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ORIGINAL ARTICLE

Analytical Process Evaluation of Biochemistry Laboratory by Using Six Sigma Method

Dilara Bal Topcu[1], [MD]
ORCID: 0000-0002-8731-0452

Ahmet Ozsoy[2], [MD]
ORCID: 0000-0003-0718-3471

Fatma Ucar[2], [MD]
ORCID: 0000-0001-7354-375X

Ali Yalcindag[2], [MD]
ORCID: 0000-0003-1846-9248

Yesim Oztas[3], [MD, PhD]
ORCID: 0000-0002-8638-9744

[1]Ankara Akyurt State Hospital, Laboratory of Clinical Biochemistry, Ankara, Turkey.

[2]Diskapi Yildirim Beyazit Training and Research Hospital, Laboratory of Clinical Biochemistry, Ankara, Turkey.

[3]Hacettepe University, Faculty of Medicine, Department of Medical Biochemistry, Ankara, Turkey.

Corresponding Author: Dilara Bal Topcu
Akyurt State Hospital, Clinical Biochemistry Laboratory, Akyurt, Ankara, Turkey.
Phone: +90 312 844 30 10 /1061
E-mail: drdilarabal@gmail.com

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ABSTRACT

Objectives: The primary purpose of medical laboratories is to provide the most accurate results appropriate to the patient's medical condition. Therefore, the reliability of each laboratory must be scientifically tested. Approximately 10 % of laboratory errors occur in the analytical phase. In this study, we aimed to evaluate analytical process performances of 14 routinely assayed parameters according to Six Sigma methodology.

Materials and Methods: Mean, standard deviation and coefficient of variation were calculated from internal quality control data for 3 months from 14 routinely assayed parameters (albumin, alanine aminotransferase, aspartate aminotransferase, chloride, creatinine, glucose, HDL cholesterol, lactate dehydrogenase, potassium, total cholesterol, total protein, sodium, triglyceride and urea) in the laboratory (Roche Cobas c501). Bias was calculated using external quality control values for same months. Total error was also calculated. Acceptable total error was determined according to the Clinical Laboratory Improvement Amendments and Turkey criteria. Sigma values were calculated and divided into four groups; as <3 unacceptable; 3-4 suited for purpose; 4-6 acceptable; >6 world-class performance.

Results: According to the Clinical Laboratory Improvement Amendments and Turkey sigma assessment, first levels of chloride, total cholesterol, glucose and urea performance were unacceptable. Moreover according to the Clinical Laboratory Improvement Amendments sigma assessment, first levels of albumin, creatinine, total protein; and both levels of sodium, chloride and urea were unacceptable. Other tests were found to be suited for purpose, acceptable or world-class performance.

Conclusions: Sigma measurements should be routinely performed in laboratories for evaluating the analytical period performance of the laboratory. That will increase its quality via regulatory preventive actions. Our study allowed us to see and improve our measurement quality by determining the three-month periodic performance of our laboratory tests.

Keywords: Internal quality control, analytical performance assessment, six sigma methodology, total allowable error, westgard rules

INTRODUCTION

Clinical laboratory results are essential to diagnose and follow up the disease and they have obviously a great impact on the quality of health services. Also, laboratory tests provide guidance for approximately 80–90 % of all diagnoses. Laboratory testing is a highly complex process in which laboratory errors were reported to occur with a frequency of 0.012 – 0.6 % for all test results [1].

While the clinical laboratories are playing a very critical role in clinical decision and medication, minimizing measurement errors should be the primary goal of clinical laboratories, to provide reliable, competent and accurate performances with a variety of defined scientific methods. These methods vary according to the stages of the total test process as pre-analytical, analytical and post-analytical. Laboratory errors are frequently seen in pre and post-analytical processes. Errors seen in the analytical phase represents the smallest proportion of overall test errors, about 7-13 % [2].

Quality control (QC) screening is a crucial process in the laboratory and ensures clinical diagnostic accuracy and quality of patient safety. QC monitoring can be done via three ways which are; internal quality control (IQC) program with the Levey-Jennings charts, the external quality control (EQC) programs, and Sigma metrics system which is newly acknowledged as analytical assessment method [3,4]. QC programs are not always sufficient for analytical stage evaluation. In addition to all these methods, a comprehensive and systematic evaluation is also required [5,6].

Objective evaluation of performance can be achieved with the Six Sigma method. The sigma level of a process can be obtained by calculation using specific equations. The sigma value represent how often errors are probably to happen. If the sigma is a low value, the process will most likely produce errors. Ideal situation or world-class performance has at least 6 sigma value. this means that there were fewer than 3.4 errors per million products in this process [7].

Systematic error of a measurement is the difference from the actual concentration of the analyte, which can be positive or negative. Systematic error is expressed as a bias [8]. Precision (repeatability) is the power of an analytical method to produce the same result of repetitive measurements made from the same sample. It is being used to measure the random errors. Random error is expressed as coefficient of variation (CV). Total analytical error (TE) is the sum of random error and systematic error. Westgard et al. formulated TE %= Bias % + (1.65× CV %) [9]. Total allowable error (TEa) is the analytical quality specification that determines acceptable limits in a single test result [10]. The TEs of the laboratory for each test should be aimed to be lower than the target TEa values that they accept as criteria. Target TEa limits can be set in different ways. There are values set by organizations such as Clinical Laboratory Improvement Amendments (CLIA), besides each country can set its own national values [11]. TEa value for some tests has recently been determined by the Analytical Standardization and Harmonization Committee in our country (Turkey) [12]. Above mentioned sigma metrics calculate from TEa, CV, and bias [13].

In this study, we aimed to evaluate analytical performance of our laboratory according to TEa and Six Sigma methodology. The tests evaluated for this purpose; albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), chloride (Cl), total cholesterol (TChol), creatinine (Crea), glucose (Glu), HDL cholesterol (HDL-c), lactate dehydrogenase (LD), potassium (K), total protein (TP), sodium (Na), triglyceride (Tg) and urea.

MATERIALS and METHODS

Mean, standard deviation (SD) and CV were calculated from period of 3 month from March 2020 to June 2020. A Cobas c501 device (Roche Diagnostics) was used to test assays: Alb, ALT, AST, Cl, TChol, Crea, Glu, HDL-c, LD, K, TP, Na, Tg and urea in the laboratory. The method of each test was traceable to the reference method. Two levels of clinical chemistry controls, PreciControl ClinChem Multi 1 and 2 (Level 1: normal control, Level 2: pathological control) used for each parameter. Bias was determined from the same period's peer laboratory group of EQC data with this calculation: [Bias % = (our lab mean- mean of peer group) × 100/ mean] of peer group. The arithmetic average of bias was used to calculate sigma values. TE calculated via Bias % + (1.65× CV %) formula. TEa

was determined according to the CLIA and Turkey (TR) criteria. CV of all assays were calculated from the 3 month IQC data as follows: CV % = (SD× 100)/ mean formula. Sigma values were calculated via (TEa % – Bias %)/ CV % formula [14]. According to sigma levels groups divided into our groups; as <3 unacceptable; 3-4 suited for purpose; 4-6 acceptable; >6 world-class performance [15].

This study was approved by the Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (06/07/2020-91/14).

RESULTS

Table 1 summarizes the calculated laboratory mean, CV %, TE %, TEa %, Bias % and sigma values depending on the CLIA and TR TEa. Table 2 and 3 summarize which Westgard rules could apply for improving future works based on depending CLIA and TR sigma values respectively [3,16].

TE values of all tests were found under the TEa limits which depends on Turkey criteria while both levels of Na and first level of Cl tests'TE values were found higher than TEa which depends on CLIA criteria.

According to the CLIA and TR sigma assessment, first levels of Cl, TChol, Glu and urea performance were unacceptable and also, according to the CLIA sigma assessment, first levels of Alb, Crea, TP and both levels of Na, Cl and urea were unacceptable.

According to the TR and CLIA sigma assessment both levels of HDL-c were higher than 6, have word-class performance (Table 2-3).

According to the CLIA sigma assessment first level of Tg were higher than 6, has word-class performance (Table 2).

According to CLIA sigma assessment both levels of LD, ALT, K and second level of AST were between 4-6 (Table 2).

According to TR sigma assessment both levels of LD, ALT and second levels of Alb. AST, Crea, K, TP, Urea, Tg were between 4-6 (Table 3).

Other tests were found to be suited for purpose, between 3-4.

DISCUSSION

Tests with small sigma values are considered to exhibit low analytical performance. It reveals the necessity of evaluating the analytical process of these tests in detail, recommending the application of suitable Westgard Sigma rules. Another benefit of using sigma values is that it gives an opportunity to make adjustments in control applications [17].

Table 1. Calculated laboratory mean, CV %, bias %, TE %, Tea % and sigma values

Analyte	Laboratory mean		CV %		Bias %	TE %		TEa % (CLIA)		TEa % (Turkey)		Sigma (CLIA)		Sigma (TR)	
	L1*	L2+	L1	L 2	-	L1	L2	L1	L2	L1	L2	L1	L2	L1	L2
Albumin (g/L)	31.9	49.4	3.4	3.2	2.7	8.4	5.4	10.0	10.0	15.0	15.0	**2.1**	3.1	3.6	4.6
ALT (U/L)	46.3	111.7	3.9	3.4	2.5	9.0	5.6	20.0	20.0	20.0	20.0	4.4	5.8	4.4	5.8
AST (U/L)	50.9	150.7	4.4	4.5	3.7	10.9	7.5	20.0	20.0	20.0	20.0	3.7	4.4	3.7	4.4
Cl (mmol/L)	87.8	108.0	3.0	2.9	1.9	**6.8**	4.8	5.0	5.0	9.0	9.0	**1.0**	**1.7**	**2.4**	3.1
TChol (mg/dL)	86.9	156.5	3.1	3.0	2.6	7.7	5.0	10.0	10.0	11.0	11.0	**2.4**	3.3	**2.7**	3.6
Crea (mg/dL)	1.1	3.9	5.4	4.3	4.0	12.9	7.2	15.0	15.0	20.0	20.0	**2.0**	3.5	3.0	4.6
Glu (mg/dL)	101.7	230.8	3.6	3.4	1.6	7.5	5.6	10.0	10.0	11.0	11.0	**2.3**	3.0	**2.6**	3.3
HDL-C (mg/dL)	26.4	66.3	2.5	2.7	3.1	7.3	4.4	30.0	30.0	30.0	30.0	10.8	11.2	10.8	11.2
LD (U/L)	167.2	313.9	3.3	3.5	2.1	7.5	5.7	20.0	20.0	21.0	21.0	5.4	5.8	5.7	6.0
K (mmol/L)	3.6	6.9	2.0	2.0	1.4	4.6	3.3	13.0	8.3	9.0	9.0	5.9	4.1	3.9	4.4
TP (g/L)	48.7	75.9	3.0	3.1	3.1	8.0	5.2	10.0	10.0	15.0	15.0	**2.3**	3.2	4.0	4.8
Na (mmol/L)	112.8	137.1	2.0	2.3	1.2	**4.6**	**3.7**	2.9	3.2	9.0	9.0	**0.8**	**1.4**	3.8	4.0
Tg (mg/dL)	118.0	225.0	3.1	2.9	3.1	8.3	4.7	25.0	25.0	15.0	15.0	7.0	8.7	3.8	5.2
Urea (mg/dL)	38.6	113.6	3.4	3.2	5.9	11.4	5.3	12.2	9.0	15.0	15.0	**1.9**	**2.8**	**2.7**	4.7

*: Level 1

+: Level 2

Table 2. Sigma values depending on CLIA assessment and recommended internal quality control rules

Sigma metrics (CLIA)	Parameters	Levels of control	Assay performance	Westgard Rules
>6	HDL-c, Tg HDL-c, Tg	1 2	World Class	1_{3s} 2 Levels, 1 Times per day
4-6	ALT, LD, K ALT, AST, LD, K	1 2	Acceptable	$1_{2.5S}$ 2 Levels, 1 Times per day
3-4	AST Alb, TChol, Glu, Crea TP	1 2	Suited for purpose	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$ 2 Levels, 2 Times per day
<3	Cl, TChol, Na, Urea, Alb, Crea, TP, Glu Cl, Na, Urea	1 2	Unacceptable	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$ 3 Levels, 2 Times per day

Table 3. Sigma values depending on TR assessment and recommended internal quality control rules

Sigma metrics (TR)	Parameters	Levels of control	Assay performance	Westgard Rules
>6	HDL-c HDL-c	1 2	World Class	1_{3s} 2 Levels, 1 Times per day
4-6	ALT, LD Alb, ALT, AST, LD, K, TP, Crea,Tg, Urea	1 2	Acceptable	$1_{2.5S}$ 2 Levels, 1 Times per day
3-4	Alb, AST, Cre, Na, Tg, K Glu, Cl, TChol Na	1 2	Suited for purpose	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$ 2 Levels, 2 Times per day
<3	Cl, TChol, Glu, Urea -	1 2	Unacceptable	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$ 3 Levels, 2 Times per day

In this study we analyzed test results for 14 parameters in a period of 3 months. Although our internal quality control values, which we routinely apply to these parameters, seem appropriate but when sigma analysis was performed, it was revealed that the performance of some tests was actually low.

Tests with sigma values depending on CLIA assessment, below 3 are at a high rate in our study but on the other hand we found TE values of all tests in appropriate TEa limits except both levels of Na and Cl which depend on CLIA criteria.

According to the CLIA and TR sigma assessment, first levels of Cl, TChol, Glu and urea performance were unacceptable and also, according to the CLIA sigma assessment, first levels of Alb, Crea, TP and both levels of Na, Cl and urea were unacceptable.

We should rigorously follow applied QC Westgard multi rules and pay extra attention to these tests. Method performance must be reformed primarily for these tests and three levels of QC should be taken twice a day with applying 13s/22s/R4s/41s rule (Table 2, Table 3).

Parameters with sigma values between 3 and 4, two levels of QC with a 13s/22s/R4s/41s rule should be taken twice a day (Table 2, Table 3).

Parameters have sigma values in the range of 4 to 6, two levels of QC with a 12.5s rule should be taken twice a day (Table 2, Table 3).

Tests with sigma values higher than 6 required only a single rejection rule of 13s, with two control measurements of each level in a run. In this way, the number of unnecessary IQC assessments can be reduced and thus cost, labor and time can be saved.

Gulbahar et al. [18] who used four different biochemical analyzers, a sigma value lower than 3 was observed mostly for tests urea, Na, and K using the TEa values of CLIA. Korkmaz [19] calculated sigma metrics for 17 assays on the Beckman Coulter UniCel DxC 800 analyzer using CLIA TEa targets and showed that sigma levels for Glu (both levels), TP (level 1) amilase (level 2) tests were lower than 3. Nanda et al. [13] calculated sigma values less than 3 for urea, TP, Alb, TChol and Cl in Cobas Integra auto analyzer.

Also our results are comparable to the results of Mao et al. for urea, Na, and Cl which were below 3 sigma. However they found differently sigma metrics between 3-6 for Glu and TChol from our study [17]. In a study by Verma et al. sigma values of Glu, urea and TChol were <3 [20]. In these studies TEa for calculating the sigma metrics are taken from the guidelines of CLIA like us.

Sigma levels of some analytes showed variations among different studies. This situation can be explained by various reasons; using the different types of analyzers, reagents, and QC materials, selecting various source of the TEa targets and using different algorithms to calculate the bias and CV, which might affect the sigma values [21].

Six Sigma is a statistical measure, which firstly discovered and used in non-healthcare industry to achieve the highest level of quality. In non-healthcare ventures, sigma level under 3 is regard as suboptimal performance. In health care the sigma performance is not recognized well however, performance level of 2 to 3 has been quoted in most assessments [22]. These results show that analytic quality is still a major problem when evaluated on the sigma scale [3].

TEa expresses the degree of error which can be tolerated in a test result. TEa based on biological variations and is acknowledged concept in laboratory medicine. CLIA values are more stringent than TR values. Utilizing more relaxed TEa values will yield better sigma values [22].

EQC assessment results should compare with reference method goal values. Using reference materials or comparison with reference methods are ideal ways. But because of financial reasons we could not perform this [23]. We calculated bias from EQC data which is the most used method in literature. Utilization of Six Sigma methodology should be easy, quick, and reliable.

The Six Sigma methodology gives us the opportunity to create our own QC strategy and conduct self-assessment. It can be very beneficial to apply this metrics for produce accurate test results into our laboratory.

CONCLUSION

Sigma measurements should be routinely performed in laboratories to assess the analytical period performance of the laboratory and improve its quality through regulatory preventive actions. Our study allowed us to see and improve our measurement quality by determining the 3-month periodic performance of our laboratory tests.

CONFLICT of INTEREST STATEMENT

Authors declare that they have no conflict of interest and financial support for this study.

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