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Performance evaluation of HbA1c measurement systems with sigma metric for 1066 laboratories in China

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ABSTRACT

Background: This study aimed to evaluate the performance of HbA1c measurement systems quantitatively with sigma metric and promote the quality improvement.
Methods: 1066 laboratories enrolled external quality assessment (EQA) and reported their internal quality control (IQC) data for HbA1c in 2017 were included in this study. The bias and coefficient of variation were collected from EQA and IQC program designed by the National Center for Clinical Laboratory. The σ values was used to assess the performance of HbA1c, and combine Westgard Sigma Rules™ to select proper quality control rules in every laboratory.
Results: Totally, There were 388,190,185,100,59,55,89 participants used Bia-Rad HPLC, TOSOH G7/G8, ARKRAY HA8160/8180, HUIZHONG MQ-2000/2000PT, Roche, Primus HPLC and "Others" system, respectively. "HUIZHONG MQ-2000/2000PT" group had the smallest variation of bias. 56.19% (599/1066) of laboratories met bias criterion and 55.63% (593/1066) satisfied imprecision criterion. However, sigma metrics indicated that 80.21% (855/1066) of 1066 laboratories needed to improve their performance of HbA1c. Moreover, "TOSOH G7/G8" group had the highest constituent ration of $\sigma \geq 3$.
Conclusions: The analytical quality of HbA1c in most laboratories need improving. Laboratories should pay more attention on the performance of HbA1c, and EQA organizers in China should improve evaluation criteria and push standardization work for HbA1c.

1. Introduction

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia, which is due to a defective insulin secretion, damaged insulin-biological effects, or both [1]. It causes various long-term complications, such as retinopathy, neuropathy, and nephropathy. The expecting worldwide prevalence of diabetes mellitus is estimated to be approximately reached 380×10^6 by 2025 [2].

The concentration of HbA1c is related to the life span of red blood cells, which 120 days, and the average concentration is of blood glucose during this period. In addition, it is not affected by fluctuation of daily glucose concentration, exercise and food. HbA1c, which reflects average blood glucose levels over a 2-to 3-month period of time, plays a key role in the diagnosis and treatment of diabetes mellitus [3].

American Diabetes Association (ADA) used HbA1c for the first time as a new diagnostic indicators in 2010 [4]. With the increasing use of HbA1c measurement systems in China, a scientific evaluation scheme to understand the quality level of different systems seems more and more essential for both clinicians and laboratory personnel. Although HbA1c is of great importance for diagnosis, the degree of standardization is not enough in China, and results vary greatly between laboratories.

Sigma is one of the indicators that quantitatively describe the performance of laboratories, which refers to "standard deviation" of statistics, indicating the degree of dispersion of data [5]. Six Sigma™ (Motorola Trademark Holdings, Libertyville, IL) is a concept that has been widely used for nearly a decade, representing an emerging quality management system to achieve the highest level of quality [6]. Six Sigma means six times standard deviation of process variation ought to be within the allowable range, or meet quality requirement of the process. Sigma metrics combine total allowable error, bias and precision, can be used to assess analytical quality.

Westgard Sigma Rules™, proposed by Westgard, is a convenient

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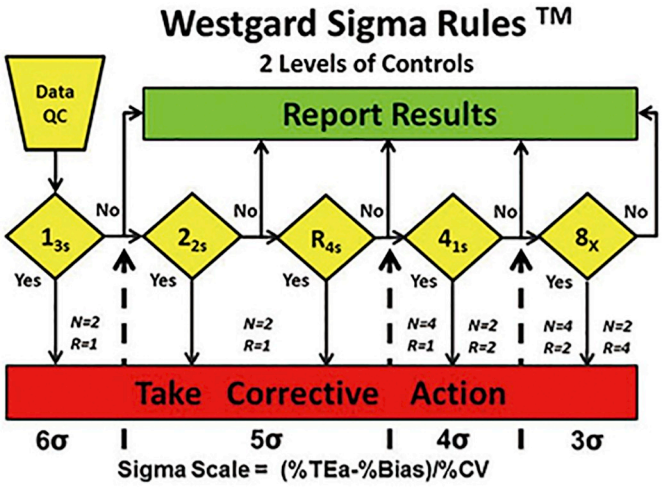

Fig. 1. The Westgard Sigma Rules for 2 levels of control materials [8].

internal quality control design tool for laboratories to choose proper rules [7]. As nearly all the laboratories detected 2 level of control materials in China, we chose Westgard Sigma Rules™ for 2 level of controls to analysis. Fig. 1 showed proper rules and number of quality control, for example, 6-sigma quality requires only a single control rule, 1_{3s}, the notation $N = 2$, $R = 1$ indicates that 2 control measurements are needed in a single run [8].

With the increasing use of HbA1c to monitor blood glucose, external quality assess (EQA) or proficiency testing and internal quality control (IQC) for HbA1c were organized by the National Center for Clinical Laboratories(NCCL),Beijing, People's Republic of China, in recent years. Data of 2017 were collected through these two programs to assess the performance of HbA1c measurement systems with Six Sigma techniques, and to provide recommendations for quality improvement.

2. Material and method

2.1. Subjects

1066 laboratories from different provinces in China were included in this study, which enrolled EQA scheme and provided IQC information of HbA1c in 2017.

2.2. Methods

The EQA samples of five lots (lots number 201711, 201712, 201713, 201714, and 201715) were distributed to laboratories by post on February 2017. Pure fresh frozen patient blood were used as EQA samples, which had satisfied Interoperability and very few matrix effects. In order to evaluate performance of different analytical systems for HbA1c, laboratories were grouped by measurement systems. After the measurement of every sample, participating laboratories were required to report results via Clinet (www.clinet.com.cn) reporting system version 1.5 before March 15. In addition, the information of measurement systems should be provided for grouping. The raw EQA data of each lot were collected through software, and outliers should be removed for analysis. In this study, target value of each lot of sample was assigned by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference method, i.e. liquid chromatography-tandem mass spectrometry. The bias is defined as [(M1-T1) + (M2-T2) + (M3-T3) + (M4-T4) + (M5-T5)]/5, in which M1～M5 are the mean measured HbA1c concentrations in EQA samples 201711～201715 [9].

The IQC program and EQA scheme for HbA1c were organized by NCCL in China. Laboratories that participated in EQA scheme of HbA1c in 2017, returned IQC information in February 2017 including cumulative coefficient of variation (CV) through Clinet (www.clinet.com.cn) reporting system version 1.5. IQC raw data were collected by Clinet (www.clinet.com.cn) evaluation system version 1.0. As long-term quality control data can ensure more stable imprecision value, it was recommended to apply cumulative CV of results in-control to calculate σ value. If there were two concentration levels reported by participants, σ value should be calculated with resultant CV, which was calculated as $[(CV_1^2 + CV_2^2)/2]^{1/2}$. If not, cumulative CV was used.

Table 1
Laboratories classification based on σ level.

σ Level	Grade
6σ	World class
5σ	Excellent
4σ	Good
3σ	Marginal
< 3σ	Unacceptable

The total allowable error (TEa) was set at 5 mmol/mol to pass the evaluation criteria, according to guidance on the use of sigma metrics for quality targets (IFCC TF-HbA1c) [10]. Based on the equation: σ = (TEa-|bias|)/CV, the σ value for HbA1c of all participants could be calculated. Laboratories were graded according to different σ level, as shown in Table 1.

2.3. Statistical analysis

All participants were divided into seven groups on the grounds of measurement systems, those were Bio-Rad HPLC, ARKRAY HA 8160/8180, TOSOH G7/G8, HUIZHONG MQ-2000/2000PT, Roche, Primus HPLC and “Others”.

Normality test was applied to determine whether data of each group and all laboratories was normal distribution, with use of SPSS Statistics version 20. As all reported results were non-normal distribution by Kolmogorov-Smirnov test, median and quartile range were the best statistical parameters to describe the central tendency and dispersion of data. Maximum, minimum were also needed calculating. In order to describe bias of each group, the median, maximum, minimum, 25th and 75th percentiles of bias were of necessity. Box plot was used to describe the distribution of bias.

The constituent ratios of σ values for each group were calculated after getting σ values. One half of TEa is the evaluation criterion of bias, which is 2.50 mmol/mol; while one third of TEa is the criterion of CV, 1.67 mmol/mol, approximately [11]. The percentages of laboratories satisfying the requirement of bias and CV were calculated, respectively. Moreover, the median and range of σ values were obtained for laboratories met both bias and CV evaluation criterions of each group. All the calculation were generated by Clinet EQA evaluation system version 1.0 and Microsoft Excel version 2016.

The ability to detect the analytical error of quality control method depends on rules and the number of control measurements. In order to show the application of standardized sigma performance verification diagram, we took one group for example, helping laboratories choose proper control rules by themselves. After logging in Clinet (www.clinet.com.cn) as administrator, total allowable error, imprecision and bias of HbA1c of laboratories using Roche system was typed, and then proper quality control rules of participants were generated automatically on standardized sigma performance verification diagram.

3. Results

3.1. Descriptive statistics

388 laboratories used Bio-Rad instruments(D-10:241 laboratories; VariantII:90 laboratories; VariantIITurbo:57 laboratories), 190