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ORIGINAL ARTICLE

Sigma Metrics used to Evaluate the Performance of Internal Quality Control in a Clinical Biochemistry Laboratory

Zhong Han [1], Wu-Qiong Zhou [1], Wei-Lin Mao [1, 2], Wei-Wei Zheng [3]

[1] *Department of Clinical Laboratory, Shengzhou People's Hospital, Shengzhou Branch of The First Affiliated Hospital of Zhejiang University, Shengzhou, China*
[2] *Key Laboratory of Digestive System Diseases of Shengzhou, Shengzhou People's Hospital, Shengzhou, China*
[3] *The First Affiliated Hospital of University of Science and Technology of China, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui Province, China*

SUMMARY

Background: **The performance of 17 routine chemical detection methods was evaluated by the Sigma (σ) index, and separate quality control standards were established according to the sigma values of different detection methods.**
Methods: **The internal quality control (IQC) and external quality assessment (EQA) data of 17 assays in the biochemical laboratory of our hospital were collected from January to June 2019. Referring to the total allowed error (TEa) standards established in the Health Industry Standards of the People's Republic of China (WS/T 403-2012), the sigma metric of each assay was calculated, the performance level for inspection was evaluated, the quality goal index (QGI) was calculated for items with analysis performance < 5 sigma, and the main causes of poor performance were determined to guide quality improvement.**
Results: **For level 1 internal quality control (IQC), five assays (AMY, Crea, UA, TP, and Na) showed a performance of ≥ 6 sigma levels. Five assays (GGT, LDH, ALP, K, and Ca) had a performance lower than 3 sigma. For level 2 IQC, nine assays (ALT, AST, CK, AMY, Crea, UA, TP, Na, and Mg) achieved 6 sigma, and four assays (GGT, LDH, ALP, and K) achieved less than 3 sigma. Among the 12 assays with a sigma value < 5, the precision of 1 assay should be improved first, the accuracy of 6 assays should be improved next, and both the precision and the accuracy of 5 assays should be improved.**
Conclusions: **The sigma metric is the best tool for evaluating the performance of different test methods. Assays with high sigma values can be evaluated with single-rule quality control, while assays with low values should be evaluated with strict quality control rules.**
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Correspondence:
Wei-Wei Zheng
Department of Clinical Laboratory
The First Affiliated Hospital of University of Science and Technology of China
Division of Life Sciences and Medicine
University of Science and Technology of China
Lujiang Road #17
Hefei, 230001 Anhui Province
China
Phone: +86 551-62283582
Email: kyan614@163.com

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KEY WORDS

Six Sigma, Westgard rule, internal quality control, quality goal index

LIST OF ABBREVIATIONS

σ - sigma
QGI - quality goal index
CV - coefficient of variation
Tea - total allowable error
IQC - internal quality control
EQA - external quality assessment

ALT - alanine aminotransferase
AST - aspartate aminotransferase
GGT - gamma-glutamyl transferase
LDH - lactate dehydrogenase
CK - creatine kinase
AMY - amylase
ALP - alkaline phosphatase
Glu - glucose
Urea - urease
Crea - creatinine
UA - uric acid
TP - total protein
Ca - calcium
Mg - magnesium
K - potassium
Na - sodium
Cl - chloride

INTRODUCTION

Sigma metrics combine deviation, inaccuracy, and total allowable error (TEa) to perform an objective and comprehensive evaluation of analytical test quality. Sigma metrics analysis provides a standardized measure for comparing the quality of testing results by evaluating the performance of the corresponding methods [1-3]. Three Sigma represents the minimum quality requirement, and six Sigma indicates the international quality level. A six sigma analysis means that 99.99966% of the results are error free, corresponding to 3.4 defects for every million opportunities [4]. Higher sigma values mean that fewer analytical errors are made, fewer suspicious test results are accepted and reported, and fewer acceptable test results are erroneously rejected and not reported [5]. In addition, the laboratory may also select appropriate quality control rules based on the review of the quality control results on the sigma scale [6,7]. In many clinical laboratories in China, the Westgard proliferation rules (1_{3s}, 2_{2s}, R_{4s}, 4_{1s}, 8_{x}) have been widely used in clinical biochemistry. With this method, a large number of false rejections may occur. However, the sigma measurement method allows the laboratory to observe the data more broadly, and bias and inaccurate estimation are combined with practical judgement of the clinical usefulness of the quality control standards of the method [8,9]. Thus, it is useful and simple to obtain and select the optimal internal quality control standard based on the Sigma metric. The purpose of this study is to perform statistical analysis and calculate the sigma values for the internal quality control data of some routine biochemical testing items. The application of the sigma value in the evaluation of internal quality control methods and detection analysis methods is discussed.

MATERIALS AND METHODS

Analyser and assays

A Hitachi 7600 analysis system was used to perform 17 routine biochemistry assays: alanine aminotransferase (ALT, IFCC reference method modified without pyridoxal phosphate), aspartate aminotransferase (AST, IFCC reference method modified without pyridoxal phosphate), gamma-glutamyl transferase (GGT, IFCC reference method), lactate dehydrogenase (LDH, IFCC reference method), creatine kinase (CK, IFCC reference method), amylase (AMY, IFCC reference method), alkaline phosphatase (ALP, IFCC reference method), glucose (Glu, hexokinase method), urease (Urea, kinetic assay method), creatinine (Crea, Jaffe kinetic), uric acid (UA, uricase and peroxidase method), total protein (TP, Biuret method), calcium (Ca, Arsenazo III method), magnesium (Mg, Xylidyl blue method), potassium (K, ion-selective electrodes method), sodium (Na, ion-selective electrodes method) and chloride (Cl, ion-selective electrodes method).

ALT, AST, GGT, ALP, and Crea were tested with reagents obtained from Kuake; LDH, AMY, Glu, Urea, UA, and TP from Meikang; CK, Ca and Mg from Diasys; and K, Na, and Cl from Hitachi. Calibration was performed with reagents from Roche, and IQC products were obtained from Beckman Coulter (lot 1: M806001, lot 2: M806003). All EQA samples were provided by the National Center for Clinical Laboratories (lots: 201901, 201902, 201911, 201912, 201921, 201922).

Total allowable error (TEa)

TEa includes random error and systematic error. The definition of the TEa requirements for different clinical biochemistry test methods are considered the starting point for managing quality. The recommended allowable error values for analytes according to the requirements of the Health Industry Standards of the People's Republic of China (WS/T 403-2012) are presented in Table 1.

Precision

The coefficient of variation (CV) was used as an imprecise representation of precision. According to the laboratory quality control data of the clinical biochemical project of our laboratory from January to June 2019, the CV values for two concentration levels of quality control products were determined (level 1 and level 2; Table 1).

Bias

Percent differences were used to estimate bias, which was calculated based on EQA samples. According to data on the metabolites, total proteins, enzymology, and electrolytes obtained in 2019, the laboratory obtained six sets of data corresponding to percentage differences. The average value of the absolute percentage differences was used to assess bias in our laboratory (Table 1).

Table 1. Coefficient of variation (CV), bias, total allowable error (TEa), sigma, and quality goal index (QGI) values of the two levels of quality control for the assays.

Parameter	Average Bias (%)	TEa	Level 1			Level 2		
			CV	Sigma value	QGI	CV	Sigma value	QGI
ALT	4.50	16	2.99	3.85	1.00	1.15	10.03	
AST	2.91	15	2.69	4.50	0.72	1.12	10.83	
GGT	13.25	11	1.45	-1.55	6.08	0.46	-4.87	19.13
LDH	8.82	11	2.25	0.97	2.62	1.27	1.72	4.64
CK	6.66	15	1.68	4.96	2.64	0.81	10.26	
AMY	7.70	15	0.98	7.47		0.75	9.78	
ALP	17.29	18	1.89	0.38	6.09	0.90	0.79	12.80
Glu	2.12	7	1.38	3.54	1.02	1.28	3.82	1.11
Urea	2.88	8	1.60	3.20	1.20	1.22	4.21	1.58
Crea	1.04	12	1.37	8.00		0.83	13.28	
UA	1.15	12	0.85	12.71		0.60	18.18	
TP	0.05	5	0.75	6.63		0.77	6.40	
Na	0.61	4	0.48	7.05		0.36	9.39	
K	5.11	6	0.85	1.05	4.00	0.50	1.78	6.78
Ca	1.84	5	1.40	2.25	0.87	1.05	3.02	1.17
Mg	0.23	15	2.50	5.91		1.23	12.06	
Cl	1.13	4	0.93	3.09	0.81	0.74	3.87	1.02

Abbreviations: ALT - alanine aminotransferase, AST - aspartate aminotransferase, GGT - gamma-glutamyl transferase, LDH - lactate dehydrogenase, CK - creatine kinase, AMY - amylase, ALP - alkaline phosphatase, Glu - glucose, Urea - urease, Crea – creatinine, UA - uric acid, TP - total protein, Ca - calcium, Mg - magnesium, K - potassium, Na - sodium, Cl - chloride.

Sigma metric calculation

Sigma metrics were calculated using the following formula:

Sigma metric = (Tea - |Bias|)/CV

Two sets of Sigma metrics were calculated, one for each of two control concentrations.

Quality goal index (QGI) ratio

The quality goal index (QGI) ratio indicates the relative degree of deviation and accuracy required to achieve the corresponding quality objectives, which was used to find the reason for the detection errors in measurements with a Sigma value < 5 [10]. The QGI ratio was calculated using the standard equation: QGI = Bias/1.5 x CV%. When QGI < 0.8, we should prioritize improving the precision; when 0.8 < QGI < 1.2, both accuracy and precision should be improved; and when QGI > 1.2, improvement of the accuracy should be prioritized.

RESULTS

The performances and sigma values of the 17 assays in the Hitachi 7600 analysis system were calculated, and the results are shown in Table 1. Table 2 summarizes the sigma metrics analyzed in terms of TEa, CV% (level 1 or 2), and Bias %. For the level 1 IQC, five assays (AMY, Crea, UA, TP, and Na) showed a performance of ≥ 6 sigma level. Five assays (GGT, LDH, ALP, K, and Ca) showed a performance of less than 3 sigma. For level 2 IQC, nine assays (ALT, AST, CK, AMY, Crea, UA, TP, Na, and Mg) achieved 6 sigma, and four assays (GGT, LDH, ALP, and K) achieved less than 3 sigma. Among the 12 assays with a sigma value < 5, the precision of 1 assay should be improved first, the accuracy of 6 assays should be improved next, and both the precision and the accuracy of 5 assays should be improved (Table 3).

The assay performances were divided into unacceptable (< 2 sigma), poor (≥ 2 sigma and < 3 sigma), marginal (≥ 3 sigma and < 4 sigma), good (≥ 4 sigma and < 5 sigma), excellent (≥ 5 sigma and < 6 sigma), and world class (≥ 6 sigma). The Westgard sigma rules were used to develop individualized internal quality control measures, and the sigma scale provided guidance for rules that should be applied based on the sigma value of each assay. For all analytes whose assay performance was < 5 sigma, a QGI < 0.8 indicated that the problem was imprecision, while a QGI > 1.2 indicated inaccuracy.

Table 2. Quality control strategies for future works.

Sigma value	Parameters		Westgard rules
	Level 1	Level 2	
σ ≥ 6	AMY, Crea, UA, TP, Na	ALT, AST, CK, AMY, Crea, UA, TP, Na, Mg	13s
5 ≤ σ < 6	Mg		13s/22s/R4s
4 ≤ σ < 5	AST, CK	Urea	13s/22s/R4s/41s
3 ≤ σ < 4	ALT, Glu, Urea, Cl	Glu, Ca, Cl	13s/22s/R4s/41s/8x
σ < 3	GGT, LDH, ALP, K, Ca	GGT, LDH, ALP, K	

Table 3. Quality goal index (QGI) and quality improvement measures of the 17 routine biochemistry assays.

QGI	Parameters		Problem
	Level 1	Level 2	
< 0.8	AST		precision
0.8 - 1.2	Cl, Ca, ALT, Glu, Urea	Cl, Glu, Ca	precision and accuracy
> 1.2	LDH, CK, K, GGT, ALP	Urea, LDH, K, ALP, GGT	accuracy

DISCUSSION

Sigma metrics can be used in many ways in the clinical laboratory, such as for determining method quality when a laboratory purchases a new analytical system or assesses the performances of new assays, selecting appropriate quality control rules, and establishing quality improvement programs [11-13]. In this study, the quality performances of 17 routine biochemistry assays tested using the Hitachi 7600 instrument were evaluated by sigma metrics in our laboratory.

For parameters AMY, Crea, UA, TP, and Na in level 1 IQC and ALT, AST, CK, AMY, CREA, UA, TP, Na, and MG in level 2 IQC, all with a sigma value > 6, the 1_{3S} rule could be used and the testing results can be reported directly. For parameters such as GGT, LDH, ALP, and K, the sigma value was found to be < 3 for both levels of IQC in our study. The QGI ratio for these parameters indicates that the problem for GGT, LDH, ALP, and K could be due to accuracy (QGI > 1.2) but that for CA, the problem could be due to both precision and accuracy (0.8 > QGI <1.2). Therefore, a very stringent IQC protocol needs to be followed, the frequency of IQC should be increased, or the laboratory should use alternate methods and reagents [14].

The Westgard rules and the levels of IQC processed can be selected for biochemical parameters with a sigma metrics level 6 or above (world-class) by assessing one level of QC per day and following the 1_{3s} Westgard rule alone. For Sigma metrics 5-6 (excellent performance), the 1_{3s}, 2_{2s}, and R_{4s} Westgard multirules should be used. For sigma level 4-5 (good performance), the 1_{3s}, 2_{2s}, R_{4s}, and 4_{1s} Westgard multirules should be used. For Sigma metrics 3 - 4 (marginal performance), the 1_{3s}, 2_{2s}, R_{4s}, 4_{1s} and 8_{x} Westgard multirules should be used. For Sigma metrics < 3 (poor performance), measures should be taken immediately to improve the assay or other methods should be used for testing [15].

As a global quality management system, the Six Sigma model is suitable for benchmarking multiple clinical chemical biomarkers. It is an effective method for the evaluation of analytical stage, the quality assessment of laboratory assays and the selection of quality control rules based on sigma values [16]. Clinical laboratories focus on accurate test results; therefore, it would be important to implement six sigma indices in daily analysis. Six Sigma measurements can be used as the evaluation method for quality control plans used frequently in clinical laboratories. To obtain accurate test results, it would be very helpful to implement these indicators in the daily analysis processes of the laboratory.

Although the Westgard Sigma rule has many advantages, there are still many points to note in its use. According to the formula used to calculate sigma, bias, imprecision, and the origin of the TEa can significantly affect the final sigma value [17,18]. During the study, it was found that long-term internal quality control data could ensure more stable imprecision estimates. Therefore, internal quality control data can be selected for half a year or more. The use of short-term calculated imprecision values may lead to inaccurate sigma estimates. The mean value can be calculated for the imprecision estimation of multiple horizontal quality control products. If high quality estimates are required, the

largest value can also be chosen for the imprecision value in the formula.

CONCLUSION

The sigma metric is the best tool for evaluating the performance of different test methods. Assays with high sigma values can be evaluated with single-rule quality control, while assays with low values should be evaluated with strict quality control rules. In addition, poor performance assays should be checked, and different alternatives could be considered to replace them [19].

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Declaration of Interest:
None of the authors have any commercial or other associations that might pose a conflict of interest.

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