



Research Article

Determination of analytical performances of NT-proBNP and aPTT tests with three methods

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Abstract

Objectives: This study aimed to evaluate the analytical performances of N-terminal pro-B-type natriuretic peptide (NT-proBNP), which has not been investigated before, and activated partial thromboplastin time (aPTT), which has been the subject of little research, using the six sigma methodology and to calculate the quality goal index values of low-performing parameters. It was aimed to evaluate the analytical process with three methods by presenting this performance with Operation specification charts, which have been done in few other studies.

Methods: Three consecutive months of internal quality control data obtained from NT-proBNP and aPTT tests, twice daily, and data obtained from a monthly external quality control program were used. Sigma values were calculated using the calculation of $\text{Sigma} = (\text{Total allowable error} - \text{bias}) / (\text{Coefficient of variation})$ and shown with Operation specification charts (OPS Specs). Quality goal index (QGI) was calculated for those with $\text{sigma} < 6$.

Results: The sigma values for levels 1 and 2 of the NT-proBNP test were calculated as 5.06 and 5.65, and the performance status was determined as very good. The sigma values for levels 1 and 2 of the aPTT test were calculated as 4.28 and 3.56, respectively, and this was evaluated as moderate and good performance. The Quality goal index values (QGI) for levels 1 and 2 of the NT-proBNP test were calculated as 0.11 and 0.12, respectively. The Quality goal index (QGI) values for levels 1 and 2 of the aPTT test were calculated as 0.90 and 0.75, respectively.

Conclusion: Both tests had moderate, good and very good performance. It is of great importance to increase quality standards in laboratory tests. In this direction, continuous improvement-oriented initiatives should be implemented to make analytical processes more competent.

Keywords: aPTT, NT-proBNP, OPS Specs, quality goal index, six sigma

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The entire testing process in clinical laboratories is divided into three stages: Preanalytical, analytical, and postanalytical. Research indicates that error rates are estimated to range from 30–75% in the preanalytical stage, 4–30% in the analytical stage, and 9–55% in the postanalytical stage [1]. Laboratories need to assess their process performance based on scientifically established quality standards. This assessment involves analyzing the rate of sample errors and rejections during the preanalytical phase, evaluating the accuracy and precision of test results in the analytical phase, and monitoring the reporting of critical values as well as test turn around times in the postanalytical phase [2]. Among

these stages, analytical quality alone is not sufficient as a standalone quality requirement; however, other quality parameters hold no significance unless analytical quality is achieved. Laboratories must ensure accurate test results before addressing other quality criteria [3].

The Six Sigma approach is a technique applied in quality control and process enhancement. It aims to detect defects and minimize mistakes and variations [4]. Six sigma quality management is not just a tool for defining process performance; it is also a methodology aimed at reducing the error rate within the process. In automated analytical systems, it is important to determine the situations where precision error, accuracy error,

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or both errors occur together, which are among the test-specific reasons, in order to ensure the quality improvement of tests. These performance data can also be evaluated by calculating the quality goal index (QGI) [5]. The six sigma method allows for an objective assessment of performance. The sigma level of a process can be determined by using specific equations. The sigma value indicates the frequency of potential errors. A low sigma value suggests that the process is more likely to produce errors. Ideal or world-class performance should have a minimum of 6 sigma values, which translates to fewer than three or four errors per million products [6].

In this study, the research was planned by prioritizing the feedback from clinicians to the laboratory regarding the tests. Considering this situation, it was aimed to evaluate the analytical performances of N-terminal pro-B-type natriuretic peptide (NT-proBNP), which has not been investigated before, and activated partial thromboplastin time (aPTT), which is a subject of little research, using the six sigma methodology and to calculate the quality target index (QGI) values of the parameters showing low performance. It was aimed to evaluate the analytical process with three methods by presenting this performance with Operation Specification Charts (OPSspecs charts), which have been done in few other studies.

Materials and Methods

The study was approved by the Bursa City Hospital Scientific Research Ethics Committee (no: 2024-21/23, date: 11/12/2024), following the principles of the Declaration of Helsinki.

For the six sigma methodology calculations, three consecutive months of NT-proBNP tests performed on the Cobas 8000 Modular Analyzer System (Cobas, Mannheim, Germany) and aPTT tests performed on the Cobas t 711 (Roche Diagnostics Mannheim, Germany) coagulation analyzer, two-level internal quality control (IQC) data per day and data obtained from the monthly external quality control (RIQAS, UK) program were used retrospectively. All stages of the study were carried out conformity the Helsinki Declaration.

Calculation of sigma values of tests

To calculate sigma values; The mean, standard deviation (SD), coefficient of variation (CV%), bias (%) and total analytical error calculations of the tests must be made. The calculations were made as follows:

CV values (%) = (SD/Mean of IQC data)×100

For CVmean (mean %CV) values, 2-level internal quality control results were used.

CVmean = (CV1²+CV2²)^{1/2}

The bias (%) values were calculated using the formula provided below:

Bias (%) = [(IQC data mean of our laboratory–target mean of IQC data)/target mean of IQC data]×100.

The total analytical error for each parameter and control level was determined using the formula outlined below: Total analytical error = Bias+(1.65x CVmean)

Sigma values were calculated for each parameter and each control level.

Sigma = (TEa-Bias)/CV formula was used [7].

Evaluation of analytical performance of tests using OPSspecs charts

OPSspecs charts can also be used as quality planning and performance evaluation tools in clinical laboratories [8]. In the study, sigma levels of the tests were shown on OPSspecs charts.

Calculation of quality goal indices of tests

The Quality Goal Index (QGI) is a recent parameter that reflects the extent to which both accuracy and precision align with the applicable quality targets and helps identify which factor may be responsible for the issue [9]. Quality goal index calculation; QGI = Bias/(1.5×CV) formula was used [10].

Statistical analysis

All calculations were made using Microsoft Office Excel 2021 software.

Results

In the study, two levels, three-month average %CV, %Bias values, %TEa ratios of NT-proBNP and aPTT tests are shown (Table 1). The mean, standard deviation (SD), and coefficient of variation (CV%) of the tests were calculated using internal quality control data collected over a 3-month period.

In the study, the sigma value of Level 1 for the NT-proBNP test was calculated as 5.06 and the sigma value of Level 2 was calculated as 5.65. For the aPTT test, the sigma value of Level 1 was calculated as 4.28 and the sigma value of Level 2 was calculated as 4.85.

Table 1. CV%, Bias%, total analytical error and TEa values of NT-proBNP and aPTT tests						
Parameter	CV (%)		CVmean	Bias (%)	Total analytical error	TEa (%)
	Level 1	Level 2				
NT-proBNP	5.74	5.13	7.70	0.98	16.19	30
aPTT	2.66	3.20	4.15	3.61	11.91	15

CV: Coefficient of variation; TEa: Total allowable error; NT-proBNP: N-terminal pro-B-type natriuretic peptide; aPTT: Activated partial thromboplastin time; CLIA 2025: Clinical laboratory improvement amendments 2025.

Table 2. Sigma values of NT-proBNP and aPTT tests, performance status of these values and recommended control rules

Parameter	Sigma		Performance		Recommended internal control rules	
	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2
NT-proBNP	5.06	5.65	Very good or excellent, individual quality control rules apply	Very good or excellent, individual quality control rules apply	$1_{2.5S}$	$1_{2.5S}$
aPTT	4.28	3.56	Good, multiple quality control rules are applied	Medium requires quality control procedure. More than 1 analytical run and multiple measurements per run	$1_{2.5S}$	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$

NT-proBNP: N-terminal pro-B-type natriuretic peptide; aPTT: Activated partial thromboplastin time.

Table 3. Recommended control rules based on sigma values

Sigma	Performance description	Recommended control rules	R (number of measurements)	N (number of controls)
<3 sigma	Bad, quality improvement plan should be implemented	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$	2 or 4	R=2 for N=4 R=4 for N=2
≥3-<4 sigma	It is fit for purpose but more than one quality study should be done and multiple rules should be used	$1_{3S}/2_{2S}/R_{4S}/4_{1S}$	1 or 2	R=1 for N=4 R=2 for N=2
≥4-<6 sigma	Fit for purpose	$1_{2.5S}$	1	2
≥6 sigma	World class	1_{3S}	1	2

Table 4. Performance criteria according to sigma values

Sigma	Performance criteria
<2- sigma	Unacceptable, not valid as a measurement procedure
>2- sigma ve <3- sigma	Bad, quality improvement plan should be implemented
>3- sigma ve <4- sigma	Medium requires Quality Control (QC) procedure. More than 1 analytical run and multiple measurements per run
>4- sigma ve <5- sigma	Good, multiple quality control rules are applied
>5- sigma ve <6- sigma	Very good or excellent, individual quality control rules apply
≥6- sigma	world class

culated as 3.56. According to these measured sigma values, performance statuses and recommended control rules according to these performances are shown (Table 2).

The quality control Westgard rules used depending on the sigma metric value of the analytes are shown [7] (Table 3).

The performance criteria created depending on the sigma metric value of the analytes are shown [7, 11] (Table 4).

In this study, sigma values of NT-proBNP and aPTT tests are shown with OPSpecs charts [12] (Fig. 1). The sigma of the line closest to the operation point we obtained gives our process sigma level.

The criteria for interpreting the quality goal index ratios of analytes are as follows; <0.8 QGI: Indicates that there is precision error, 0.8–1.2 QGI: Indicates that there is precision and accuracy error, and >1.2 QGI: Indicates that there is accuracy error. In this study, the quality goal indices of the

tests have been calculated and the error types corresponding to these results are shown (Table 5).

Discussion

The six sigma methodology, in addition to identifying the causes of errors, provides recommendations on control measures. The sigma method, which can be applied to every step of the total testing process, is used to evaluate laboratory performance [13]. In this research, the analytical performance of NT-proBNP and aPTT parameters was assessed using the six sigma approach, QGI, and OPSpecs charts.

No study was found in the literature review on the NT-proBNP test. However, a study was found on the BNP (brain natriuretic peptide) test. Accordingly: Üstündag et al. [14] calculated sigma values for the BNP test using the six sigma methodology. They reported that sigma values varied between 0.76 and 2.06 at dif-

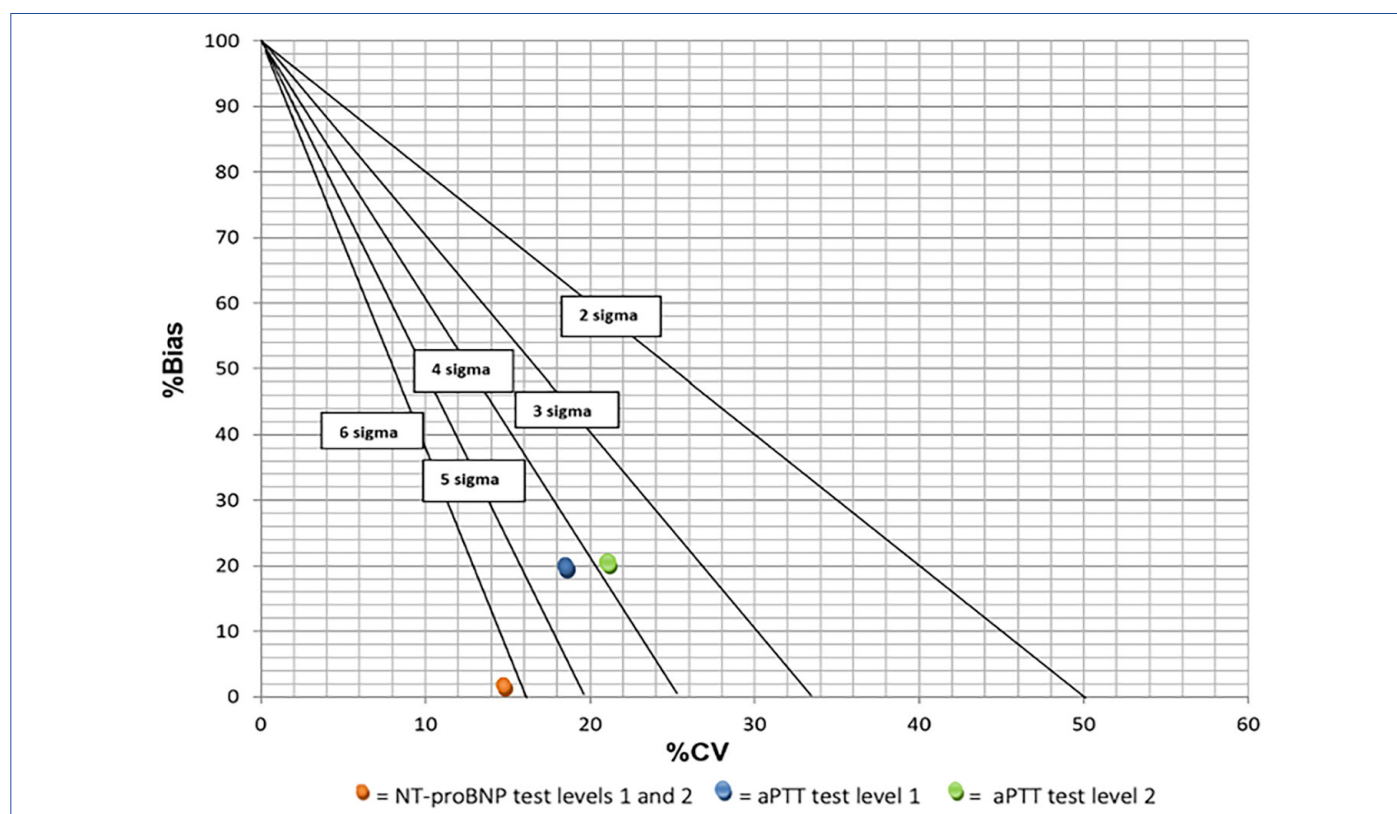


Figure 1. OPSpecs chart for NT-proBNP and aPTT parameters for levels 1 and 2.

CV: Coefficient of variation; aPTT: Activated partial thromboplastin time; OPSpecs: Operation Specification Charts; NT-proBNP: N-terminal pro-B-type natriuretic peptide.

ferent quality control levels and that the problem in the BNP study was uncertainty according to the calculated QGI levels.

Studies evaluating aPTT performance are as follows. El-Neanaey et al. [15] calculated sigma values of aPTT tests in a study they conducted and found sigma values of the test to be >3 at normal and pathological levels, according to their findings. Hollestelle et al. [16] showed that sigma values for aPTT in two laboratories were higher than 3. Aksit et al. [17] found level 1 and level 2 sigma values for aPTT to be 5.27 and 4.31, respectively. Üge et al. [11] calculated the normal and high level sigma values of the aPTT test as 4.51 and 4.31, respectively. They reported that they found the QGI calculation for the aPTT test as 0.41 and 0.36, respectively, at normal and high levels.

Total allowable error (TEa) refers to the maximum acceptable difference between the actual concentration of an analyte

and the value reported by the laboratory, ensuring the result is considered accurate and trustworthy [18]. The TEa values for NT-proBNP and aPTT parameters were sourced from the CLIA 2025 database [19]. In this study, the total analytical error rate for the NT-proBNP test was determined to be 16.19, which is below the permissible total error rate set by CLIA (30%). Likewise, the total analytical error rate for the aPTT test was calculated as 11.91, which is also lower than the CLIA allowable total error rate of 15% (Table 1).

Since the sigma values of the NT-proBNP test in this study were calculated as 5.06 and 5.65 for levels 1 and 2, respectively, its performance was evaluated as very good or excellent and it was recommended to apply single quality control rules in the form of the 12.5S rule. Since the sigma value of the level 1 control for the aPTT test was found to be 4.28, its performance was; It was evaluated as good and the 12.5S

Table 5. Sigma values of NT-proBNP and aPTT tests and QGI ratios for sigma <6

Parameter	Sigma		QGI		Performance	
	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2
NT-proBNP	5.06	5.65	0.11	0.12	Precision error	Precision error
aPTT	4.28	3.56	0.90	0.75	Precision and accuracy error	Precision error

NT-proBNP: N-terminal pro-B-type natriuretic peptide; aPTT: Activated partial thromboplastin time; QGI: Quality goal index.

rule was recommended to be applied as multiple quality control rules. The sigma value of the level 2 control of the aPTT test was found to be 3.56, accordingly its performance was evaluated as moderate and it was recommended to perform multiple analytical runs as 13s/22s/R4s/41S and multiple measurements per run (Table 2, 3).

The sigma values calculated in this study were calculated as 5.06 for level 1 of the NT-proBNP test and 5.65 for level 2. For the aPTT test, it was calculated as 4.28 for level 1 and 3.56 for level 2. When evaluated in terms of performance criteria according to sigma values, a sigma value less than 3 is an indicator of a poor performance procedure. Good performance is shown by a sigma level higher than 3 [20] (Table 4).

OPSpecs charts describe the deviations from the allowable precision and accuracy for a method and specify the internal quality control rules required to monitor the performance of the method. The inaccuracy plot is shown on the y-axis, while the imprecision plot is represented on the x-axis. The operating point is the combination of the deviations in both precision and accuracy [21]. The sigma values are plotted on the OPSpecs charts (Fig. 1). OPSpecs charts assist in evaluating the quality of an analytical process by offering a sigma value. For each sigma metric, the appropriate Westgard rule (along with the optimal number of QC levels) can be selected to maximize error detection while minimizing false rejections. It is evident that the sigma metric can be enhanced in two ways: By decreasing bias or by reducing the CV [12].

The quality goal index (QGI), introduced by Westgard, incorporates both repeatability (precision) and accuracy elements. It is used to pinpoint the source of error in measurements with a sigma value less than 6. A QGI score of <0.8 indicates that precision needs to be improved, a QGI score of >1.2 indicates that accuracy needs to be improved, and a QGI score between 0.8 and 1.2 indicates that both precision and accuracy need to be improved [19]. For the NT-proBNP test, the QGI values were determined to be 0.11 and 0.12 for levels 1 and 2, respectively. Similarly, the QGI values for the aPTT test were calculated as 0.90 and 0.75 for levels 1 and 2, respectively. The QGI values for the NT-proBNP test point to precision errors at both levels, while the aPTT test values indicate precision and accuracy errors at level 1 and accuracy errors at level 2 (Table 5). These results highlight the need for improvements in both precision and accuracy.

Conclusion

The process performance of laboratories should be evaluated in accordance with internationally accepted scientific quality criteria. In order to ensure higher accuracy, reliability and repeatability, it is of great importance to increase quality standards in laboratory tests. In this direction, continuous improvement-oriented initiatives should be implemented to make analytical processes more effective.

Ethics Committee Approval: The study was approved by the Bursa City Hospital Scientific Research Ethics Committee (no: 2024-21/23, date: 11/12/2024).

Informed Consent: Informed consent was obtained from all participants.

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