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Research Article

Evaluation of analytical phase performance of coagulation parameters by sigmametric methodology

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Abstract

Objectives: This study aimed to evaluate the analytical performance of coagulation tests (prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer) using the Six Sigma methodology, focusing on identifying areas for improvement to enhance healthcare quality.

Methods: Internal quality control (IQC) and external quality control (EQC) data from September 2023 to February 2024 were collected for coagulation parameters analyzed by four Cobas T711 analyzers. Sigma values were calculated using IQC, EQC, and total allowable error (TEa) data. The sigma value for each parameter was calculated according to the formula "(TEa%–bias %)/CV%." The outpatient sample analyzers were labeled A1, A2, and A3. The one that analyzes samples from emergency and intensive care patients was labeled B.

Results: Across analyzers A1, A2, A3, and B, sigma values varied for different coagulation parameters. Notably, the D-dimer parameter consistently exhibited excellent performance (sigma >6) for all analyzers. In contrast, some analyzers showed poor performance for aPTT and PT parameters at level 1 (A1 and A3 for aPTT, B for INR). Fibrinogen performance varied, with some analyzers showing excellent performance (sigma >6) and others falling below acceptable levels.

Conclusion: By identifying areas of low performance, particularly in aPTT and INR parameters, this study highlights the importance of continuous quality improvement in laboratory testing. Addressing issues identified through the Six Sigma methodology can enhance the reliability of laboratory results and ultimately improve patient care. Further research and initiatives focused on analytical process improvement are needed to achieve higher quality standards in laboratory testing.

Keywords: Analytical performance, coagulation, quality control, Six Sigma

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The results of laboratory tests are very important for making healthcare decisions. Identifying and reducing laboratory errors is critical. Pre-analytical, analytical, and post-analytical stages of the laboratory procedure are all subject to error [1]. While errors frequently occur throughout the pre- and post-analytical phases, it is crucial to address the causes of analytical errors to guarantee patient safety. Enhancing analytical performance requires the implementation of both external quality control (EQC) and internal quality control (IQC) programs. Whereas EQC evaluates test trueness, IQC offers insights into test precision. The Six Sigma approach has grown in significance for assessing analytical performance since it integrates results from IQC and EQC [2].

Sigma metric methodology has become increasingly important in laboratory quality management, particularly in evaluating the performance of analytical methods and analyzers. This methodology incorporates the concepts of precision, bias, and analytical quality requirements into a comprehensive framework for assessing a laboratory's ability to produce accurate and reliable results [3]. Sigma metrics quantify assay performance by calculating the number of standard deviations between the mean of the target value and the nearest specification limit. The Sigma metric methodology allows laboratories to pinpoint areas needing improvement, establish achievable quality goals, and track the effectiveness of improvement efforts over time. Therefore, the Sigma metric methodology is

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important not only for identifying poor performance but also for offering practical guidance for improvement [4].

Sigma calculation entails utilizing the coefficient of variation (CV) data from IQC, bias data from EQC, and total allowable error (TEa) values established by international organizations. The corresponding Sigma values denote the following performance levels: poor performance (<3), indicating inadequate quality; appropriate quality necessitating stringent control measures (3–3.99); good quality (4–4.99); very good quality (5–5.99); and excellent (≥6), representing world-class performance [5]. Thus, the Six Sigma methodology is rapid, cost-effective, and provides information about analytical performance.

Coagulation parameters are particularly important in patients with bleeding and thrombosis conditions. Additionally, they are among the most requested test groups for emergency department patients. Given their critical role in patient care, reliable results from coagulation tests are crucial for ensuring patient safety and maintaining laboratory quality. In this study, we aimed to evaluate the analytical performance of the coagulation tests (prothrombin time (PT/INR), activated partial thromboplastin time (aPTT), fibrinogen, and D-dimer) on four coagulation analyzers using the Six Sigma methodology.

Materials and Methods

This study was conducted at the Medical Biochemistry Laboratory of Ankara Etlik City Hospital after obtaining ethical approval (Decision number: AEŞH-BADEK-2024-364, Date: 24.04.2024). Between September 2023 and February 2024, sigma values were calculated using IQC and EQC data of coagulation parameters analyzed by Cobas T711 analyzers (Roche, Germany). All four coagulation analyzers in our laboratory were included, with three analyzing samples from outpatients (labeled as A1, A2, and A3) and one from emergency and intensive care patients (labeled as B).

Using the 6-month IQC (Roche, Germany) data, standard deviation (SD), mean, and CV values were calculated for each parameter and analyzer at both control levels (level 1 and level 2).

CV% = (SD/mean) ×100

EQC data were obtained from the EQC service provider (Bio-Rad, United States of America). Bias values were calculated from 6-month EQC data.

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

The TEa values of INR, aPTT, and fibrinogen parameters were obtained from the Clinical Laboratory Improvement Amendments (CLIA) 2019 database, and the D-dimer TEa value was obtained from the American Association of Bioanalysts (AAB) [6, 7].

CV% and bias% values were calculated each month for both control levels regarding aPTT, INR, fibrinogen, and D-dimer parameters. The averages of CV% and bias% for six months were calculated for each control level. The mean sigma value and total error (TE) were calculated using the 6-month mean CV% and bias% values for each control level. For levels with sigma values below 3, the quality goal index (QGI) was calculated to determine whether IQC, EQC, or both caused the problem. QGI scores of <0.8, >1.2, and 0.8–1.2 indicate imprecision, inaccuracy, and both imprecision and inaccuracy, respectively [8].

The formulations used are as follows:

Sigma (σ) = (TEa% – bias%)/CV%

TE = Bias% + 1.65×CV%

QGI = Bias% / (1.5×CV%)

Results

Analyzer A1: The sigma values of <3 (level 1) and 3–3.99 (level 2) were determined for aPTT (Table 1). The sigma value for both control levels of INR was determined to be in the range of 4–4.99. Sigma values of 3–3.99 (level 1) and 5–5.99 (level 2) were determined for fibrinogen. For the D-dimer test, >6 sigma values were determined for both control levels (Fig. 1).

Analyzer A2: The sigma value for both control levels of aPTT was determined to be in the range of 3–3.99. Sigma values for INR were 3–3.99 (level 1) and 4–4.99 (level 2). Sigma values of 4–4.99 (level 1) and >6 (level 2) were determined for fibrinogen. For the D-dimer test, >6 sigma values were determined for both control levels (Fig. 2).

Analyzer A3: The sigma values of <3 (level 1) and 3–3.99 (level 2) were determined for aPTT. The sigma value for both control levels of INR was determined to be in the range of 4–4.99. Sigma values of 3–3.99 (level 1) and >6 (level 2) were determined for fibrinogen. For the D-dimer test, >6 sigma values were determined for both control levels (Fig. 3).

Analyzer B: The sigma value for both control levels of aPTT was determined in the range of 4–4.99. Sigma values for INR were <3 (level 1) and 3–3.99 (level 2). Sigma values of 3–3.99 (level 1) and 4–4.99 (level 2) were determined for fibrinogen. For the D-dimer test, >6 sigma values were determined for both control levels (Fig. 4).

Discussion

Minimizing laboratory errors is very important for patient safety. Particularly, the Six Sigma metric methodology plays a pivotal role in evaluating laboratory analysis processes. The unique perspective provided by combining IQC and EQC programs used in monitoring analytical performance is noteworthy. In addition to identifying error sources, the Six Sigma metric offers recommendations for control measures, emphasizing the importance of proactive measures and error detection. In this study, we evaluated the analytical performance of coagulation parameters on four coagulation analyzers using the Six Sigma metric methodology. We observed that the sigma value of level 1 of the aPTT parameter was <3 in both analyzers A1 and A3. Moreover, in the B analyzer, the sigma value of the level 1 INR parameter was <3. We found that the sigma values for both control levels of the D-dimer parameter were >6 for all four devices.

Table 1. Average six months data results of the four coagulation analyzers, regarding control levels 1 and 2

Analyzers	Tests	CV (%)	Bias (%)	TEa (%)	Sigma	Total error	Quality goal Index	Problem
A1	aPTT-L1	2.92	6.39	15	2.95	11.2	1.46	Inaccuracy
	aPTT-L2	2.32			3.70	10.3		
	INR-L1	2.31	5.24	15	4.23	9.04		
	INR-L2	2.12			4.61	8.73		
	Fibrinogen-L1	4.33	3.78	20	3.75	10.9		
	Fibrinogen-L2	2.71			5.99	8.24		
	D-dimer-L1	2.57	3.36	30	10.4	7.61		
	D-dimer-L2	2.60			10.2	7.66		
A2	aPTT-L1	2.65	6.61	15	3.17	10.9		
	aPTT-L2	2.23			3.77	10.3		
	INR-L1	2.84	5.84	15	3.22	10.5		
	INR-L2	2.21			4.13	9.50		
	Fibrinogen-L1	4.04	1.37	20	4.61	8.03		
	Fibrinogen-L2	2.46			7.56	5.44		
	D-dimer-L1	3.67	1.54	30	7.75	7.59		
	D-dimer-L2	2.44			11.7	5.56		
A3	aPTT-L1	2.91	6.86	15	2.80	11.7	1.57	Inaccuracy
	aPTT-L2	2.27			3.58	10.6		
	INR-L1	2.21	4.85	15	4.60	8.49		
	INR-L2	2.24			4.53	8.55		
	Fibrinogen-L1	4.19	3.30	20	3.98	10.2		
	Fibrinogen-L2	2.69			6.21	7.74		
	D-dimer-L1	2.41	1.84	30	11.7	5.82		
	D-dimer-L2	2.71			10.4	6.31		
B	aPTT-L1	2.23	5.68	15	4.18	9.36		
	aPTT-L2	2.25			4.14	9.40		
	INR-L1	3.21	5.91	15	2.83	11.2	1.23	Inaccuracy
	INR-L2	3.02			3.01	10.9		
	Fibrinogen-L1	4.65	3.14	20	3.63	10.8		
	Fibrinogen-L2	3.42			4.93	8.78		
	D-dimer-L1	2.82	1.48	30	10.1	6.13		
	D-dimer-L2	2.23			12.8	5.16		

CV: Coefficient of variation; TEa: Total allowable error; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; L1: Level 1; L2: Level 2.

Westgard's study, which assessed the performance of coagulation parameters on the Sysmex CS5100 analyzer using the Six Sigma metric methodology, found sigma values >6 for both control levels of the PT parameter. Additionally, for the aPTT parameter, sigma values were found to be <3 for level 1 and 5–5.99 for level 2 [7]. In Shaikh et al. [9]'s study assessing the performance of PT and fibrinogen parameters on the Sysmex CS-2000i analyzer using the Six Sigma metric methodology, sigma values <3 were identified for both control levels of PT. Moreover, for fibrinogen, sigma values were <3 for level 1 and 3–3.99 for level 2. In the study by Aksit et al. [10] on the Sysmex CS2500 analyzer evaluating the performance of coagulation parameters using the Six Sigma metric methodology and utilizing six months of data, sigma values <3 were identified for PT at level 2, and for fibrinogen, sigma values were <3 for both control levels. They observed a distribution ranging from 3 to 5.99 for other parameters and control levels. By calculating the Quality Goal Index (QGI) for parameters exhibiting low performance, they identified that the issues with these parameters were related to imprecision. In our study, the identified issues associated with parameters exhibiting low performance were attributed to inaccuracy. In the study conducted by Uge et al. [11], using three months of data to evaluate the performance of PT and aPTT parameters using the Six Sigma metric methodology, sigma values of 4–4.99 were determined for level 1 of PT and 3–3.99 for level 2. Furthermore, for aPTT, sigma values of 4–4.99 were identified for both control levels.

Variations in sigma values across studies may result from differences in instruments used, variations in internal quality control materials and calibrators, and the utilization of different external quality assurance programs. Moreover, considering the perceived influence of the number of partic-

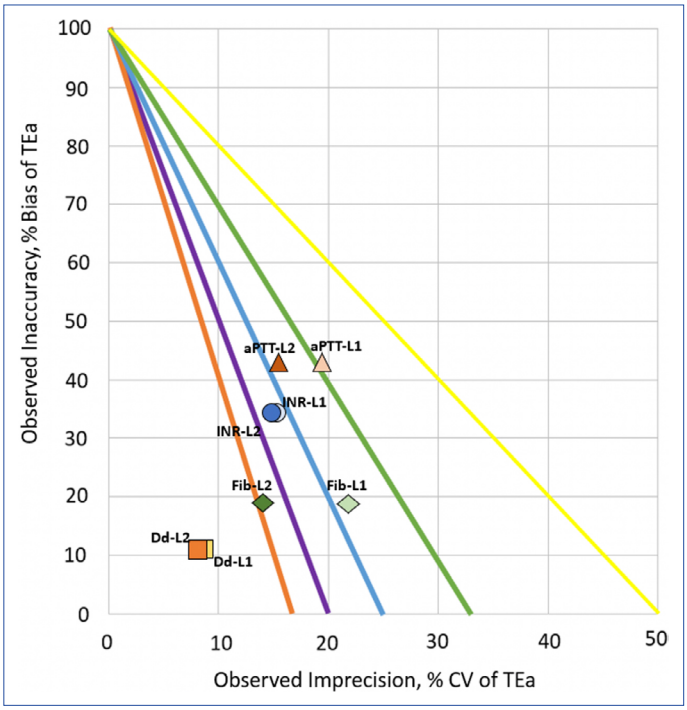

Figure 1. Normalized operating specifications chart for coagulation analyzer A1, showing 6 months average sigma values (September 2023-February 2024).

CV: Coefficient of variation; TEa: Total allowable error; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; Fib: Fibrinogen; Dd: D-dimer; L1: Level 1; L2: Level 2. In the figure, the area between the orange line and the abscissa and ordinate indicates greater than 6 sigma, the area between the orange and purple lines indicates 5-6 sigma, the area between the purple and blue lines indicates 4-5 sigma, the area between the blue and green lines indicate 3-4 sigma and the area between the green and yellow lines indicates 2-3 sigma.

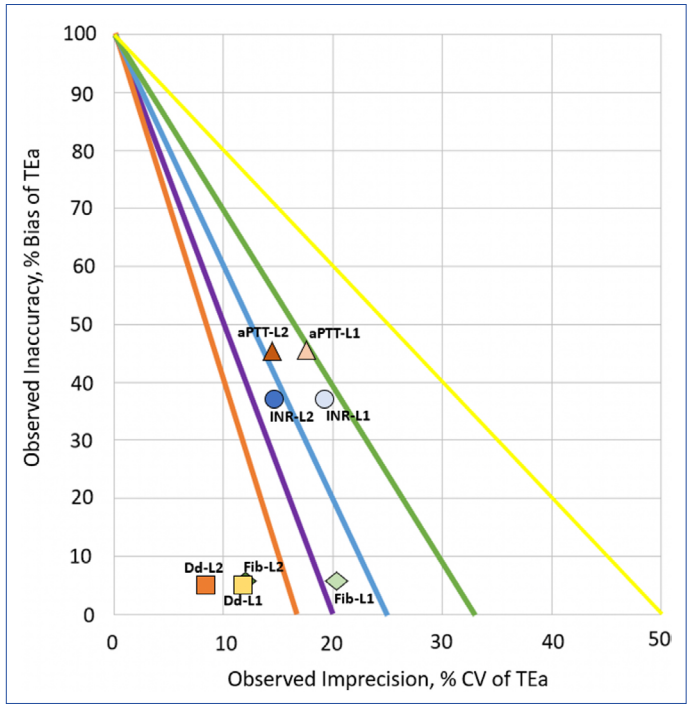

Figure 2. Normalized operating specifications chart for coagulation analyzer A2, showing 6 months average sigma values (September 2023-February 2024).

CV: Coefficient of variation; TEa: Total allowable error; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; Fib: Fibrinogen; Dd: D-dimer; L1: Level 1; L2: Level 2. In the figure, the area between the orange line and the abscissa and ordinate indicates greater than 6 sigma, the area between the orange and purple lines indicates 5-6 sigma, the area between the purple and blue lines indicates 4-5 sigma, the area between the blue and green lines indicate 3-4 sigma and the area between the green and yellow lines indicates 2-3 sigma.

ipants in the EQC programs, the participant count holds significance. The acquisition of TEa data from different sources also contributes to variability. Sigma values calculated with higher TEa recommendations indicate better performance as a formulation necessity. In this context, El Sharkawy suggests harmonization for sigma calculations [12]. We used the TEa sources in our study because they have been used in studies in the current literature. In particular, the EFLM biological variation-based targets are very narrow and may be difficult to achieve under routine laboratory conditions. In addition, different implementations, such as using IQC or EQC data for bias calculation, may have contributed to the different results. Our study found that the control levels with poor performance (<3 sigma) were level 1. We also found that the CV% values of poorly performing level 1 controls were higher than level 2 controls. Level 1 control levels are normal control levels, and level 2 control levels are also pathological levels. Generally, analyses are performed at lower concentrations than pathological controls in normal level controls. The reason why we detected higher CV% values may be the possibility that those studied at low concentrations generally have higher CV% values than those studied at high concentrations.

Our study identified that the issues with parameters exhibiting low performance were attributed to inaccuracy, as revealed by the QGI. High bias in EQC results may be due to problems with the transport of the control material, improper storage of the control material, or random error during the analyzer's analysis of the control material. In addition, it is important in EQC programs to compare external quality results with a peer group using the same method and analyzer. The EQC program we use compares our external quality results according to the peer group when the number of peer groups is 9 or higher and with laboratories using the same measurement method when the number of peer groups is less than 9. Since the number of peer groups for aPTT and PT was insufficient, our external quality results were compared with laboratories with the same method (approximately 1000). We could have obtained lower bias results if the peer group was provided. Additionally, when evaluating parameters with high bias values, the acceptability of the Z score used in assessing EQC results within acceptable ranges (+2>x>-2) also supports the notion that the high bias is linked to the scarcity of participants in the peer group. Thus, despite Z scores falling within acceptable ranges, the presence of high bias values presents challenges for the Six Sigma metric methodology. In this context, there are also proposals that the Six Sigma methodology should be revised or that different formulations should be employed [13].

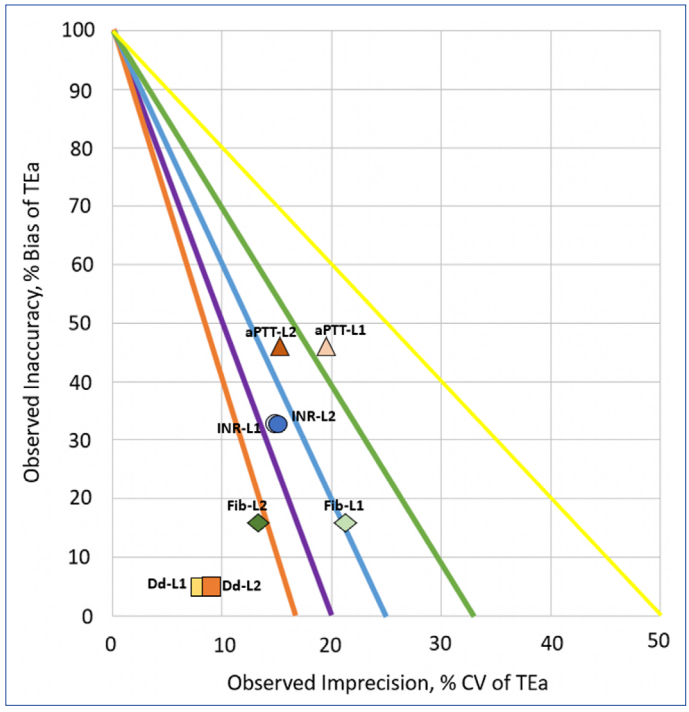

Figure 3. Normalized operating specifications chart for coagulation analyzer A3, showing 6 months average sigma values (September 2023-February 2024).

CV: Coefficient of variation; TEa: Total allowable error; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; Fib: Fibrinogen; Dd: D-dimer; L1: Level 1; L2: Level 2. In the figure, the area between the orange line and the abscissa and ordinate indicates greater than 6 sigma, the area between the orange and purple lines indicates 5-6 sigma, the area between the purple and blue lines indicates 4-5 sigma, the area between the blue and green lines indicate 3-4 sigma and the area between the green and yellow lines indicates 2-3 sigma.

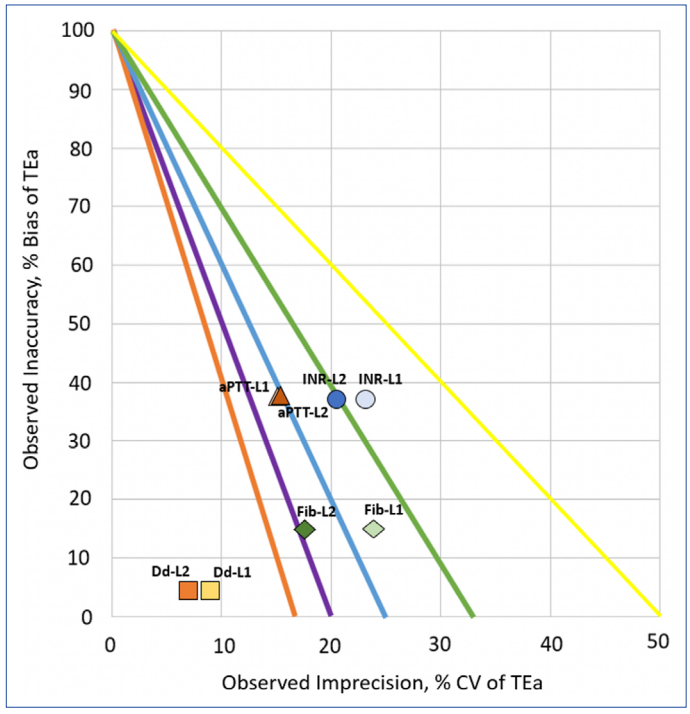

Figure 4. Normalized operating specifications chart for coagulation analyzer B, showing 6 months average sigma values (September 2023-February 2024).

CV: Coefficient of variation; TEa: Total allowable error; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; Fib: Fibrinogen; Dd: D-dimer; L1: Level 1; L2: Level 2. In the figure, the area between the orange line and the abscissa and ordinate indicates greater than 6 sigma, the area between the orange and purple lines indicates 5-6 sigma, the area between the purple and blue lines indicates 4-5 sigma, the area between the blue and green lines indicate 3-4 sigma and the area between the green and yellow lines indicates 2-3 sigma.

According to the sigma levels obtained in our study, we will apply Westgard multirules in terms of IQC. In our study, we will apply Westgard multirule $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_{x}$ for control levels <4 sigma values, Westgard multirule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ for control levels between 4 and 4.99 sigma values, and Westgard multirule $1_{3s}/2_{2s}/R_{4s}$ for control levels between 5 and 5.99 sigma values.

The outstanding performance of the D-dimer parameter across all four instruments, reaching world-class standards at both control levels, reflects positively on our laboratory's performance. Additionally, the absence of poor performance in any device or control levels for fibrinogen is noteworthy and holds significant implications for our laboratory in terms of patient safety. Our laboratory works very intensively, so there are lot changes approximately once a month due to kit consumption. A potential limitation of our study may stem from inter-lot variations observed across months. Nevertheless, the satisfactory CV values for our internal quality suggest that this factor has minimal impact. In a multicenter study by Kitchen et al. [14] evaluating the performance of the Cobas T711 coagulation analyzer, they found that the Cobas T711 coagulation analyzer was reliable and accurate in routine practice for analyzing coagulation parameters. Our study is notable for being the first to employ the Six Sigma metric methodology to assess performance using the Cobas T711 coagulation analyzer. Furthermore, evaluating four different analyzers adds further interest to our findings.

In conclusion, we have identified areas in our laboratory that need improvement by evaluating the analytical performance of coagulation parameters using the Sigma metric method. Conducting assessments and improvement initiatives focused on the analytical process can help improve the reliability of laboratory results.

Ethics Committee Approval: The study was approved by The Ankara Etlik City Hospital Scientific Ethics Committee (No: 2024-364, Date: 24/04/2024).

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