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Research Article

Total analytical error assessment of Yerköy State Hospital biochemistry laboratory

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Abstract

Objectives: In 2016, the maximum allowable CV% and allowable total error limits (TEa-TR) for 15 test parameters were specified by the Ministry of Health of Turkey and put into practice. Our study aimed to assess the analytical performance of 15 test parameters studied in our laboratory in terms of the TEa-TR criteria and demonstrate the effect of the method of CV% use in the TAE formula on the performance of tests when two-level internal quality control (IQC) was employed.

Methods: Total analytical error (TAE) was calculated using the formula TAE%=(CV%×1.65)+bias%. Two different procedures were followed for TAE calculation. TAE_1 and TAE_2 were separately calculated for each control level using the CV% values obtained from the data of IQC at two different levels used for each test. In addition, TAE_3 values were found for each test parameter in line with the total CV% value (Total CV%=$\sqrt{(CV1^2+CV2^2)}$) obtained using the IQC data from two different levels.

Results: When CV% values were separately taken for each control level, the maximum allowable CV% value was exceeded in two tests at IQC Level 2, whereas the TEa-TR limit was exceeded in two tests at IQC Level 1 and in 2 tests at IQC Level 2 during the 6-month period. According to the TEa-TR formula, the allowable CV% was exceeded 19 times in 13 out of 15 tests, and TEa limits were exceeded 15 times in 10 tests during the 6-month period.

Conclusion: When the total CV% was calculated from Level 1 and Level 2 according to the TEa-TR formula, both the maximum allowable CV% and allowable TEa% limits were exceeded many times. However, when the CV% and TAE values were calculated separately for different levels of IQC samples, the analytical performance of the tests were found better. We think that calculating the TAE and CV% values separately is more useful in showing the analytical performance of the test at different levels.

Keywords: Allowable total error in Turkey, analytical performance, quality control, total analytical error

Although clinical biochemistry laboratory professionals are not in direct contact with patients in practice, the results obtained from clinical laboratories are extremely important for clinicians in the diagnosis and follow-up of the disease [1]. The regular examination of the accuracy and consistency of the data obtained in the biochemistry laboratory is highly important to obtain accurate, precise, and comparable results [1, 2]. In the clinical laboratory, errors can arise at all stages of the laboratory testing process [3]. Approximately, 10% of the errors in the total testing process emerge in the analytical process [4]. Although analytical process errors account for a very small part of the test errors, they are important for laboratory professionals as they are easy to standardize and control [5]. Clinical laboratory professionals should reduce errors as much as possible in the analytical phase by periodically assessing them with quality control processes [5-8]. The concept of total analytical error (TAE) was first defined by Westgard et al. [9] in 1974, and a formula was developed to assess analytical performance (TAE%=(CV%×1.65)+bias%). TAE is the sum of the random and systematic errors reflected in a test result [10-12]. TEa means the maximum amount of error that can be tolerated without compromising the clinical benefit of the test [13]. Its value is different for each test parameter and may be specified based on the clinical importance of the test, clini-

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cal experiences, biological variability of the analyte, or current research data. There is no worldwide standardization for TEa limits. Different recommendations for TEa limits for the same test parameter based on different formulae and data sources have been given by different organizations such as the Clinical Laboratory Improvement Amendments (CLIA), Richtlinien der Bundesarztekämmer (Rilibak), and Royal College of Pathologists of Australasia (RCPA) [14, 15]. Moreover, there are also TEa limits based on biological variation developed by Ricós et al. [16, 17]. The Analytical Standardization and Harmonization Committee, established by the Ministry of Health, Department of Medical Laboratory Services in Turkey, determined the targets for total error (TEa-TR) and the maximum allowable coefficient of variation (CV%-TR) for 15 test parameters [albumin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), chloride (Cl), total cholesterol, creatinine, glucose, HDL-cholesterol, lactate dehydrogenase (LDH), potassium (K), total protein, sodium, triglyceride, and urea)] and published them in a circular dated October 13, 2016 [18]. In the same circular, laboratory professionals are requested to conduct an internal quality control (IQC) study at least once and at minimum two levels when the test is studied for the parameters stated in Table 1.

Clinical laboratory professionals can identify their analytical performance by comparing the calculated TAE values to the TEa limits. For the safety of patients, TAE should not exceed the TEa limit [13, 19]. While the CV% value of each IQC level is used separately for the CV% values used in the TAE formula in the literature [20-22], it is suggested to use a single total CV% value (Total CV%=$\sqrt{(CV1^2+CV2^2)}$) using the TEa-TR formula.

Regarding the performance assessment of the analytical process, studies using the CLIA, Rilibak, and biological variation-based TEa criteria are found in the literature. However, the number of studies using the national TEa criteria determined for Turkey is limited. In our study, we aimed to compare the performance of 15 test parameters specified in the circular with the TEa limits and the maximum allowable CV% values determined by the Analytical Standardization and Harmonization Committee and find out whether our laboratory performance achieved the targeted quality. In the present study, we also aimed to compare the CV% values calculated for two levels of IQC both separately and with the TAE values calculated by obtaining a single total CV% via the TEa-TR formula.

Materials and Methods

This study was conducted with the approval of Yozgat Bozok University Clinical Research Ethics Committee. In this study, the IQC and external quality control (EQC) data of albumin, ALT, ALP, AST, Cl, total cholesterol, creatinine, glucose, HDL-C, LDH, K, total protein, Na, triglyceride, and urea tests, which were studied using the Beckman Coulter AU 680 (Beckman Coulter, Inc., Brea, CA, USA) analyzer in Yerköy State Hospital Biochemistry Laboratory between June 2020 and November 2020, were retrospectively examined for the 6-month period. For the study period, the duration recommended by the Clinical Laboratory and Standards Institute (CLSI) C24-A3 guidelines was followed [13]. The units of the assessed test parameters and the methods used in our laboratory are presented in Table 2.

Table 1. The total error limits and the maximum allowable CV% values determined by the Ministry of Health, Department of Medical Laboratory Services

Test Name	Allowable total error of the Ministry of Health (%)	The maximum CV% recommended by the Ministry of Health
Albumin	15	7.5
ALT	20	10
ALP	30	10
AST	20	10
Cl	9	5
Total cholesterol	11	5
Creatinine	20	10
Glucose	11	5
HDL-C	30	10
LDH	21	10
K	9	5
Total protein	15	7.5
Na	9	5
Triglyceride	15	7.5
Urea	15	7.5

CV: Coefficient of variation; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; Cl: Chloride; HDL-C: High-density lipoprotein cholesterol; LDH: Lactate dehydrogenase; K: Potassium; Na: Sodyum.

Precision is the repeatability of results. It provides information about the random error component of TAE and is expressed as CV%. On the other hand, bias is an expression of the distance of the analyte result from the actual value and provides information about the systematic error component of TAE. The value 1.65 is the Z-score in case of which 95% of the results are considered normal in the one-way analysis of the normal distribution [9].

Bias% values were obtained from the KBUDEK EQC program assessment reports from June to November. Absolute values of bias were used in TAE calculation.

For each test, two-level IQC samples (low level and high level) were used. Among the values obtained from the two-level IQC, measured on different days of every month during the study (20 days/month, twice a day), CV1% (for low-level IQC) and CV2% (for high-level IQC) were calculated using formula (2).

With formula (3),

TAE was calculated separately for the CV% values found for each IQC level (TAE_1 and TAE_2).

TAE_3 was calculated from the total CV% (Total CV%=$\sqrt{(CV1^2+CV2^2)}$).

Table 2. The names, units and laboratory study methods of the test parameters assessed

Test name	Test unit	Study method
Albumin	g/dL	Bromcresol green
ALT	U/L	Tris buffer without Pyridoxal Phosphate
ALP	U/L	AMP optimized to IFCC
AST	U/L	Tris buffer without Pyridoxal Phosphate
Cl	mmol/L	ISE, indirect
Total cholesterol	mg/dL	Cholesterol Oxidase-Abell Kendall
Creatinine	mg/dL	Modified Jaffe's, kinetic
Glucose	mg/dL	Hexokinase
HDL-C	mg/dL	Direct HDL, Clearance method
LDH	U/L	L to P, IFCC
K	mmol/L	ISE, indirect
Total protein	g/dL	Biuret reaction, end point
Na	mmol/L	ISE, indirect
Triglyceride	mg/dL	Lipase/ Glycerol phosphate Dehidrogenase-peroxidase
Urea	mg/dL	Urease, kinetic

ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; IFCC: International Federation of Clinical Chemistry; AST: Aspartate aminotransferase; Cl: Chloride; ISE: Ion Selective Electrode; HDL-C: High-density lipoprotein cholesterol; LDH: Lactate dehydrogenase; K: Potassium; L: Lactate; P: Pyruvate; Na: Sodyum.

TAE is calculated using IQC data to obtain CV% and EQC data to obtain bias% values:

$$\text{Bias\%}=\frac{(\text{Laboratory result-mean of peer group})}{(\text{mean of peer group})}\times 100 \quad (1)$$

$$\text{CV\%}=\frac{SD}{(Xmean)}\times 100 \quad (2)$$

$$\text{TAE\%}=(\text{CV\%}\times 1.65)+\text{bias\%} \quad (3)$$

Results

TAE_1 and TAE_2 values calculated using CV1%, CV2%, and bias% values obtained during the 6-month period for 15 test parameters and total CV% and TAE_3 values calculated using total CV% are given in Table 3.

When CV% values were taken separately for each level of control, the CV%-TR limit was exceeded only in two tests at IQC Level 2 (CV2%) during the 6-month period.

In the case of total CV% calculation, the CV%-TR limit was exceeded 19 times in 13 out of 15 tests during the 6-month period. The CV%-TR limits were exceeded by 21.1%. Limits were exceeded 9.5 times more in calculations with total CV% compared to calculations with CV% values of each level.

According to the TAE results obtained when CV% values of each level were assessed separately, TEa-TR limits were exceeded in two tests at IQC Level 1 (TAE_1) and in two tests at IQC Level 2 (TAE_2).

Following the TAE calculation with total CV% upon obtaining a single CV% with the TEa-TR formula, it was observed that the TEa-TR limits were exceeded 15 times in 10 tests, and TEa-TR limits were exceeded by 16.7% during the 6-month period.

Compared to the TAE calculations with CV% values of each level, the TAE value exceeded TEa-TR limits 3.75 times more in TAE calculations with total CV%.

Discussion

It is of great importance to deliver test results in time and accurately so that clinicians can make decisions on diagnosis, treat-ment, and follow-up [23]. This requires the implementation of quality systems and risk management guidelines [24]. In order to implement them, it is necessary to determine the quality targets expected for each test and ensure that these targets are achieved in routine tests [24, 25]. Before Westgard, Carey, and Wold introduced the concept of TAE in 1974, laboratory professionals considered precision (CV%) and accuracy (bias%) as separate sources of error and evaluated them separately. They made repeated measurements to reduce the effect of uncertainty, and leaving bias to measure the quality of the test result. However, clinical laboratories make a single measurement for each patient sample for the desired tests and report the result. Accordingly, the analytical quality of a test result did not depend on the separate effect of precision and accuracy of a method, but their overall or total effect. Westgard et al. [9] introduced the concept of TAE in which both precision and accuracy would be used to assess the method performance of a test and suggested that the result should be compared with the predefined allowable total error (TEa). For this, they suggested that the TAE value could be found by calculating bias (accuracy) from a method comparison experiment and CV from a repeatability experiment. Thus, the formula TAE=(CV%×1.65)+bias% was obtained in the 95% confidence interval.

The CV value, which indicates analytical precision, refers to the repeatability of the test results. Concerning the use of control material at two or more levels, there are practices on the use of a total CV value, calculated from CV values of different levels, in the TAE formula [18-26] in addition to separate TAE calculation for each level by calculating the CV values of each level [20-22]. The Centers for Disease Control and Prevention reported that the use of total CV was appropriate only when all measured error sources were calculated using the same analyte mean and recommended that total CV% could be used if there were uncertainties of different components of the same level (e.g., analytical variability, variability from centrifugation, and variability in sample preparation) [27]. In the CLSI EP15-A2 document, it is stated

Table 3. TAE_1 and TAE_2 values were calculated using CV1%, CV2%, and bias% values calculated for the test parameters assessed, and total CV% and TAE_3 values calculated using total CV%

		IQC1			IQC2				
Test Name	**Month**	**CV1%**	**Bias%**	**TAE_1%**	**CV2%**	**Bias%**	**TAE_2%**	**Total CV%***	**TAE_3**%**
Albumin	June	1.27	1.76	3.85	1.03	1.76	3.45	1.64	4.46
	July	1.08	1.90	3.68	1.73	1.90	4.75	2.04	5.27
	August	1.98	1.95	5.22	1.82	1.95	4.95	2.69	6.39
	September	1.99	2.07	5.36	1.93	2.07	5.26	2.77	6.65
	October	1.98	2.07	5.33	2.48	2.07	6.16	3.17	7.31
	November	1.58	2.48	5.09	1.56	2.48	5.06	2.22	6.15
ALT	June	2.99	4.36	9.29	1.61	4.36	7.02	3.40	9.97
	July	2.53	4.89	9.06	2.86	4.89	9.61	3.82	11.19
	August	7.35	5.28	17.40	8.30	5.28	18.97	**11.09**	**23.57**
	September	2.71	5.08	9.56	2.59	5.08	9.36	3.75	11.27
	October	2.73	5.58	10.09	2.37	5.58	9.49	3.62	11.55
	November	3.90	5.42	11.86	2.81	5.42	10.06	4.81	13.36
ALP	June	7.0	3.76	15.31	6.62	3.76	14.69	9.63	19.66
	July	5.74	3.69	13.16	3.70	3.69	9.80	6.83	14.96
	August	9.63	2.87	18.76	9.73	2.87	18.92	**13.69**	25.46
	September	8.18	3.25	16.74	4.47	3.25	10.62	9.32	18.63
	October	4.52	4.02	11.48	3.59	4.02	9.94	5.77	13.55
	November	5.41	4.17	13.09	4.85	4.17	12.17	7.27	16.16
AST	June	4.23	4.28	11.26	1.92	4.28	7.45	4.65	11.95
	July	1.78	4.05	6.99	2.27	4.05	7.80	2.88	8.82
	August	7.49	4.05	16.41	8.52	4.05	18.11	**11.34**	**22.77**
	September	1.92	4.26	7.43	1.81	4.26	7.25	2.64	8.62
	October	2.13	4.05	7.56	2.51	4.05	8.19	3.29	9.48
	November	3.74	4.03	10.20	2.98	4.03	8.94	4.78	11.92
Cl	June	1.40	0.12	2.43	1.34	0.12	2.34	1.94	3.33
	July	2.76	0.27	4.83	3.24	0.27	5.62	4.26	7.30
	August	3.19	0.36	5.63	3.02	0.36	5.35	4.39	7.62
	September	2.28	0.56	4.32	2.41	0.56	4.54	3.32	6.04
	October	4.96	0.87	**9.05**	4.38	0.87	8.10	**6.62**	**11.79**
	November	3.91	0.83	7.28	3.63	0.83	6.82	**5.34**	**9.64**
Total cholesterol	June	2.55	1.49	5.69	1.57	1.49	4.08	2.99	6.43
	July	4.21	2.85	9.80	3.27	2.85	8.25	**5.33**	**11.65**
	August	4.07	2.68	9.39	2.94	2.68	7.53	**5.02**	10.97
	September	1.55	2.62	5.17	1.8	2.62	5.59	2.38	6.54
	October	3.19	2.23	7.49	2.62	2.23	6.55	4.13	9.04
	November	4.0	2.07	8.67	2.76	2.07	6.62	4.86	10.09
Creatinine	June	4.04	2.31	8.97	2.95	2.31	7.17	5.00	10.56
	July	3.01	1.66	6.62	2.13	1.66	5.17	3.69	7.74
	August	4.06	1.66	8.36	7.54	1.66	14.10	8.56	15.79
	September	1.75	1.46	4.35	1.74	1.46	4.33	2.47	5.54
	October	3.57	1.29	7.18	2.93	1.29	6.12	4.62	8.91
	November	1.65	1.43	4.16	2.05	1.43	4.82	2.63	5.78
Glucose	June	1.69	1.69	5.48	1.81	1.69	5.68	2.48	5.78
	July	2.03	2.03	5.70	4.10	2.03	9.11	4.58	9.58
	August	2.93	2.20	7.03	4.55	2.20	9.70	**5.41**	**11.13**
	September	1.55	1.97	4.53	1.48	1.97	4.42	2.14	5.52
	October	4.28	0.71	7.78	2.91	0.71	5.52	**5.18**	9.26
	November	3.07	0.60	5.66	3.48	0.60	6.34	4.64	8.26

Table 3. Cont.

		IQC1			IQC2				
Test Name	**Month**	**CV1%**	**Bias%**	**TAE$_1$%**	**CV2%**	**Bias%**	**TAE$_2$%**	**Total CV%***	**TAE$_3$**%**
HDL-C	June	4.57	4.87	12.41	4.27	4.87	11.92	6.25	15.20
	July	2.77	2.77	7.74	1.90	2.77	6.31	3.36	8.31
	August	7.78	2.39	15.23	9.47	2.39	18.01	**12.26**	22.62
	September	5.39	1.98	10.87	3.27	1.98	7.37	6.30	12.38
	October	9.23	1.36	16.59	5.89	1.36	11.08	**10.95**	19.43
	November	4.50	1.25	8.67	3.69	1.25	7.34	5.82	10.85
LDH	June	9.06	0.75	15.70	5.01	0.75	9.02	**10.35**	17.84
	July	9.84	2.85	19.08	4.82	2.85	10.80	**10.96**	20.93
	August	6.56	0.38	11.21	6.03	0.38	10.33	8.91	15.09
	September	6.34	1.15	11.61	3.65	1.15	7.18	7.32	13.23
	October	4.65	1.30	8.98	3.04	1.30	6.32	5.56	10.47
	November	6.38	1.02	11.55	3.89	1.02	7.44	7.47	13.35
K	June	1.60	1.55	4.19	2.10	1.55	5.01	2.64	5.91
	July	1.64	1.20	3.91	2.09	1.20	4.65	2.66	5.59
	August	3.13	1.22	6.39	**5.16**	1.22	**9.74**	**6.04**	**11.18**
	September	2.7	1.19	5.64	2.66	1.19	5.58	3.79	7.45
	October	4.5	1.45	8.87	3.15	1.45	6.65	**5.49**	**10.52**
	November	2.8	1.44	6.06	2.55	1.44	5.65	3.79	7.69
Total protein	June	3.45	2.77	8.46	4.19	2.77	9.68	5.43	11.73
	July	2.75	2.36	6.89	5.07	2.36	10.72	5.77	11.88
	August	6.40	2.19	12.75	7.30	2.19	14.24	**9.71**	**18.22**
	September	2.03	2.10	5.45	3.03	2.10	7.10	3.65	8.12
	October	3.04	2.21	7.22	1.57	2.21	4.80	3.42	7.86
	November	1.65	2.03	4.75	1.85	2.03	5.08	2.48	6.12
Na	June	1.60	1.22	3.86	1.96	1.22	4.46	2.53	5.40
	July	2.20	0.74	4.37	3.55	0.74	6.60	4.18	7.64
	August	2.39	0.77	4.71	2.81	0.77	5.40	3.69	6.86
	September	2.90	0.58	5.37	2.38	0.58	4.51	3.75	6.78
	October	4.79	0.56	8.47	3.78	0.56	6.80	**6.10**	**10.64**
	November	3.27	0.57	5.96	3.08	0.57	5.65	4.49	7.98
Triglyceride	June	3.55	4.46	10.32	3.56	4.46	10.33	5.03	12.76
	July	3.68	6.00	12.08	4.21	6.00	12.95	5.59	15.23
	August	7.15	6.97	**18.77**	6.83	6.97	**18.24**	**9.89**	**23.29**
	September	4.25	6.03	13.04	3.65	6.03	12.05	5.60	**15.28**
	October	4.03	8.01	14.66	3.23	8.01	13.34	5.16	**16.54**
	November	3.09	5.62	10.72	2.45	5.62	9.67	3.94	12.14
Urea	June	3.58	1.79	7.69	3.56	1.79	7.66	5.05	10.12
	July	3.51	1.63	7.42	2.15	1.63	5.18	4.12	8.43
	August	3.26	1.80	7.18	**7.79**	1.80	14.66	**8.44**	**15.74**
	September	2.40	1.48	5.44	2.31	1.48	5.30	3.33	6.98
	October	3.38	1.54	7.12	3.96	1.54	8.08	5.21	10.14
	November	2.75	1.64	6.17	2.50	1.64	5.76	3.72	7.77

Tests with poor statistical performance were shown in bold. *: Total CV%: Total CV%=$\sqrt{(CV1^2+CV2^2)}$; **: TAE3%: TAE values calculated by converting to a single CV% using the TEa-TR formula. CV: Coefficient of variation; TAE: Total analytical error; IQC: Internal quality control; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; Cl: Chloride; HDL-C: High-density lipoprotein cholesterol; LDH: Lactate dehydrogenase; K: Potassium; Na: Sodyum.

that separate calculations are required for each level [28]. Westgard et al. [29] support the idea that an approach similar to the suggestion that sigmametric calculation, which observed that the formula using the total CV value exceeded TEa limits at a higher rate and prevented us from seeing the good performance of each level.

Conclusion

We think that the CV% and TAE values should be calculated separately for different control levels of each test parameter, and the CV% and TAE values calculated for each level should be compared separately with the maximum allowable CV% and TEa limits in the performance assessment. The purpose of using two or more IQC samples is to assess analytical performance at different levels. We believe that the use of total CV% prevents the separate assessment of test performance for each level. Calculation of the TAE value of each level will be a more appropriate approach.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the Yozgat Bozok University Clinical Research Ethics Committee (No: 2017-KAEK-189_2021.03.10_01, Date: 10/03/2021).

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