RESEARCH ARTICLE

Quality specification and status of internal quality control of cardiac biomarkers in China from 2011 to 2016

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Background: This study aimed to investigate the status of internal quality control (IQC) for cardiac biomarkers from 2011 to 2016 so that we can have overall knowledge of the precision level of measurements in China and set appropriate precision specifications.

Methods: Internal quality control data of cardiac biomarkers, including creatinine kinase MB (CK-MB) ($\mu\text{g/L}$), CK-MB(U/L), myoglobin (Mb), cardiac troponin I (cTnI), cardiac troponin T (cTnT), and homocysteines (HCY), were collected by a web-based external quality assessment (EQA) system. Percentages of laboratories meeting five precision quality specifications for current coefficient of variations (CVs) were calculated. Then, appropriate precision specifications were chosen for these six analytes. Finally, the CVs and IQC practice were further analyzed with different grouping methods.

Results: The current CVs remained nearly constant for 6 years. cTnT had the highest pass rates every year against five specifications, whereas HCY had the lowest pass rates. Overall, most analytes had a satisfactory performance (pass rates >80%), except for HCY, if one-third TEa or the minimum specification were employed. When the optimal specification was applied, the performance of most analytes was frustrating (pass rates < 60%) except for cTnT. The appropriate precision specifications of Mb, cTnI, cTnT and HCY were set as current CVs less than 9.20%, 9.90%, 7.50%, 10.54%, 7.63%, and 6.67%, respectively. The data of IQC practices indicated wide variation and substantial progress.

Conclusion: The precision performance of cTnT was already satisfying, while the other five analytes, especially HCY, were still frustrating; thus, ongoing investigation and continuous improvement for IQC are still needed.

KEYWORDS

analytical phase, biochemical markers, health care, quality control, quality indicators, quality specification

1 | INTRODUCTION

According to World Health Organization estimates, 16.7 million people around the globe die of cardiovascular diseases (CVD) each year, and nearly 25 million deaths are estimated to occur worldwide by the

year 2020. CVD is more common in China than in all economically developed countries in the world added together.¹ Recently, cardiac biomarkers have become a major focus of attempts to improve CVD risk scores. The use of such biomarkers is attractive because they integrate signals from different pathophysiological pathways, including

signals for cardiac, vascular, and renal health.² In the 2012 report of the European Society of Cardiology/American College of Cardiology, the essential criterion for myocardial infarction was defined as elevated cardiac biomarkers.³

Therefore, the accuracy of these cardiac biomarkers tests become more and more important in the diagnosis of CVD, and the advances in test technology have also contributed to the increased importance of laboratory tests. However, there is no denying that many diagnostic errors are associated with laboratory testing, and many of these errors are preventable.⁴ Accordingly, evaluating the quality performance of medical laboratories has become increasingly important not only for reducing costs, but also for providing evidence of testing-related diagnostic errors. It has been demonstrated that the optimal analyzing performance and correct measurements can improve the quality of patient care.⁵ Quality indicators (QIs) can be especially useful for quantifying the quality of interested aspects by comparing them against defined criteria.^{6,7} The percentage coefficient of variation (CV) can be treated as one of the QIs for monitoring the precision of measurements in the analytical phase of laboratory work.⁸

To monitor the precision of measurements, laboratories should perform routine internal quality control (IQC). Additionally, ISO 15189 also requires that laboratories design IQC procedures to verify the attainment of the intended quality of results.⁹ However, how can laboratories evaluate their levels of analyzing precision? Comparing CVs with different quality specifications can let them know whether their laboratory performances have met the specific quality criterion and provide them with corresponding directions to make an effort. Meanwhile, in this study, the national IQC investigation launched by the National Center for Clinical Laboratories (NCCL) of China in 2011 can also provide participating laboratories more useful information, including the whole national situation of precision and their own positions compared to others. For organizing this continuous survey of cardiac biomarker IQC data, we can not only have overall knowledge of the precision level of cardiac biomarker measurements, but also the tendency of CVs and pass rates against different precision specifications from 2011 to 2016. Eventually, this national survey can help laboratories set appropriate precision specifications for each analyte of cardiac biomarkers.

2 | MATERIALS AND METHODS

2.1 | Subjects

The subjects of this continual IQC investigation were laboratories located within different provinces in China that participated in a cardiac biomarkers EQA scheme organized by NCCL, which is the official EQA provider in China. In 2011, the number of laboratories participating in the IQC investigation for creatinine kinase MB (CK-MB) ($\mu\text{g/L}$), CK-MB (U/L), myoglobin (Mb), cardiac troponin I (cTnI), cardiac troponin T (cTnT), and homocysteine (HCY) were 130, 140, 214, 177, 156, and 134, respectively. Additionally, 91.5% (119/130), 73.6% (103/140), 81.3% (174/214), 85.9% (152/177), 85.3% (133/156), and 88.8%

(119/134) of laboratories submitted their IQC data for CK-MB ($\mu\text{g/L}$), CK-MB (U/L), Mb, cTnT, cTnT, and HCY in the following 5 years, respectively.

2.2 | Methods

The IQC data for cardiac biomarkers were collected in April every year from 2011 to 2016 via an additional part of the Clinet (www.clinet.com.cn) EQA reporting system version 1.5, which was developed by NCCL in China. The survey questionnaires were distributed to participating laboratories, and they were requested to submit the IQC information, which included the manufacturers, the lot number of quality control (QC) materials, the QC rules, the number of concentration levels for in-control QC materials, the mean value of each concentration level, the current CVs of measurements, the principle of the assay, and the manufacturers of instruments, reagents, and calibrators.

The CV was calculated as the standard deviation divided by the mean value multiplied by 100. These two parameters (standard deviation and mean value) were derived from the in-control IQC results, which were judged by QC rules set by laboratories themselves. As different laboratories performed different numbers of concentration levels of QC materials, we only analyzed the CVs of level 1, for which more laboratories reported the data. Then, the percentages of laboratories meeting quality specifications (ie, pass rates) for current CVs were calculated according to five precision criteria, including two criteria based on total error allowance (TEa) (1/3TEa and 1/4TEa) and the other three quality specifications (minimal, desirable, and optimal allowable precision criteria) derived from biologic variation data.

The acceptable CV was defined as less than corresponding precision criterion. The pass rates were defined as the ratio of "number of laboratories with acceptable CVs" to "the total number of laboratories of each group." According to different grouping rules such as year, test principle, or manufacturer of instrument, all participating laboratories could be divided into several groups for a particular biomarker. Then, pass rate for each group was calculated and compared among different groups. The appropriate precision specification was chosen from these five kinds of specifications to allow approximate 80% laboratories meet the chosen precision criterion.

2.3 | Analytical quality specifications

The 1/3TEa, 1/4TEa, and the specifications from biologic variation database including the minimum, desirable, and optimal allowable precision requirement were used as the quality criteria to evaluate the precision of IQC. The details of the quality requirements are shown in Table S1.

2.3.1 | Quality specifications derived from CLIA'88

The TEa of 1/4TEa and 1/3TEa specifications was from the quality requirements (TEa) set by Clinical Laboratory Improvement Amendment (CLIA'88).¹⁰

2.3.2 | Quality specifications derived from the biologic variation database

(i) Minimal specification for precision defined by $CV_A < 0.75 CV_I$ (CV_I = within-subject biologic variation; CV_A = the analytical precision); (ii) Desirable specification defined by $CV_A < 0.50 CV_I$; (iii) Optimal specification defined by $CV_A < 0.25 CV_I$.¹¹ Within-subject and between-subject CV values were updated and compiled by Dr. Carmen Ricos and colleagues.¹²

2.4 | Statistical analysis

The distributions of current CVs were described with abnormal distribution statistical parameters, including median and interquartile range (IQR) using the 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). The outliers are defined as values of CVs outside of a 95% confidence interval. The Friedman M test was performed to compare

the current CVs among different years followed by the Bonferroni method for multiple comparisons between groups. While Kruskal-Wallis H tests or Mann-Whitney U-tests were used to compare the current CVs among different subgroups in the same year for a certain analyte. A value of $P < .05$ was considered to be statistically significant.

3 | RESULTS

In the survey, we found that most laboratories (61.3%-79.9%) performed only one level concentration of QC measurements, and fewer laboratories (20.0%-34.4%) reported two levels of QC information (Figure 1). The percentage of laboratories that repeated their QC measurements increased during the study period.

As there are no standardized national QC levels for the measurements during routine IQC practice, and the results of CVs varied very much among different laboratories. The median (IQR) for each cardiac biomarker analyte is shown in Table 1, along with the

FIGURE 1 Percentages of laboratories according to the number of concentration levels of quality control measurements performed within one analytical run for six items from 2011 to 2016

■ 2011 ■ 2012 ■ 2013 ■ 2014 ■ 2015 ■ 2016

TABLE 1 Number of participant laboratories, distribution of current CVs, and percentages of laboratories meeting quality specifications (%)

	Y	Number of labs	Current CVs			Allowable Precision specifications based on CLIA'88 and biologic variation				
			Median	IQR	P*	1/3TEa	1/4TEa	Minimum	Desirable	Optimal
CK-MB ($\mu\text{g/L}$)	2011	119	5.30	4.65	.112	90.7	71.4	95.0	81.5	42.9
	2012	119	4.94	3.33		94.0	80.2	98.8	87.4	44.3
	2013	119	4.87	3.78		96.6	79.5	98.9	93.2	45.5
	2014	119	5.00	3.70		90.1	77.6	94.2	86.9	44.6
	2015	119	5.19	4.16		90.9	74.7	95.8	86.4	42.3
	2016	119	5.30	3.78		91.4	75.5	98.9	88.0	37.9
CK-MB (U/L)	2011	103	4.96	4.48	.324	91.3	74.8	95.1	90.3	49.5
	2012	103	4.70	4.26		86.6	78.2	95.0	85.7	51.3
	2013	103	4.90	4.32		89.8	76.3	94.9	88.1	52.5
	2014	103	4.70	4.82		90.0	73.8	96.1	87.8	52.4
	2015	103	4.70	4.10		88.7	76.8	95.1	87.2	51.4
	2016	103	4.65	4.33		89.6	75.9	95.3	88.6	52.5
Mb ($\mu\text{g/L}$)	2011	174	4.92	4.41	.092	90.2	74.1	91.4	71.8	31.0
	2012	174	4.68	4.02		92.9	77.0	94.1	84.5	27.6
	2013	174	4.86	2.88		93.5	84.7	95.2	83.9	29.0
	2014	174	4.70	3.66		91.7	80.3	93.7	77.7	31.4
	2015	174	4.83	3.69		91.8	79.0	93.1	74.9	27.8
	2016	174	5.30	3.78		91.4	75.5	93.3	69.9	22.6
cTnI ($\mu\text{g/L}$)	2011	152	6.99	5.38	.987	82.7	54.6	81.6	50.0	17.1
	2012	152	6.40	5.39		81.5	58.5	83.9	56.6	18.0
	2013	152	5.48	4.44		90.1	68.3	92.3	64.4	20.2
	2014	152	5.80	4.82		83.6	64.5	86.6	61.0	21.1
	2015	152	6.55	4.57		84.0	61.9	86.5	56.3	16.0
	2016	152	5.90	4.23		89.5	68.1	91.2	64.9	20.5
cTnT ($\mu\text{g/L}$)	2011	133	4.32	3.93	.765	95.4	81.5	98.5	98.5	84.6
	2012	133	4.30	3.88		94.4	79.8	100.0	100.0	80.9
	2013	133	5.00	3.55		100.0	82.2	100.0	100.0	84.4
	2014	133	4.32	3.99		94.9	81.6	100.0	100.0	81.6
	2015	133	4.67	3.81		92.7	81.0	100.0	99.4	82.7
	2016	133	4.15	3.86		95.5	80.4	100.0	100.0	82.1
HCY ($\mu\text{mol/L}$)	2011	119	4.80	3.60	.981	74.8	52.9	73.1	40.3	9.2
	2012	119	5.00	3.63		75.6	51.2	72.0	36.6	11.0
	2013	119	4.95	3.83		71.3	52.1	67.5	36.7	7.0
	2014	119	4.52	3.30		79.0	58.5	74.4	44.5	11.9
	2015	119	4.20	2.98		79.1	64.6	78.4	48.5	12.7
	2016	119	4.48	3.07		79.8	58.7	75.7	45.7	13.0

IQR, Interquartile range.

*Differences in current CVs among different years were tested with the Friedman M test.

percentages of laboratories meeting different quality specifications. As we can see, three analytes had excellent results, including CK-MB($\mu\text{g/L}$), Mb, and cTnT. The percentages of laboratories whose CVs met the 1/3TEa specification for these three analytes were all above 90% every year (90.1%-96.6% for CK-MB($\mu\text{g/L}$); 90.2%-93.5% for Mb; 92.7%-100% for cTnT), whereas the pass rates

varied greatly from 22.6% (Mb in 2016) to 90.0% (cTnT in 2012) when the optimal precision criteria were applied. The analytes of CK-MB(U/L) and cTnI had a satisfactory result, for which the acceptable laboratories whose current CVs met the 1/3TEa specification were above 80% (81.5%-90.1% for cTnI; 86.6%-91.3% for CK-MB(U/L)). Similarly, the percentages varied greatly from 16.0%

(cTnI in 2012) to 52.5% (CK-MB(U/L) in 2012) when the optimal allowable precision specification was used. Frustratingly, there was still an analyte (ie, HCY) with a performance that was not satisfactory, such that the percentages of laboratories whose CVs met the $1/3TEa$ specification were below 80% (71.3%-79.8%). There was no significant difference in current CVs for all cardiac biomarkers among years from 2011 to 2016 (all $P > .05$). See Table 1 for more information.

3.1 | Setting appropriate quality specification for analytical precision

According to the precision performance of current CVs in these 6 years, the quality specifications of analytical precision for CK-MB ($\mu\text{g/L}$), CK-MB (U/L), Mb, cTnI, cTnT, and HCY were set as

current CVs less than 9.20% (desirable), 9.90% (desirable), 7.50% ($1/4TEa$), 10.54% (minimum), 7.63% (optimal), and 6.67% ($1/3TEa$), respectively.

3.2 | Precision analysis from test principles

As shown in Figure 2, the test principles of CK-MB($\mu\text{g/L}$), CK-MB(U/L), Mb, cTnT, and HCY used by most laboratories were the electrochemiluminescence assay (ECLA), the inhibition immunoassay (IIA), the ECLA, the ECLA, and the enzymatic cycling assay (ECA), respectively. The main testing method of cTnI changed substantially over 6 years. Additionally, some principles of the assay were eliminated. For example, the chemiluminescence immunoassay (CLA) was not used in HCY testing since 2015. Additionally, some new methods, such as the dot immunogold filtration assay (DIGFA), were introduced into laboratories and used for

FIGURE 2 Percentages of laboratories using each type of test method for six items from 2011 to 2016. AECLA, acridinium-ester-labeled chemiluminescence immunoassay; ECLA, electrochemiluminescence assay; CLA, chemiluminescence immunoassay; DIGFA, dot immunogold filtration assay; CEA, chemiluminescent enzyme immunoassay; IFA, immunofluorescence method; CLMA, chemiluminescent microparticle immunoassay—AMPPD; MEIA, microparticle enzyme immunoassay; DCM, dry chemistry method; IIA, inhibition immunoassay; RM, rate method; IMT, immunoturbidimetry; FEIA, fluorescence enzyme immunoassay; and ECA, enzymatic cycling assay

TABLE 2 Current CVs of each group categorized by principles of the assay from 2011 to 2016

	Principle of assay	2011		2012		2013		2014		2015		2016	
		M	IQR	M	IQR	M	IQR	M	IQR	M	IQR	M	IQR
CK-MB ($\mu\text{g/L}$)	AECLA	4.74	3.95	5.49	2.43	5.01	2.78	5.30	2.94	5.88	3.65	5.41	3.67
	ECLA	4.05	5.38	4.10	3.57	3.80	2.77	3.75	3.36	3.61	3.25	4.36	3.07
	CLA	5.10	7.77	4.90	2.25	5.42	3.35	5.26	3.66	4.90	3.42	5.14	3.32
	DIGFA	-	-	-	-	-	-	5.95	3.70	7.92	3.51	8.11	4.06
	CEA	5.83	5.26	5.40	4.32	6.26	4.52	10.39	9.94	6.17	9.57	9.00	4.04
	IFA	-	-	-	-	-	-	5.44	5.13	5.10	4.22	5.06	2.80
	CLMA	7.73	3.43	5.93	5.57	7.20	5.14	5.08	3.86	4.98	4.32	4.90	3.56
	MEIA	7.00	3.79	4.83	2.69	6.80	4.05	4.66	2.85	5.00	2.98	4.73	2.09
	Others	5.50	3.26	5.02	4.88	5.31	4.12	4.20	5.03	5.55	4.01	5.67	4.49
CK-MB (U/L)	DCM	4.78	3.46	4.70	3.17	4.36	3.09	4.00	5.73	5.00	4.14	4.60	5.58
	IIA	5.16	4.84	4.44	4.99	6.00	4.40	4.91	4.83	4.66	4.53	4.69	3.53
	RM	4.96	4.19	5.51	4.46	3.40	4.44	4.70	4.37	4.69	3.89	4.45	4.21
	Others	3.20	3.50	4.20	4.60	4.62	7.24	3.34	3.81	5.30	4.56	5.30	3.56
Mb ($\mu\text{g/L}$)	AECLA	4.96	3.08	4.46	2.23	5.2	2.30	5.47	3.69	4.64	3.21	4.51	3.07
	ECLA	3.18	4.16	3.61	3.35	3.85	3.03	3.89	2.55	3.96	3.26	3.57	3.48
	CLA	5.03	5.00	4.71	2.45	4.20	1.44	4.70	3.61	4.77	2.89	4.82	2.78
	DIGFA	-	-	-	-	-	-	4.46	3.23	7.38	4.68	6.51	2.34
	CEA	4.74	2.75	5.05	4.23	4.63	2.75	10.50	9.23	7.10	978	8.20	4.79
	CLMA	8.47	6.91	6.48	4.28	4.85	3.99	5.01	4.37	4.91	2.56	4.00	3.78
	MEIA	4.94	3.42	5.02	3.39	5.33	3.41	3.79	3.25	4.71	3.14	4.75	3.69
	IMT	6.30	5.53	6.60	5.12	5.95	3.59	5.00	4.70	4.70	4.67	4.80	4.16
	Others	5.64	5.08	6.04	4.26	4.71	3.32	4.43	2.74	5.52	4.59	5.15	3.47
cTnI ($\mu\text{g/L}$)	AECLA	6.17	4.92	6.00	5.58	5.47	4.18	5.40	5.83	6.70	4.10	5.81	4.40
	CLA	5.90	4.70	5.40	3.30	4.16	3.33	5.96	4.00	5.83	4.02	5.22	3.28
	DIGFA	-	-	-	-	-	-	8.66	3.28	9.48	5.74	6.57	3.79
	CEA	8.08	4.56	7.76	7.26	6.04	5.13	6.60	6.49	7.56	5.00	9.01	1.38
	CLMA	7.58	5.77	8.00	5.48	7.52	4.99	5.98	3.35	6.50	5.27	5.80	3.11
	MEIA	7.56	4.40	7.05	2.96	6.65	4.64	6.00	5.05	6.65	5.59	5.45	4.56
	IMT	5.80	9.48	-	-	-	-	7.20	7.21	6.03	4.03	5.43	6.38
	FEIA	5.89	9.93	5.01	7.51	4.99	3.31	4.23	3.94	4.45	3.98	3.88	4.39
	Others	7.93	5.52	5.70	5.28	7.09	9.72	4.34	3.20	6.15	3.70	6.15	4.27
cTnT ($\mu\text{g/L}$)	ECLA	3.87	3.69	4.29	4.28	4.30	3.53	4.18	3.85	4.45	3.89	4.15	3.78
	Others	7.80	6.50	4.86	1.68	5.17	1.72	4.68	4.75	5.99	6.48	4.06	4.12
HCY ($\mu\text{mol/L}$)	CLA	8.01	3.24	8.03	3.79	5.56	3.85	7.78	7.50	6.00	3.80	4.46	1.92
	RM	-	-	-	-	-	-	-	-	4.73	3.24	4.94	3.57
	IMT	6.12	3.23	6.00	7.78	7.85	4.60	5.56	4.24	5.14	3.89	4.20	2.26
	ECA	4.02	2.78	4.10	2.84	5.00	3.33	4.79	3.55	4.09	2.78	4.43	3.47
	Others	5.35	3.12	5.37	3.14	3.30	3.50	4.71	3.09	5.05	4.85	4.65	2.53

AECLA, acridinium-ester-labeled chemiluminescence immunoassay; ECLA, electrochemiluminescence assay; CLA, chemiluminescence immunoassay; DIGFA, dot immunogold filtration assay; CEA, chemiluminescent enzyme immunoassay; IFA, immunofluorescence method; CLMA, chemiluminescent microparticle immunoassay—AMPPD; MEIA, microparticle enzyme immunoassay; DCM, dry chemistry method; IIA, inhibition immunoassay; RM, rate method; IMT, immunoturbidimetry; FEIA, fluorescence enzyme immunoassay; ECA, enzymatic cycling assay; IQR, interquartile range.

testing cardiac biomarkers after 2011. In addition, Table 2 shows the detailed information on current CVs grouped by test principles. Although the CVs among different groups divided by principles of assays were not significantly different every year, and although there is no consistent trend for CVs of each group from 2011 to 2016, we found that ECLA had the minimum CVs for each analyte every year (all $P < .001$).

3.3 | Precision analysis by instrument manufacturers

The manufacturers of instruments used by laboratories mainly include Abbott, Beckman, Roche, Siemens, Lepu (Beijing), and Hitachi. Beckman and Roche had bigger proportions than other instrument producers for each analyte.

TABLE 3 Acceptable laboratories with desirable precision specification from manufacturers of instruments

Manufacturers of the instruments	Percentage of laboratories meeting desirable precision specification %(n/N)					
	2011	2012	2013	2014	2015	2016
CK-MB ($\mu\text{g/L}$)						
Abbott	88.9 (9/10)	88.9 (9/10)	80.0 (8/10)	84.6 (8/10)	76.3 (8/11)	90.0 (9/10)
Beckman	93.2 (41/44)	88.9 (39/44)	89.3 (39/44)	94.7 (29/31)	93.2 (31/33)	93.9 (20/21)
Roche	77.5 (31/40)	90.0 (36/40)	100.0 (40/40)	93.7 (33/35)	95.1 (29/31)	96.8 (33/34)
Siemens	75.0 (12/16)	76.2 (12/16)	100.0 (16/16)	81.6 (16/19)	91.5 (16/18)	90.7 (15/16)
Lepu (Beijing)	-	-	-	94.4 (8/9)	85.7 (9/10)	60.0 (6/10)
Others	66.7 (6/9)	58.8 (5/9)	88.9 (8/9)	69.4 (10/15)	73.6 (12/16)	79.5 (22/28)
CK-MB (U/L)						
Abbott	100.0 (5/5)	100.0 (4/4)	-	80.0 (4/5)	85.7 (4/5)	100.0 (1/1)
Beckman	86.2 (26/30)	82.4 (24/29)	85.7 (24/28)	82.8 (26/31)	85.7 (21/25)	82.8 (27/33)
Roche	96.2 (26/27)	88.9 (21/24)	90.5 (38/42)	100.0 (26/26)	92.5 (19/20)	95.7 (25/26)
Siemens	-	-	-	81.8 (4/5)	73.9 (8/11)	82.4 (7/8)
Hitachi	91.7 (13/14)	86.7 (14/16)	80.0 (12/15)	94.1 (14/15)	87.5 (24/27)	87.7 (15/17)
Others	88.0 (24/27)	85.7 (26/30)	90.7 (17/18)	78.6 (17/21)	85.7 (13/15)	91.3 (16/18)
Mb ($\mu\text{g/L}$)						
Abbott	81.2 (15/18)	73.9 (12/16)	80.0 (15/19)	77.6 (9/12)	80.6 (15/18)	80.8 (11/14)
Beckman	68.0 (34/50)	73.9 (35/47)	82.9 (39/47)	68.2 (24/35)	75.5 (23/30)	79.1 (25/31)
Roche	77.1 (37/48)	79.7 (35/44)	90.3 (38/42)	90.1 (38/42)	82.8 (35/42)	86.8 (32/37)
Siemens	67.9 (19/28)	81.2 (21/26)	88.2 (24/27)	78.6 (18/23)	87.5 (18/20)	85.1 (22/26)
Lepu (Beijing)	-	-	-	100.0 (6/6)	52.4 (3/6)	60.0 (4/7)
Others	66.7 (20/30)	64.7 (27/41)	75.0 (29/39)	70.7 (40/56)	64.7 (38/58)	65.3 (39/59)
cTnI ($\mu\text{g/L}$)						
Abbott	65.2 (15/23)	68.8 (14/21)	56.2 (13/23)	71.9 (18/25)	61.1 (12/20)	75.0 (3/4)
Beckman	53.2 (33/62)	51.8 (32/62)	56.1 (35/62)	54.9 (27/50)	48.1 (20/41)	67.8 (26/38)
Siemens	30.6 (11/36)	57.5 (19/33)	85.7 (28/33)	60.3 (14/24)	63.9 (12/19)	75.0 (12/16)
Lepu (Beijing)	-	-	-	25.5 (1/4)	28.6 (3/9)	68.0 (8/12)
Others	55.2 (17/31)	55.8 (20/36)	68.2 (23/34)	67.7 (33/49)	60.0 (38/63)	59.6 (49/82)
cTnT($\mu\text{mol/L}$)						
Roche	100.0 (130/130)	100.0 (129/129)	100.0 (129/129)	100.0 (128/128)	99.2 (127/128)	100.0 (128/128)
others	100.0 (3/3)	100.0 (4/4)	100.0 (4/4)	100.0 (5/5)	100.0 (5/5)	100.0 (5/5)
HCY ($\mu\text{mol/L}$)						
Abbott	33.3 (2/3)	60.0 (3/5)	40.0 (2/5)	37.5 (3/8)	50.0 (4/8)	44.4 (4/9)
Beckman	50.0 (3/6)	50.0 (3/6)	50.0 (3/6)	46.8 (22/47)	47.8 (22/46)	51.2 (22/43)
Roche	45.5 (5/11)	50.0 (4/8)	33.3 (3/9)	50.0 (10/20)	52.9 (9/17)	52.9 (9/17)
Siemens	28.6 (2/7)	40.0 (2/5)	50.0 (3/6)	45.5 (5/11)	38.5 (5/13)	45.5 (5/11)
Hitachi	36.1 (13/36)	34.4 (11/32)	39.4 (13/33)	54.2 (13/24)	48.1 (13/27)	44.8 (13/29)
Olympus	45.5 (10/22)	34.6 (9/26)	37.5 (9/24)	-	-	-
Others	38.7 (12/31)	34.2 (13/38)	37.8 (14/37)	55.6 (5/9)	62.5 (5/8)	40.0 (4/10)

Further analysis of the percentages of laboratories meeting desirable precision criteria indicated that the pass rates of different manufacturers were not significantly different ($P > .05$) in the same year except that Roche held higher pass rates for CK-MB(U/L) ($P < .001$), and the pass rates of a certain instrument manufacturer were also not significantly different among different years. Surprisingly, the producer of Lepu (Beijing) had a very variable rate (eg, ranging from 27.3% to 100% for Mb). For more information, see Table 3.

3.4 | Investigation of IQC practice

In the survey, laboratories were asked to report what control rules they used. We found that the constituent ratio of control rules had obviously changed (Figure 3). Fewer and fewer laboratories did not

understand how to choose QC rules, while more and more laboratories began to use combined QC rules from 1_{2s} , 1_{3s} , 2_{2s} , R_{4s} , 4_{1s} , and 10_x in a period between 2011 and 2016.

The IQC frequency or average time interval between two IQC measurements was calculated according to the submitted number of IQC results per month. Most laboratories performed one QC run every 1-2 days ($>60\%$), and fewer laboratories could do more than one QC run every day ($<10\%$). For more information, see Figure 4.

4 | DISCUSSION

The program described in this manuscript is the first national continuous long-term survey on IQC of cardiac biomarker measurements in

FIGURE 3 Percentages of laboratories according to the control rules for six items from 2011 to 2016. 1_{2s} —one point out of 2 standard deviation (SD); 1_{3s} —one point outside 3 SD; 2_{2s} —(across runs) 2 consecutive values outside the same 2SD or (with run) 2 consecutive values outside the same 2 SD; R_{4s} —The range (difference) between two controls within a run exceeds 4 SDs. This rule is only to be used within a run, not across runs; 4_{1s} —4 consecutive control values on one side of the mean and further than 1 SD from the mean. This can be within one control across 4 consecutive runs or within 2 controls across 2 consecutive runs; 10_x —10 consecutive values on one side of the mean. This can be within one control across 10 consecutive runs or within 2 controls across 5 consecutive runs

FIGURE 4 Percentages of laboratories according to control frequency for six items from 2011 to 2016

■ One QC run more than 2 days
■ More than one QC run every day

■ One QC run every 1-2 days

medical laboratories in China. The results suggested that the precision level of different analytes varied very much. Additionally, the precision performance of some analytes (including CK-MB(μg/L), Mb, and cTnT) has been satisfactory in the first year of investigation and can be maintained in the following years, while the results of others, such as HCY, were not so good first and did not achieve obvious improvement from 2011 to 2016.

Among these six analytes of cardiac biomarkers, cTnT had the most satisfactory performance, with the annual average passing rates against 1/3TEa, 1/4TEa, and specifications based on biologic variation including minimum, desirable, and optimal specification being up to 95.6%, 82.6%, 99.8%, 99.7%, and 83.8%, respectively. In contrast, HCY got the lowest pass rates based on these five quality specifications every year, and the mean annual rates were only approximately 76.6%, 56.3%, 73.5%, 42.0%, and 10.8%, respectively. The great difference among these two analytes is due to several factors, such as the inherent performance of the analytical system composed of an instrument, calibration and reagent, principles of the assay, IQC practice, including QC materials, rules and frequency,

operation of laboratory practitioners, and so on. Therefore, laboratory quality management should require certain actions, such as training staff, compiling a standard operating procedure (SOP) of specific analyte measurement, calibrating instruments, or changing reagents to enhance the performance of the analytes that did not have satisfactory results.

Quality indicators as stated in ISO 15189 are “a measure of the degree to which a set of inherent characteristics fulfills requirements”.⁹ It is a tool that can inform laboratory management of how well their laboratory performance meets the needs and requirements of users and the quality of all operational processes. Therefore, CVs can be regarded as one of the QIs for monitoring the precision of examination processes. Laboratories can monitor QIs of CVs by performing the IQC procedure and periodically (usually monthly) reviewing the indicator by comparing CVs with appropriate quality specifications to evaluate their laboratory examination precision and to ensure its appropriateness.

There are many ways to set analytical quality specifications in laboratory medicine. The Stockholm Conference held from April

24-26, 1999, achieved a global consensus on the setting of analytical quality specifications in laboratory medicine and advocated for the ubiquitous application of a hierarchical structure of approaches (the hierarchy has five levels).^{13,14} After 15 years, the Organizers 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" was held in Milan on November 24-25, 2014 and simplified the hierarchy and represented it using three different models, which were based on the following: (i) the effects of analytical performance on clinical outcomes; (ii) components of biologic variation of the measurements; and (iii) state-of-the-art techniques.¹⁵ In this study, we choose two kinds of analytical precision criteria that were based on biologic variation and state-of-the-art approaches. The specifications based on biologic variation are the model 2 in the Milan consensus, whereas the 1/3TEa and 1/4TEa derived from CLIA'88 are model 3. Generally, a model higher in the hierarchy may be given high priority, so minimum, desirable, and optimal precision requirements derived from biologic variation data seem more reasonable for IQC precision evaluation.

As we can see, the pass rates against the optimal specification were all very low for these six kinds of cardiac markers. When the minimum specification was employed, the precision performance became the best with even a 100% pass rate for cTnT measurement. It reminds us of the fact that these two extreme criteria (ie, too stringent or loose) may not be suitable as precision criteria for cardiac markers. Therefore, organizers such as the NCCL of China should choose an appropriate quality requirement according to the performance that a specific analyte can achieve nationwide, and laboratories should also choose suitable precision criteria by comparing their CVs with our data. After continuous investigation of current CVs of cardiac biomarkers and precision analysis of it, we can set quality specifications for these six analytes. To allow 80% of laboratories to meet the precision criteria, we can choose a desirable specification ($CV\% < 9.20\%$) for CK-MB($\mu\text{g/L}$), a desirable specification ($CV\% < 9.90\%$) for CK-MB(U/L), 1/4TEa ($CV\% < 7.50\%$) for Mb, 1/3TEa ($CV\% < 7.03\%$) for cTnI, and an optimal specification ($CV\% < 7.63\%$) for cTnT and 1/3TEa ($CV\% < 6.67\%$) for HCY. Furthermore, these precision specifications can be updated with an annual IQC investigation in the future.

Through continual IQC investigation, we can have the knowledge of which instrument vendors were the most popular. For cardiac biomarker examination, Beckman and Roche had bigger proportions than other instrument producers. Additionally, Roche held higher pass rates for CK-MB(U/L) than other instrument producers. The pass rate of Lepu (Beijing) fluctuated. As such, it is recommended that laboratories should choose mainstream instrument vendors with smaller CVs, such as Roche for CK-MB(U/L), instead of Lepu. Similarly, we know the situation of testing methods used in cardiac biomarkers examination. Ultimately, we found that ECLA had the minimum CVs for each analyte every year. For cTnI, more and more laboratories began using CLA and DIGFA with fewer and fewer laboratories using AECLA, which may be due to a slow turnaround time. Bailin

Zhang, et al¹⁶ have studied a label-free detection of cTnI with a photonic crystal biosensor that can shorten turnaround time. For cTnT, testing methods remained the same, which may be due to the small CVs obtained by ECLA. Overall, the test method of cTnI measurement is changing during these years and still needs to be improved in precision performance. However, ECA is used in most laboratories in China and the proportion of its use is almost unchanged. Other methods, such as HPLC and enzymatic assays are used by most laboratories in America.¹⁷⁻¹⁹ Brunelli T, et al²⁰ have demonstrated that these different analytic methods produced highly correlated and comparable results. However, study of the precision performance for the HCY testing methods is few. At least, the precision of HCY measurement in China based on this survey needs to be improved vigorously in the future. Therefore, laboratories of which the precision performance were not so satisfactory can consider changing another testing method, such as ECLA used in CK-MB($\mu\text{g/L}$), Mb, cTnI, and cTnT testing. Because IQC practice can also affect the measurement quality, IQC rules and frequency were also investigated in the survey. Appropriate IQC practice can balance the rate of false rejection and error detection. For IQC rules, fewer and fewer laboratories were unfamiliar with the Westgard rules. In contrast, more and more laboratories began using combined rules, which both suggested that many laboratories have known how to choose appropriate IQC rules according to their own quality performance, which may be based on sigma metrics analysis.²¹ Data on QC frequency demonstrated that most laboratories perform one QC every 1-2 days. Fortunately, fewer and fewer laboratories performed one QC more than 2 days except for cTnI. These may suggest that laboratories have begun to realize the importance of IQC. However, it is not necessary for laboratories to perform QC measurements too often. Assay-specific IQC systems developed by Kinns et al²² and an IQC system specifically aimed at the analytical run length for quantitative tests that was developed by NCCL in China²³ can be both used to determine the IQC frequency. Only the IQC rules and frequency were set according to the laboratory's own quality performance, and the IQC plays an effective role in monitoring the accuracy of testing results.

Unfortunately, we did not find a consistent changing tendency for current CVs from 2011 to 2016. Some reasons could be attributed to the results. First, testing methods for cardiac biomarker examination may have not been improved over the last few years. Second, the QC process used to monitor the stability of the analytical system may also maintain the same approach. Third, it may be the main reason that laboratories did not recognize the importance of quality assurance by controlling the CVs within the limits of requirements, so laboratories did not take any actions to improve analytical precision at all. Finally, it may be the results of small sample size which is also a disadvantage of this investigation. Meanwhile, we did not distribute harmonized national QC materials, so the inherent essence of QC materials such as homogeneity and stability may be different among laboratories, which may lead to the variation of CVs. It was also the main deficiencies of the research. Additionally, laboratories must change the QC material lots from 2011 to 2016, so the difference in the different QC material lots can also lead to big changes in CVs. Our previous investigation on

hemoglobin A1c has shown that CVs were influenced by vendors of QC materials.²⁴

It is a good beginning and a meaningful thing for NCCL in China to collect the IQC data from EQA participants using an additional part of EQA network platform and conducting some further statistical analysis although there were many limitations that existed in this national continual survey on IQC practice for cardiac biomarkers. However, we can conclude that the measurement precision of laboratories in China has yet to be improved, especially for some analytes, such as HCY. Laboratories can choose the quality specifications established in the paper that can be updated when necessary or set the appropriate quality specifications for themselves and then strive for it.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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