Imprecision Investigation and Analysis of Routine Chemistry in China

Yang Fei, Wei Wang, Falin He, Kun Zhong, and Zhiguo Wang*

National Center for Clinical Laboratories (NCCL), Beijing Hospital, Dong Dan, Beijing, China

Background: This study aims to investigate the imprecision of internal quality control of routine chemistry analytes so that we can have an overall knowledge of imprecision level of measurement in laboratories in China. **Methods:** The internal quality control information including two kinds of coefficient of variations (CVs) of 22 analytes were collected via an on-line questionnaire. Then, the percentages of laboratories meeting the quality requirement for each analyte were calculated according to five imprecision criteria. **Results:** Among these 22 analytes, creatine kinase got the most satisfied result, the percentages of laboratories whose current CV met 1/3 total allowable error (1/3TEa), 1/4TEa, and the specifications

based on biological variation were 99.3%, 95.9%, 99.6%, 99.9%, and 90.6%, respectively, while Na got the lowest satisfaction rate according to these specifications, which were 4.15%, 22.4%, 4.2%, 9.0%, and 1.3%, respectively. From an overall perspective, most of the 22 analytes got a satisfied result when applying the criteria defined by CLIA'88, while only a small amount of laboratories can meet the requirement when applying the specifications derived from biological variation. **Conclusions:** There is huge space for us to enhance and substantial effort is needed in improving and implementing quality management in China. J. Clin. Lab. Anal. 30:444–450, 2016. © 2015 Wiley Periodicals, Inc.

Key words: coefficient of variation; internal quality control; precision; quality specification; routine chemistry

INTRODUCTION

Laboratory testing is an integral part of modern medicine as it impacts patient management regarding both screening, early diagnosis, prognosis, appropriate treatment, and monitoring (1). With the testing technical advancing, our requirements on laboratory medicine for high quality are increasing. Assessing the quality of medical laboratories has become increasingly important not only for pressures to reduce costs, but also for the evidence of testing-related diagnostic errors (2). It has been demonstrated that performance and outcome measures improve the quality of patient care (3). In particular, quality indicators (QIs) represent valuable tools for quantifying the quality of selected aspects of care by comparing it against a defined criterion.

The percentage coefficient of variation (CV, expressed in percentage), which was calculated as the standard deviation (s) divided by the mean value multiplied by 100, can be treated as one of the QIs for monitoring the imprecision of measurement in the analysis phase of clinical laboratory. Only when the precision of our measurement

system is satisfied, we can get an accurate and reliable result. Laboratories can evaluate the imprecision of their measurement systems by monitoring monthly or long-time CVs of internal quality control (IQC) data, and the comparison of CVs with the quality specification (allowable imprecision criteria) can give them a direction to make effort. There are several quality requirements for the evaluation of CVs of IQC, such as 1/3 total allowable error (TEa), 1/4TEa, and the specifications based on biological variation including the minimal, desirable, and optimal allowable imprecision. So far the allowable limits

Grant sponsor: Beijing Natural Science Foundation in 2014; Grant number: No. 7143182.

Contract grant sponsor: Beijing Natural Science Foundation; Contract grant number: 7143182.

*Correspondence to: Zhiguo Wang, National Center for Clinical Laboratories (NCCL), Beijing Hospital, No. 1, Da Hua Road, Dong Dan District, Beijing 100730, China. E-mail: zgwang@nccl.org.cn

Received 10 October 2014; Accepted 11 July 2015

DOI 10.1002/jcla.21877

Published online in Wiley Online Library (wileyonlinelibrary.com).

of external quality assessment are often treated as TEa. Then, the 1/4 TEa and 1/3TEa can be calculated for each analyte. Laboratories in china often use these two specifications as criteria in the evaluation of the precision of their IQC (4). However, combining the biological variation and clinical requirements, the allowable imprecision specifications based on biological variation are suitable for all kind of laboratories regardless of the size and conditions, therefore gained a consensus recommendation among experts and laboratory staffs (5). The CVs of 22 analytes of routine chemistry item in different laboratories in China were collected and then analyzed according to several imprecision specifications so that we can have an overall knowledge of imprecision level of measurement for routine chemistry item in laboratories in China.

MATERIALS AND METHODS

Subjects

Participant laboratories of the routine chemistry External Quality Assessment EQA program organized by National Center for Clinical Laboratories (NCCL) in china.

Methods

The IQC information including the current and long-term cumulative CVs of 22 analytes, which were potassium (K), sodium (Na), chlorine (Cl), calcium (Ca), phosphorus (P), glucose (Glu), urea nitrogen (Urea), uric acid (UA), creatinine (Cre), albumin (Alb), total protein (TP), total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), aspartate transaminase (AST), bilirubin (TBil), alkaline phosphatase (ALP), amylase (AMY), creatine kinase (CK), lactic dehydrogenase (LDH), magnesium (Mg), and gamma-glutamyl transpeptidase (GGT) in February 2014 were collected via the online questionnaire developed by the NCCL of china, which is the official proficiency testing provider in China.

The survey questionnaires were distributed to the participant laboratories who took part in the routine chemistry EQA program, and they were asked to return the questionnaire with the following information: whether they perform IQC, number of the controls, mean value of each control, current CV, and cumulative CV of results in-control, principle of analytes, analyzer, reagent, and calibrator. Then, the percentages of laboratories meeting the quality requirement for each analyte were calculated according to five imprecision criteria, which were 1/3TEa, 1/4TEa, and the specifications based on biological variation including the minimal, desirable, and optimal allowable imprecision.

TABLE 1. Allowable Imprecision Specifications Based on CLIA'88 and Biological Variation

Analytes	1/3TEa	1/4TEa	Minimum performance	Desirable performance	Optimum performance
K	2.87	2.16	2.60	2.4	1.2
Na	0.99	0.74	0.53	0.4	0.175
Cl	1.67	1.25	0.90	0.6	0.30
Ca	3.03	2.27	1.43	1	0.475
P	3.57	2.68	6.38	4.3	2.125
Glu	3.33	2.5	4.28	2.9	1.425
Urea	3	2.25	9.23	6.2	3.075
UA	5.67	4.25	6.75	4.5	2.25
Cre	6.25	4.69	3.98	2.7	1.325
Alb	3.33	2.50	2.33	1.6	0.775
TP	3.33	2.50	2.03	1.4	0.675
TC	3.33	2.50	4.05	2.7	1.35
TG	8.33	6.25	15.68	10.5	5.225
ALT	6.67	5.00	18.23	12.2	6.075
AST	6.67	5.00	8.93	6	2.975
TBil	5.33	4	17.85	11.9	5.95
ALP	10.00	7.50	4.80	3.2	1.6
AMY	10.00	7.50	6.53	4.4	2.175
CK	10.0	7.50	17.10	11.4	5.7
LDH	6.67	5.00	6.45	4.3	2.15
Mg	8.33	6.25	2.70	1.8	0.9
GGT	6.67	5.00	10.35	6.9	3.45

Analytical Quality Specifications

The 1/3TEa, 1/4TEa, and the specifications based on biological variation including the minimal, desirable, and optimal allowable imprecision were used as the quality specifications to evaluate the precision of IQCs for 22 analytes of routine chemistry item. The details of the quality specifications are shown in Table 1.

Based on TEa

Based on the quality requirements (TEa) provided by Clinical Laboratory Improvement Amendment (CLIA'88), NCCL set the criteria of TEa for these routine chemistry analytes. Accordingly, the 1/4 TEa and 1/3TEa can be calculated for each analyte. Laboratories in China often use these two specifications as criteria in the evaluation of the imprecision of their IQCs.

Based on Biological Variation

There were three levels of quality specifications for precision derived from biological variation, which were (1) desirable performance defined by $CV_A < 0.50CV_I$ (where CV_A means analytical precision and CV_I means the within-subject biological variation), (2) optimum performance defined by $CV_A < 0.25CV_I$, and (3) minimum performance defined by $CV_A < 0.75CV_I$. The data we use

TABLE 2. Number of Participant Laboratories, Median, 25th, and 75th of Current CVs and Percentages of Laboratories Meeting Quality Requirements (%)

Analytes	Number of participant laboratories	Current CVs of Chinese laboratories			Allowable Imprecision specifications based on CLIA'88 and biological variation				
		Median	25th	75th	1/3TEa	1/4TEa	Minimum	Desirable	Optimal
K	1,115	1.49	1.01	2.26	84.5	72.7	81.3	78.1	36.8
Na	1,110	1.11	0.78	1.60	41.5	22.4	9.0	4.2	1.3
Cl	1,108	1.34	0.97	2.01	65.8	44.8	21.4	6.0	1.5
Ca	1,122	2.17	1.51	3.10	73.4	54.8	23.1	7.8	1.5
P	1,069	2.30	1.56	3.46	76.6	60.3	94.1	84.9	45.0
Glu	1,242	1.86	1.30	2.78	83.3	70.2	89.0	76.7	31.5
Urea	1,229	2.59	1.90	3.71	61.3	37.8	98.4	93.4	63.1
UA	1,206	1.69	1.15	2.76	94.4	88.8	96.9	90.1	66.5
Cre	1,215	2.60	1.65	4.06	91.7	81.5	74.2	52.4	15.4
Alb	1,215	1.89	1.27	2.90	80.9	67.9	63.5	38.4	6.3
TP	1,217	1.72	1.20	2.57	84.9	74.3	62.9	35.0	5.0
TC	1,210	1.91	1.30	2.88	81.1	67.7	86.4	72.2	27.3
TG	1,211	2.48	1.63	3.67	96.1	92.4	99.3	98.3	88.8
ALT	1,268	3.20	2.13	4.75	92.2	79.6	99.7	99.1	89.0
AST	1,226	2.82	1.94	4.14	92.7	84.3	96.2	90.6	53.4
TBil	1,183	3.23	2.14	4.82	80.4	64.5	99.6	98.1	84.2
ALP	1,168	3.08	2.17	4.60	98.5	94.6	78.1	54.0	12.3
AMY	931	2.20	1.43	3.44	98.7	96.5	95.1	84.4	49.5
CK	1,112	2.18	1.51	3.47	99.3	95.9	99.9	99.6	90.6
LDH	1,135	2.60	1.79	3.90	93.6	86.0	92.8	79.7	38.2
Mg	861	3.40	2.27	4.80	94.8	87.0	35.8	14.3	1.7
GGT	1,174	2.25	1.57	3.50	94.6	88.8	99.1	94.9	74.4

referred to the intra- and interindividual biological variation list provided by Ricos and updated by Westgard in the website of <http://www.westgard.com/biodatabase1.htm> (6). Accordingly, we set the minimum, desirable, and optimum quality specifications for each analyte.

Statistical Analysis

The distributions of CV were described with nonnormal distribution statistical parameters, including median, the 25th percentile (25th), and the 75th percentile (75th), with the use of SPSS 13.0. The percentages of laboratories that met the quality requirements of precision are calculated and shown in Tables 2 and 3.

RESULTS

The numbers of laboratories answered the questionnaires for tests of 22 routine chemistry analytes are approximate 1,000 (from 861 to 1,268), as shown in Tables 2 and 3. As there are no harmonized national controls for the measurements during routine IQC practice, the results of CVs varied very much among different laboratories.

The imprecision of measurement was defined as the percentage CV, which was calculated as the standard

deviation (s) divided by the mean value multiplied by 100. Two different kinds of CV were collected, which were CV of results in-control in February and cumulative CV of data in-control. To calculate the former one, laboratories had to collect all the results of controls in February which were in-control judged by their own quality control rules, that is to say they should remove all the results out-of-control (outlier) and calculate. To calculate the cumulative CV, laboratories had to collect all the results of controls from the first day on which the same lot of control was used to the last day until February. Also, outliers were removed for analysis.

The distributions of the current and cumulative CVs of each analyte are shown in Figures 1 and 2, respectively. The outliers marked by small circle or star in Figures 1 and 2 were automated flagged by SPSS 13.0, which represented the value of CV exceed the confidence interval (5%, 95%). As shown in these two figures, the CVs of controls among clinical laboratories in China varied remarkably.

The medians, 25th, and 75th of these two kinds of CVs for each analyte are shown in Tables 2 and 3, so are the percentages of laboratories whose CV meeting the quality requirement according to five imprecision criteria.

As we can see, for the current CVs, 11 analytes got an excellent result, which were UA, Cre, TG, ALT, AST, ALP,

TABLE 3. Number of Participant Laboratories, Median, 25th, and 75th of Cumulative CVs and Percentages of Laboratories Meeting Quality Requirements (%)

Analytes	Number of participant laboratories	Cumulative CVs of Chinese laboratories			Allowable Imprecision specifications based on CLIA'88 and biological variation				
		Median	25th	75th	1/3TEa	1/4TEa	Minimum	Desirable	Optimal
K	1,115	1.74	1.22	1.74	80.1	64.2	76.1	70.5	24.2
Na	1,110	1.28	0.90	1.87	31.1	13.1	5.5	2.8	1.3
Cl	1,108	1.55	1.12	2.28	56.7	33.0	14.1	4.0	0.9
Ca	1,122	2.48	1.75	3.44	66.2	44.9	15.5	4.9	1.2
P	1,069	2.67	1.80	5.66	70.8	50.6	92.6	79.6	35.6
Glu	1,242	2.20	1.50	3.25	76.6	59.1	85.6	67.3	22.6
Urea	1,229	2.95	2.15	4.19	52.2	28.1	97.8	91.9	53.5
UA	1,206	2.12	1.42	3.20	92.2	84.8	95.7	86.3	53.8
Cre	1,215	3.00	1.96	4.57	89.8	76.6	68.1	42.8	10.4
Alb	1,215	2.23	1.50	3.31	75.5	59.1	53.2	29.1	4.0
TP	1,217	2.00	1.40	2.98	82.2	66.7	52.8	25.0	3.5
TC	1,210	2.30	1.60	3.35	74.9	57.2	82.2	62.6	16.0
TG	1,211	2.83	1.90	4.33	95.7	90.8	99.1	97.8	84.6
ALT	1,268	3.59	2.50	5.00	88.8	75.4	99.2	98.4	85.5
AST	1,226	3.18	2.25	4.66	90.7	79.1	95.8	87.6	43.2
TBil	1,183	3.74	2.55	5.40	74.3	54.5	99.2	96.9	80.0
ALP	1,168	3.59	2.56	5.05	97.3	91.7	70.9	43.4	8.0
AMY	931	2.60	1.79	3.99	97.5	94.1	92.5	80.6	36.1
CK	1,112	2.76	1.83	4.22	97.8	93.5	99.8	99.0	86.2
LDH	1,135	3.00	2.02	4.60	90.7	81.3	90.0	72.6	28.1
Mg	861	3.78	2.58	5.20	92.7	83.3	28.2	9.8	1.4
GGT	1,174	2.63	1.87	3.97	93.4	85.0	98.7	93.4	68.5

AMY, CK, LDH, Mg, and GGT. The percentages of laboratories whose CV met the 1/3TEa specification for these analytes were all above 90% (ranges from 91.7% (Cre) to 99.3% (CK)), whereas the percentages varied greatly from 1.4% (Mg) to 90.6% (CK) when the optimal allowable imprecision specification was used. The analytes of K, Glu, Alb, TP, TC, and TBil got a satisfactory result, for which the percentages of laboratories whose CV met the 1/3TEa specification were above 80% (ranges from 80.4% (TBil) to 84.9% (TP)), whereas the percentages varied greatly from 5.0% (TP) to 84.2% (TBil) when the optimal allowable imprecision specification was employed. However, there are still five analytes (Na, Cl, Ca, P, and Urea) whose results were not so satisfied, the percentages of laboratories whose CV met the 1/3TEa specification for these analytes were below 80% (ranges from 41.5% (TBil) to 76.6% (TP)). See Table 2 for more information.

While for the cumulative CVs, nine analytes got an excellent result, which were UA, TG, AST, ALP, AMY, CK, LDH, Mg, and GGT. The percentages of laboratories whose CV met the 1/3TEa specification for these analytes were all above 90%, whereas the percentages varied greatly from 1.4% (Mg) to 86.2% (CK) when the optimal allowable imprecision specification was used. The analytes of UA, Cre, TP, and ALT got satisfactory results,

for which the percentages of laboratories whose CV met the 1/3TEa specification were 80.1%, 89.8%, 82.2%, and 88.8%, whereas the percentages were 24.2%, 10.4%, 3.5%, and 85.5% when the optimal allowable imprecision specification was employed, respectively. However, there still were nine analytes (Na, Cl, Ca, P, Glu, Urea, Alb, TC, and Urea) whose results were not so satisfied, for which the percentages of laboratories whose CV met the 1/3TEa specification were below 80%. For details, see Table 3.

Poorer quality resulted when applying the specifications derived from within biological variation with the optimal allowable imprecision than when applying the criteria defined by CLIA'88 for these analytes except for Urea and TBil, which were the other way around.

DISCUSSION

Laboratories in this survey located in different areas of China and could be considered as representatives of Chinese clinical laboratories with better medical facilities and more concerns on their performance than those who did not participant in the national EQA program. The results of our investigation suggested that the CVs of these analytes of routine chemistry item varied very much among different laboratories in China. Among these

Fig. 1. Current CVs of 22 analytes of routine chemistry.

22 analytes, CK got the most satisfied result. The percentages of laboratories whose current CV met 1/3TEa, 1/4TEa, and the specifications based on biological variation including the desirable, minimal, and optimal allowable imprecision for CK were 99.3%, 95.9%, 99.6%, 99.9%, and 90.6%, respectively. While the analyte Na got the lowest satisfaction rate according to these allowable imprecision specifications, which were 41.5%, 22.4%, 4.2%, 9.0%, and 1.3%, respectively. The great difference between these two analytes attribute to several factors such as the methods of measurement, operation of laboratory staff, performance of instrument, calibration and maintenance of instrument, usage and storage of reagents and quality control materials, and so on. Laboratories can pay more attention on analytes that still have big gaps with these specifications and make effort to improve their performance.

CV can be treated as one of the QIs for monitoring the imprecision of measurement in the analysis phase of clinical laboratory. Laboratories can evaluate the imprecision of their measurement systems by monitoring monthly or long-time CVs of IQC data, and the comparison of CVs with the quality specification (allowable imprecision criteria) can give them a direction to make effort. There are several quality requirements for the evaluation of CV based on existing state-of-the-art techniques, expert opinion, and biological variation, having been developed over a period of time (7–9). Consequently, the

conference on Strategies to Set Global Quality Specifications in Laboratory Medicine was held by International Union of Pure and Applied Chemistry, International Federation of Clinical Chemistry, and World Health Organization in Stockholm, April 24–26, 1999. The consensus recommendation of the Stockholm Conference was that a hierarchy of quality models should be used. In descending order, the hierarchy of quality specifications was based on (a) clinical outcome, (b) BV, (c) published professional recommendations, (d) regulatory bodies and EQA schemes, and (e) current state of the art (10). The three-level quality goals based on biological variation are in the second level of the Stockholm hierarchy. And in this study, we evaluated the CVs against the specification based on biological variation mentioned above and criteria from CLIA'88, which are in the fourth level of the Stockholm hierarchy apparently. That is to say they are lower than the former specifications. As we know, a model higher in the hierarchy should be preferred over a lower one, performance specifications based on within-subject biological variation seem more reasonable for IQC imprecision evaluation. Laboratories can choose a suitable quality specification by comparing their CVs with our data and make effort for it.

As we can see, poorer quality resulted when applying the specifications derived from within biological variation with the optimal allowable imprecision than when applying the criteria defined by CLIA'88 for these

Fig. 2. Cumulative CVs of 22 analytes of routine chemistry.

analytes except for Urea and TBil, which were the other way around. This means the criteria defined by CLIA'88 in China for these analytes were less stringent than the specifications derived from within biological variation, except for Urea and TBil. There were two kinds of CVs in our survey, which were CV of results in-control in February and cumulative CV of data in-control. The current CV represents the imprecision of the measurement systems in February 2014 while the cumulative CV stands for the total imprecision over time. These two kinds of CV had a similar distribution in our survey. From an overall perspective, most of the 22 analytes got a satisfy result when applying the criteria defined by CLIA'88, while only a small number of laboratories can met the requirement when applying the specifications derived from within biological variation with the optimal allowable imprecision. That is to say there is huge space for us to enhance and substantial effort is needed in improving and implementing quality management so that we can get a better result on the imprecision of measurement systems among different laboratories all over China.

Altogether, the imprecision of measurement of laboratories in China has yet to be improved, and we should make effort to change this situation. For one aspect, laboratories should chose suitable quality based on their own conditions and strive for it. For the other aspect, the government should strengthen supervisory management of clinical laboratories and offer more opportunity for

further education on management and a platform of communication for laboratories (11). Only by joint efforts of both sides, we can improve our performance and get a better result.

ACKNOWLEDGMENTS

We appreciate those participant laboratories and institutions that attended the EQA schemes for this survey. We also thank Clinet website (www.clinet.com.cn) that gave computer technology support to establish the network platform for survey and relevant services.

REFERENCES

1. Plebani M, Laposata M, Lundberg GD. The brain-to-brain loop concept for laboratory testing 40 years after its introduction. *Am J Clin Pathol* 2011;136:829–833.
2. Epner PL, Gans JE, Graber ML. When diagnostic testing leads to harm: A new outcomes-based approach for laboratory medicine. *BMJ Qual Saf* 2013;22(Suppl 2):ii6–ii10.
3. Mainz J, Krog BR, Bjornshave B. Nationwide continuous quality improvement using quality indicators: the Danish National Indicator Project. *Int J Qual Health Care* 2004;16(Suppl 1): i45–i50.
4. Bai Y, Wang ZG, Wang W, Li SN, Zhong K. Analysis of the coefficient of variation of internal quality control of routine chemistry in China. *Lab Med* 2011;32:2002–2004.
5. Skiek M. Acceptability limits based on biology goals in haematology EQAS. *Accred Qual Assur* 2005;10:112–115.

6. Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV. Desirable specifications for total error, imprecision, and bias, derived from intra- and inter-individual biologic variation. Available from: <http://www.westgard.com/biodatabase1.htm>. Accessed on April 2011.
7. Tonks DB. A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories. *Clin Chem* 1963;9:217–233.
8. Barnett RN. Medical significance of laboratory results. *Am J Clin Pathol* 1968;50:671–676.
9. Cotlove E, Harris EK, Williams GZ. Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. 3. Physiological and medical implications. *Clin Chem* 1970;16:1028–1032.
10. Kallner A, McQueen M, Heuck C. The Stockholm Consensus Conference on quality specifications in laboratory medicine, 25–26 April 1999. *Scand J Clin Lab Invest* 1999;59:475–476.
11. Hu LT, Wang ZG. Quality control practice of thyroid disease related tests and imprecision analysis in China. *Clin Lab* 2014;60(2):301–308.