55%-2.13%	0.98%	0.85%-1.25%	2.89%	2.44%-3.84%	1.64%	1.33%-2.28%

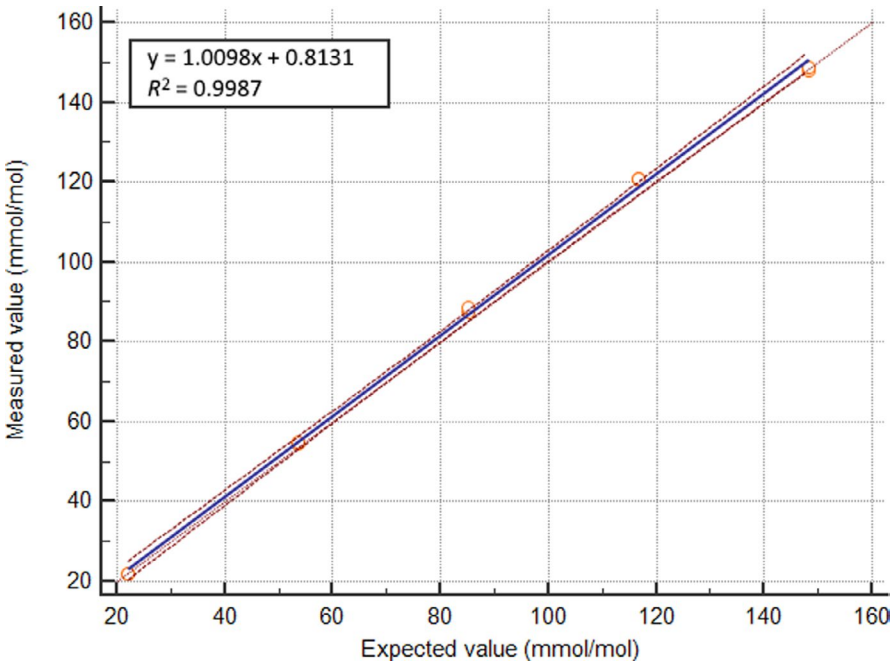

FIGURE 1 Linearity of the Norudia HbA_{1c} assay

2.6 | Accuracy assessment using assigned HbA1c target values

The accuracy of the Norudia HbA_{1c} assay was evaluated by comparing its results from 13 commutable specimens of known HbA_{1c} reference target values (ranging from 31.0-102.95 mmol/mol) measured by the KCDC. The samples were stored at −70°C and thawed before use. Passing-Bablok regression and Bland-Altman plots of the Norudia HbA_{1c} assay against the reference values were obtained.

2.7 | Assessment of effect of Hb variants

The most common worldwide Hb variants such as Hb S, C, E, and D are rarely found in Korea. Instead, Hb G-Coushatta and Hb Queens are the most common Hb β- and α-chain variants. In this study, we evaluated the interference of Hb variants on the HbA_{1c} assay by measuring 16 samples with known Hb variants (7 Hb G-Coushatta, 5 Hb Queens, 2 Hb Ube-4, 1 Hb Chad, and 1 Hb Yamagata) which are relatively common in Korea.[10] For variant analysis, in addition to the Norudia, D100, and G11, the Tina-Quant immunoassay (Roche Diagnostics) was also compared. The % differences to HbA_{1c} reference target values obtained via IFCC-RMP (ranging from 31.41-62.85 mmol/mol) were compared between the Norudia, D100, G11, and Tina-Quant HbA_{1c} assays.

2.8 | Statistical analysis

All statistical analyses were implemented in MedCalc version 14.8.1 (MedCalc Software), and statistical significance was defined as $P < .05$.

3 | RESULTS

3.1 | Precision

Low- and high-concentration HbA_{1c} QC material from two different manufacturers (Sekisui and Bio-Rad) were used for precision evaluation. For the Sekisui QC material, the CV for repeatability for low

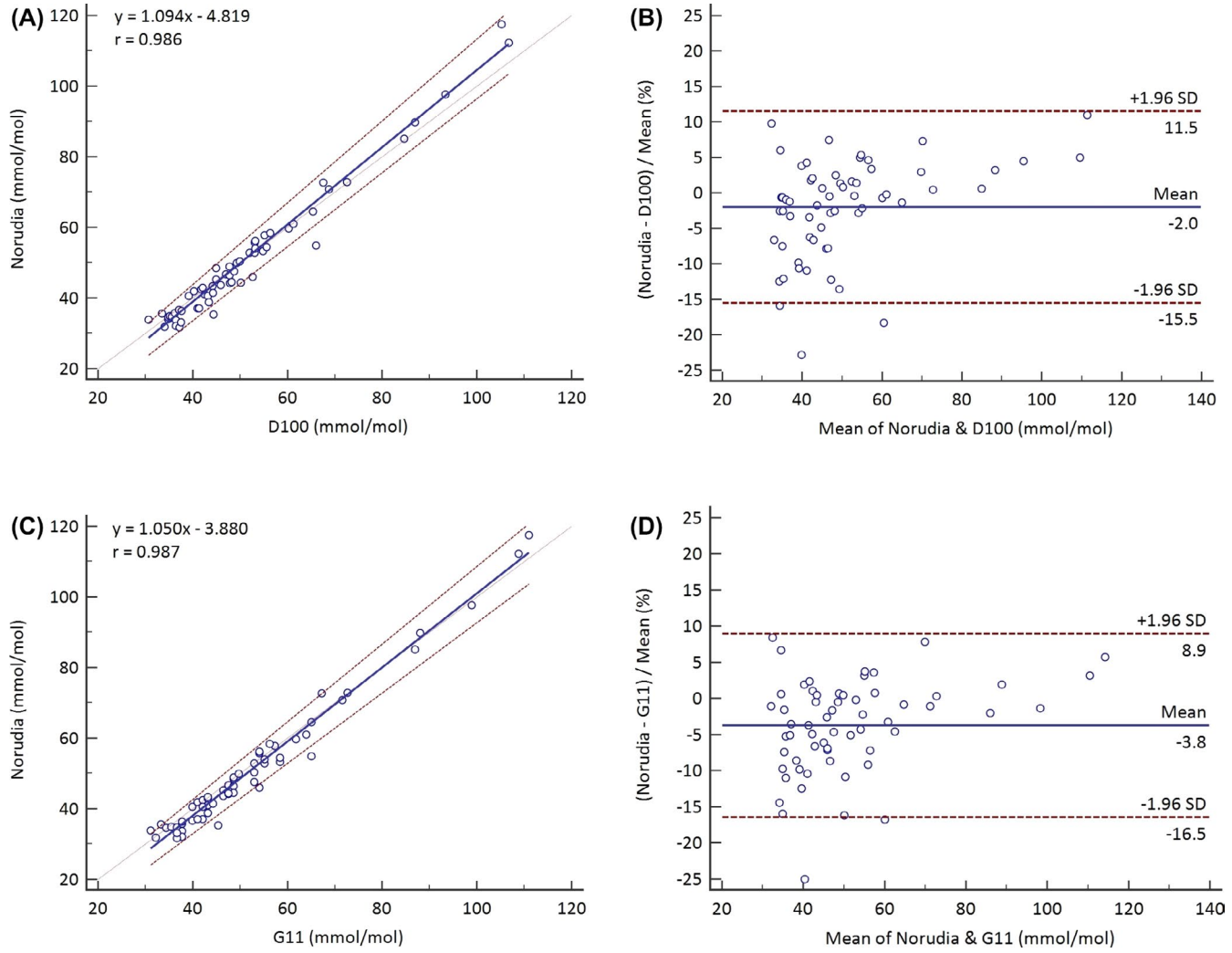

FIGURE 2 Comparison of the Norudia with the D100 and G11 HbA_{1c} assay. (A) Passing-Bablok regression of HbA_{1c} results of the Norudia against the D100 assay. The blue solid line and red dotted lines represent the linear curve and 95% confidence interval (CI), respectively. (B) Bland-Altman plot showing the % difference of HbA_{1c} values against the mean of the two assays (D100 and Norudia). The blue solid line and red dotted lines represent the mean and 1.96 standard deviation (SD) borders, respectively. (C) Passing-Bablok regression of HbA_{1c} results of the Norudia against the G11 assay. (D) Bland-Altman plot showing the % difference of HbA_{1c} values against the mean of the two assays (G11 and Norudia)

and high concentrations were 1.12% and 0.66%, respectively, and the CV for within-laboratory results for low and high concentrations were 1.73% and 0.98%, respectively. For the Bio-Rad QC material, repeatability for low and high concentrations was 1.50% and 0.75%, respectively, and within-laboratory results for low and high concentrations were 2.89% and 1.64%, respectively. Comprehensive imprecision results with 95% confidence intervals (CI) are shown in Table 1.

3.2 | Linearity

Over a measured HbA_{1c} range of 21.3-143.7 mmol/mol, the Norudia HbA_{1c} assay showed excellent linearity, with a coefficient of determination (R^2) of 0.9987 (Figure 1).

3.3 | Carryover

The calculated carryover between high and low HbA_{1c} values of the Norudia HbA_{1c} assay was −0.09%, which is below the preset acceptance criteria of 1.0%.

3.4 | Comparative analysis with routine HbA1c diagnostic assays

Passing-Bablok regression between the Norudia HbA_{1c} assay and D100 assay gave a slope of 1.094 with a 95% CI of 1.047-1.159 and an intercept of −4.819 (95% CI, −8.283 to −2.621) (Figure 2A). The Pearson correlation coefficient (r) between the two assays was

0.986. The mean % difference shown on the Bland-Altman plot was −1.981 (95% CI −3.761 to −0.201) (Figure 2B). Three outliers out of limit of agreement with lower values of Norudia HbA_{1c} assay were observed.

Likewise, Passing-Bablok regression between the Norudia HbA_{1c} assay and G11 assay gave a slope of 1.050 (95% CI 0.998 - 1.100) and an intercept of −3.880 (95% CI −7.049 to −1.338) (Figure 2C). The Pearson correlation coefficient between the two assays was 0.987. The mean % difference observed on the Bland-Altman plot was −3.783 (95% CI −5.458 to −2.108) (Figure 2D). Two outliers out of limit of agreement with lower values of Norudia HbA_{1c} assay were observed.

3.5 | Accuracy assessment using assigned HbA1c target values

Commutable, reference samples with known HbA_{1c} reference target values (ranging from 31.0-102.95 mmol/mol) obtained via RMP were measured using the Norudia, D100, and G11 assays. The Norudia assay showed the lowest mean bias (−1.72%) of the 3 assays. Regression of the Norudia assay against the reference HbA_{1c} value gave a slope of 0.995, an intercept of −0.579, and a correlation coefficient of determination (R^2) of 0.995 (Figure 3A), while Bland-Altman plotting of the 13 reference samples measured via the Norudia assay gave a mean % difference of −1.715 (Figure 3B).

3.6 | Assessment of effect of Hb variants

HbA_{1c} values from samples with known Hb variants occurring in the Korean population (Coushatta, Queens, Ube-4, Chad) were measured via the Norudia, D100, G11, and Tina-Quant assays. When compared to the MS-confirmed HbA_{1c} values (ranging from 31.41-62.85 mmol/mol), the Norudia showed the best overall performance with % differences to MS-confirmed HbA_{1c} values ranging from a low of −6.15% (mean value, Queens) to a high of 3.59% (mean value, Ube-4). Summarized HbA_{1c} measurements of the NORUDAI, D100, G11, and Tina-Quant assays are shown in Table 2.

4 | DISCUSSION

In this study, we evaluated the analytical performance of the Norudia HbA_{1c} assay, via tests for precision, linearity, carryover, comparative

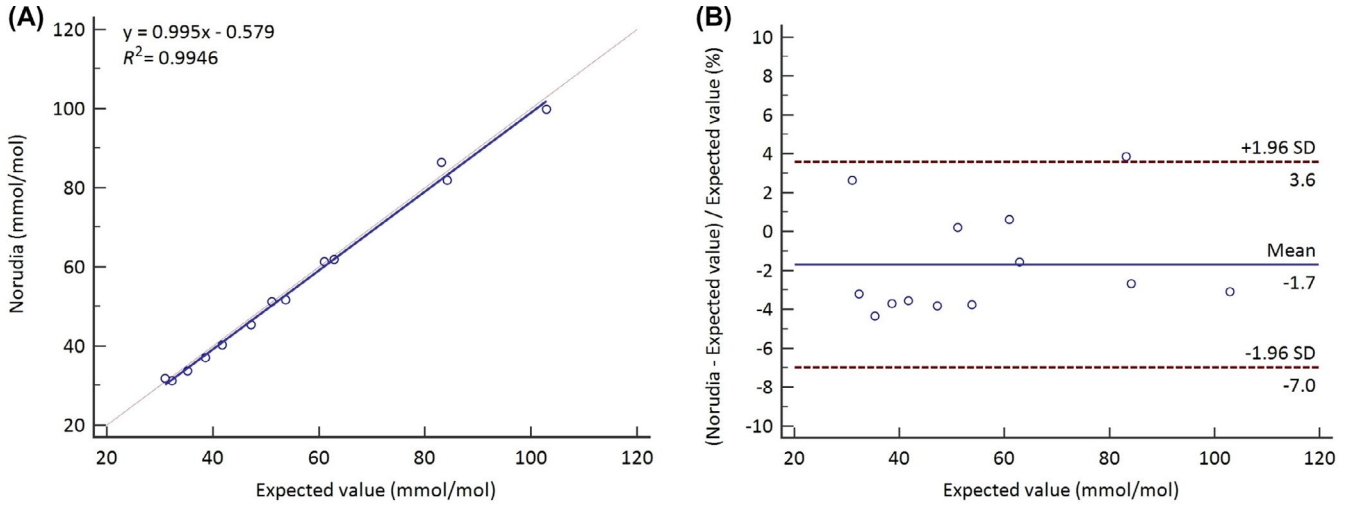

FIGURE 3 Regression plot (A) of the Norudia HbA_{1c} assay against the reference target HbA_{1c} value; Bland-Altman plot (B) of the % bias of the Norudia results against the target value

TABLE 2 Mean ± SD of percentage differences (%) to HbA_{1c} reference target values with known Hb variants

	Hb variants				
Methods	G-Coushatta (n = 7) (31.4-62.9)[a]	Queens (n = 5) (33.4-37.8)[a]	Ube-4 (n = 2) (35.9 and 37.9) [a]	Chad (n = 1) (35.8) [a]	Yamagata (n = 1) (34.5) [a]
Norudia	−3.57 ± 3.27	−6.15 ± 3.09	3.59	−3.90	−3.46
G11	−46.63 ± 5.84	−23.74 ± 11.41	−14.10	−45.11	−168.27
D100	−5.10 ± 5.03	5.59 ± 9.14	11.02	−4.66	1205.73
Tina-Quant	−1.65 ± 3.78	0.16 ± 4.00	8.15	−1.30	7.64

[a]HbA_{1c} value or range (mmol/mol) measured by reference measurement procedure.

analysis with other routine assays, accuracy comparison to target values, and effects of Hb variants.

The Norudia HbA_{1c} assay showed excellent precision, with CV for repeatability ranging from 0.66 - 1.50%, and CV for within-laboratory results ranging from 0.98%-2.89% (Table 1). Although imprecision results for the Bio-Rad QC material seemed to show slightly higher values, no significant difference to the Sekisui QC material was observed. Most importantly, all within-laboratory CV are <3%, which comply with standard analytical consensus.[15] Due to the nature of the conversion between IFCC and NGSP units, analytical goals must be set according to the used units.[16-18] Thus, when HbA_{1c} values are converted to NGSP units, all recalculated CV (data not shown) are <2%, which are in compliance with not only the CLSI/NGSP guideline (recommended <5% intralaboratory CV),[19] but also the stricter Laboratory Medicine Practice Guideline (LMPG) provided by the National Academy of Clinical Biochemistry (NACB) (recommended <2% laboratory CV).[20] Notwithstanding, the "most imprecise" result from the precision evaluation was the within-laboratory CV (2.89%) of the low (24.8 mmol/mol) Bio-Rad QC control, which is an acceptable value but not ideal. However, it must be taken into account that such low HbA_{1c} values are rarely observed in patients or suspected patients, with the majority of clinical decision limits covering the 40-64 mmol/mol range (5.8%-8.0% in NGSP units); thus, the aforementioned imprecision will not be a hindrance to the assay's performance in clinical settings.

As HbA_{1c} is used not only in the diagnosis of DM, but also in other various situations including treatment evaluation and follow-up, linearity is required over a wide range of HbA_{1c} concentrations. The Norudia assay showed commendable linearity over the range of 21.3-143.7 mmol/mol, with an R^2 value of 0.999 (Figure 1), and all measured results were within 5% of the expected target value. Furthermore, no carryover effect was observed, which allows for the reliable measurement of randomly ordered samples as would be observed in true clinical settings.

When compared with two commonly used HbA_{1c} diagnostic assays, the D100 and G11, via Passing-Bablok regression, the Norudia assay showed good correlation. A closer analysis revealed small proportional and systematic differences between Norudia and D100, and Norudia and G11. Although Bland-Altman plots also showed minor negative biases of −2.0% and −3.8% between Norudia and D100, and Norudia and G11, respectively (Figures 2B and 3B), the Norudia actually gave higher values at high HbA_{1c} concentrations. This was not a completely unexpected observation, as HPLC-based HbA_{1c} methods have previously been reported to show negative biases at higher HbA_{1c} concentrations.[7,8]

Moreover, the accuracy of the 3 methods was compared using 13 reference samples provided by the KCDC, with corresponding target HbA_{1c} values obtained via IFCC-RMP. The Norudia assay proved to be the most accurate method, with a mean bias of −1.72%, which was significantly lower than both the G11 (mean bias −2.17%) and the D100 (mean bias −4.67%) assays.

Utilizing known Hb variant samples, the HbA_{1c} measurements of the Norudia, D100, G11, and Tina-Quant assays were compared to MS-confirmed HbA_{1c} values (Table 2). The Norudia gave the most consistent and reliable HbA_{1c} values for all samples, with mean % differences to the true HbA_{1c} value only ranging from a low of −6.15% (Hb Queens) to a high of 3.59% (Hb Ube-4). This was followed by the Tina-Quant assay, with mean % differences to the true HbA_{1c} value ranging from a low of −1.65% (Hb G-Coushatta) to a high of 8.15% (Hb Ube-4). However, similar to the results of our previous study,[10] the D100 showed significant positive interference from the Hb Yamagata sample (1205.73% difference to MS-confirmed value), while the G11 assay showed consistently significant negative interference in all analyzed samples. Hemoglobin variants have persistently hindered the accurate measurement of HbA_{1c}, and the interference caused by the most common variants, such as Hb S, E, C, and D, has been well documented in previous studies.[21-24] Interestingly, although the estimated Hb variant prevalence in Korea is 1/2700, it is the rarer Hb G-Coushatta, Queens, Ube-4, Chad, and Yamagata variants, rather than the aforementioned common variants, which are relatively common in the Korean population.[25] Despite their rarity, the confounding effect of these rarer variants has also been reported,[26,27] thus emphasizing the need to improve the coverage of rare variants in established methods. The Norudia HbA_{1c} assay's performance was not affected by the rare Hb variants G-Coushatta, Queens, Ube-4, Chad, and Yamagata, proving its clinical robustness in this aspect.

Despite the excellent overall performance of the Norudia HbA_{1c} assay, there are a few limitations to the study. The study involved the comparison of the Norudia, an enzymatic assay, with only the D100 and G11, which are HPLC methods; ideally, we would have liked to compare the Norudia to another enzymatic assay. However, the HPLC method is currently the most popular method in Korea and is utilized in approximately 70% of clinical laboratories for HbA_{1c} testing, whereas the enzymatic methods are only used in approximately 3% of clinical laboratories nationwide [28]; thus, we believe the comparison scheme in our study is sufficient for major representation of the current clinical situation. Another limitation of the study is the relatively small number of samples available for the method comparison study. Although the CLSI EP9 guideline recommends a minimum of 40 samples for method comparison, we only have small numbers of samples, especially over 80 mmol/mol, which may not be enough to evaluate the exact differences between methods at high HbA1c levels. The third limitation is that our variant analysis did not include the internationally common variants such as Hb S, E, C, and D, and this can be attributed to the rarity of such variants in the Korean population. Nonetheless, the number of foreigners residing in Korea is increasingly becoming a large minority,[29] which will alleviate the lack of availability of variant samples and simultaneously require urgent variant evaluation of routine HbA_{1c} assays. Despite the many advantages of the HPLC method, it possesses the fundamental disadvantage of Hb

variants exerting different effects in response to slight differences in the method protocol.

In conclusion, the Norudia HbA_{1c} assay showed excellent precision, linearity, and minimal carryover effect. When compared with commonly used routine HbA_{1c} assays (Bio-Rad D100, Tosoh G11, and for variant analysis, the Roche Tina-Quant), the Norudia showed the highest accuracy to the true HbA_{1c} value determined via IFCC-RMP and was least affected by known Hb variants. These results suggest that the Norudia can be used immediately in the clinical laboratory and will promote higher-quality diagnosis and treatment follow-up of HbA_{1c} in diabetic patients.

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CONFLICT OF INTEREST

The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, preparation of article, or final approval of article. The authors declare no other conflict of interest.

ETHICAL APPROVAL

This research was approved by the Seoul National University Hospital Institutional Review Board (IRB number B-1711/430-302).

DATA AVAILABILITY STATEMENT

All data generated and analyzed during this study are included in this published article. Please contact the authors for data requests.

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