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Research Article

Evaluation of analytical quality of coagulation parameters by sigmametric methodology

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Abstract

Objectives: The total testing process in the laboratory is divided into pre-analytical, analytical, and post-analytical phases. Evaluating the quality of these phases and carrying out improvement studies will increase the quality of the healthcare system. In this study, we aimed to evaluate the analytical phase of the coagulation tests using the six-sigma methodology, which is a quality management tool that aims at zero error.

Methods: The coefficient of variation (CV%) values were calculated from the two-level internal quality control (IQC) data between January and June 2022 of the coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer). External quality control (EQC) data were retrieved from the EQC program of external quality assurance services and used in the calculation of bias %. Total allowable error (TEa) data were obtained from the database of international organizations. The sigma value for each parameter was calculated according to the formula "(TEa%–Bias %)/ CV%."

Results: Level 1 and level 2 sigma values were calculated as 4.41 and 2.93 for PT; 5.27 and 4.31 for aPTT; 2.72 and 2.73 for fibrinogen, and 4.36 and 4.08 for D-dimer.

Conclusion: Among coagulation tests in which we evaluated their analytical performances using the six sigma methodology, PT (level 2) and fibrinogen (level 1 and 2) showed poor performance (sigma value <3). We decided to follow the tests with $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$ Westgard control rules. Using these tests improvement can be achieved in the analytical process, and the overall testing process may improve by performing pre-analytical, post-analytical, and analytical assessments.

Keywords: Coagulation, quality control, six sigma

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Laboratory services greatly impact clinical decision-making processes, and contribute up to 70% of the most important decisions made about the hospitalization of patients, drug treatments, radiotherapy, chemotherapy, surgical procedures, and discharge [1, 2]. The total testing process starts with a test requested by the patient or the attending physician and continues with the analysis of the test and reporting of the results. This process consists of pre-analytical, analytical, and post-analytical phases, which are completed after the interpretation of the results by the clinician. Laboratory errors in each phase can affect test results and therefore; it is aimed to detect and minimize all possible sources of error [3, 4].

Most laboratory errors occur in the pre-analytical and post-analytical phases, while a smaller proportion of them are in the analytical phase. For this reason, greater emphasis is placed on the quality of test results in the pre-analytical and post-analytical phases, while less emphasis is placed on improving the quality in the analytical phase [5]. Although laboratory errors occur less frequently in the analytical phase, still analytical phase should be taken into consideration and correctly managed as

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a whole to increase the quality of healthcare provided to the patients. Implementation of internal quality control (IQC) and external quality control (EQC) programs has a great impact on improving the quality of the analytical process [6]. However, assessing analytical quality can be challenging. Therefore, the six sigma approach or methodology combines three elements, namely, total allowable error (TEa), bias, and precision, both to measure quality in a more standardized, objective, and quantitative way and also to evaluate test performance [7].

The six sigma methodology was first defined by the Motorola company and has become widespread in many areas including the flight industry where safety is a priority. In recent years, the six sigma methodology has been applied as a quality indicator of the processes performed in many medical laboratories. Medical laboratories can use the six sigma methodology to improve the quality of healthcare system and increase patient safety [8–10].

A low sigma value is considered an indication of an error or defect. The defect value is measured at 3.4 defects per million. The respective sigma values indicate poor performance (<3), appropriate quality requiring strict control measurements (3–3.99), good quality (4–4.99), very good quality (5–5.99), and excellent (≥6) world-quality performances [11].

The importance of the tests and the frequency of use may vary according to the conditions of the day. One of the best examples of this is that coagulation tests (especially D-dimer) come to the fore in the evaluation and follow-up of patients during the COVID process. Therefore, in our study, we aimed to evaluate the analytical performance of these tests by calculating the sigma values of the analytical stage of coagulation tests and to determine which control strategies will be applied in IQC evaluation studies.

Materials and Methods

This study was carried out in the Medical Biochemistry Laboratory of University of Health Sciences Tepecik Training and Research Hospital with the approval of the ethics committee (Approval date: November 15, 2021; Decision no: 2021/11–03). Between January and June 2022, IQC and EQC data of four coagulation parameters tested in our biochemistry laboratory were used to calculate their sigma levels.

Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer levels were studied in the Sysmex CS2500 (Sysmex Inc., Kobe, Japan) coagulation system. The mean, standard deviation (SD), and coefficient of variation (CV) of the tests were calculated using 6-month IQC data with the same lot number. The CV% of the tests was calculated with the formula "CV(%)=(SD /mean)×100". EQC data for the same period (January–June 2022) were obtained from the external quality assurance services (Biorad, United States of America) EQC program and used to calculate the bias (%).

The bias % values were determined by the following formula:

Bias (%)=[(laboratory mean –peer group mean)/peer group mean]×100.

TEa is determined according to the criteria of international organizations by considering the biological variation (BV) and the performance of the analytical method. The TEa values of PT, aPTT, and fibrinogen parameters were obtained from the clinical laboratory ımprovement changes (CLIA) 2019 database, and the D-dimer TEa value was obtained from the American Bioanalysts Association (AAB) [12].

Total error (TE), sigma value, and quality goal index (QGI) for each parameter and each control level were calculated with the formulas: TE=Bias+1.65 CV, Sigma=(TEa-bias)/CV and QGI =Bias / (1.5×CV). QGI was used to determine whether the assessment of imprecision, accuracy, or both imprecision and inaccuracy was targeted for analytes which low sigma values. QGI scores of <0.8, >1.2, and 0.8–1.2 indicate imprecision, inaccuracy, and both imprecision and inaccuracy, respectively [13].

Results

Mean, target value, SD, and CV, bias of four coagulation parameters measured in January–June 2022, and TEa values estimated based on the criteria of AAB and CLIA organizations and sigma values calculated according to these TEa values are shown in Table 1. As seen in Figure 1 and Table 2, while the 6-months sigma value of PT (level 2) and fibrinogen (level 1 and 2) were <4, the sigma value of D-dimer (level 1 and 2) and PT (level 1) were 4–4.99. Level 1 and level 2 sigma values of the aPTT test were found to be 5–5.99 and 4–4.99, respectively. The calculated TE of all parameters was lower than the TEa. Table 3 shows the QGI values calculated for parameters with low sigma levels (<4). Imprecision problems were found in the measurements for PT (levels 2), and fibrinogen (levels 1 and 2) tests with a QGI value of <0.8. The quality control strategy is shown in Table 4.

Discussion

Improving the quality of medical laboratory tests is an active field of laboratory medicine and the six sigma approach is one of the important tools used for this purpose. Six sigma quality standards analyze possible causes of failure, identify solutions, and take bias and CV into account to systematically and comprehensively evaluate quality management in clinical laboratories while optimizing the quality control program [14]. In our study, both control levels in fibrinogen parameters and the sigma value of the control level 2 of PT were found to be < 4 sigma, and the level 1 control sigma value of aPTT was between 5 and 5.99. Each control level sigma values of the D-dimer, the sigma values of the control level 1 of PT, and the control level 2 of aPTT were found to be between 4 and 4.99.

In the literature, there are few studies evaluating the performance of coagulation parameters using the six sigma methodology. Shaikh et al. [15] examined 7 years of coagulation test data and found 4005 errors. Of these, 2350 (58.7%) were found in the pre-analytical, 11 (0.3%) in the analytical,

Table 1. Mean, target value, SD, CV, bias, TEa, and sigma values of coagulation tests for the January-June 2022

	Test	IQC	Mean	Target value	SD	CV (%)	Bias (%)	TEa (%)	Sigma
January	PT	Level 1	11.9	11.7	0.42	3.51	0.85	15	4.03
		Level 2	20.3	19.9	0.76	3.77			3.75
	aPTT	Level 1	24.7	24.1	0.64	2.61	0.84	15	5.42
		Level 2	45.1	44.2	1.33	2.94			4.82
	Fibrinogen	Level 1	251.2	268	10.9	4.32	3.32	20	3.86
		Level 2	90.4	89	2.99	3.30			5.05
	D-dimer	Level 1	268.5	290	14.6	5.44	0.45	30*	5.43
		Level 2	2607	2570	161.2	6.18			4.78
February	PT	Level 1	11.9	11.7	0.45	3.72	1.32	15	3.68
		Level 2	20.4	19.9	0.84	4.09			3.35
	aPTT	Level 1	25.3	24.1	0.72	2.83	0.91	15	4.98
		Level 2	45.7	44.2	1.28	2.80			5.03
	Fibrinogen	Level 1	264.9	268	12.7	4.80	0.76	20	4.01
		Level 2	89.8	89	4.62	5.15			3.74
	D-dimer	Level 1	256.8	290	7.49	2.92	7.62	30*	7.67
		Level 2	2400	2570	91.1	3.79			5.90
March	PT	Level 1	11.8	11.7	0.38	3.21	2.25	15	3.97
		Level 2	19.5	19.9	0.74	3.79			3.36
	aPTT	Level 1	25.2	24.1	0.66	2.62	1.71	15	5.08
		Level 2	46.6	44.2	1.63	3.50			3.80
	Fibrinogen	Level 1	254.3	268	14.9	5.89	2.69	20	2.94
		Level 2	75.9	89	3.60	4.74			3.65
	D-dimer	Level 1	261	290	9.68	3.71	10.54	30*	5.25
		Level 2	2550	2570	93.6	3.67			5.30
April	PT	Level 1	11.9	11.7	0.23	1.91	1.95	15	6.83
		Level 2	18.8	19.9	0.53	2.84			4.59
	aPTT	Level 1	24.6	24.1	0.66	2.69	1.46	15	5.03
		Level 2	46.4	44.2	1.34	2.89			4.68
	Fibrinogen	Level 1	250.7	268	16.9	6.73	4.17	20	2.35
		Level 2	76.8	89	5.23	6.81			2.32
	D-dimer	Level 1	289	290	14.10	4.88	8.55	30*	4.40
		Level 2	2617	2570	111.3	4.26			5.04
May	PT	Level 1	11.9	11.7	0.26	2.16	2.11	15	5.97
		Level 2	19.4	19.9	0.74	3.82			3.37
	aPTT	Level 1	24.4	24.1	0.58	2.36	0.22	15	6.26
		Level 2	46.9	44.2	1.72	3.67			4.03
	Fibrinogen	Level 1	241.4	268	13.7	5.67	6.44	20	2.39
		Level 2	78.4	89	5.05	6.44			2.10
	D-dimer	Level 1	272.5	290	13.7	5.03	4.31	30*	5.10
		Level 2	2623	2570	159.1	6.07			4.23
June	PT	Level 1	11.9	11.7	0.32	2.72	3.45	15	4.25
		Level 2	19.6	19.9	0.78	3.97			3.71
	aPTT	Level 1	24.9	24.1	0.66	2.66	1.57	15	5.05
		Level 2	46.2	44.2	1.46	3.16			4.24
	Fibrinogen	Level 1	245.5	268	13.9	5.68	2.96	20	3.00
		Level 2	79.4	89	4.53	5.70			2.99
	D-dimer	Level 1	268	290	11.9	4.46	6.60	30*	5.24
		Level 2	2570	2570	127.5	4.96			4.72

*: American Association of Bioanalysts Total Allowable Error value. SD: Standard deviation; CV: Coefficient of variation; TEa: Total allowable error; IQC: Internal quality control; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

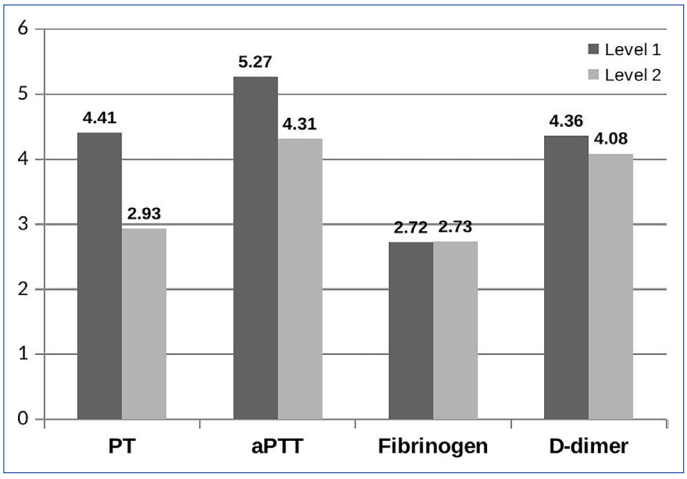

Figure 1. The 6 months sigma values of 4 coagulation parameters.
PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

and 1644 (41%) in the post-analytical stages. The average sigma value obtained was 4.8, and 12 (80%) of the 15 indicators examined reached the sigma value of 4. In a study conducted by Westgard using the Sysmex CS5100 system, although sigma values of ≥6 were observed at both control levels of PT, and sigma values of <3, and 5.9 were reported for aPTT levels 1, and 2, respectively [16]. Hollestelle et al. [17] calculated the sigma levels of PT, aPTT, and fibrinogen tests using BV data together with IQC and EQC data retrieved from three laboratories that used different devices and reagents. Using the maximum BV values for the desired TEa, the sigma values of three laboratories for fibrinogen and two laboratories for PT and aPTT were found to be higher than 3. Using the median BV values, a sigma level of over 3 was achieved for fibrinogen by two laboratories, and for PT testing by the third laboratory. Using the minimum BV, only one laboratory achieved a sigma level above 3 for fibrinogen analysis and no other test had a sigma level above 3. Ahmed El-Neanaey et al. [18] found mean sigma values ranging from 3 to 5.9 for PT and aPTT parameters at both control levels in two different coagulation devices. In another study, the sigma values calculated according to CLIA 2019 TEa of PT and aPTT analyzed on the Stago STA Compact (Diagnostica Stago, Inc., Rome, Italy) coagulation system were <4, and it was determined that the control results should be evaluated according to Westgard multirules $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$ [19]. Katar et al. [20] calculated D-

Table 2. Sigma metrics and total error of parameters (6 months)

Tests	Average CV (%)		Average bias (%)	TEa	TE (calculated)		Sigma	
	Level 1	Level 2			Level 1	Level 2	Level 1	Level 2
PT	2.95	4.44	1.99	15	6.86	9.32	4.41	2.93
aPTT	2.63	3.22	1.12	15	4.56	5.53	5.27	4.31
Fibrinogen	6.10	6.08	3.39	20	13.45	13.42	2.72	2.73
D-dimer	5.42	5.79	6.35	30*	15.29	15.90	4.36	4.08

*: American Association of Bioanalysts Total Allowable Error value. CV: Coefficient of variation; TEa: Total allowable Error; TE: Total error; PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

Table 3. Quality goal index values of parameters with sigma level <4

Test	IQC	Sigma	Average CV(%)	Average bias(%)	QGI	Problem
PT	Level 2	2.93	4.44	1.99	0.30	Imprecision
Fibrinogen	Level 1	2.72	6.10	3.39	0.37	Imprecision
	Level 2	2.73	6.08	3.39	0.37	Imprecision

IQC: Internal quality control; CV: Coefficient of variation; QGI: Quality goal index; PT: Prothrombin time

Table 4. Recommended internal quality control strategy

Parameter	Sigma value		Westgard rules
	Level 1	Level 2	
PT	4.41	2.93	$1_{3s}/2_{2s}/R_{4s}/41s$ (Level 1); $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$ (Level 2)
aPTT	5.27	4.31	$1_{3s}/2_{2s}/R_{4s}$ (Level 1); $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (Level 2)
Fibrinogen	2.72	2.73	$1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$
D-dimer	4.36	4.08	$1_{3s}/2_{2s}/R_{4s}/4_{1s}$

PT: Prothrombin time; aPTT: Activated partial thromboplastin time.

dimer sigma values pertaining to the quality control results of 3-months (November, December and January) using Roche Diagnostics' Cobas e 601 automatic analyzer, and determined ≥6 for two IQC levels for the months November and December, but D-dimer sigma levels in January were determined as 4.14, and 2 for levels 1, and 2, respectively.

Differences in sigma levels between studies may stem from the differences in instruments, reagents, quality control materials, or calibrators. Another reason may be the lack of standardization in obtaining the %bias values used in the calculation of the sigma levels since some researchers use IQC and others EQC values. In addition to all these, obtaining TEa values from different sources may cause sigma values to be calculated differently.

In our study, sigma values of PT (levels 2), and fibrinogen (levels 1 and 2) tests were <4, which were found appropriate to evaluate the control results according to Westgard multirules $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$. It was seen that IQC results for the D-dimer (levels 1, and 2), PT (levels 1), and aPTT (levels 2) tests with a sigma value between 4 and 4.99 should be evaluated according to Westgard multirules $1_{3s}/2_{2s}/R_{4s}/4_{1s}$. For the aPTT (level 1) test with a sigma value between 5 and 5.99, it was seen that IQC results should be evaluated according to $1_{3s}/2_{2s}/R_{4s}$. Imprecision problems were found in the measurements for PT (levels 2), and fibrinogen (levels 1 and 2) tests with a QGI value of <0.8.

Imprecision problem is the expression of random error. A random error is a potentially positive or negative error whose magnitude and direction cannot be predicted. Random error is generally caused by instrument instability, temperature changes, stability of the calibration curve, personnel change, variations in processes such as pipetting, mixing, or timing [21]. Therefore, all the above possible causes should be reviewed to identify the source of error in tests with QGI values <0.8.

The limitation of our study we can say that the Operating Specifications chart (OPSpecs) that visually shows the performance in sigma evaluations was not used.

Conclusion

We ensured that the parts that need to be improved in our laboratory can be revealed by evaluating the analytical quality of the coagulation parameters using the sigma metric method. We think that productivity can be increased in the whole test process by conducting evaluation and improvement studies for the pre-analytical, post-analytical, and analytical phases.

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

Ethics Committee Approval: The study was approved by The University of Health Sciences Izmir Tepecik Training and Research Hospital Non-interventional Research Ethics Committee (No: 2021/11–03, Date: 15/11/2021).

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