RESEARCH ARTICLE

Internal quality control status for BNP and NT-proBNP in China from 2014 to 2017

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Background: This study aimed to investigate and analyze the status of internal quality control (IQC) for BNP and NT-proBNP from 2014 to 2017, so as to have an integral understanding of quality performance of measurement in clinical laboratories in China.

Methods: The 4-year IQC information for BNP and NT-proBNP of participant laboratories were collected through EQA reporting system. Percentages of laboratories meeting different quality requirements (pass rates) for current coefficient of variations (CVs) were calculated afterwards. Further analysis for current CVs and pass rates among different years and measurement systems were conducted. Finally, we analyzed and summarized IQC practice and its changes in 4 years.

Results: The current CVs for BNP and NT-proBNP have decreased significantly from 2014 to 2017, and pass rates both presented significant increasing trends. NT-proBNP had higher pass rates than BNP regardless of 1/3TEa or 1/4TEa specification was used. The main measurement systems for two analytes were different. For NT-proBNP, current CVs of Roche has decreased significantly among 4 years and were significantly lower than Radiometer and BioMérieux in 2015. Current CVs of Abbott also had decreasing tendency for BNP. Analysis of IQC practice indicated that control rules and IQC frequency had made great progress in 4 years.

Conclusion: The imprecision performance of measurement of BNP and NT-proBNP has improved with decreasing of current CVs and increasing of pass rates in 4 years. However, it still needs continual improvement. Clinical laboratories in China should take active actions to promote performance of BNP and NT-proBNP measurement.

KEYWORDS

BNP, imprecision, internal quality control, NT-proBNP, quality specification

1 | INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (eg, breathlessness, ankle swelling and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.¹

Epidemiological studies show that about 26 million people worldwide suffer from HF.^{2,3} Diagnosis of HF should be based on clinical symptoms, signs, and the presence of cardiac abnormalities. However, symptoms and signs are often non-specific and can bring challenges to diagnosis, especially for HF with preserved ejection fraction (HFpEF, left ventricular ejection fraction $\geq 50\%$) and HF with mid-range ejection fraction (HFmrEF, left ventricular ejection fraction is 40%-49%).⁴ Natriuretic peptides, particularly B-type natriuretic peptide (BNP) and

N-terminal pro-B type natriuretic peptide (NT-proBNP) were found to be elevated in the circulation of patients with cardiovascular diseases (CVD), including myocardial infarction and HF.^{5,6} BNP is mainly synthesized and secreted by ventricular cardiomyocytes. In human plasma, it consists of 32 amino acids and has various biological activities such as relaxing blood vessels and diuresis. NT-proBNP does not have any known biological activity and is more stable than BNP.⁶ The elevated level of BNP and NT-proBNP has been one of the diagnostic criteria of HFpEF and HFmrEF.^{1,7} They have been recommended as first-line biomarkers for the diagnosis of acute and chronic HF and can also be used to rule out acute dyspnea not due to HF and to assess prognosis.⁸⁻¹⁰ At present, there are differences in measurement systems and methods for detecting BNP and NT-proBNP in clinical laboratories around the world.^{11,12} It is worthwhile paying more attention to the accuracy of measurement for BNP and NT-proBNP in all laboratories, as it can directly affect the patient's diagnosis and treatment.

Internal quality control (IQC) is regarded as an effective tool to discover errors and plays an important role in improving the precision level of clinical laboratories and ensuring accuracy and reliability of test results.¹³ The coefficient of variation (CV) is an indicator that describes the degree of data variation and is calculated as the standard deviation divided by the mean value multiplied by 100. Derived from IQC data, CV can be used to monitor the imprecision of measurement and reflect the quality of laboratory analysis phase.¹⁴ Therefore, laboratories can evaluate and control the imprecision level of BNP and NT-proBNP by monitoring CVs and performing appropriate IQC programs. Although the IQC program has been developed in China for many years, the beginning of IQC for BNP and NT-proBNP is relatively late. There has been no previous long-term IQC survey for BNP and NT-proBNP in China and relevant research results are lacking. Therefore, we carried out this investigation through collecting and analyzing 2014-2017 IQC results of BNP and NT-proBNP of clinical laboratories in China, and assessed percentages of laboratories meeting allowable imprecision quality specifications to determine whether the quality performance of Chinese clinical laboratories had been improved and IQC practice had made progress from 2014 to 2017.

2 | MATERIALS AND METHODS

2.1 | Subjects

Clinical laboratories in various provinces in China, which continuously participated in an external quality assessment (EQA) program for BNP and NT-proBNP from 2014 to 2017. EQA program is officially organized by the National Center for Clinical Laboratories (NCCL) in China.

2.2 | Methods

The IQC information for BNP and NT-proBNP of participant laboratories were collected annually in each April from 2014 to 2017 through

Clinet (www.clinet.com.cn) EQA reporting system version 1.5, which were developed by the NCCL in China. When participating in the EQA program of these two analytes, laboratories are required to report their IQC information simultaneously. For incomplete or improper IQC information, the corresponding laboratories were asked to add completed information, including suppliers of control materials, lot number of control materials, control rules and IQC frequency, mean value and standard deviation of control materials, current CVs, manufacturers of instruments, reagents and calibrators, analytical methods every year.

At present, the control materials for BNP and NT-proBNP are purchased by laboratories from different suppliers or prepared by the laboratories themselves, not provided by the NCCL. Therefore, laboratories test their own control materials and monitor current and cumulative CVs to evaluate the within-laboratory imprecision level. To calculate current CVs, laboratories have to collect all in-control results judged by their own quality control rules in April yearly. But the calculation of cumulative CVs is based on all in-control results from the first day on which the same lot of control materials is used to the last day until April.¹⁴ Considering the difference in collecting time among various laboratories, this study only used current CVs to make sure the data could be compared and analyzed.

Percentages of laboratories meeting the quality requirements for BNP and NT-proBNP were calculated by quality specifications based on biological variation and total error allowance (TEa) provided by evaluation criteria for EQA in laboratory medicine in China. If the current CVs were lower than an evaluation criterion, the precision of the laboratory was considered acceptable under the quality requirements of the standard. The pass rates of each group, which were divided and analyzed by year, measurement systems, 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

This study used allowable imprecision quality specifications derived from biological variation and TEa recommended by evaluation criteria for EQA in laboratory medicine in China. There were three levels of quality specifications based on biological variation: minimum, desirable, and optimum performances, which were respectively calculated and defined as $0.75CV_I$, $0.50CV_I$, and $0.25CV_I$, CV_I , the

TABLE 1 Percentages of laboratories using different number of concentration levels of control materials for BNP and NT-proBNP from 2014 to 2017

Year	BNP (%)			NT-proBNP (%)		
	One	Two	Three	One	Two	Three
2014	60.9	23.64	15.45	60.95	35.87	3.17
2015	64.20	19.75	16.05	58.26	38.02	3.72
2016	70.27	18.92	10.81	62.39	34.07	3.54
2017	79.17	11.11	9.72	56.81	38.03	5.16
Average	68.64	18.36	13.01	59.60	36.50	3.90

FIGURE 1 Distribution of current CVs (%) for BNP and NT-proBNP from 2014 to 2017 (Different boxes represent current CVs for different years. The upper and lower ends of boxes stand for the 75th and 25th percentiles, respectively. The horizontal lines in the box represent the median, and the horizontal lines at the top and bottom outside the box are the maximum and minimum, small circles, and pentagons indicate outliers)

intrasubject biological variation, was provided by Ricos and updated by Westgard on the website (<http://www.westgard.com/biodatabase1.htm>). Unfortunately, BNP does not have quality specifications based on biological variation. For NT-proBNP, the minimum, desirable, and optimum specifications were 7.5%, 5%, and 2.5%, respectively. Total error (TE), introduced by Westgard,¹⁵ is composed of systematic error and random error. The TE model can be expressed as: $TE = \text{average bias} + Z \times \text{imprecision}$ (Z defines the level of confidence, the value is usually 1.65).¹⁶ The evaluation criteria for EQA of

two analytes in China are given as TEa, so the NCCL set the criteria of TEa for these two analytes (both were 30%). Accordingly, the $1/3TEa$ and $1/4TEa$ can be calculated for them: $1/3TEa$ for BNP and NT-proBNP was 10% and $1/4TEa$ was 7.5%.

2.4 | Statistical analysis

The distribution of current CVs was represented by the 25th, 50th (median), and 75th percentiles. For each analyte, Friedman M test

was used to compare current CVs among different years (multiple comparisons between groups using Bonferroni's method). The comparison of current CVs among different groups in the same year used Kruskal-Wallis H tests or Mann-Whitney U tests. χ^2 test was performed to compare the pass rates and constituent ratio among different years or groups (also including Cochran-Armitage trend test and McNemar's test). Statistical processing and analysis was carried out by IBM SPSS Statistics Version 21.0 (SPSS Inc, Chicago, IL, USA) and Microsoft Excel 2016 software (Microsoft Inc, Redmond, Washington, DC, USA). The differences were considered to be statistically significant when the value of $P < 0.05$.

3 | RESULTS

In April 2014, 110 and 314 clinical laboratories in China submitted their IQC information for BNP and NT-proBNP, respectively. Among them, there were 72(65.45%) and 212(67.52%) laboratories participating in this investigation continuously in the following 3 years.

The number of concentration levels of control materials tested by various laboratories throughout the country was different. The percentages of laboratories that only detected one level of control materials in 4 years were 68.64% for BNP and 59.60% for NT-proBNP on average. Laboratories which adopted two levels of control materials were 18.36% and 36.50%, respectively. Unfortunately, laboratories which measured three levels were approximately 10% or less. Detailed results are shown in Table 1. As most laboratories only submitted IQC data for one level of control materials, and most of them tested level 1, the following analysis of current CVs was performed for level 1.

3.1 | Imprecision analysis

From 2014 to 2017, the distribution of current CVs for BNP and NT-proBNP is shown in Figure 1. For these two analytes, there were significant differences in current CVs among 4 years (both $P < 0.001$). Further analysis of the current CVs of BNP between any 2 years showed that significant differences existed between 2014 and 2017, 2015, and 2017 (both $P < 0.001$). For NT-proBNP, significant differences in current CVs were between following 2 years: 2014 and 2015 ($P = 0.005$), 2014 and 2016 ($P < 0.001$), 2014 and 2017 ($P < 0.001$), 2015 and 2017 ($P < 0.001$). The current CVs for BNP and NT-proBNP in 2017 were significantly lower than those in 2014 and 2015.

Percentages of laboratories meeting allowable imprecision quality specifications (ie, pass rates) from 2014 to 2017 are shown in Figure 2. Using the loosest 1/3 TEa as the evaluation criterion, the pass rates of the two analytes was high (86.9%-93.4% for BNP, 94.6%-97.8% for NT-proBNP). With the more rigorous 1/4TEa criterion, the pass rates of the two analytes decreased. However, we conducted Cochran-Armitage trend test and found the pass rates has an increasing trend over the 4 years (72.1%-92.8% for BNP, $P = 0.012$; 82.6%-94.0% for NT-proBNP, $P < 0.001$). Compared with BNP, NT-proBNP had higher pass rates regardless of whether 1/3TEa or

FIGURE 2 Percentages of laboratories meeting different allowable imprecision quality specifications for BNP and NT-proBNP from 2014 to 2017 (Only NT-proBNP had allowable imprecision quality specification based on biological variation, including minimum, desirable, and optimum specification)

1/4TEa was used in 2016 ($\chi^2 = 11.773$ and 10.472 , respectively, both $P = 0.001$). In addition, when applying the desirable and optimum allowable imprecision specifications based on biological variation, the pass rates for NT-proBNP were lower than that using 1/3TEa or 1/4TEa criterion, but it still increased gradually from 2014 to 2017 (55.98%-74.76% for desirable, 10.87%-22.83% for optimum).

3.2 | Imprecision analysis by measurement systems

The instruments, reagents, and calibrators used in one laboratory were all purchased from one manufacturer. For all participant laboratories in China, measurement methods for these two analytes were immunoassays. After investigating which measurement systems laboratories used, we found that the main measurement systems for BNP were Abbott, Siemens and Beckman, and for NT-proBNP were Roche, Johnson & Johnson (referred to as J&J), Radiometer and BioMérieux. The instruments in all systems above were large biochemical analysis instruments instead of bedside instruments (detailed information are shown in Table S1 in supplementary materials). From 2014 to 2017, there was no significant change in the constituent ratio of the main measurement systems for two analytes (both $P > 0.05$). For BNP, the most popular measurement system was Abbott (about 50%), followed by Siemens (about 25%), and Beckman (about 18%). For NT-proBNP, Roche owned the largest constituent ratio (about 80%), followed by J&J (about 6%), Radiometer (about 5%) and BioMérieux (about 4%).

Further analysis of the current CVs and pass rates of main measurement systems for the two analytes are displayed on Tables 2 and

TABLE 2 Current CVs and pass rates of different measurement systems of BNP from 2014 to 2017

Year	Measurement systems	Percentage of laboratories % (N/Total)	Current CVs (%)		Allowable imprecision quality specifications ^b	
			Median	IQR ^a	1/3TEa	1/4TEa
2014	Abbott	55.7 (34/61)	6.70	3.18	91.18	61.76
	Siemens	26.2 (16/61)	5.17	3.33	93.75	81.25
	Beckman	11.5 (7/61)	4.90	0.80	100	100
2015	Abbott	54.1 (33/61)	6.79	2.28	84.85	69.70
	Siemens	24.6 (15/61)	4.87	2.38	100	93.33
	Beckman	16.4 (10/61)	4.83	2.82	100	80.00
2016	Abbott	54.1 (33/61)	5.20	3.06	84.85	75.76
	Siemens	23.0 (14/61)	4.89	1.74	100	92.86
	Beckman	18.0 (11/61)	4.80	3.02	90.91	81.82
2017	Abbott	50.8 (31/61)	4.80	2.13	93.55	90.32
	Siemens	23.0 (14/61)	4.94	3.48	92.86	92.86
	Beckman	19.7 (12/61)	5.29	2.83	100	100

^aInter quartile range (IQR) is equal to the difference between the upper and lower quartiles, IQR = Q3 – Q1.

^bAllowable imprecision quality specifications for BNP were based on TEa provided by evaluation criteria for EQA in laboratory medicine in China.

TABLE 3 Current CVs and pass rates of different measurement systems of NT-proBNP from 2014 to 2017

Year	Measurement systems	Percentage of labs % (N/Total)	Current CVs (%)		Allowable imprecision quality specifications ^b (%)				
			Median	IQR ^a	1/3TEa	1/4TEa	Minimum	Desirable	Optimum
2014	Roche	79.9 (147/184)	4.38	2.84	95.24	82.99	82.99	56.46	12.24
	J&J	6.0 (11/184)	4.73	3.34	90.91	90.91	90.91	54.55	9.09
	Radiometer	3.3 (6/184)	5.43	2.40	100	83.33	83.33	33.33	0
	BioMérieux	4.9 (9/184)	4.82	2.51	100	77.78	77.78	66.67	0
2015	Roche	80.4 (148/184)	4.00	2.87	95.27	91.89	91.89	66.89	15.54
	J&J	6.5 (12/184)	3.94	2.53	100	83.33	83.33	75.0	8.33
	Radiometer	4.3 (8/184)	5.50	0.99	100	100	100	12.5	0
	BioMérieux	3.8 (7/184)	7.30	4.80	85.71	71.43	71.43	14.29	0
2016	Roche	78.8 (145/184)	3.65	2.59	97.24	93.10	93.10	72.41	19.31
	J&J	7.1 (13/184)	3.96	3.75	100	84.62	84.62	61.54	7.69
	Radiometer	4.9 (9/184)	4.5	4.05	100	100	100	66.67	22.22
	BioMérieux	3.8 (7/184)	4.84	4.70	100	71.43	71.43	57.14	14.29
2017	Roche	78.8 (145/184)	3.48	2.39	97.93	95.86	95.86	77.24	24.14
	J&J	7.1 (13/184)	3.79	3.78	100	92.31	92.31	69.23	23.08
	Radiometer	6.0 (11/184)	3.54	3.21	90.91	90.91	90.91	72.73	18.18
	BioMérieux	3.8 (7/184)	5.05	3.75	100	85.71	85.71	42.86	14.29

^aInter quartile range (IQR) is equal to the difference between the upper and lower quartiles, IQR = Q3 – Q1.

^bAllowable imprecision quality specifications for NT-proBNP were based on biological variation and TEa provided by evaluation criteria for EQA in laboratory medicine in China.

3. There was no significant difference in the concentration distribution of control materials among the main measurement systems. For BNP, current CVs of Abbott have decreased over the 4 years, and current CVs in 2017 were significantly lower than in 2014 and 2015 ($P = 0.004$ and 0.001 , respectively). In 2015, current CVs of Abbott were significantly higher than Siemens ($P = 0.004$). For NT-proBNP,

current CVs of Roche have decreased significantly over the 4 years ($P < 0.001$), and we conducted further comparisons between any 2 years, the results indicating that there were significant differences between following 2 years: 2014 and 2015 ($P = 0.022$), 2014 and 2016 ($P = 0.001$), 2014 and 2017 ($P < 0.001$). In 2015, current CVs of Roche were significantly lower than Radiometer and BioMérieux

FIGURE 3 Percentages of laboratories using different control rules for BNP and NT-proBNP from 2014 to 2017 (Group 1: single IQC rule; Group 2: 12S/13S; Group 3: 13S/22S; Group 4: multiple, combination of rules from 12S, 13S, 22S, R4S, 41S, 10X but exclude 12S/13S, 13S/22S; Group 5: unclear, including laboratories did not submit control rules or not provide specific description about Westgard rules)

($P = 0.026$ and 0.002 , respectively). Furthermore, analysis of the percentages of laboratories meeting quality requirements showed that pass rates of Roche increased significantly over the 4 years when using the 1/4TEa and desirable quality specifications ($P = 0.002$ and 0.001 , respectively). Compared with the 1/3TEa and 1/4TEa criteria, the adoption of the stricter desirable and optimum specifications derived from biological variation could significantly decreased the pass rates of Roche (conducted by McNemar's test, all $P < 0.001$).

3.3 | Investigation of IQC practice

In this study, laboratories were required to submit control rules for BNP and NT-proBNP. We found that the constituent ratio of control rules had changed from 2014 to 2017 (Figure 3). For BNP and NT-proBNP, approximately 25% and 40% of laboratories did not submit clear control rules (Group 5) in 2014, many of which used ambiguous descriptions such as "L-J," "Westgard," and "Westgard rules." Fortunately, the constituent ratio has dropped sharply to 3% and 7% by 2017. Simultaneously, instead of using single control rule (Group 1), more and more laboratories have chosen appropriate control rules which were combined with 1_{2S} , 1_{3S} , 2_{2S} , R_{4S} , 4_{1S} , $10_{\bar{X}}$ (37%-57% for BNP and 35%-60% for NT-proBNP in Group 4).

FIGURE 4 Percentages of laboratories with different IQC frequency for BNP and NT-proBNP from 2014 to 2017 (Group 1: time interval (days) between two IQC measurement is less than 1 day; Group 2: time interval is 1-2 days; Group 3: time interval is 2-3 days; Group 4: time interval is 3-4 days; Group 5: time interval is more than 4 days.)

Laboratories used $1_{2S}/1_{3S}$ and $1_{3S}/2_{2S}$ changed slightly (Group 2, 3).

The frequency of internal quality control (IQC frequency) was calculated based on the number of monthly IQC observations reported by participating laboratories. From 2014 to 2017, the constituent ratio of IQC frequency has also changed (Figure 4). For BNP, the time intervals that most laboratories perform IQC twice were not exceeding 1 day (Group 1). Moreover, we found that the percentages of laboratories in that group has increased over the 4 years, but there was no statistical difference (36.7%-46.7%, $P > 0.05$). The percentages of laboratories which performed an IQC between 1 and 2 days, 2 and 3 days, 3 and 4 days (Group 2, 3, 4) were all decreased with no statistical difference (33.3%-31.6%, 11.7%-6.7%, 6.7%-1.7%, respectively). NT-proBNP showed a similar tendency as mentioned for BNP. However, it is worth noting that in 2014 most laboratories performed an IQC between 1 and 2 days, and from 2016 on the interval became less than 1 day. Less and less laboratories performed an IQC for more than 4 days (7.61%-5.98% for NT-proBNP in Group 5).

4 | DISCUSSION

Under the circumstance of the high incidence of CVD, BNP and NT-proBNP are very important biomarkers for the diagnosis of acute

and chronic HF and for the assessment of prognosis. Therefore, the accuracy of their laboratory measurement is particularly important. Regarded as an effective tool to ensure the accuracy and reliability of testing results, IQC should be given more attention and application. This study is the first long-term IQC investigation to evaluate the overall imprecision performance of BNP and NT-proBNP in clinical laboratories in China. The results indicated that with the decrease in current CVs, the imprecision performance of BNP and NT-proBNP in Chinese clinical laboratories has improved from 2014 to 2017, and the percentages of laboratories meeting quality specifications have increased. In the meantime, the IQC practice (including control rules and IQC frequency) and measurement systems also had some changes over the 4 years.

Quality indicators, stated in ISO 15189 are "a measure of the degree to which a set of inherent characteristics fulfills requirements."¹⁷ As one of the quality indicators in the analysis phase, CVs can be applied to evaluate the degree to which a laboratory meets quality requirements as well. Our study used quality specifications based on biological variation and TEa provided by evaluation criteria for EQA in laboratory medicine in China. We found that from 2014 to 2017, the current CVs of BNP and NT-proBNP decreased and pass rates increased, reflecting the improvement of imprecision performances of these two analytes. Besides, the results of pass rates indicated that when 1/4TEa criterion was used, pass rates of two analytes could both exceed 90% in 2017. And for NT-proBNP, pass rates in 2017 could reach 75% when applying the desirable quality specifications derived from biological variation.

There are many aspects that may affect the imprecision performance of BNP and NT-proBNP, including technical and management levels. In this study, we explored some key factors including measurement systems and IQC practice. The main measurement systems for BNP and NT-proBNP were different. The former were Abbott, Siemens, and Beckman, and for the latter, Roche hold the highest constituent ratio (about 80%), indicating that Roche was more widely used than other systems for NT-proBNP. Our study found that current CVs of Roche were higher than those of Radiometer and BioMérieux in 2015, and that the imprecision level of Roche has improved over the period of 4 years. This may be related to improvement of Roche's reagents, calibrators or high quality of after-sales maintenance of instruments and still needs further observation and studies. Similarly, the imprecision level of Abbott also has improved over the 4 years under study. It is suggested that laboratories should choose main measurement systems with more stable and smaller CVs.¹⁸ Based on results of this study, we recommended Roche for measurement system of NT-proBNP.

Actually, good IQC practice can effectively increase the error detection rate and reduce the rate of false rejection.^{19,20} In this study, we evaluated the control rules and IQC frequency. We found that with great importance laboratories attaching to IQC and effective training provided by the NCCL, more and more laboratories gradually understand the concept of control rules and start using multiple control rules. At the same time, IQC frequency has also changed. About 47% of laboratories performed IQC at intervals not exceeding

1 day, and the percentages of laboratories performing an IQC for more than 2 days also had a decrease. Both the control rules and IQC frequency have improved, demonstrating the untiring efforts made by laboratory managers and the NCCL. It is worth mentioning that laboratories do not need to choose too complex control rules, nor do they need to perform IQC too often.²¹⁻²³ Laboratory managers can make reasonable choices based on their own situation.

However, there are still some limitations in this study. Firstly, there were only 72 laboratories continuously submitting IQC information for BNP over the 4-year period in China, which was far less than for NT-proBNP. This may not be enough to reflect the current status of IQC for BNP all over China. Moreover, most of the participant laboratories belonged to tertiary hospitals (66 and 180 laboratories for BNP and NT-proBNP, percentages were 91.67% and 84.91%, respectively) with better reagents and instruments, which may not fully represent the imprecision level of entire laboratories in China. Secondly, management documents require that there should be at least two concentration levels of control materials for each analyte in the medical laboratory.^{24,25} However, until 2017, there were still more than half of laboratories carrying out only one concentration level of control materials, indicating that more than half of laboratories failed to perform IQC as required. Besides, the measurement range of each level was also not specified, so there may be an overlap between two levels.²⁶ Thirdly, there is currently no allowable imprecision quality specifications based on biological variation for BNP currently. Quality specifications based on TEa, which are provided by evaluation criteria for EQA in laboratory medicine, are only at level 4 of the quality specifications hierarchy model, while the quality specifications based on biological variation are at level 2. The advantages of quality specifications based on biological variation are that it can be used in all laboratories according to medical requirements (regardless of the size, type, and location of the laboratory). It is widely accepted because it is simple to use and easy to understand.^{27,28} According to the results of our study, approximately 90% of laboratories can meet 1/4TEa, so it is recommended to use 1/4TEa as the criterion to evaluate the imprecision level of measurement of BNP. In the future, we need to include more laboratories and select different types of hospitals for further study. We should not only assess the imprecision level within a laboratory, but evaluate the inter-laboratory imprecision level as well. The NCCL is also supposed to organize more training programs about quality management, which could strengthen the awareness of quality management and improve the ability of clinical laboratory managers. We appeal to more laboratories in China to participate in the IQC programs.

In this study, we collected and analyzed the IQC data of BNP and NT-proBNP in 72 and 212 Chinese clinical laboratories, respectively, from 2014 to 2017. The results indicated that over the 4 years, the imprecision performance of the two analytes has improved with the decreasing of current CVs. The pass rates have increased and there has been great progress in IQC practice. However, the overall imprecision level and percentages of laboratories meeting stringent quality specifications still need to be improved. Clinical laboratories

in China need to strengthen the concept of IQC and take active actions to ensure the accuracy and reliability of results of BNP and NT-proBNP, so as to provide greater assistance for clinical diagnosis and treatment.

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CONFLICT OF INTEREST

All the authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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