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Technical Report

Tools for evaluating the performance of HbA1c analyzer: Sigma Metric and Quality Goal Index Ratio

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Abstract

Objectives: Sigma metric model is one of the most popular quality management system tools used for Six Sigma process improvement. This model provides three features that improve the results: low inaccuracy, less deviation, and correct performance of the analytical method. Internal quality control and external quality assessment programs are routinely carried out in all clinical laboratories to evaluate and continually improve the analytical quality. The Six Sigma model is a global quality management system that can also be applied in the determination of glycated hemoglobin (HbA1c). In recent years, this model has been supported by Quality Goal Index (QGI). In this study, we aimed to evaluate the analytical performances of Arkray HA8180V HbA1c analyzer according to internal and external quality Sigma metrics and QGI.

Methods: The data have been evaluated according to two internal control materials (Bio-DPC and KBUDEK External Quality Program) to calculate Sigma levels [Sigma=(TEa%-bias%)/CV%] and quality target indexes (QGI=bias/1.5×CV), where TEa is the total analytical error and CV is the coefficient of variation. QGI is a metric that can distinguish between techniques to deal with sensitivity and accuracy issues as well as calibrator lot changes.

Results: The mean Sigma levels for low and high quality control materials were found to be 5.17 and 2.51, respectively. QGI was found to be 0.8-1.2 for both levels.

Conclusion: The performance of HA8180V HbA1c analyzers was found to be acceptable compared to Sigma metrics. The values of OGI between 0.8 and 1.2 indicate inaccurate and inconsistent result. However, when evaluated as a whole with Sigma values, the results of the devices were found reliable.

Keywords: Hemoglobin A1c, quality control, quality goal index, sigma metric

Hemoglobin is a protein that exists in red blood cells and helps in carrying oxygen. After the synthesis of hemoglobin, many modified hemoglobin types are formed by post-translational modifications. Among these types, hemoglobin A1c (HbA1c) is most commonly found [1, 2]. The International Federation of Clinical Chemistry (IFCC) defines HbA1c as hemoglobin that is irreversibly glycated at one or both N-terminal valines of the β-chains [3]. Analysis of glycated hemoglobin (HbA1c) in blood provides evidence about an individual's average blood glucose levels during the previous two to three months, which is the predicted half-life of red blood cells (RBCs) [4]. As only 0.5% change in HbA1c level is acceptable as a clinically significant change [5, 6], accurate measurement of HbA1c is very important. Therefore, it is important to ensure that a change in HbA1c level is not because of analytical variation [6].

At present, more than 20 different assay methods are being used to measure the level of HbA1c in clinical laboratories. These methods are based on different analytical principles, such as immune turbidimetry, cation-exchange chromatography, and high-performance liquid chromatography (HPLC) [7, 8]. The diagnostic industry recognizes the relevance of the HbA1c concentration in diabetes management, and various commercial tests have been developed in this respect [9]. The high analytical quality of the HbA1c test can be achieved us-

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ing special HPLC systems. Although current QCs in laboratory medicine focus on the performance and efficiency of analytical processes, they still have room for improvement [10].

Quality parameters, inaccuracy and imprecision are basic parameters of methods performance validation as measure of systematic and random error. Those parameters are presented by coefficient of variation (CV) and bias, but also can be used for calculation of total error (TE) [11]. Combining effects of systemic and random error in form of total error makes validation results of complete analytical process more evident [12].

Six Sigma metrics combine bias, precision, and TEa and can be used for assessing the quality of the analytic phase [13]. The exact number of errors made can be quantified by employing Sigma metrics in the laboratory. A high Sigma value indicates that a laboratory's reports of false test results are low. With the aid of Six Sigma principles and metrics, it is possible to achieve the desired quality [14]. Recently, the IFCC Task Force on the Implementation of HbA1c Standardization (TF-HbA1c) suggested a consensus statement regarding the quality targets for HbA1c concerning the Sigma metrics model as the model of choice [15].

Quality Goal Index (QGI) indicates the reason behind a lower value of Sigma: because of lower precision, lower accuracy, or a combination of both. QGI represents the relative extent to which both bias and precision meet their respective quality goals [16].

Materials and Methods

We used the Adams HA-8160V (Arkray KDK, Kyoto, Japan) for HbA1c analysis; the assay principle is based on reverse phase cation-exchange HPLC. The Adams HA-8160V HbA1c analyzer is fully automated and uses reversed-phase cation-exchange chromatography with a colorimetric method of detection (measured at a wavelength of 415 nm and a blanking wavelength of 500 nm). The concentration of HbA1c is expressed as a percentage of the ratio of the hemoglobin peak area to the total hemoglobin peak area (Fig. 1). Two levels of internal quality control (IQC) materials were used daily with mean values 5.0% (range 4.70-5.9%) and 10.8% (range 8.6-11.0%) for IQC1 and IQC2, respectively (extend SURE ® HbA1c liquid control IQC1 and IQC2). The lot number (7089) of the controls was the same with the same mean values all year. CV% was calculated by using the mean from IQC1 and IQC2: CV%=(standard deviation×100)/laboratory mean (IQC).

Monthly bias% was calculated from 12 external quality assessment (EQA) data which were performed monthly [KBUD External Quality Control Program (KBUDEK)] by the following formula: [(our result - peer group mean)/peer group mean]×100 [17]. The mean bias was calculated by dividing bias% by 12. External Quality Control (EQC) data were collected using KBUDEK program in January 2019-December 2019. In the calculation of Sigma values, 10% was used as TEa level, which was suggested by Clinical Laboratory Implementation Amendments 1988 (CLIA 88). The Sigma values were calculated using the following formula: Sigma=(TEa%-bias%)/CV%. The analytical performance of the HbA1c analyzer was evaluated using the obtained Sigma levels. The TEa is the amount a test result may deviate from the "true value" and still be acceptable. The quantitative relationship between the quality of a measurement procedure characterized by the Sigma metric and the appropriate QC procedure(s) can be illustrated by applying a Sigma scale to a critical error plot. A critical-error graph is simply a power function graph that also displays the size of error that is medically important and needs to be detected by the QC procedure: The critical dimensions of systematic and random errors that should be detected by the QC procedure can be calculated from the quality requirement and the observed uncertainty and inaccuracy with the following equa-

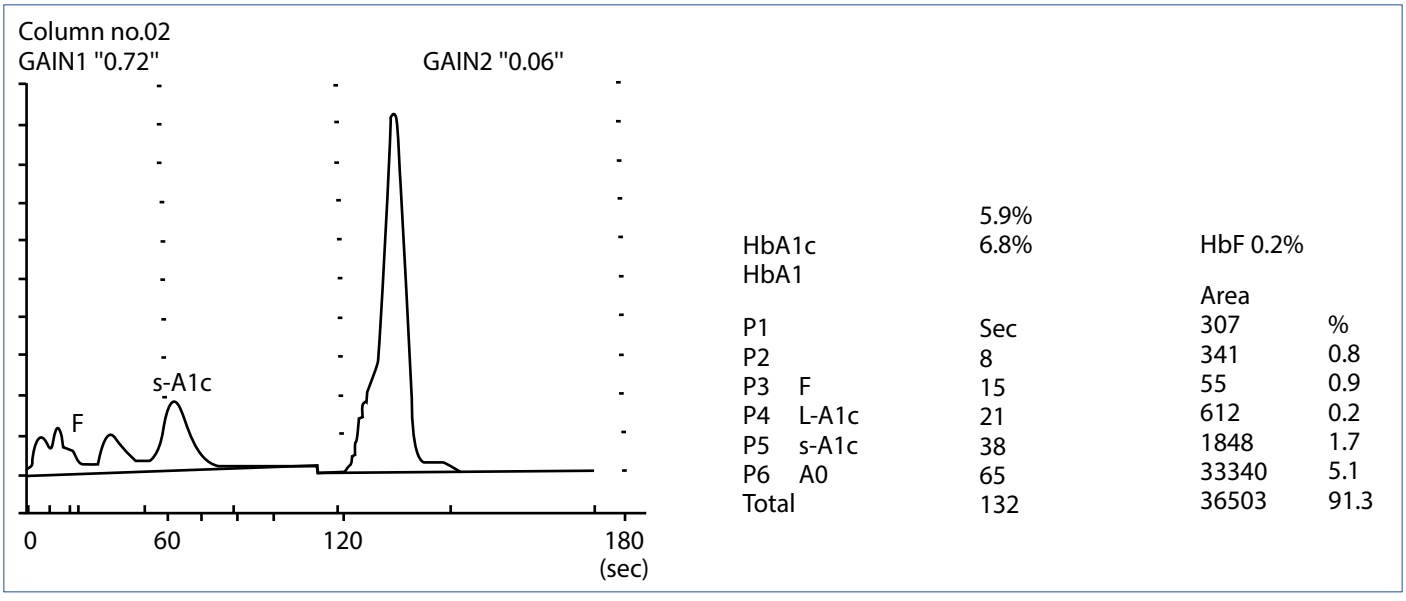

Figure 1. The peak of HbA1c within hemoglobin variant determination in the Adams HA-8160VA analyzer.

tions: SEcrit=[(TEa - biasmeas)/smeas]-z. where TEa is a quality requirement in the form of an allowable total error, biasmeas is the observed inaccuracy of the method (and is considered as an absolute value in these calculations), smeas is the observed imprecision of the method, and z defines the tail of the distribution that is allowed to exceed the quality requirement and is often chosen as 1.65 to set a maximum defect rate of 0.05 or 5%. If QGI <0.8, it indicates uncertainty. QGI of 0.8-1.2 indicates both uncertainty and falsity, and QGI >1.2 indicates falsity. A statistical analysis of the data was evaluated using Microsoft Excel 2016.

Results

According to CLIA 88 values, we found Sigma IQC1=5.17, and IQC2=2.51 (Tea=10). CV%, TEa, bias, Sigma, and QGI values of IQC1 and IQC2 are shown in Table 1. As the IQC2 Sigma value is <3, the QGI value is checked to determine the source of the problem. The QGI value for IQC2 was 0.76. This indicates the imprecision problem. Mean CVs were 1.47% and 2.10% for IQC1 and IQC2, respectively. Bias, CV%, and Sigma of 12 EQC results are shown in Table 2. We found an average Sigma EQC=3.69. According to CLIA 88 values, we found Sigma IOC1=5.17 and IQC2=2.51 (Tea=10). CV%, TEa, bias, Sigma, and QGI values of IQC1 and IQC2 are shown in Table 1. As the IQC2 Sigma value is <3, the QGI value is checked to identify the source of the problem. The QGI value for IQC2 was 0.76. This illustrates the problem of imprecision. The calculated average Sigma metric was 3.69, and ΔSEcrit was 2.04. When EQC was evaluated in terms of QGI, no accuracy problem was observed. EQC results had an imprecision problem. One of the SDI values was 1.45, which is considered acceptable to marginal performance.

Discussion

In our study, the Sigma levels of the Adams Arkray HbA1c analyzer used for the routine HbA1c measurements are at the level recommended by TEa CLIA criteria (TEa=10) (Sigma IOC1=5.17 and IQC2=2.52). We found the average Sigma level of IQC1 and ICQ2 as 3.84. The 1-year EQC Sigma average was found to be 3.69, which indicates that the analytical quality of the Adams HA-8160V analyzer is appropriate when evaluated at the Sigma scale. According to the study conducted by the International Federation of Clinical Chemistry (IFCC) Task Force on the development of quality control targets in HbA1c measurements, it was determined that the Sigma metric model should be preferred, and the Sigma level should be at least 2 for HbA1c measurements in routine laboratories.

The analytical mathematical model was one of the key elements in the development of quality objectives. Sigma met-

Table 1. Sigma, SDI ,QGI, BIAS, CV% and TEA values calculated for Internal quality controls data (level 1(IQC1) and level 2(IQC2))

Control	CV%	BIAS	TEA	Sigma	SDI	Problem	QGI	Problem
IQC1	1.47	-2.40	4.83	3.52	1.71	Acceptable to marginal performance	1.09	Imprecision and inaccuracy
IQC2	2.10	-4.72	-1.26	5.36	-0.33	Acceptable	0.76	Imprecision

SDI: Standart deviation index; QGI: Quality Goal Index; BIAS: Systematic error; CV: Coefficient of variation; TEA: Total analytical error; QCI: Quality goal index; IQC: Internal Quality Control.

Table 2. Sigma, SDI, QGI, BIAS, TEA and CV% values calculated for External quality control data (KBUDEK)

Months	BIAS	CV%	TEA% (CLIA)	SIGMA	SDI	Problem	QGI	Problem
January	6.5	4.49	10	3.1	0.99	Acceptable	0.97	Imprecision and inaccuracy
February	4.6	4.2	10	3.83	1.45	Acceptable to Marginal performance	0.73	Imprecision
March	3.6	4.7	10	6.14	1.2	Acceptable	0.51	Imprecision
April	2	3.32	10	2.41	0.37	Acceptable	0.4	Imprecision
May	2.5	4.09	10	1.83	1.09	Acceptable	0.41	Imprecision
June	7.1	2.2	10	1.32	0.77	Acceptable	0.66	Imprecision
July	5.9	1.96	10	2.09	0.55	Acceptable	0.79	Imprecision
August	1.6	2.27	10	3.7	0.6	Acceptable	0.25	Imprecision
September	3	1.43	10	4.9	0.6	Acceptable	0.37	Imprecision
October	2.8	2.27	10	3.17	0.92	Acceptable	0.62	Imprecision
November	1.3	2.3	10	9.43	0.6	Acceptable	0.38	Imprecision
December	1.6	3.5	10	2.4	0.34	Acceptable	0.8	Imprecision

SDI: Standart deviation index; QGI: Quality Goal Index; BIAS: Systematic error; TEA: Total analytical error; CV: Coefficient of variation.

ric model and quality target index are current and important methods in analytical performance evaluation [18, 19]. Bozkaya et al. [20] conducted a study that evaluated the analytical quality of the HbA1c analyzer according to Sigma metrics. The mean Sigma levels for low and high quality control materials were found to be 3.0 and 4.1, respectively. Literature studies on the evaluation of the analytical performance of HbA1c analyzers over Sigma metrics are very limited. Huysal et al. [21] used Six Sigma methodologies to evaluate the analytical performance of HbA1c analyzer test results. In their study, bias values and process Sigma levels obtained from external quality reports were evaluated. Although Six Sigma methodologies can be used effectively in evaluating analytical performance and regulating IQC-EQC applications, two factors should be considered when calculating the Sigma value. First, different Sigma values can be obtained based on the TEa reference selected. Second, different Sigma values and different bias values can be obtained depending on the IQC sample level and analyte concentration level of the external quality material. Depending on the selected TEa reference, different Sigma values can be obtained. For example, if we had taken TEa value as 6% according to National Glycohemoglobin Standardization Program (NGSP) instead of CLIA, we would have obtained Sigma values as <3 for IQC1 and IQC2. By applying biological variability and the Six Sigma model, Wang and colleagues evaluated the analysis performance of six different HbA1c analyzers. Generally, the analytical performance of 6 HbA1c analyzers in their laboratory was good. However, 50% (3/6) and 67% (4/6) of the HbA1c analyzers have reached the acceptable level in the biological variation and Six Sigma model, respectively [22].

Standardization and monitoring of the analytical performance of HbA1c tests are critical [23]. There is a need for nationwide use of tests in international standards and a certification program for laboratories. Arkray Adams HA-8160 HbA1c is a widely used analyzer [24]. The Sigma metric method can be used to ensure quality, and problems can be revealed with the quality target index.

Conflict of Interest: No conflict of interest was declared by the authors.

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