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Technical Report

Sigma metric evaluation with different TEa targets in clinical biochemistry

Seniz Korkmaz

Central Laboratory, Karacabey State Hospital, Bursa, Turkey

Abstract

Objectives: The aim of this study was to evaluate the analytical performances of various clinical biochemistry analytes by the sigma metrics method according to different total allowable error (TEa) targets and to determine the causes of errors that lead to low sigma score by using Quality Goal Index (QGI).

Methods: The study was carried out in the Central Laboratory of Bursa Karacabey State Hospital. Twelve analytes that were studied on the Roche Cobas c 501 autoanalyzer were included in the study. Internal (level 1 and 2) and external quality control data for the period March–August 2020 were obtained retrospectively. The TEa targets were obtained from the Clinical Laboratory Improvement of 2019 (CLIA 2019), biological variation database (BVD), Rili-BAEK, and Turkish data. QGI was calculated for analytes with sigma score <3 according to CLIA.

Results: According to the TEa goals of four different guides, different sigma scores were obtained. Three parameters with sigma scores <3 were determined according to TEa targets of CLIA, 8 according to BVD, and 6 according to Rili-BAEK, while there were no parameters with sigma score <3 according to the TEa targets of Turkey. Number of parameters with sigma scores >6 were 7, 10, 6, and 18 according to TEa targets of CLIA, BVD, Rili-BAEK, and Turkey, respectively. When QGI was calculated, it was found that there was inaccuracy problem for albumin and chlorine L1 and imprecision for chlorine L2.

Conclusion: Laboratories should determine the appropriate TEa targets and use the sigma metrics method and QGI as a quality improvement tool. In the light of the obtained data, necessary quality improvements should be made, and the reliability of the results should be increased.

Keywords: Hemoglobin A1c, quality control, quality goal index, sigma metric

The results provided by the clinical laboratories influence 70%-75% of medical decisions; therefore, the quality of laboratory services directly affects the quality of health care. Laboratory results should be accurate, reliable, timely concluded, and useful to clinical decisions [1].

Strict quality control is one of the main conditions for laboratories to provide consistent results. The performance of analytical methods is observed by analyzing samples whose concentration is known and comparing the obtained values with the lower and upper acceptable limit intervals. Internal quality control (IQC) is necessary for daily monitoring of the imprecision and accuracy of the analytical method while external quality control (EQC) is important for monitoring the long-term accuracy of the analytical method, and the two methods are complementary to each other [2]. Accuracy is "the closeness of the agreement between the result of a measurement and the true concentration of the analyte." Accuracy is thus influenced by both bias and imprecision and in this way reflects the total error. Precision has been defined as "the closeness of agreement between independent results of measurements obtained under stipulated conditions" [3]. The bias, which is an indicator of accuracy and systematic errors, is defined as "the difference between the reference value and the value obtained by the analysis" [4]. The main analytical criteria for measuring clinical laboratory tests are accuracy and reproducibility, which are measured by bias and standard deviation (SD), respectively [5]. Total allowable error (TEa) is an analytical quality requirement that sets a limit for both the imprecision

Address for correspondence: Seniz Korkmaz, MD. Central Laboratory, Karacabey State Hospital, Bursa, Turkey
Phone: +90 506 358 48 32 **E-mail:** senizkorkmaz@gmail.com **ORCID:** 0000-0001-5779-9499
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(random error) and bias (systematic error) that are tolerable in a single measurement or single test result [6].

Various additional quality indicators have been developed for laboratories to incorporate into their quality management principles. The Six Sigma method is one of the popular quality management system tools used for process improvement [7]. The Six Sigma strategy measures the degree to which any process deviates from its goal. The sigma metric approach is seen as the evolution of total quality management by clarifying the goals for a more quantitative assessment of process performance and process improvement. The sigma value indicates how often defects are likely to occur; the higher the sigma value, the less likely the process will produce defects [8]. Six Sigma (σ) is a world-class quality target, while Three Sigma is the minimum acceptable level in the sigma metric quality assessment [9]. In the Westgard proposal, the target range is determined according to the TEa. Accordingly, the sigma score for the analytical course of each analyte is calculated by the sigma equation [10].

Quality Goal Index (QGI) refers to a relative extent to which both accuracy and imprecision meet their own quality goals [11]. It is used to examine the cause of the low sigma score in analytes. QGI <0.8 indicates that an improvement in precision is required, QGI between 0.8 and 1.2 indicates an improvement in precision and accuracy, and QGI >1.2 indicates an improvement in accuracy [12].

Our study aimed to compare the TEa goals determined by the government circular in Turkey with other guidelines, evaluate the effect of different TEa goals on sigma values, and determine the causes of errors that lead to low sigma scores.

Materials and Methods

Our study was conducted in the Central Laboratory of Karacabey State Hospital in Bursa. IQC and EQC data studied in the March-August period of 2020 were obtained retrospectively.

Albumin (ALB), alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST), glucose (GLU), chlorine (Cl), total cholesterol (CHOL), creatinine (CREA), lactate dehydrogenase (LDH), triglyceride (TG), total protein (TP), and urea analytes, which were studied on the Roche Cobas c 501 (Roche Diagnostics, Tokyo, Japan) autoanalyzer, were included in the study. ALB was studied using BCG colorimetric method, while ALP was studied using IFCC (ALP-AMP), ALT and AST were studied using IFCC (UV without P5P) methods. GLU was determined by hexokinase enzymatic method, Cl by ISE indirect, CHOL by enzymatic colorimetric (CE-CHOD-POD) method, CREA by Jaffe colorimetric kinetic method (alcaline picrate), LDH by pyruvate-lactate method, TG by enzymatic endpoint (GPO) method, TP by biuret, and urea by urease and GDH kinetic method.

CV% values were calculated using the formula CV(%)=(SD/x) × 100 from two levels of IQC samples studied daily (PreciControl ClinChem Multi 1 and 2, Roche Diagnostics GmbH, Mannheim, Germany). (L1=IQC level 1 and L2=IQC level 2).

Bias was calculated using the monthly EQC reports (Oneworld System Accuracy, Canada) from March to August using the formula bias%=[(test result-average EQC value of test)/average EQC value of test]×100. Six months' average bias% values for each test were used in calculating sigma values.

The sigma value was calculated using the formula: sigma (σ)=(TEa%-bias%)/CV%. TEa targets were obtained from CLIA 2019 (Clinical Laboratory Improvement of 2019), biological variation database (BVD) (desirable), Rili-BAEK, and Turkish government data [13-16]. The minimum acceptance limit for sigma was considered to be 3 sigma level. QGI was calculated by the formula: QGI=bias/1.5×CV% [12].

All calculations were performed using the Microsoft Excel software.

Results

The 6-month average CV% values were 1.35-3.26 for L1 and 1.22-3.76 for L2 (Table 1). The CV% values of all parameters were below 5%, which indicates good repeatability. The mean bias% values and sigma values calculated for both levels based on different TEa targets, and QGI ratios are presented in Table 1.

The parameters were divided into three groups according to their sigma levels. Tests with sigma levels below 3 and having poor quality performance constituted group 1. Group 2 tests were the tests with sigma values between 3.0 and 5.99 and had an acceptable quality performance. Group 3 tests were the tests that had sigma levels above 6, meaning a world-class quality. Table 2 shows the distribution of analytes grouped according to the calculated sigma values.

Because they were calculated using different TEa targets, the sigma metric performances of the analytes were also found to be different. Three parameters with sigma scores <3 were determined according to CLIA, 8 according to BVD, and 6 according to Rili-BAEK, while there were no parameters with sigma score <3 according to the TEa targets of Turkey. The number of parameters with sigma scores >6 were 7, 10, 6, and 18 according to CLIA, BVD, Rili-BAEK, and Turkey, respectively. To determine the reason for the poor performance of the analytes with sigma <3 according to CLIA, QGI was calculated. There were inaccuracy problems for ALB and Cl L1 and imprecision problems for Cl L2.

Discussion

Sigma metrics are used in many fields in clinical laboratories, such as monitoring and auditing the performance of tests, establishing individual quality criteria, and quality improvement plans [5, 10, 17]. In our study, the analytical performances of clinical biochemistry analytes were evaluated sigma metrically. For each analyte, four different sigma values were calculated based on the CLIA, BVD, Rili-BAEK, and Turkey TEa targets with the same CV% and bias values. We aimed to determine

Table 1. CV%, bias%, TEa, and sigma values for all analytes for L1 and L2, and QGI ratios

				CLIA		BVD		Rili-BAEK		Turkey			
	CV%	Bias	TEa	TEa	σ	TEa	σ	TEa	σ	TEa	σ	QGI	Problem
ALB													
L1	2.33	1.32	5.16	8	2.9*	4.07	1.2	12.5	4.8	15	5.9	2.05	inacc
L2	1.86		4.39		3.6		1.5		6.0		7.4		
ALP													
L1	3.26	5.00	10.38	20	4.6	12.04	2.2	11	1.8	30	7.7		
L2	3.76		11.21		4.0		1.9		1.6		6.6		
ALT													
L1	2.46	0.05	4.11	15	6.1	27.48	11.1	11.5	4.6	20	8.1		
L2	2.57		4.30		5.8		10.7		4.4		7.7		
AST													
L1	1.58	0.74	3.35	15	9.0	16.69	10.1	11.5	6.8	20	12.2		
L2	1.61		3.39		8.9		9.9		6.7		12.0		
GLU													
L1	1.63	1.25	3.94	8	4.1	6.96	3.5	11	6.0	11	6.0		
L2	1.71		4.06		4.0		3.3		5.7		5.7		
Cl													
L1	2.14	0.74	4.28	5	2.0*	1.5	0.4	4.5	1.8	9	3.9	1.06	imp inacc
L2	1.57		3.33		2.7*		0.5		2.4		5.3	0.78	imp
CHOL													
L1	1.89	2.37	5.49	10	4.0	9.01	3.5	7	2.4	11	4.6		
L2	1.35		4.60		5.7		4.9		3.4		6.4		
CREA													
L1	2.57	1.27	5.51	10	3.4	8.87	3.0	11.5	4.0	20	7.3		
L2	2.31		5.09		3.8		3.3		4.4		8.1		
LDH													
L1	1.42	1.61	3.95	15	9.4	11.4	6.9	9	5.2	21	13.7		
L2	1.37		3.86		9.8		7.2		5.4		14.2		
TG													
L1	2.47	2.09	6.16	15	5.2	25.99	9.7	9	2.8	15	5.2		
L2	1.57		4.68		8.2		15.2		4.4		8.2		
TP													
L1	1.35	0.56	2.79	8	5.5	3.63	2.3	6	4.0	15	10.7		
L2	1.22		2.57		6.1		2.5		4.5		11.9		
Urea													
L1	1.53	0.25	2.77	9	5.7	15.55	10.0	10.5	6.7	15	9.7		
L2	1.65		2.97		5.3		9.3		6.2		8.9		

*The minimum acceptance limit for sigma was considered to be 3 sigma level according to CLIA. QGI was calculated. TEa: Total allowable error; CLIA: Clinical Laboratory Improvement; BVD: Biological variation database; CV: Coefficient of variation; QGI: Quality Goal Index; ALB: Albumin; ALP: Alkaline phosphatase; ALT: Alanine transaminase; AST: Aspartate transaminase; GLU: Glucose; Cl: Chlorine; CHOL: Total cholesterol; CREA: Creatinine; LDH: Lactate dehydrogenase; TG: Triglyceride; TP: Total protein; inacc: Inaccuracy; imp: Imprecision.

the most appropriate target for our laboratory by evaluating the analytical performance of the tests according to different targets. The reason for the poor performance was examined using QGI for analytes with sigma <3 according to CLIA, which was evaluated as poor performance. According to the result, necessary corrective and preventive actions were initiated.

As in the case of ALB, the CLIA, BVD, Rili-BAEK, and Turkey TEa targets were 8, 4.07, 12.5, and 15, respectively. ALB sigma values were found to be 2.9-3.6 according to CLIA, 1.2-1.5 according to BVD, 4.8-6.0 according to Rili-BAEK, and 5.9-7.4 according to Turkey. QGI for ALB L1 was >1.2, and ALB had undesired accuracy at this level. When the ALB EQC reports were examined, it was seen that the values were close to the average and performed well. Sigma values for Cl were <3 according to CLIA, BVD, and Rili-BAEK. Cl L1 had undesired accuracy and precision, while Cl L2 had undesired precision. Based on Turkey

Table 2. Distribution of analytes according to the sigma values

	CLIA		BVD		Rili-BAEK		Turkey	
Groups	**Level 1**	**Level 2**	**Level 1**	**Level 2**	**Level 1**	**Level 2**	**Level 1**	**Level 2**
Group 1 (σ<3)	ALB Cl	Cl	ALB ALP Cl TP	ALB ALP Cl TP	ALP Cl CHOL TG	ALP Cl		
Group 2 (σ=3-6)	ALP GLU CHOL CREA TG TP Urea	ALB ALP ALT GLU CHOL CREA Urea	GLU CHOL CREA	GLU CHOL CREA	ALB ALT CREA LDH TP	ALT GLU CHOL CREA LDH TG TP	ALB Cl CHOL TG	GLU Cl
Group 3 (σ>6)	ALT AST LDH	AST LDH TG TP	ALT AST LDH TG Urea	ALT AST LDH TG Urea	AST GLU Urea	ALB AST Urea	ALP ALT AST GLU CREA LDH TP Urea	ALB ALP ALT AST CHOL CREA LDH TG TP Urea

CLIA: Clinical Laboratory Improvement; BVD: Biological variation database; ALB: Albumin; Cl: Chlorine; ALP: Alkaline phosphatase; CHOL: Total cholesterol; TP: Total protein; TG: Triglyceride; GLU: Glucose; ALT: Alanine transaminase; CREA: Creatinine; LDH: Lactate dehydrogenase; AST: Aspartate transaminase.

criteria Cl had good performance with 3.9 and 5.3 sigma values. Cl CVs were 2.14-1.57 and showed good repeatability and performed well in EQC reports. Because the ALB and Cl TEas of other guides were lower than Turkey's, sigma values were found to be lower. When the cause of the poor performance was investigated, no problems were found in the CV and bias values of the analytes. Therefore, it was concluded that the TEa targets of Turkey are more suitable for our laboratory.

In this study, we have observed that three parameters with sigma scores <3 were determined according to CLIA, 8 according to BVD, and 6 according to Rili-BAEK, while there were no parameters with sigma score <3 according to Turkey. Considering the number of parameters with low performance, BVD and Rili-BAEK are close to each other, while Turkey's criteria seem optimistic.

Goel et al. [18] compared the CLIA and BVD criteria in the Siemens Dimensions Rxl device. According to the CLIA, BUN (L2-3), ALT (L2-3), AST (L2), TP (L2), and GLU (L2) were found to be sigma <3, while according to BVD, ALP, ALB, TP, GLU, and HDL for both levels, AST, BUN, CREA, ALT, and calcium for L2 were found to be sigma <3. When they evaluated QGI for ALB, ALP, and TP, they found that there was an error in inaccuracy and imprecision for ALB and imprecision for ALP and TP. Erçin [19] reported sigma scores <3 for CHOL [pathologic level (PL)] and for ALB, GLU, CREA, Cl, and TG in both levels according to CLIA. Sigma scores were <3 for CHOL (PL) and ALP, ALB, GLU, CREA, and Cl in both levels according to BVD, and only TG (for both levels) sigma score was <3 according to Rili-BAEK in Abbott Architect c8000 plus (IL 60064, USA) autoanalyzer. He found that there were problems with imprecision and inaccuracy for ALB (normal level) and TG (for both levels) and with imprecision in ALB (PL), GLU, CREA, Cl, and CHOL (PL). Xia et al. [20] have found CHOL, GLU, and TP sigma values to be <3 according to BVD, and CREA sigma values to be <3 according to CLIA. Parallel to our results, Cakmak et al. [21] have stated that ALB, ALP, Cl, and TP tests did not meet the BVD TEa targets. In a similar study, Oktay and Ayyıldız [22] have compared the performances of two biochemistry analyzers according to CLIA targets. The sigma values of ALB, direct bilirubin, Cl, sodium, urea, and TG for IQC L1, and the sigma values of ALB, Cl, and sodium for IQC L2 were <3 on analyzer 1. The sigma values of Cl and sodium for IQC L1, and the sigma values of ALB, direct bilirubin, Cl, and sodium for IQC L2 were <3 on analyzer 2.

The choice of TEa is of critical importance in obtaining the sigma value. A low TEa produces an incorrect low sigma value, while a high TEa can cause one to overlook errors with an incorrect high sigma value. Although there are many different TEa targets for clinical biochemistry, the optimal ones should be determined according to each laboratory's respective conditions and requirements. The requirements should be neither

too low nor too high. If necessary, appropriate targets can be determined from different sources according to the experience of laboratories instead of setting targets from a single source. Although we adhere to the regulations of the Ministry of Health in Turkey, we can set the more stringent TEa of different guidelines as a target. The sigma assessment should be repeated periodically. The necessary corrective-preventive actions should be planned, and repetition of errors should be avoided by identifying the possible causes of low sigma values. Tests with high sigma values can use simple IQC rules to reduce false rejection, while stricter rules should follow tests with low sigma values.

Conflict of Interest: No conflict of interest was declared by the authors.

Ethics Committee Approval: The study was approved by The Bursa City Hospital Clinical Research Ethics Committee (No: 2021-24/12, Date: 29/12/2021).

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References

1. International Organization for Standardization (ISO). ISO/IEC 17025. General requirements for the competence of testing and calibration of laboratories, 2005.
2. Burtis CA, Bruns DE. Tietz fundamentals of clinical chemistry and molecular diagnostics. In: Klee GG, Westgard JO, editors. Quality Management. 7th ed. USA: Elsevier Inc; 2015. p. 97–102.
3. Burtis CA, Bruns DE. Tietz fundamentals of clinical chemistry and molecular diagnostics. In: Linnet K, Boyd JC, editors. Selection and analytical evaluation of methods-with statistical techniques. 7th ed. USA: Elsevier Inc; 2015. p. 12.
4. Plebani M. Errors in clinical laboratories or errors in laboratory medicine? Clin Chem Lab Med 2006;44(6):750–9. [CrossRef]
5. Zhang C, Zhao H, Wang J, Zeng J, Wang Z. The application of six sigma techniques in the evaluation of enzyme measurement procedures in China. Clin Lab 2015;61:461–5. [CrossRef]
6. Clinical and Laboratory Standards Institute. EP21A. Estimation of total analytical error for clinical laboratory methods. Wayne, PA: 2003.
7. Coskun A, Inal T, Unsal I, Serteser M. Six sigma as a quality management tool: evaluation of performance in laboratory medicine quality management and six sigma. InTechOpen: Rijeka, Croatia; 2010. p. 248–61. [CrossRef]
8. Nevalainen D, Berte L, Kraft C, Leigh E, Picaso L, Morgan T, et al. Evaluating laboratory performance on quality indicators with the six sigma scale. Arch Pathol Lab Med 2000;124(4):516–9.
9. Harry M, Schroeder R, Six Sigma: The breakthrough strategy revolutionizing the world's top corporation. New York, NY: Random House, Doubleday; 2000.
10. Shaikh MS, Moiz B. Analytical performance evaluation of a high-volume hematology laboratory utilizing sigma metrics as standard of excellence. Int J Lab Hematol 2016;38(2):193–7.
11. Westgard JO, Westgard SA. An assessment of σ metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. J Vet Diagn Invest 2008;20:536–44.
12. Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of sigma metrics for analytic quality using performance data from proficiency testing surveys and the CLIA criteria for acceptable performance. Am J Clin Pathol 2006;125(3):343–54. [CrossRef]
13. Federal Register. clinical laboratory improvement amendments of 1988 (CLIA) proficiency testing regulations related to analytes and acceptable performance. Federal Register; 2019. p. 1536–67.
14. Westgard JO. WestgardQC, Quality requirements. Available at: https://www.westgard.com/biodatabase1.htm. Accessed Apr 12, 2022.
15. Revision of the "Guideline of the German Medical Association on quality assurance in medical laboratory examinations – Rili-BAEK" (unauthorized translation). LaboratoriumsMedizin 2015;39(1):26–69. [CrossRef]
16. T.C. Sağlık Bakanlığı. İzin verilen toplam hata sınırları. Genelge 2016/18. Available at: https://shgmtetkikdb.saglik.gov.tr/Eklenti/2581/0/genelge-201618izin-verilen-toplam-hata-sinirlaripdf.pdf. Accessed Apr 12, 2022.
17. Tran MT, Hoang K, Greaves RF. Practical application of biological variation and Sigma metrics quality models to evaluate 20 chemistry analytes on the Beckman Coulter AU680. Clin Biochem 2016;49(16–17):1259–66. [CrossRef]
18. Goel P, Malik G, Prasad S, Rani I, Manhas S, Goel K. Analysis of performance of clinical biochemistry laboratory using Sigma metrics and Quality Goal Index. Pract Lab Med 2020;23:e00195. [CrossRef]
19. Erçin U. Sigma values according to different %TEa standards and evaluation of the analytical phase. Türk Klinik Biyokimya Derg 2021;19(2):99–107.
20. Xia J, Chen SF, Xu F, Zhou YL. Quality specifications of routine clinical chemistry methods based on sigma metrics in performance evaluation. J Clin Lab Anal 2018;32(3):e22284. [CrossRef]
21. Cakmak O, Altun Z, Ayan NN. Evaluation of analytical performance specifications of routine clinical biochemistry tests with biological variation-based total allowable error criteria. Int J Med Biochem 2018;1(3):91–8. [CrossRef]
22. Oktay SB, Ayyıldız SN. Assessment of analytical process performance using the Six Sigma method: A comparison of two biochemistry analyzers. Int J Med Biochem 2021;4(2):97–103.