Evaluation of Analytical Performance of Clinical Chemistry Assays Using Six Sigma

Altı Sigma Kullanılarak Klinik Kimya Testlerinin Analitik Performansının Değerlendirilmesi

Gökhan Çakırca **Tülin Yazıcı**

Department of Medical Biochemistry, Şanlıurfa Mehmet Akif İnan Education and Research Hospital, Şanlıurfa, Turkey

Başvuru Tarihi: 11 Haziran 2019 **Kabul Tarihi:** 23 Ağustos 2019

ABSTRACT

Aim: Six sigma is a quality management tool used to evaluate analytical process performance. We evaluated the performance of biochemical and immunological tests on a Roche Cobas 8000 device in our laboratory using sigma metrics.

Materials and Methods: Six-month (September 2018 to February 2019) data on internal quality control (IQC) and external quality control (EQC) were extracted for each assay. The precision and bias were calculated for IQC and EQC, respectively. The sigma values for each assay were calculated using precision, bias, and total allowable error (TEa) ratios of CLIA 2019.

Results: Sigma values of ALB, GLU, Ca, CI, CREA, Na, K, TP, urea, and complement C3 were below 3. ALT, AST, Amylase, P, GGT, HDL-C, CHOL, LDH, LDL-C, T-BIL, UIBC, UA, CRP, complement C4, IgA, and IgM were between 3 and 6 sigma. Sigma values of CK, D-BIL, lipase, and IgG were greater than 6.

Conclusion: Because most sigma values were above 3, the analytical performances of assays in our laboratory were acceptable. However, parameters with sigma values less than 3 should be strictly monitored.

Keywords: Six sigma; analytical process performance; quality assessment; CLIA 2019.

Gökhan Çakırca : https://orcid.org/0000-0003-1526-5899
Tülin Yazıcı : https //orcid.org/0000-0001-8535-0437

Yazışma adresi: Gökhan Çakırca
Department of Medical Biochemistry, Şanlıurfa Mehmet Akif İnan Education and Research Hospital, Şanlıurfa, Turkey
e-mail: cakirca.gokhan@gmail.com

ÖZET

Amaç: Altı sigma, analitik süreç performansını değerlendirmek için kullanılan bir kalite yönetim aracıdır. Bu çalışmada, sigma ölçümlerini kullanarak laboratuarımızdaki Roche Cobas 8000 cihazında biyokimyasal ve immünolojik testlerin performansını değerlendirdik.

Gereç ve Yöntem: Biyokimyasal ve immünolojik testlerinin altı aylık (Eylül 2018 - Şubat 2019), iç kalite kontrol (İKK) ve dış kalite kontrol (DKK) verileri çıkarıldı. Sigma değerleri, İKK verilerinden elde edilen varyasyon katsayısı (CV), DKK verilerinden elde edilen bias ve CLIA 2019'un toplam izin verilebilir hata (TEa) oranları kullanılarak hesaplandı.

Bulgular: ALB, GLU, Ca, CI, CREA, Na, K, TP, üre ve kompleman C3'ün sigma değerleri 3'ün altındaydı. ALT, AST, Amilaz, P, GGT, HDL-C, CHOL, LDH, LDL-C, T-BİL, UIBC, UA, CRP, kompleman C4, IgA ve IgM testlerinin sigma değerleri 3-6 aralığında bulundu. CK, D-BIL, lipaz ve IgG'nin sigma değerleri 6'dan büyük idi.

Sonuç: Sigma değerlerinin çoğu 3'ün üzerinde olduğu için, laboratuarımızda biyokimyasal ve immünolojik testlerin genel olarak analitik performansı kabul edilebilir. Bununla birlikte, sigma değeri 3'ten küçük olan testler sıkı kalite kontrol kurallarıyla izlenmelidir.

Anahtar Kelimeler: Altı sigma; analitik işlem performansı; kalite değerlendirme; CLIA 2019.

INTRODUCTION

Information provided by clinical laboratories has a major impact on patient management and safety, and thus it is important to provide reliable laboratory results to physicians (1). The testing process consists of three main stages: preanalytical, analytical, and postanalytic. Errors in these stages may adversely affect test results. Therefore, strict quality control (QC) practices in the clinical laboratory are essential for the safety and care of patients (2).

QC includes internal quality control (IQC) and external quality control (EQC). IQC is performed daily and provides continuous monitoring of the analytical system. EQC is run once per month and provides an objective evaluation of laboratory performance using an external agency. However, the exact number of defects or errors in the laboratory cannot be evaluated by running EQC and IQC. This problem can be solved by employing sigma metrics calculated from total error (TE), precision (CV), and bias (3).

Sigma metric levels represent a specific value of defects (or errors) per million (dpm) opportunities. For example, six sigma focuses on regulating a process to six standard deviations, corresponding to 3.4 dpm. Lower sigma levels represent more errors and less confidence in test results (4). Sigma metrics provide a scientific basis for selection of test-specific QC procedures in clinical laboratories and creates a more quantitative study framework. Thus, false rejection and control costs in the laboratory can be reduced (5). This study investigated the analytical performance of biochemical and immunological tests using six sigma metrics and to establish the correct QC strategy for each test.

MATERIALS AND METHODS

Study design

This study was performed in the clinical biochemistry laboratory of Sanliurfa Mehmet Akif Inan Training and Research Hospital, Sanliurfa, Turkey, which has a 500-bed capacity. Approval for this study was obtained from Harran University Ethics Committee.

The EQC and IQC data from 34 routine biochemical and immunological analytes were extracted for a period of 6 months from September 2018 to February 2019. A COBAS 8000 device (Roche Diagnostics) was used to test biochemical and immunological assays: albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), amylase, aspartate aminotransferase (AST), calcium (Ca), cholesterol (CHOL), creatine kinase (CK), Chloride (CI), creatinine (CREA), direct bilirubin (D-BIL), γ -glutamyl transferase (GGT), glucose (GLU), high density lipoprotein cholesterol

(HDL-C), iron, lactate dehydrogenase (LDH), low density lipoprotein cholesterol (LDL-C), lipase, magnesium (Mg), sodium (Na), phosphorus (P), potassium (K), total bilirubin (T-BIL), total protein (TP), triglyceride (TG), unsaturated iron-binding capacity (UIBC), urea, uric acid (UA), C-reactive protein (CRP), immunoglobulins (IgG, IgA, IgM), complement C3 and C4.

Sigma calculation

Two-level IQC materials (PreciControl ClinChem Multi 1 and 2, Roche Diagnostics) provided by the manufacturer of the device were assayed daily prior to analyses of blood samples. The coefficients of variation (CV %) of all assays were calculated from the 6-month IQC data as follows: CV%=(standard deviation×100)/mean (6).

Trueness (bias %) for each assay was calculated for each month separately from the EQC data with the following formula: Bias % = (our lab mean–mean of peer group) × 100 /mean of peer group (7). The arithmetic average of bias% was used to calculate sigma values.

The total errors (TEs) of parameters were selected from the Clinical Laboratories Improvement Act of 2019 (CLIA 2019) guidelines (8). There were no TE targets for the Ca, lipase, D-BIL, and K parameters in the CLIA guidelines, so TE values of the Ricos biological variation database (9) were obtained.

The sigma metrics for above-mentioned assays were determined as follows: Sigma metric= (TE%−|Bias%|)/CV% (10). Sigma value was determined for both the level 1 and 2 of IQC. Sigma values are generally categorized into unacceptable (<3 sigma), good (3≤sigma <6), and world class (≥6 sigma) (11,12).

RESULTS

Bias%, CV%, and sigma values of clinical chemistry and immunological tests are shown in Table 1. A sigma value > 6 was found for CK, D-BIL, lipase, and IgG for both levels of IQC. Iron and Mg showed a sigma value of >6 for IQC-1 and 5.83 and 5.80 for IQC-2, respectively. ALP and TG showed a sigma value of >6 for IQC-2 and 5.03 and 5.62 for IQC-1, respectively. Sigma values of ALT, AST, Amylase, P, GGT, HDL-C, CHOL, LDH, LDL-C, T-BİL, UIBC, UA, CRP, C4, IgA and IgM for both levels of IQC were in the range of 3 to 6. Sigma values of ALB, Ca, CI, CREA, GLU, Na, K, TP, urea and C3 for both levels of IQC were lower than 3. The QC strategy for future studies according to sigma values are provided in Table 2 (5,13).

DISCUSSION

In laboratories, sigma metrics can be used to assess the performance of tests or analyzers and to establish optimal QC rules and practices (14). Laboratories can determine which assays are world-class (>6 sigma) quality and which assays are unacceptable (<3 sigma). Assays with low sigma values should be improved with a strict QC strategy. This provides an improvement over the classic rule (control ± 2 SD), which is considered of equal quality for all analytes (15).

In the present study, sigma metrics were calculated to evaluate the quality performance of 34 assays on the Roche Cobas 8000 device. CLIA 2019 TE targets, bias, and precision were used to calculate the sigma values of the assays. We observed sigma values < 3 for ALB, Ca, CI, CREA, GLU, Na, K, TP, urea, and C3 at both QC levels. In Singh et al. (16), who used the Olympus AU400 instrument, a sigma value lower than 3 was observed for urea, Na, and K using the TE values of CLIA 1988. Bozkaya et al. (17) calculated sigma metrics for 13 assays on the Olympus AU680 analyzer using CLIA 1988 TE targets and showed that sigma levels for urea, Na, K, and CI tests were lower than 3. Another study showed that sigma values for urea, Na, K, and CI were below 3 using the TE values of CLIA 1988 in the Beckman-Coulter AU 5800 autoanalyzer (5).

Table 1. Bias%, TEa %, CV% and sigma values of the tests
Tablo 1. Testlerin % Bias, % TEa, % CV ve sigma değerleri

Parameter	TE (%)	Average Bias (%)	IQC-1			IQC-2	
			CV (%)	Sigma		CV (%)	Sigma
ALB (g/L)	8	2.17	3.31	1.76		2.73	2.14
ALP (U/L)	20	2.49	3.48	5.03		2.89	6.06
ALT (U/L)	15	2.10	3.44	3.75		2.73	4.73
Amylase (U/L)	10	1.18	2.24	3.94		2.29	3.85
AST (U/L)	15	1.79	3.36	3.93		2.44	5.41
Ca (mg/dL)	2.55[a]	1.53	2.48	0.41		2.42	0.42
CHOL (mg/dL)	10	1.36	2.73	3.16		2.30	3.76
CK (U/L)	20	1.71	2.83	6.46		2.74	6.68
Cl (mmol/L)	5	1.51	2.18	1.60		1.91	1.83
CREA (mg/dL)	10	3.47	3.62	1.80		3.50	1.87
D-BIL (mg/dL)	44.5[a]	1.17	4.42	9.80		3.42	12.67
GGT (U/L)	15	1.87	3.12	4.21		2.67	4.92
GLU (mg/dL)	8	2.34	2.12	2.67		2.24	2.53
HDL-C (mg/dL)	20	5.60	2.68	5.37		4.22	3.41
Iron (µg/dL)	15	2.81	1.96	6.22		2.09	5.83
LDH (U/L)	15	1.43	2.46	5.52		2.46	5.52
LDL-C (mg/dL)	20	1.76	4.51	4.04		4.73	3.86
Lipase (U/L)	37.88[a]	3.79	2.72	12.53		2.72	12.53
Mg (mg/dL)	15	2.29	2.02	6.29		2.19	5.80
Na (mmol/L)	5	0.95	1.61	2.52		1.63	2.48
P (mg/dL)	10	2.62	2.42	3.05		2.36	3.13
K (mmol/L)	5.61[a]	0.96	1.69	2.75		1.66	2.80
T-BİL (mg/dL)	20	1.91	5.00	3.62		3.82	4.74
TP (g/L)	8	1.56	2.56	2.52		2.40	2.68
TG (mg/dL)	15	0.78	2.53	5.62		2.12	6.71
UIBC (µg/dL)	20	3.99	5.01	3.20		4.97	3.22
Urea (mg/dL)	9	2.75	3.36	1.86		3.05	2.05
UA (mg/dL)	10	1.49	1.98	4.30		1.98	4.30
CRP (mg/L)	30	3.22	4.53	5.91		4.62	5.80
Complement C3 (g/L)	15	1.85	5.75	2.29		6.44	2.04
Complement C4 (g/L)	20	4.67	4.28	3.58		3.92	3.91
IgA (g/L)	15	3.21	3.49	3.38		2.57	4.59
IgG (g/L)	20	1.93	2.65	6.82		2.93	6.17
IgM (g/L)	20	2.17	5.17	3.45		4.55	3.92

a= Ricos desirable TE

Table 2. Internal quality control strategy for future works based on sigma values (5,13).
Tablo 2. Sigma değerlerine dayalı sonraki çalışmalar için iç kalite kontrol stratejisi (5,13).

Sigma value	Assay performances	Number of controls	Measurements	Recommended rule
> 6	World class	2	1	1_{3S}
4-6	Suited for purpose	2	1	$1_{2.5S}$
3-4	Marginal	2	2	1_{3S} / 2_{2S} / R_{4S} / 4_{1S}
<3	Unacceptable	3	2	1_{3S} / 2_{2S} / R_{4S} / 4_{1S}

Compared to the above studies, the number of tests with sigma values below 3 were higher in our study. This can be explained by the fact that CLIA 2019 standards are more stringent than CLIA 1988 standards. Using ALT as an example, the TEa targets for CLIA 1988 and CLIA 2019 were 20% and 15%, respectively. Hens et al. (15) stressed that the use of different TE standards leads to variable sigma values that make it difficult to interpret clinical chemistry assays. In addition, differences in QC data collection

(e.g., time interval), differences in choosing the source of bias, selected IQC criteria, the concentrations of the controls, as well as different manufacturers, analyzers, methods, and reagents may explain the different sigma values across studies (10,12,15,18). The performance of the method should be improved primarily for tests with sigma values < 3. For these tests, three levels of quality control with the $1_{3S}/2_{2S}/R_{4S}/4_{1S}$ rule should be performed twice a day. In addition, we should periodically calculate sigma values to observe changes in test quality by applying these stringent QC procedures. Besides, sigma levels of assays may increase the use of different analyzers and methods (12).

In our study, amylase, CHOL, P, UIBC, complement C4, IgM (both controls); ALT, AST, T-BIL, and IgA (IQC-1); and HDL-C and LDL-C (IQC-2) were between 3 and 4 sigma. For these tests, the $1_{3S}/2_{2S}/R_{4S}/4_{1S}$ rule should be used to ensure accurate test results.

For assays such as GGT, LDH, UA, and CRP (both controls); ALP, HDL-C, LDL-C, and TG (IQC-1); and ALT, AST, iron, Mg, T-BIL, and IgA (IQC-2) between 4 and 6 sigma, QC monitoring should be performed using the $1_{2.5S}$ rule.

A simple 1_{3S} rule should be used for tests with sigma values > 6 (CK, D-BIL, lipase, and IgG (both controls); iron and Mg (IQC-1); and ALP and TG (IQC-2)). For these tests, quality control strategies do not need to be strict and patient results can be reported safely. In this way, control costs and turnaround time (TAT) can be reduced by minimizing false rejection and re-runs.

The use of EQA peer group report in the calculation of bias is the main limitation of our study. Freidecky et al. (19) emphasized that EQA results should be based on comparison with reference method goal values.

CONCLUSIONS

In our laboratory, D-BIL with a sigma value of 12.67 showed the best performance, while Ca had the lowest sigma value of 0.41. Tests with high sigma metric values may use simple IQC rules, while tests with low sigma metric values should be monitored with strict IQC rules. Therefore, each laboratory should establish an IQC strategy for each test using sigma metrics.

REFERENCES

1. Cakirca G. The Evaluation of Error Types and Turnaround Time of Preanalytical Phase in Biochemistry and Hematology Laboratories. Iran j Pathol 2018;13(2):173-8.
2. Plebani M, Sciacovelli L, Marinova M, Marcuccitti J, Chiozza ML. Quality indicators in laboratory medicine: a fundamental tool for quality and patient safety. Clin Biochem 2013;46(13-14):1170–4.
3. Nanda SK, Ray L. Quantitative application of sigma metrics in medical biochemistry. J Clin Diagn Res 2013;7(12):2689-91.
4. Westgard S, Bayat H, Westgard JO. Analytical Sigma metrics: a review of Six Sigma implementation tools for medical laboratories. Biochem Med (Zagreb) 2018;28(2):020502.
5. Mao X, Shao J, Zhang B, Wang Y. Evaluating analytical quality in clinical biochemistry laboratory using Six Sigma. Biochem Med (Zagreb) 2018;28(2):020904.
6. Hill P, Uldall A, Wilding P. Fundamentals for external quality assessment (EQA). Available at: http://www.ifcc.org/ ifcc!les/docs/fundamentals-for-eqa.pdf. Accessed February 12th 2016.
7. EQAS Program User Guide. Version 12.2015 Available at: http://www.qcnet.com/Portals/0/PDFs/EQASUserGuide.pdf. Accessed February 5th, 2018.
8. US Department of Health and Human Services. Clinical laboratory improvement amendments of 1988 (CLIA) proficiency testing regulations related to analytes and acceptable performance 2019. https://www.govinfo.gov/content /pkg/FR-2019-02-04/pdf/2018-28363.pdf. Accessed March 18, 2019.
9. Westgard QC. Quality requirements: desirable biological variation database specifications 2019. https://www.westgard.com/biodatabase1.htm. Accessed March 18, 2019.
10. Westgard SA. Utilizing global data to estimate analytical performance on the Sigma scale: A global comparative analysis of methods, instruments, and manufacturers through external quality assurance and proficiency testing programs. Clin Biochem 2016;49(9):699-707.

11. Zhang C, Zhao H, Wang J, Zeng J, Wang Z. The application of six sigma techniques in the evaluation of enzyme measurement produces in China. Clin Lab 2015;61(5-6):461–5.
12. Gülbahar Ö, Kocabıyık M, Çıracı MZ, Demirtaş C, Uçar F, Bayraktar N, et al. The use of six sigma methodology to evaluate the analytical performances of clinical chemistry analyzers. Turk J Biochem 2018;43(1):1-8.
13. Westgard JO, Westgard SA. Quality control review: implement ing a scientifically based quality control system. Ann Clin Biochem 2016;53(Pt 1):32-50.
14. Schoenmakers CH, Naus AJ, Vermeer HJ, van Loon D, Steen G. Practical application of Sigma Metrics QC procedures in clinical chemistry. Clin Chem Lab Med 2011;49(11):1837–43.
15. Hens K, Berth M, Armbruster D, Westgard S. Sigma metrics used to assess analytical quality of clinical chemistry assays: importance of the allowable total error (TEa) target. Clin Chem Lab Med 2014; 52(7):973-80.
16. Singh B, Gowami B, Gupta VK, Chawla R, Mallika V. Application of sigma metrics for the assessment of quality assurance in clinical biochemistry laboratory in India: a pilot study. Ind J Clin Biochem 2011;26(2):131–5.
17. Bozkaya G, Murat Aksit M, Aksit MZ. Evaluation of clinical chemistry tests in emergency laboratory by sigma metrics. Turk J Biochem 2018;43(1):9–14.
18. Cao S, Qin X. Application of Sigma-metrics in assessing the clinical performance of verified versus non-verified reagents for routine biochemical analytes. Biochem Med (Zagreb) 2018;28(2):020709.
19. Friedecky B, Kratochiva J, Budina M. Why do different EQA schemes have apparently different limits of acceptability? Clin Chem Lab Med 2011;49(4):743–5.