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RESEARCH ARTICLE

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National continuous surveys on internal quality control for HbA1c in 306 clinical laboratories of China from 2012 to 2016: Continual improvement

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Background: This study aimed to evaluate whether the quality performance of clinical laboratories in China has been greatly improved and whether Internal Quality Control (IQC) practice of HbA1c has also been changed since National Center for Clinical Laboratories (NCCL) of China organized laboratories to report IQC data for HbA1c in 2012.

Methods: Internal Quality Control information of 306 External Quality Assessment (EQA) participant laboratories which kept reporting IQC data in February from 2012 to 2016 were collected by Web-based EQA system. Then percentages of laboratories meeting four different imprecision specifications for current coefficient of variations (CVs) of HbA1c measurements were calculated. Finally, we comprehensively analyzed analytical systems and IQC practice of HbA1c measurements.

Results: The current CVs of HbA1c tests have decreased significantly from 2012 to 2016. And percentages of laboratories meeting four imprecision specifications for CVs all showed the increasing tendency year by year. As for analytical system, 52.1% (159/306) laboratories changed their systems with the change in principle of assay. And many laboratories began to use cation exchange high-performance liquid chromatography (CE-HPLC) instead of Immunoturbidimetry, because CE-HPLC owed a lower intra-laboratory CVs. The data of IQC practice, such as IQC rules and frequency, also showed significant variability among years with overall tendency of meeting requirements.

Conclusion: The imprecision performance of HbA1c tests has been improved in these 5 years with the change in IQC practice, but it is still disappointing in China. Therefore, laboratories should actively find existing problems and take action to promote performance of HbA1c measurements.

KEYWORDS
clinical laboratory, coefficient of variation, diabetes, diagnosis, HbA1c, imprecision, internal quality control, quality specification

1 | INTRODUCTION

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism in which glucose is underutilized and overproduced, causing hyperglycemia.[1] The current worldwide prevalence of diabetes mellitus is estimated to be approximately 250×10^6, and it is expected to reach 380×10^6 by 2025.[2]

Measurement of glycated proteins, primarily HbA1c which reflects average blood glucose levels over a 2- to 3-month period of time, is widely used for routine monitoring of long-term glycemic status in patients with diabetes.[3] But less pre-analytic instability and biological variability for the HbA1c measurement make analytical quality specification more tight. So it is necessary to strictly control of inter-assay standardization, assay precision and trueness. Moreover, it is required

that the test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay.[3]

However, in the past few years, the lack of standardization for HbA1c assay in China leaded to the great difference in inter-laboratory results and the availability of HbA1c tests was only limited to certain laboratories. At present, many kinds of assay methods are used by laboratories in China and some laboratories still use methods non-standardized. In 2012, the preliminary survey conducted by National Center for Clinical Laboratories (NCCL) of China on Internal Quality Control (IQC) practice of HbA1c indicated disappointing assay performance for intra-laboratory CVs.[4] IQC as a part of technical requirements in ISO 15189 document[5] that laboratories shall design quality control (QC) procedures that verify the attainment of the intended quality of results, plays a significant role in laboratories' daily practice. The coefficient of variation (CVs) derived from the data of IQC reflects the imprecision of measurement which represents the quality of clinical laboratories in the analysis phase.

With increasing use of assays certified and standardized by more laboratories and more training programs about QC held by Chinese NCCL available to laboratory manager in recent years, we speculate that the assay performance would be improved. Therefore, we carried out this investigation on IQC practice of HbA1c assay through national External Quality Assessment (EQA) program by NCCL and then assessed the percentages of laboratories meeting four different quality specifications of imprecision to judge whether the quality performance of clinical laboratories in China has been greatly improved from 2012 to 2016 and whether IQC practice has also been changed with time.

2 | MATERIALS AND METHODS

2.1 | Subjects

Laboratories distributed to Chinese different provinces, which participated in Hb1Ac EQA program organized by NCCL that is the official proficiency testing provider in China.

2.2 | Methods

The IQC information for HbA1c was collected annually in each February from 2012 to 2016 via Clinet (www.clinet.com.cn) EQA reporting system version 1.5, which was developed by NCCL of China. Before the formal investigation, the pilot investigation which involved 346 laboratories was conducted by NCCL in 2011. However, the information reported by many laboratories were improper or incomplete in the pilot survey, so we perfected the questionnaire in 2012 and required that laboratories should submit the information including vendor of control materials, number of controls, control rules, mean value of each control, current CVs of February in-control, principle of assay, analyzer, reagent, and calibrator of each concentration level every year. The current CVs were derived from the results of controls in February every year, which were in-control judged by their own IQC rules.

Then, the percentages of laboratories meeting the quality specification for HbA1c were calculated according to four imprecision criteria including the one based on National Academy of Clinical Biochemistry (NACB) and the other requirements derived from biological variation (minimal, desirable, and optimal allowable imprecision). The pass rates of each group, which may divided by year, principle of assay, or type of hospitals, etc., defined as the ratio of "number of laboratories with acceptable performance" to "the total number of laboratories of each group".

2.3 | Analytical quality specifications

The Stockholm Conference held in 1999 achieved a global consensus on the setting of analytical quality specifications in laboratory medicine and advocated the ubiquitous application of a hierarchical structure of approaches. The hierarchy has five levels, which based on: (1) clinical outcomes; (2) biological variation; (3) published professional recommendations; (4) regulatory bodies or organisers of EQA schemes; and (5) current state of the art as demonstrated by data from EQA or PT scheme or found in current publications on methodology.[6,7] After 15 years, the Organisers and Scientific Programme Committee of the 1st Strategic Conference of the European Federation of Clinical Chemistry and Laboratory Medicine on 'Defining analytical performance goals 15 years after the Stockholm Conference on Quality Specifications in Laboratory Medicine', held in Milan on November 24-25, 2014, simplified the hierarchy and represented it by three different models, which were respectively based on: (1) the effect of analytical performance on clinical outcomes; (2) components of biological variation in the measurand, and (3) state-of-the-art.[8] In this study, we choose two kinds of analytical imprecision criteria based on biological variation and state-of-the-art.

The NACB recommended CVs <2% within laboratory,[9] which become our first precision criteria. Other three imprecision criteria for HbA1c measurement were derived from biological variation. (1) Minimal specification for imprecision defined by CV_A <.75 CV_I (CV_I = within-subject biologic variation; CV_A = the analytical precision); (2) Desirable specification for imprecision defined by CV_A <.50 CV_I; (3) Optimal specification for imprecision defined by CV_A <.25 CV_I.[10] Within-subject and between-subject CV values of analytes were updated and compiled by Dr. Carmen Ricos and colleagues (http://www.westgard.com/biodatabase1.htm).[11] Accordingly, we set the minimum, desirable and optimal quality specifications for analytical imprecision (CVs) as 1.43%, 0.90%, and 0.48%, respectively.

2.4 | Statistical analysis

The distributions of current CVs are presented as median and several percentiles (i.e., 5th, 25th, 75th, 95th percentiles). Friedman M test was performed to compare the current CVs among different years (followed by the Bonferroni method for multiple comparisons between groups). The chi-square test was performed to compare for pass rates and constituent ratios among different groups (followed by the

Bonferroni method for multiple comparisons between groups). The differences in current CVs among groups in the same year were tested by Kruskal-Wallis *H* tests or Mann-Whitney *U*-tests. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Armonk, NY, USA) and Excel (Microsoft, Redmond, WA, USA) (2007 version). A value of $P<.05$ was considered to be statistically significant.

3 | RESULTS

Three hundred and thirty-one clinical laboratories from Chinese different provinces submitted their IQC data of HbA1c assays in February 2012 through Clinet EQA reporting system, with 306 laboratories (92.4%) reporting their IQC information of February in the following 4 years. As there are no harmonized national control materials for HbA1c for daily IQC, QC materials among laboratories varied widely with respect to manufactures and measurements. Those who used controls of two levels of mass fraction were asked to submit the data of both levels. We did not define the range of measurement for each level, so there may be an overlap between the two levels. Table 1 shows the distribution of measurement of the QC materials in Level 1 and Level 2. There were fewer laboratories reporting the data of two levels, so the following subgroup analyses of the current CVs in the essay were for level 1.

3.1 | Imprecision analysis

The distribution of current CVs for level1 and level 2 were shown in Table 1. For Level 1, the current CVs of 2012 showed significant higher than other years (all $P<.005$). On the contrary, the current CVs of 2016 was smaller than other years significantly (all $P<.005$). Furthermore, the current CVs between following 2 years have no significant difference: 2013 and 2014 ($P=.254$); 2013 and 2015 ($P=.024$); 2014 and 2015 ($P=.043$). For Level 2, there were no certain regulations for the current CVs change. Current CVs in 2012 was significant higher than 2013 ($P=.002$), 2015 ($P<.001$), and 2016 ($P=.003$). It did not show significant difference between other years ($P>.005$).

The percentages of acceptable laboratories meeting different four allowable imprecision specifications for current CVs of HbA1c all showed the increasing tendency year by year from 2012 to 2016 (Table 1). As for level 1, Laboratories owned higher pass rates when the NACB specification (from 39.9% to 63.4%) was applied, followed by minimum allowable imprecision specification (from 24.5% to 40.7%), desirable specification (from 8.0% to 18.1%), and optimum specification (from 3.2% to 4.9%).

3.2 | Imprecision analysis by type and category of hospital

The distribution of current CVs (Supplemental Material) among laboratories in different types and categories of hospitals were both different each year. When laboratories were sorted by type of hospital, the current CVs of laboratories in tertiary hospital were significant different among years ($P<.001$) and its pass rates based on NACB also expressed increasing tendency year by year from 2012 to 2016; secondary hospital did not have the change, that is, there was no significant difference in its current CVs among different years ($P=.184$) and no consistent tendency for pass rates from 1 year to another. When laboratories were sorted by category of hospital, the current CVs were only significant different in general hospital among years ($P<.001$).

TABLE 1 Mass fraction and current CVs of control materials and percentages of laboratories meeting different quality requirements for HbA1c (%)

Year	Number of labs[a]	Mass fraction		Current CVs			Allowable imprecision specifications based on NACB and biological variation			
		Median	IQR[b]	Median	IQR[b]	*P**	NACB[c]	Minimum	Desirable	Optimal
Level 1										
2012	306	5.68	0.57	2.60	2.88	<.001	39.9	24.5	10.1	4.9
2013	306	5.67	0.49	2.09	1.77		47.0	23.1	8.0	3.6
2014	306	5.35	0.64	1.90	1.58		53.5	26.2	8.5	3.2
2015	306	5.34	0.58	1.90	1.56		54.3	33.2	12.5	4.3
2016	306	5.45	0.63	1.61	1.52		63.4	40.7	18.1	4.9
Level 2										
2012	147	9.46	0.68	2.39	2.35	<.001	44.2	32.0	12.2	4.1
2013	158	9.60	0.97	1.83	1.49		56.3	28.1	13.3	3.1
2014	173	9.58	0.78	1.78	1.46		63.7	38.9	8.3	0.6
2015	171	9.69	0.73	1.53	1.13		69.9	46.8	20.5	3.2
2016	177	9.83	0.67	1.49	0.94		72.3	52.5	19.1	3.5

[a]The data in this row reflect the number of laboratories which have submitted the information of current CVs for level 1 and level 2.
[b]Interquartile range (IQR) is equal to the difference between the upper and lower quartiles, IQR=Q3-Q1.
[c]Analytical imprecision criteria based on National Academy of Clinical Biochemistry (NACB) was set as <2% within laboratory.
*Differences in current CVs in different years were tested by Friedman M test.

3.3 | The changes of IQC practice from 2012 to 2016

The constituent ratio of vendors of control materials for HbA1c did not change significant (χ^2=28.41, *P*=.1). Bio-Rad (from 45.1% to 56.5%) was the primary supplier of control materials for HbA1c, followed by TOSOH (from 10.9% to 15.2%) and Roche (from 5.5% to 11.9%) (Table 2). It is worth noting that a proportion of laboratories (about 5.0%) was using in-house controls. Further analyzing the current CVs of different QC material's producers, we can found that QC materials produced by Roche owed higher CVs than other manufacturers; on the contrary, TOSOH has smaller current CVs. Furthermore, the current CVs of different vendors all showed a decreasing tendency from 2012 to 2016 as a whole (Table 2). As for QC concentration, Roche also had

TABLE 2 Current CVs of each group categorized by control material vendors for HbA1c from 2012 to 2016 (%)[a]

		Mass fraction		Current CVs	
Manufacturer of control materials	Percentage of labs % (N/total)	Median	IQR[b]	Median	IQR[b]
2012					
Bio-Rad	45.1 (138/306)	5.70	0.32	2.12	1.93
TOSOH	10.9 (33/306)	5.52	0.29	1.30	0.77
Roche	11.9 (36/306)	6.20	0.88	4.10	2.86
RANDOX	5.5 (17/306)	5.68	0.35	4.02	2.97
In-house preparation	5.1 (16/306)	6.10	0.67	2.16	1.91
Others	21.5 (66/306)	5.52	0.67	3.00	3.17
2013					
Bio-Rad	51.6 (158/306)	5.61	0.21	2.00	1.09
TOSOH	12.0 (37/306)	5.53	0.45	1.11	0.94
Roche	10.0 (31/306)	6.10	0.60	3.27	2.19
RANDOX	4.8 (14/306)	5.63	0.34	4.21	5.39
In-house preparation	2.4 (7/306)	5.90	0.89	1.44	1.25
Others	19.2 (58/306)	5.43	0.56	2.71	3.06
2014					
Bio-Rad	54.6 (167/306)	5.34	0.22	2.01	1.36
TOSOH	14.9 (45/306)	5.56	0.39	1.49	1.00
Roche	7.1 (22/306)	6.30	0.84	3.32	2.37
RANDOX	4.3 (13/306)	5.38	0.55	2.00	2.12
In-house preparation	2.8 (9/306)	5.80	1.23	2.39	2.58
Others	16.3 (50/306)	5.37	0.45	1.79	1.58
2015					
Bio-Rad	54.5 (166/306)	5.33	0.21	1.98	1.46
TOSOH	15.1 (46/306)	5.16	0.79	1.26	1.08
Roche	6.1 (19/306)	5.70	0.45	2.59	1.97
RANDOX	3.6 (11/306)	5.56	0.54	2.14	3.22
In-house preparation	5.4 (16/306)	5.67	1.09	1.82	1.41
Others	15.4 (47/306)	5.39	0.32	1.64	2.66
2016					
Bio-Rad	56.5 (173/306)	5.39	0.23	1.76	1.51
TOSOH	15.2 (47/306)	5.09	0.20	1.12	1.18
Roche	5.5 (17/306)	5.79	0.36	2.54	1.23
RANDOX	4.2 (13/306)	5.50	0.61	1.97	1.98
In-house preparation	5.9 (18/306)	5.72	1.15	1.52	1.27
Others	12.7 (39/306)	5.40	0.41	1.25	1.69

[a]The subgroup analyses of the current CVs and mass fraction were both for level 1.
[b]Interquartile range (IQR) is equal to the difference between the upper and lower quartiles, IQR=Q3-Q1.

a bigger mass fraction than other QC vendors. See Table 2 for more information about the distribution of QC concentration.

In addition, the constituent ratio of principles of assay has changed with time (P<.001). The proportion of Immunoturbidimetry (from 45.1% to 56.5%) used by laboratories has decreased year by year, while the proportion of Automated cation exchange HPLC (CE-HPLC; from 39.8% to 81.2) has increased with year. The proportion of other methods changed very little for its own smaller percentages (Table 3). As for mass fraction of QC materials, the concentration distribution is not different significantly among different test principles (Table 3). Further analysis of the current CVs of different assay methods showed as Table 3. The current CVs of CE-HPLC is smaller than Immunoturbidimetry every year (P<.001). When four kinds of imprecision criteria were employed, the pass rates of CE-HPLC was also higher than Immunoturbidimetry every year (Table 3). Comparing the current CVs of laboratories (n=227) which using Immunoturbidimetry in 2012 while changed using CE-HPLC in the following years and the laboratories which kept using Immunoturbidimetry without change, we can discover: the current CVs of 2012: 4.02 (2.31, 7.80) vs. 4.04 (1.98, 6.98), respectively (P=.569); 2016: 1.45 (0.89, 3.16) vs. 2.58 (1.12, 3.46), respectively (P=.002). To help inform laboratory practitioners about the lab test performance, we also list the information of manufacturers for the different test principles in 2016, which were showed in Table 4.

As for analytical system, 52.1% (159/306) laboratories changed their systems from 2012 to 2016 with the change in principle of assay. The current CVs between laboratories did not change analytical systems and those changed systems revealed no significant difference in 2012 (Z=0.10, P=.920) but significant difference in 2016 (Z=3.07, P=.002).

TABLE 3 Mass fraction, Current CVs and pass rates for each group categorized by principle of assay[a]

Principle of assay[b]	Percentage of labs % (N/total)	Mass fraction (%)		Current CVs (%)		Allowable imprecision specifications based on NACB and biological variation (%)			
		Median	IQR[c]	Median	IQR[c]	NACB[d]	Minimum	Desirable	Optimal
2012									
Immunoturbidimetry	42 (129/306)	5.64	0.51	3.77	2.82	12.9	11.3	1.6	1.6
CE-HPLC	39.8 (122/306)	5.63	0.43	1.50	1.81	53.5	33.5	14.8	6.5
AC-HPLC	9.8 (30/306)	5.38	0.63	2.27	1.00	37.5	6.2	0	0
Others	8.3 (25/306)	5.33	0.38	3.73	5.65	18.2	18.2	9.1	9.1
2013									
Immunoturbidimetry	25.3 (77/306)	5.64	0.60	3.78	2.50	19.4	11.3	1.6	0
CE-HPLC	63.3 (194/306)	5.63	0.43	1.82	1.20	60.1	31.4	10.5	5.9
AC-HPLC	7.7 (24/306)	5.38	0.60	1.86	1.42	58.8	11.8	11.8	0
Others	3.7 (11/306)	5.33	0.52	3.03	2.10	18.2	9.1	9.1	0
2014									
Immunoturbidimetry	16.3 (50/306)	5.62	0.59	3.41	2.69	27.5	7.5	5.0	5.0
CE-HPLC	72.2 (221/306)	5.53	0.43	1.80	1.18	61.6	31.3	10.7	3.4
AC-HPLC	6.9 (21/306)	5.58	0.42	2.29	1.66	33.3	0	0	0
Others	4.6 (14/306)	5.83	0.54	2.15	1.13	18.2	9.1	0	0
2015									
Immunoturbidimetry	13.2 (40/306)	5.64	0.57	2.86	2.03	29.4	17.6	2.9	2.9
CE-HPLC	80 (26/306)	5.63	0.43	1.74	1.42	58.7	35.8	15.9	4.5
AC-HPLC	5.7 (17/306)	5.38	0.63	2.15	1.90	46.7	20	0	0
Others	4.2 (13/306)	5.53	0.58	2.66	3.81	36.4	27.2	9.1	5.4
2016									
Immunoturbidimetry	9 (28/306)	5.34	0.33	2.58	2.14	31.8	22.7	0	0
CE-HPLC	81.2 (248/306)	5.43	0.43	1.60	1.33	66.3	42.3	19.9	5.1
AC-HPLC	7.8 (24/306)	5.58	0.60	1.70	2.98	63.2	36.8	10.5	5.3
Others	2 (6/306)	5.33	0.58	0.77	0.35	32.1	21.0	7.8	0

[a]The subgroup analyses of the current CVs, mass fraction and pass rates were all for level 1.
[b]CE-HPLC, Automated cation exchange HPLC; AC-HPLC, Automated affinity chromatography HPLC; others, including low pressure liquid chromatography, particulate chromatography and enzymatic analysis.
[c]Interquartile range (IQR) is equal to the difference between the upper and lower quartiles, IQR=Q3-Q1.
[d]Analytical imprecision criteria based on National Academy of Clinical Biochemistry (NACB) was set as <2% within laboratory.

TABLE 4 Current CVs of level 1 by manufacturers for the different test principles in 2016

Principle of assay[a]	Manufacturer of instruments	Percentage of labs % (N/total)	Current CVs (%)		
			25th	Median	75th
Immunoturbidimetry	Roche	53.6 (15/28)	1.70	2.39	3.15
	Siemens	14.3 (4/28)	1.42	3.13	6.04
	Hitachi	10.7 (3/28)	0.93	4.49	—
	Beckman	14.3 (4/28)	2.57	3.80	4.42
	Abbott	7.1 (2/28)	2.69	3.10	—
CE-HPLC	Bio-Rad	49.2 (122/248)	1.51	1.92	2.81
	Tosoh	26.2 (65/248)	0.79	1.17	1.99
	ARKRAY	18.1 (45/248)	0.66	1.10	2.08
	Medconn	4.8 (12/248)	1.76	3.05	3.62
	Primus	0.8 (2/248)	1.67	2.38	—
	Roche	0.8 (2/248)	2.28	2.67	—
AC-HPLC	Primus	66.7 (16/24)	1.37	1.83	4.30
	Tosoh	12.5 (3/24)	1.20	1.34	12.08
	Medconn	8.3 (2/24)	1.05	0.98	—
	ARKRAY	8.3 (2/24)	0.31	1.22	—
	Bio-Rad	4.2 (1/24)	—	—	—
Others	Others	100 (6/6)	0.76	3.49	5.97

[a]CE-HPLC, Automated cation exchange HPLC; AC-HPLC, Automated affinity chromatography HPLC; Others, including low pressure liquid chromatography, particulate chromatography and enzymatic analysis.

In the survey, laboratories were asked to report what control rules they used. We found that the constituent ratio of control rules has changed significantly (Table 5). The proportion of laboratories using single IQC rule (1_{2s} or 1_{3s}) (from 18.3% to 7.6%) has decreased from 2012 to 2016. Satisfyingly, more and more laboratories (from 1.3% to 42.4%) have known about the concepts of IQC rules clearly and were able to choose their appropriate control rules which were combined one or more rules of $1_{2s,}$ 1_{3s}, 2_{2s}, R_{4s}, 4_{1s}, and $10_{\bar{x}}$ based on analyzing performance. It's interesting to find that laboratories which can use combined rules (e.g., $1_{2s}/1_{3s}$ and $1_{3s}/2_{2s)}$ had a higher pass rates than laboratories which used single IQC rule or did not know the concept of QC rules clearly.

Internal Quality Control frequency or average time intervals between two IQC measurements which were calculated based on the reported number of IQC observation per month has also changed with time. Most laboratories (>80%) performed one IQC measurement every more than 1 day before 2015. While in 2016, up to 34.4% laboratories performed more than one IQC per day. The median of average time intervals of 2012 to 2016 were 36.0, 28.8, 32.7, 30.0, 26.7 hours, respectively. Accordingly, further analysis of the pass rates against four criteria indicated that laboratories which ran one QC or more per day got a better result for current CVs. See Table 5 for more information.

4 | DISCUSSION

The program described in this manuscript is the first long term IQC practice survey evaluating the overall knowledge of imprecision level of HbA1c measurement in clinical laboratories of China. The results indicated that the quality performance of clinical laboratories in China has been greatly improved from 2012 to 2016 with CVs decreased and percentages meeting four different imprecision criteria increased and IQC practices including IQC rules, the frequency of IQC, principle of assay, analyzer, reagent and calibrator, have also been changed with time.

The percentage CVs (expressed in percentage) can also be regarded as one of the quality indicators of analytical phase which defined as the measure of the degree to which a set of inherent characteristic fulfills requirements.[5] Therefore, CVs as a quality indicator can indicate the imprecision of measurement in the analysis phase and measure how well an organization meets the needs and requirements of users and the quality of operational processes. Laboratories can monitor the monthly or long-time CVs of IQC data to evaluate the imprecision performance of the measurement systems. And comparison of CVs with the corresponding quality specification can give laboratories some suggestions to make effort. In this study, we choose four imprecision criteria which are intra-laboratory CVs <2.0% recommended by NACB and minimum (CVs <1.43%), desirable (CVs <0.90%) and optimal (CVs <0.48%) specification based on biological variation. The results indicated that the current CVs of laboratories has become smaller and smaller; naturally, the pass rates based on the four imprecision specifications, especially on NACB, has increased greatly in these 5 years.

There are many aspects that can affect the performance of HbA1c measurements, including technical and management level. In this survey, we explored several important factors which are hospital type,

TABLE 5 Proportion of laboratories by control rules or control frequency and percentages of acceptable laboratories against different allowable imprecision specifications for HbA1c (%)[a]

	Proportion of laboratories					Allowable imprecision specifications based on NACB and biological variation[b]			
IQC practice	2012	2013	2014	2015	2016	NACB[c]	Minimum	Desirable	Optimal
IQC rules									
Single IQC rule	18.3	18.5	10.9	7.9	7.6	30.8	21.7	5.6	0
$1_{2s}/1_{3s}$	4.0	3.3	2.5	8.2	9.3	50.8	40.2	19.5	5.1
$1_{3s}/2_{2s}$	10.8	14.4	14.2	20.0	19.0	60.1	39.8	18.6	0
$1_{2s}/1_{3s}/2_{2s}$	2.2	3.3	5.5	8.6	10.1	63.2	43.2	16.5	6.9
$1_{3s}/2_{2s}/R_{4s}$	5.0	4.5	8.0	12.1	15.6	65.2	42.1	17.9	5.4
One or more from the rules of 1_{2s}, 1_{3s}, 2_{2s}, R_{4s}, 4_{1s} and $10_{\bar{x}}$	15.1	18.1	16.7	37.5	32.9	59.5	39.9	13.2	6.5
Other rules	2.2	0.8	0.4	2.5	4.2	48.9	30.2	8.9	5.3
Unclear	42.4	37.0	41.8	3.2	1.3	35.6	20.5	6.8	0
IQC frequency									
One QC run every more than 2 days	27.5	14.7	12.4	14.7	7.9	33.2	25.6	0	0
One QC run every 1-2 days	71.9	84.5	85.9	82.4	57.7	61.2	39.4	18.9	5.2
More than one QC run per day	0.6	0.8	1.8	2.8	34.4	67.8	40.3	20.1	7.9

[a]The subgroup analyses of the current CVs, mass fraction and pass rates were all for level 1.
[b]The pass rates against four criteria were for the 2016 data.
[c]Analytical imprecision criteria based on National Academy of Clinical Biochemistry (NACB) was set as <2% within laboratory.

assay methods and IQC practice. Comparing with other hospitals, we found that imprecision performance of tertiary or general hospital become better and better with steady increasing pass rates year by year, which may be related to the fact that these hospital focus more on their performance and can actively take action to achieve continual improvement than other types of hospitals. Excitingly, NGSP certified laboratories of China become more and more (http://www.ngsp.org), but these laboratories almost belong to tertiary or general hospital. It was demonstrated that the certification project by NGSP may help decrease intra-laboratory imprecision level in participant laboratories in China, which were also demonstrated by other survey.[12-14]

HbA1c test plays a critical role in the management of the patient with diabetes, but prior Expert Committees have not recommended use of the HbA1c for diagnosis of diabetes, in part due to lack of standardization of the assay. However, HbA1c assays are now highly standardized by NGSP and International Export Committee has also recommended the use of HbA1c test to diagnose diabetes.[15] Unfortunately, many laboratories of China used HbA1c assay methods which have not been certificated by NGSP and have documented traceability to the DCCT Reference Method in the past few years. But at present, more and more laboratories begin to use NGSP certified methods and reagents (updated monthly in the NGSP Web site of http://www.ngsp.org, though a part of laboratories still use methods non-standardized, whose change can be seen in our survey. Further analyses of pass rates and current CVs of different assay methods in the same year from 2012 to 2016 revealed the different inter-assay performance that the imprecision performance of CE-HPLC is better than Immunoturbidimetry and other methods, which was consistent with the survey by NCCL in 2012.[4] Moreover, CE-HPLC method is the DCCT reference and also a CLSI-designated comparison method.[13] The assay has demonstrated good long-term precision.[12] Therefore, the overall precision of Chinese laboratories improved with CE-HPLC method used by more laboratories naturally.

A wide variation in laboratory practice will affect the implementation and review of IQC. A poor approach can lead to a spectrum of scenarios from validation of incorrect patient results to over investigation of falsely rejected analytical runs. So IQC rules designed appropriately based on the required quality and assay performance can optimize error detection and reduce the rate of false rejection. As we can see, the percentages (from 18.3% to 7.6%) of laboratories choosing single IQC rule which is inherently problematic due to the high level of false rejections or low error detection has decreased. And the percentages of laboratories (from 42.4% to 1.3%) misunderstood or confused the concepts of IQC rules also become less and less, followed by more laboratories beginning to combine two or more IQC rules derived from Westgard rules.[16] These all indicated laboratory managers has recognized the importance of IQC and the effectiveness of training or education on IQC by NCCL of China. Not only the IQC rules are becoming more and more efficient, but the frequency of measurement of control materials also becomes more and more satisfactory. In the survey, we also found that laboratories which can combined two or more QC rules and run one QC or more per day had a higher pass rates against four different imprecision requirements, which confirmed the importance of designing appropriate QC rules and performed IQC

measurements in a proper frequency. Today, though, most laboratories still perform one QC every 1-2 days, it is time for Chinese laboratories to achieve the goal that laboratory personnel can decide their IQC frequency based on laboratory situation. Furthermore, the data of the survey suggested that there were no significant difference in pass rates between laboratories using two kinds of QC rules and three kinds of rules. Therefore, it is not necessary for laboratories to use very complex QC rules. Similarly, laboratories do not need perform IQC too often. Fortunately, there has been assay-specific IQC systems developed by Kinns et al.[17] It is considered from selection of IQC material to selection of IQC rules in the each stage of the IQC system. Chinese NCCL also developed a IQC system specifically aimed at the analytical run length for quantitative tests in clinical laboratory.[18]

Although the current CVs of HbA1c has decrease and pass rates against four different imprecision criteria has increased, the performance of HbA1c measurement in China is still frustrating. The pass rates against NACB, minimum, desirable and optimal specification were only 72.3%, 52.5%, 19.1%, and 3.5% in 2016, respectively. Comparing with the study of Woodworth et al.[19] and CAP survey,[20] the performance of HbA1c instruments in our study was really worse. In their investigation, many assay methods can achieve intra-laboratory CVs of <2%. As the specifications based on biological variability belong to the second of the Stockholm hierarchy, while the recommendation of NACB belongs to the third, the former is tighter than the latter. Hence, we should choose a appropriate imprecision specification for evaluating laboratory performance.

However, there were still many deficiencies which exist in this national continual survey on IQC practice for HbA1c. First of all, as there are no harmonized national control materials for HbA1c IQC, control materials among laboratories varied widely with respect to manufactures and measurements and we cannot compare the mean values between laboratories. For example, QC materials produced by Roche owed a bigger mass fraction than other manufacturers. But we can have the knowledge of how many concentration levels of QC materials tested by laboratories. As the data show, unfortunately, only about 50% laboratories performed 2 or 3 concentration levels of IQC materials for HbA1c, which is recommended by many authorities.[5,9] In our following research, we may choose control materials which produced by the same manufacturers and belong to the same level to establish the program of inter-laboratory comparison for IQC. Second, the participant laboratories in the survey is almost tertiary hospital which have better medical facilities and higher management level, so they cannot represent the overall medical level in China. But this survey is a pilot study of IQC practice for HbA1c, we will involve different types and categories of hospital in the next investigation. Finally, we did not give participant laboratories specific suggestions on how to improve their IQC performance but just a data report, which will also become our next work. Accordingly, NCCL as a governmental regulator can play a more critical role on the improvement of HbA1c measurement.

In this survey, IQC information of 306 EQA participant laboratories which kept reporting IQC data in February from 2012 to 2016 were collected by Web-based EQA system. The results suggest that the Current CVs of HbA1c tests have decreased and acceptable percentages of allowable imprecision of HbA1c against specifications derived from NACB and biological variability have increased from 2012 to 2016 with the change in HbA1c assay methods and IQC practices. But the imprecision performance of HbA1c measurement is still disappointing, so clinical laboratories in China should actively find the problem exist and take action immediately. On the other hand, NCCL of China can do more such as perfecting the questionnaire further and give more information and directions to laboratories for continual improvement.

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