

ORIGINAL ARTICLE

Precision and Trueness Verification of Routine Biochemistry Tests using CLSI EP15-A3

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ABSTRACT

Background: Method verification is a fundamental requirement to ensure reliable test results in diagnostic and therapeutic processes. This study aimed to verify the precision and trueness of routine biochemistry assays on the Beckman Coulter AU680 analyzer according to the Clinical and Laboratory Standards Institute (CLSI) EP15-A3 and to evaluate analytical performance based on biological variation (BV)-derived specifications.

Methods: Twelve routine biochemical analytes, including albumin, alkaline phosphatase (ALP), alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase (LDH), amylase, glucose, total cholesterol, total protein, triglycerides, urea, and uric acid, were evaluated. Two levels of Bio-Rad Lyphochek Assayed Chemistry Controls (lots 89701 and 89702) were analyzed using a 5 × 5 experimental design. Repeatability and within-laboratory precision were estimated using one-way ANOVA and compared with the manufacturer's claims and CLSI EP15-A3 upper verification limits (UVL). Trueness was assessed using Unity Real Time peer group means as the target values. The results falling outside the verification intervals were further evaluated against the BV-based allowable bias limits. The total analytical error (TAE) was calculated by combining the bias and within-laboratory imprecision estimates derived from the CLSI EP15-A3 verification protocol, and was subsequently evaluated against BV-based specifications.

Results: Repeatability CV values ranged from 0.37% to 1.51%, and within-laboratory CV values ranged from 0.56% to 3.70%. Although several observed CV values exceeded the manufacturer's claims, all remained below the CLSI EP15-A3 UVL, confirming acceptable analytical precision. Trueness was verified by compliance with verification intervals or by bias values remaining within the allowable BV-based limits. Optimal bias performance was achieved for ALP, LDH, total protein, triglycerides, and urea at both control levels, whereas the remaining analytes met the desirable bias specifications. All analytes fulfilled either the optimal or desirable BV-based total error specifications, and none exceeded the desirable allowable limits.

Conclusions: All evaluated assays demonstrated satisfactory analytical performance and successfully met the CLSI EP15-A3 verification criteria. Furthermore, this integrated verification approach may assist laboratories in generating objective evidence to support quality assurance activities and comply with ISO 15189:2022 accreditation requirements.

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KEYWORDS

method verification, CLSI EP15-A3, precision, trueness, biological variation

INTRODUCTION

Clinical laboratories serve as a critical link between patients and clinicians, and the analytical quality of the tests they provide directly influences clinical decision-making processes. Even when the same analytical instruments and methodologies are used, numerous variables, such as laboratory conditions, quality control (QC) practices, instrument maintenance and calibration processes, and operator experience, can cause test result accuracy and reliability to vary from one laboratory to another [1]. Validation is the process by which a manufacturer objectively demonstrates that a measurement procedure or system operates as intended and meets desirable performance characteristics. In contrast, verification is the process of confirming through objective data whether a measurement procedure validated by the manufacturer meets the performance requirements stated by the manufacturer under the operating conditions of the implementing laboratory [2,3]. Even if a manufacturer-provided analytical method is to be used without any modifications, it must be independently verified by the implementing laboratory prior to routine use in accordance with ISO 15189 accreditation requirements [4]. Verification may also be performed to demonstrate whether the measurement procedure has returned to the expected analytical performance level following the implementation of corrective actions after a failure in external quality assessment [5,6].

Although measures to improve quality in clinical laboratories have increased significantly in recent years, substantial variations in method performance verification among laboratories remain [7-9]. The CLSI EP15-A3 guideline (Evaluation Protocol 15: User Verification of Precision and Estimation of Bias) provides a standardized approach for verifying manufacturer-claimed precision and assessing trueness using materials with assigned target values [5,10]. Precision describes the agreement between repeated measurements under specified conditions and is expressed as standard deviation (SD) or coefficient of variation (CV). Trueness reflects the agreement between the measured mean and the target value, whereas their difference is expressed as a bias [11,12]. Before beginning the experiment, acceptable analytical performance characteristics of precision and bias must be defined [10]. The performance requirements can be derived by following one of the three models in accordance with the Milan hierarchy. Once these analytical performance specifications (APS) are defined, the laboratory must verify that they are met [13-15]. In modern laboratory quality management, in addition to verifying precision and trueness, comprehensive analytical performance indicators, such as the total analytical error (TAE), are widely used [16,17]. This study aimed to verify the precision and trueness of routine biochemistry tests performed on the Beckman Coulter AU680 automated analyzer in accordance with the CLSI EP15-A3 guidelines. In addition, TAE was calculated to evaluate the analytical performance more

comprehensively, and the suitability of the methods for routine clinical use was investigated by comparing the findings with APS based on biological variation (BV) [18].

MATERIALS AND METHODS

This study was conducted at the Biochemistry Laboratory of Yerköy Şehit Korgeneral Osman Erbaş State Hospital. Verification experiments were performed between November 6 and 10, 2023, following approval by the Yozgat Bozok University Clinical Research Ethics Committee (approval date: October 19, 2023; approval no. 2017-KAEK-189_2023.10.19_07). All measurements were performed on a Beckman Coulter AU680 (Beckman Coulter Inc., Brea, CA, USA) automated analyzer using the manufacturer's original reagents and calibrators. Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, glucose, lactate dehydrogenase (LDH), total cholesterol, total protein (TP), triglycerides (TG), urea, and uric acid levels were measured. The measurement principles for the test parameters are listed in Table 1. Manufacturer precision claims used for CLSI EP15-A3 verification were obtained from the corresponding analyte-specific Instructions for Use (IFU) documents provided by Beckman Coulter. The referenced IFUs were as follows: albumin (BLOS6X02 Rev.10, April 2020), ALP (BLOS6X04 Rev.10, April 2020), ALT (BLOS6X07 Rev.09, December 2018), AST (BLOS6X09 Rev.09, December 2018), amylase (BLOS6X82 Rev.10, April 2020), glucose (BLOS6X21 Rev.12, June 2019), LDH (BLOS6X28 Rev.09, October 2019), total cholesterol (BLOS6X16 Rev.13, February 2019), TP (BLOS6X32 Rev.08, April 2020), TG (BLOS6X118 Rev.08, December 2018), urea (BLOS6X34 Rev.12, June 2019), and uric acid (BLOS6X98 Rev.13, April 2020). Verification studies were conducted using commercially available internal QC materials. Two different levels of Bio-Rad Lyphochek® Assayed Chemistry Control (Bio-Rad Laboratories, USA) QC materials were used. Level 1 (lot no. 89701) and 2 (lot no. 89702) QC materials were used in this study. Target values for the analytes were determined based on the peer group cumulative averages obtained using the Unity Real Time inter-laboratory QC program (Bio-Rad Laboratories). The instrument was calibrated prior to the study, and it was confirmed that the QC results fell within the expected limits. Commercial internal QC materials at two different levels were used for each parameter, and each level was analyzed five times daily over five days (5×5 experimental design). Thus, 25 measurements were obtained for each control level.

Statistical analysis for precision verification

Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). The

measurement results were evaluated for the presence of outliers using the Grubbs test for each control level, as recommended by the CLSI EP15-A3 guidelines. Individual results were compared with the corresponding Grubbs critical limits (mean $\pm$ G $\times$ SD) [5]. In the analyses, no statistically significant outliers were found for any of the 12 analytes included in the study. Therefore, no data were excluded, and all measurement results were included in the precision and trueness analyses.

Precision was evaluated for repeatability (within-run precision) and within-laboratory (WL) precision. Variance components were calculated using one-way ANOVA. The within-run variance (V_W) was assumed equal to the within-run mean square obtained from ANOVA (MS_2), while the between-run variance (V_B) was calculated as $V_B = (MS_1 - MS_2)/n_0$, where MS_1 represents the between-run mean square, MS_2 the within-run mean square, and n_0 the average number of results per run. The WL (total variance) was calculated as $V_{WL} = V_W + V_B$. SD components were obtained by taking the square roots of the variance values, yielding the repeatability SD: $s_r = \sqrt{V_W}$, the between-run SD: $s_b = \sqrt{V_B}$, and the WL SD: $s_{WL} = \sqrt{V_{WL}}$. Coefficients of variation were calculated as $CV(\%) = (SD/\bar{x}) \times 100$, and the obtained CV_r and CV_{WL} values were compared with the repeatability and WL precision claims reported by the manufacturer. When the observed precision exceeded the manufacturer's performance claims, the upper verification limits (UVL) were calculated according to CLSI EP15-A3. For repeatability, the degrees of freedom were calculated as $df_R = N - k$, where N is the total number of measurements and k is the number of runs. For WL precision, the degrees of freedom were determined using the ratio $\rho = \sigma_{WL}/\sigma_R$ (σ_{WL} : manufacturer's WL precision claim; σ_R : manufacturer's repeatability claim), and the corresponding degrees of freedom were obtained from CLSI EP15-A3 Table 6. The UVL factor (F) was obtained from Table 7 and the UVL was calculated as $UVL = F \times \sigma$ (manufacturer's claim) [5]. Precision was considered verified when the observed precision values were below the calculated UVL values.

Statistical analysis for trueness verification

Trueness verification was performed in accordance with the CLSI EP15-A3 guideline [5]. The standard error of the laboratory mean ($se_{\bar{x}}$), was calculated using the estimates of WL imprecision (s_{WL}) and repeatability (s_R) obtained from the precision study, according to the

following formula: $se_{\bar{x}} = \sqrt{\frac{1}{n_{run}} \left[s_{WL}^2 - \frac{(n_{rep}-1)}{n_{rep}} s_R^2 \right]}$

Here, n_{run} denotes the number of runs performed in the experiment, n_{rep} represents the number of replicate measurements per run.

The cumulative mean of the peer group was accepted as the target value (TV). The standard error of the target value (se_{RM}), was calculated by dividing the peer group

SD by the square root of the number of participating laboratories ($se_{RM} = SD_{RM}/\sqrt{n_{Lab}}$). The combined standard error (se_C), $se_C = \sqrt{se_{\bar{x}}^2 + se_{RM}^2}$ was calculated using the formula. The tau value was determined as $\tau = se_{RM}/se_{\bar{x}}$. The combined degrees of freedom (df_c) were obtained from Table 15A of the CLSI EP15-A3 guideline based on the number of participating laboratories and the tau (τ) value. The m coefficient, used in the calculation of the verification interval was obtained from Student's t -distribution corresponding to the df_c . An alpha level of 0.05 was assumed for a 95% confidence interval. Given that two samples were analyzed, the probability term was taken as $1 - \frac{\alpha}{2n} = 0.9875$. Verification interval was calculated using the following formula: $VI = TV \pm m \times se_C$. The bias value was calculated using the formulas: $Bias = \bar{X} - TV$ and $Bias(\%) = \frac{\bar{X} - TV}{TV} \times 100$. Trueness was considered to be verified when the mean value was within the verification interval. For results outside the verification interval, bias was evaluated against APS based on BV. Trueness was deemed acceptable if the percentage bias (%bias) was lower than the allowable bias derived from BV [5].

Total Analytical Error Assessment

The TAE was calculated for each analyte and QC level by combining systematic and random analytical errors, according to the following equation [17]:

$$TAE(\%) = |Bias(\%)| + 1.65 \times CV_{WL}(\%)$$

where bias (%) was determined from the difference between the laboratory mean and the target value obtained from the Unity Real Time peer-group program, and CV_{WL} (%) represented within-laboratory imprecision estimated according to CLSI EP15-A3. The calculated TAE values were compared with the BV-based APS obtained from the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) BV Database [18].

Measurement uncertainty estimation

The measurement uncertainty (MU) was estimated in accordance with ISO/TS 20914 using data generated during the CLSI EP15-A3 verification study [19]. The within-laboratory standard uncertainty (u_{Rw}) was derived from the within-laboratory precision estimates obtained during the precision verification study, whereas the calibration uncertainty (u_{Cal}) was obtained from the manufacturer's calibrator documentation. The bias component was not included in the uncertainty budget because trueness verification demonstrated that the observed bias was within the predefined allowable APS and, therefore, was considered not to contribute significantly to the overall MU, as recommended by ISO/TS 20914.

The combined standard uncertainty (u_c) was calculated as: $u_c = \sqrt{u_{Rw}^2 + u_{Cal}^2}$. The expanded MU (U) was then calculated using a coverage factor of $k = 2$,

corresponding to an approximate 95% level of confidence: $U = k \times uc$.

The relative expanded uncertainty was calculated as: $U\% = (U / \text{mean}) \times 100$.

The calculated expanded uncertainty values were compared with the BV-based maximum allowable uncertainty (MAU) specifications provided by the EFLM BV Database [18].

RESULTS

Precision verification

Table 2 provides the detailed results of the precision verification studies conducted according to CLSI EP15-A3 for the 12 routine biochemistry tests. The repeatability CVs of albumin for levels 1 and 2 were 0.678 and 0.743%, respectively, whereas the WL CVs were 1.020 and 0.782%, respectively. For albumin level 1, the repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. For albumin level 2, the repeatability CV exceeded the manufacturer's claim but met the UVL target; however, the WL CV for level 2 met the manufacturer's claim. The repeatability CVs of ALP for levels 1 and 2 were 1.505 and 0.661%, respectively, whereas the WL CVs were 2.920 and 2.291%, respectively. For ALP levels 1 and 2, the repeatability and WL CVs met the manufacturer's claims. The repeatability CVs of ALT for levels 1 and 2 were 1.446 and 0.871%, respectively, whereas the WL CVs were 3.696 and 2.858%, respectively. For ALT levels 1 and 2, repeatability CVs met the manufacturer's claims, but WL CVs exceeded the manufacturer's claims but met the UVL targets. The repeatability CVs of AST for levels 1 and 2 were 1.386 and 0.541%, respectively, whereas the WL CVs were 1.864 and 2.047%, respectively. For AST level 1, the repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. For AST level 2, the repeatability CV met the manufacturer's claim; however, the WL CV exceeded the manufacturer's claim but met the UVL target. The repeatability CVs of amylase for levels 1 and 2 were 0.844 and 0.703%, respectively, whereas the WL CVs were 1.379 and 2.188%, respectively. For amylase levels 1 and 2, repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. The repeatability CVs of glucose for levels 1 and 2 were 0.678 and 0.371%, respectively, whereas the WL CVs were 0.885 and 0.594%, respectively. For glucose level 1, the repeatability and WL CVs met the manufacturer's claims. For glucose level 2, the WL CV met the manufacturer's claim; however, the repeatability CV for level 2 exceeded the manufacturer's claim but met the UVL target. The repeatability CVs of LDH for levels 1 and 2 were 1.410 and 0.606%, respectively, whereas the WL CVs were 2.142 and 1.303%, respectively. For LDH level 1, the repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. For LDH level 2, the repeatability and WL CVs met the

manufacturer's claims. The repeatability CVs of total cholesterol for levels 1 and 2 were 0.512 and 0.614%, respectively, whereas the WL CVs were 0.560 and 0.714%, respectively. For total cholesterol levels 1 and 2, the repeatability CVs exceeded the manufacturer's claims, but met the UVL targets. For total cholesterol levels 1 and 2, the WL CVs met the manufacturer's claims. The repeatability CVs of TP for levels 1 and 2 were 0.383 and 0.551%, respectively, whereas the WL CVs were 0.789 and 0.933%, respectively. For TP levels 1 and 2, repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. The repeatability CVs of TG for levels 1 and 2 were 0.854 and 1.055%, respectively, whereas the WL CVs were 1.249 and 2.533%, respectively. For TG level 1, the repeatability and WL CVs exceeded the manufacturer's claims but met the UVL targets. For TG level 2, the WL CV exceeded the manufacturer's claim but met the UVL target; however, the repeatability CV for level 2 met the manufacturer's claim. The repeatability CVs of urea for levels 1 and 2 were 0.972 and 0.958%, respectively, whereas the WL CVs were 0.951 and 1.565%, respectively. For urea levels 1 and 2, the repeatability and WL CVs met the manufacturer's claims. The repeatability CVs of uric acid for levels 1 and 2 were 0.534 and 0.632%, respectively, whereas the WL CVs were 1.330 and 1.109%, respectively. For uric acid levels 1 and 2, the repeatability and WL CVs met the manufacturer's claims (Table 2, Figure 1).

Trueness verification

Table 3 presents the detailed results of trueness verification studies conducted in accordance with CLSI EP15-A3 for the 12 routine biochemistry tests. For ALP, ALT, uric acid, LDH, TP, and albumin tests, trueness was verified, as the grand mean values obtained from the two QC levels were within the verification interval. For level 1 TG and level 2 AST, although the grand mean values were outside the verification interval, trueness was verified as the bias value fell within the allowed bias goal. For the urea, glucose, amylase, and total cholesterol tests, although the grand mean values of levels 1 and 2 were outside the verification interval, trueness was verified because the bias value fell within the allowed bias goal.

After evaluating the calculated bias values using the analytical performance characteristics derived from BV, it was ascertained that the bias values for five analytes - ALP, LDH, TP, TG, and urea - were below the optimal BV specifications at both control levels. Furthermore, AST and total cholesterol met the optimal specifications at level 1, whereas albumin and ALT met these specifications at level 2. Among the remaining parameters that did not meet the optimal criteria, amylase, glucose, and uric acid satisfied the desirable deviation specifications at both QC levels, whereas AST and total cholesterol met the desirable criteria at level 2, and albumin and ALT met them at level 1. In summary, the nine analytes achieved optimal analytical performance for at least one

Table 1. Analytical measurement principles of the routine biochemical analytes analyzed on the Beckman Coulter AU680.

Analyte	Analytical principle
Albumin	Photometric color test (bromocresol green)
ALP	Kinetic colorimetric (pNPP)
ALT	IFCC kinetic UV (without P-5'-P)
AST	IFCC kinetic UV (without P-5'-P)
Amylase	Enzymatic colorimetric (blocked maltoheptaoside)
Glucose	Enzymatic UV (hexokinase/G6PD)
LDH	IFCC kinetic UV (lactate → pyruvate)
Total cholesterol	Enzymatic colorimetric (cholesterol oxidase-peroxidase)
Total protein	Biuret method
Triglycerides	Enzymatic colorimetric (GPO-POD)
Urea	Enzymatic UV (urease-GLDH)
Uric acid	Enzymatic colorimetric (uricase-peroxidase)

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, IFCC: International Federation of Clinical Chemistry and Laboratory Medicine, UV - ultraviolet, pNPP - p-nitrophenyl phosphate, P-5'-P - pyridoxal-5'-phosphate, G6PD - glucose-6-phosphate dehydrogenase, GPO-POD - glycerol phosphate oxidase-peroxidase, GLDH - glutamate dehydrogenase.

QC level, whereas amylase, glucose, and uric acid analytes met the desirable targets (Table 4 and Figure 2). The TAE values ranged from 1.70% to 11.53% for all analytes and control levels. All calculated TAE values were below the corresponding desirable BV-based total allowable error (TEa) specifications. At level 1, the TAE values ranged from 2.38% for albumin to 11.53% for ALT. According to BV-derived APS, AST, total cholesterol, TG, urea, and uric acid achieved optimal performance, whereas albumin, ALP, ALT, amylase, glucose, LDH, and TP met the desirable performance criteria. At level 2, the TAE values ranged from 1.70% for albumin to 10.04% for amylase. Albumin, ALP, ALT, glucose, LDH, total cholesterol, TG, urea, and uric acid achieved optimal performance, whereas AST, amylase, and TP met the desirable performance specifications (Table 5).

Expanded MU estimates calculated according to ISO/TS 20914 using CLSI EP15-A3 verification data are presented in Table 6. The expanded uncertainty (U%) ranged from 1.56% to 11.1% across the evaluated analytes and QC levels. All analytes satisfied the corresponding MAU specifications, except albumin, for which U% slightly exceeded the MAU at both QC levels. The lowest U% was observed for glucose level 2 (1.56%), whereas the highest was observed for urea level 1 (11.1%).

DISCUSSION

The primary responsibility of a laboratory is to produce reliable results that support accurate clinical decision-making, which requires verification of measurement procedures before their implementation in routine practice. The purpose of method verification is to confirm that analytical performance achieved under routine laboratory conditions complies with the manufacturer's performance claims and predefined quality requirements. This process provides objective evidence supporting analytical performance and implementation of the measurement procedure within the laboratory quality management system [2,4,5].

According to the CLSI EP15-A3 guideline, the materials used to validate precision and trueness should represent at least two concentration levels close to clinical decision points. While patient samples, patient sample pools, or commercial QC materials may be used in precision verification studies, certified reference materials, materials from interlaboratory QC programs, materials from external quality assessment programs, or proficiency testing with pre-assigned target values may be used in trueness assessment [5]. In this study, commercial internal QC materials were preferred as study materials to verify the precision of the test parameters and estimate bias.

The EP15-A3 guideline emphasizes that, particularly in experimental designs with small sample sizes (5×5), there is a high probability that precision estimates obtained by the user could exceed the manufacturer's claims solely by chance. In such designs, it is noted that precision estimates obtained by the user may exceed the

Table 2. Evaluation of precision verification for 12 routine biochemistry analytes based on CLSI EP15-A3.

Parameter (n = 25)	QC Level	Mean (IFU)	CV _R (%)	σ _R (%)	UVL _R (%)	CV _{WL} (%)	σ _{WL} (%)	UVL _{WL} (%)
Albumin (g/L)	L1	47.2	0.678	0.520	0.680	1.020	0.810	1.199
	L2	23.1	0.743	0.580	0.758	0.782	0.990	1.497
ALP (U/L)	L1	38	1.505	2.100	2.745	2.920	4.200	6.518
	L2	360	0.661	1.300	1.699	2.291	2.300	3.479
ALT (U/L)	L1	19	1.446	2.100	2.745	3.696	2.700	3.724
	L2	55	0.871	1.200	1.569	2.858	2.100	3.176
AST (U/L)	L1	58	1.386	1.100	1.438	1.864	1.600	2.290
	L2	378	0.541	0.800	1.046	2.047	1.400	2.117
Amylase (U/L)	L1	51	0.844	0.710	0.928	1.379	1.160	1.717
	L2	132	0.703	0.560	0.732	2.188	1.380	2.211
Glucose (mg/dL)	L1	53.87	0.678	0.700	0.915	0.885	0.900	1.241
	L2	293.87	0.371	0.300	0.392	0.594	0.700	1.121
LDH (U/L)	L1	157	1.410	1.130	1.477	2.142	1.540	2.174
	L2	237	0.606	0.890	1.163	1.303	1.360	1.977
TC (mg/dL)	L1	236.7	0.512	0.400	0.523	0.560	0.600	0.872
	L2	95.9	0.614	0.500	0.654	0.714	0.800	1.184
TP (g/L)	L1	73.33	0.383	0.340	0.444	0.789	0.700	1.086
	L2	35.57	0.551	0.500	0.654	0.933	0.840	1.244
TG (mg/dL)	L1	378.78	0.854	0.720	0.941	1.249	1.030	1.474
	L2	41.59	1.055	1.060	1.386	2.533	1.760	2.606
Urea (mg/dL)	L1	11.83	0.972	2.280	2.980	0.951	3.250	4.651
	L2	58.32	0.958	1.030	1.346	1.565	2.380	3.693
UA (mg/dL)	L1	2.89	0.534	1.110	1.451	1.330	1.710	2.486
	L2	6.53	0.632	1.550	2.026	1.109	2.440	3.612

CLSI: Clinical and Laboratory Standards Institute, QC: quality control, IFU: instructions for use, CV_R: coefficient of variation of repeatability, σ_R: repeatability declared by the manufacturer in IFU, UVL_R: upper verification limit of repeatability, CV_{WL}: coefficient of variation of within-lab, σ_{WL}: within-lab CV declared by the manufacturer in IFU, UVL_{WL}: upper verification limit of within-lab, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, TP: total protein, TG: triglycerides, UA: uric acid.

manufacturer's claims with approximately a 50% probability, which could lead to incorrect "failure" decisions. Therefore, the CLSI recommends calculating a UVL representing the upper 95th percentile of the expected error. Thus, the probability of the experiment failing by chance alone was reduced to 5% [5,9].

In our study, the fact that repeatability CV values ranged from 0.371% to 1.505% and within-laboratory CV values ranged from 0.560% to 3.696% indicated that low analytical imprecision was achieved for the majority of the evaluated parameters. Although the observed precision estimates exceeded the manufacturer's claims for some parameters, all estimates remained within the UVLs defined by CLSI [5]. When our within-laboratory imprecision estimates were compared with the BV targets, it was observed that the optimal or desirable targets were met for all parameters. These find-

ings indicate that the analytical system used demonstrates acceptable analytical precision under routine laboratory conditions. Notably, the repeatability CV for albumin at level 1 (0.678%) was only marginally below the corresponding UVLR (0.680%), representing a borderline yet acceptable verification result according to CLSI EP15-A3. Although the verification criteria were fulfilled, this finding suggests that albumin should be monitored more closely through routine internal QC to ensure sustained analytical performance.

In the trueness assessment, the Unity Real Time peer-group mean was used as the target value, consistent with CLSI EP15-A3 recommendations when certified reference materials or reference measurement procedures were unavailable [5]. The uncertainty of the target value (seRM) was incorporated into the calculations. Trueness was considered verified when the laboratory

Table 3. Evaluation of trueness verification for 12 routine biochemistry analytes based on CLSI EP15-A3.

Parameter (n = 25)	QC Level	Grand Mean (x)	se _x	N _{lab}	se _{RM}	se _c	m	TV	VI (TV ± m*se _c)	Bias	Allowed Bias
Albumin (g/L)	L1	40.280	0.366	317	0.059	0.371	3.1634	40.0	38.827 - 41.173	0.280	0.480
	L2	25.695	0.184	314	0.041	0.189	3.1634	25.8	25.203 - 26.397	0.105	0.155
ALP (U/L)	L1	115.080	1.160	85	0.676	1.342	2.8412	112.5	108.688 - 116.312	2.580	3.038
	L2	491.248	0.990	83	2.886	3.051	2.2990	486.8	479.786 - 493.814	4.448	13.144
ALT (U/L)	L1	26.852	1.548	200	0.130	1.554	3.4954	25.47	20.047 - 30.893	1.382	2.063
	L2	93.540	1.229	198	0.425	1.301	3.1634	91.93	87.815 - 96.045	1.610	3.769
AST (U/L)	L1	43.40	0.622	79	0.169	0.645	3.1634	42.27	40.23 - 44.31	1.130	1.141
	L2	180.216	0.889	78	0.636	1.094	2.685	185.9	182.963 - 188.837	5.684	10.039
Amylase (U/L)	L1	74.960	0.516	29	0.356	0.627	2.7515	80.61	78.885 - 82.335	5.650	6.046
	L2	416.680	0.937	30	1.635	1.885	2.3289	391.5	387.111 - 395.889	25.18	29.363
Glucose (mg/dL)	L1	74.776	0.290	354	0.132	0.317	2.9686	76.09	75.149 - 77.031	1.314	1.750
	L2	268.312	0.220	353	0.448	0.499	2.2990	273.7	272.553 - 274.847	5.388	6.295
LDH (U/L)	L1	155.080	0.774	166	0.942	1.220	2.3909	153.4	150.484 - 156.316	1.680	2.454
	L2	342.960	0.529	167	2.00	2.069	2.2699	342.0	337.304 - 346.699	0.960	5.472
TC (mg/dL)	L1	261.092	0.144	163	0.855	0.867	2.2699	266.5	264.532 - 268.468	5.408	5.597
	L2	95.172	0.204	161	0.340	0.396	2.3289	98.83	97.908 - 99.752	3.658	4.151
TP (g/L)	L1	66.96	0.318	323	0.106	0.335	3.1634	66.1	65.04 - 67.16	0.855	1.190
	L2	42.85	0.354	320	0.069	0.370	3.1634	42.2	41.03 - 43.37	0.653	0.760
TG (mg/dL)	L1	160.600	0.442	285	0.364	0.572	2.5931	165	163.517 - 166.483	4.400	8.415
	L2	83.720	1.051	285	0.204	1.071	3.1634	86.49	83.102 - 89.878	2.770	4.411
Urea (mg/dL)	L1	31.881	0.172	110	0.113	0.206	2.7515	32.67	32.103 - 33.237	0.789	0.980
	L2	95.760	0.585	110	0.316	0.665	2.8412	97.70	95.811 - 99.589	1.940	2.931
UA (mg/dL)	L1	4.388	0.560	322	0.010	0.555	3.4954	4.55	2.611 - 6.489	0.162	0.255
	L2	9.360	0.426	319	0.014	0.427	3.4954	9.70	8.208 - 11.192	0.340	0.543

CLSI: Clinical and Laboratory Standards Institute, QC: quality control, se_x: standard error of mean, N_{lab}: number of participant laboratories in interlaboratory QC, se_{RM}: standard error of the reference material, se_c: combined standard error, m: multiplier to the student's *t*-quantile, TV: target value, VI: verification interval, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, TP: total protein, TG: triglycerides, UA: uric acid.

mean fell within the verification interval; otherwise, the observed bias was interpreted according to the selected APS to determine its clinical acceptability. It should also be acknowledged that the use of commercial QC materials may introduce commutability-related limitations, because these materials may not fully mimic the behavior of native patient samples across various measurement procedures. Consequently, matrix-related differences may have influenced the estimated bias values obtained in this study. The grand mean values obtained at both levels for ALP, ALT, uric acid, LDH, TP, and albumin tests were within the verification interval, and the manufacturer's trueness claims were verified. Although the grand mean values for TG (level 1) and AST (level 2) fell outside the verification interval, trueness was confirmed because the calculated bias value remained within the acceptable bias target. Similarly, although the grand mean values for urea, glucose, amy-

lase, and total cholesterol were outside the verification interval at both levels, trueness was verified according to CLSI EP15-A3 because the calculated bias values remained within acceptable limits. Among the available approaches for defining APS, BV-derived criteria are widely accepted for evaluating analytical quality. The EFLM BV Database provides standardized optimal, desirable, and minimum performance specifications based on systematically evaluated BV data and global meta-analysis estimates, facilitating consistent assessment of analytical performance across laboratories [15,18,20-22]. In the evaluation based on BV-based APS, the optimal performance targets were met for ALP, LDH, TP, TG, and urea analyses at both the control levels. Additionally, optimal specifications were achieved for AST and total cholesterol in the level 1 control material, and for albumin and ALT analyses in the level 2 control material. For other parameters in which the optimal criteria

Table 4. Comparison of percentage bias values with EFLM biological variation-based analytical performance specifications.

Parameter (n = 25)	QC Level	Bias %	Optimum Bias Goal	Desirable Bias Goal	Minimum Bias Goal
Albumin (g/L)	L1	0.70	0.6	1.2	1.9
	L2	-0.41	0.6	1.2	1.9
ALP (U/L)	L1	2.29	2.7	5.5	8.2
	L2	0.91	2.7	5.5	8.2
ALT (U/L)	L1	5.43	4.1	8.1	12.2
	L2	1.75	4.1	8.1	12.2
AST (U/L)	L1	2.67	2.7	5.4	8.0
	L2	-3.06	2.7	5.4	8.0
Amylase (U/L)	L1	-7.01	3.8	7.5	11.3
	L2	6.43	3.8	7.5	11.3
Glucose (mg/dL)	L1	-1.73	1.2	2.3	3.5
	L2	-1.97	1.2	2.3	3.5
LDH (U/L)	L1	1.10	1.6	3.1	4.7
	L2	0.28	1.6	3.1	4.7
TC (mg/dL)	L1	-2.03	2.1	4.2	6.3
	L2	-3.70	2.1	4.2	6.3
TP (g/L)	L1	1.30	1.8	3.6	5.4
	L2	1.54	1.8	3.6	5.4
TG (mg/dL)	L1	-2.67	5.1	10.1	15.2
	L2	-3.20	5.1	10.1	15.2
Urea (mg/dL)	L1	-2.42	3.0	6.0	9.1
	L2	-1.99	3.0	6.0	9.1
UA (mg/dL)	L1	-3.56	2.8	5.6	8.4
	L2	-3.51	2.8	5.6	8.4

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, TP: total protein, TG: triglycerides, UA: uric acid.

were not met, the calculated bias values remained within the desirable APS. This indicates that the observed deviation in the measurement procedure remained within clinically acceptable limits and that trueness was successfully verified. The inclusion of TAE provides a more clinically relevant assessment because it simultaneously incorporates both systematic and random analytical error components. All calculated TAE values remained below the corresponding BV-derived allowable limits, supporting the overall suitability of the evaluated methods for routine patient testing. For uric acid at level 1, trueness was successfully verified according to the CLSI EP15-A3 acceptance criteria, as the laboratory mean remained within the predefined verification interval. However, the relatively broad verification interval indicates limited discriminative capability of the verification procedure at this concentration level. Consequently, although the result provides statistically valid evidence that the predefined acceptance criterion was

met, it should be interpreted as a confirmation of acceptable trueness rather than as strong evidence of close agreement with the target value.

The analytical performance results obtained in this study were generally consistent with those of previous studies that evaluated the performance of Beckman Coulter AU-series analyzers. Studies conducted on AU480, AU5800, and AU680 platforms reported low imprecision, acceptable levels of bias, and compliance with analytical performance targets based on BV for the vast majority of routine clinical chemistry analytes [23-27]. Cattozzo et al. [23] reported that the CV values on the AU680 analyzer ranged from 0.4% to 2.6%, depending on the method, and that the optimal quality targets based on BV were met in 23 of the 29 analytical methods evaluated. Similarly, Lippi et al. [24] demonstrated that the intra- and inter-assay CV values of the AU5800 analyzer ranged from 0.4% to 3.0% and 0.6% to 2.8%, respectively, and that the total error limits

Table 5. Total analytical error values of the evaluated analytes and their classification according to biological variation-based analytical performance specifications.

Parameter	Level	TAE (%)	TEa Optimal (%)	TEa Desirable (%)	TAE Class
Albumin	L1	2.38	1.7	3.3	Desirable
Albumin	L2	1.70	1.7	3.3	Optimal
ALP	L1	7.11	5.2	10.4	Desirable
ALP	L2	4.69	5.2	10.4	Optimal
ALT	L1	11.53	9.3	18.5	Desirable
ALT	L2	6.47	9.3	18.5	Optimal
AST	L1	5.75	6.2	12.4	Optimal
AST	L2	6.44	6.2	12.4	Desirable
Amylase	L1	9.29	6.5	13.1	Desirable
Amylase	L2	10.04	6.5	13.1	Desirable
Glucose	L1	3.19	3.1	6.2	Desirable
Glucose	L2	2.95	3.1	6.2	Optimal
LDH	L1	4.63	3.4	6.8	Desirable
LDH	L2	2.43	3.4	6.8	Optimal
TC	L1	2.95	4.3	8.6	Optimal
TC	L2	4.88	4.3	8.6	Desirable
TP	L1	2.60	1.7	3.4	Desirable
TP	L2	3.08	1.7	3.4	Desirable
TG	L1	4.73	13.2	26.5	Optimal
TG	L2	7.38	13.2	26.5	Optimal
Urea	L1	3.99	8.4	16.8	Optimal
Urea	L2	4.57	8.4	16.8	Optimal
UA	L1	5.75	6.2	12.5	Optimal
UA	L2	5.34	6.2	12.5	Optimal

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, TP: total protein, TG: triglycerides, UA: uric acid, TAE: total analytical error, TEa: total allowable error, L1: quality control level 1, L2: quality control level 2.

based on BV were not exceeded for any parameter. Abebe [25], in a verification study conducted on the AU480 analyzer according to the CLSI EP15-A2 protocol, reported low imprecision for glucose, total cholesterol, creatinine, AST, and ALT, and demonstrated that all parameters met the desired performance targets based on BV. Glibert et al. [26], however, reported that total CV values on the AU5800 analyzer ranged from 0.4% to 3.2%, and that optimal or desired quality targets were met for the vast majority of the analytes examined. Nevertheless, the detection of significant inter-method deviations in some parameters underscores the importance of harmonizing analytical systems. In a study by Lin et al. [27], who evaluated AU series analyzers in various body fluids, it was reported that intra- and inter-day precision values were below 5% for most analytes, and strong correlations were obtained in inter-system comparisons. Collectively, these findings sug-

gest that AU-series analyzers exhibit consistently acceptable analytical performance across different laboratory settings, analyte panels, and experimental designs. The concordance between our findings and those reported in previous studies supports the robustness and reliability of the AU680 platform in terms of precision and trueness verification.

Importantly, while earlier studies primarily focused on conventional analytical performance characteristics, the present study extends these observations by integrating BV-based APS and TAE assessment into the verification process. This approach provides a more clinically meaningful interpretation of analytical performance by considering not only statistical acceptability but also the potential impact of analytical errors on patient care and clinical decision-making. Minor differences observed between studies may stem from variations in reagent lots, calibration procedures, QC materials, target value

Table 6. Expanded measurement uncertainty estimated from CLSI EP15-A3 verification data according to ISO/TS 20914.

Parameter	Level	uRw	uCal	U	U%	MAU
Albumin	L1	0.41	0.66	1.56	3.86	3.80
Albumin	L2	0.20	0.66	1.38	5.37	3.80
ALP	L1	3.36	2.35	8.20	7.13	9.00
ALP	L2	11.3	2.35	22.9	4.68	9.00
ALT	L1	0.99	0.78	2.53	9.40	18.9
ALT	L2	2.67	0.78	5.57	5.95	18.9
AST	L1	0.81	0.76	2.22	5.12	12.9
AST	L2	3.69	0.76	7.53	4.18	12.9
Amylase	L1	1.03	1.41	3.49	4.67	10.1
Amylase	L2	9.12	1.41	18.5	4.43	10.1
Glucose	L1	0.66	1.35	3.01	4.02	7.10
Glucose	L2	1.59	1.35	4.18	1.56	7.10
LDH	L1	3.32	2.73	8.59	5.55	6.60
LDH	L2	4.47	2.73	10.5	3.05	6.60
TC	L1	1.46	1.55	4.26	1.63	8.10
TC	L2	0.68	1.55	3.39	3.56	8.10
TP	L1	0.53	0.04	1.06	1.58	3.90
TP	L2	0.40	0.04	0.80	1.88	3.90
TG	L1	2.01	2.21	5.97	3.72	29.7
TG	L2	2.12	2.21	6.13	7.32	29.7
Urea	L1	0.30	1.74	3.53	11.1	19.7
Urea	L2	1.49	1.74	4.59	4.77	19.7
UA	L1	0.06	0.03	0.13	2.99	12.5
UA	L2	0.10	0.03	0.22	2.31	12.5

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, TP: total protein, TG: triglycerides, UA: uric acid, uRw: within-laboratory standard uncertainty derived from within-laboratory precision, uCal: standard uncertainty associated with the calibrator, U: expanded measurement uncertainty ($k = 2$), U%: relative expanded measurement uncertainty, MAU: maximum allowable uncertainty, L1: quality control level 1, L2: quality control level 2.

assignment methods, experimental design, and local laboratory conditions. Consequently, beyond manufacturer claims or literature-reported performance data, it is crucial for each laboratory to conduct method verification studies under its own operating conditions to ensure analytical reliability. Although the analytical performance of AU series analyzers has been evaluated in numerous previous studies, the originality of the present study lies not in the analytical platform itself, but in the comprehensive verification strategy employed in this study. To the best of our knowledge, this is one of the first studies from Türkiye to apply the CLSI EP15-A3 protocol to a broad panel of routine biochemical analytes on the Beckman Coulter AU680 platform while simultaneously incorporating updated EFLM BV-based APS and TAE assessment. By integrating precision verification, trueness evaluation, BV-derived quality goals, and TAE analysis within a single framework, this ap-

proach provides a more clinically meaningful assessment of analytical performance. Furthermore, it offers a practical model for laboratories seeking to demonstrate analytical competence and support compliance with ISO 15189:2022 accreditation requirements.

MU is a key component of analytical quality assessment and is becoming increasingly important in clinical laboratory practice, particularly within the framework of ISO 15189:2022 requirements. Assessment of MU may provide additional information regarding the reliability and clinical interpretability of laboratory results by quantitatively expressing the uncertainty associated with reported measurement results [4,28]. A recent study by Michaelis et al. demonstrated that expanded MU calculated using the Nordtest protocol from CLSI EP15-A3 verification data showed satisfactory agreement with estimates obtained from one year of internal QC data. The authors suggested that verification data

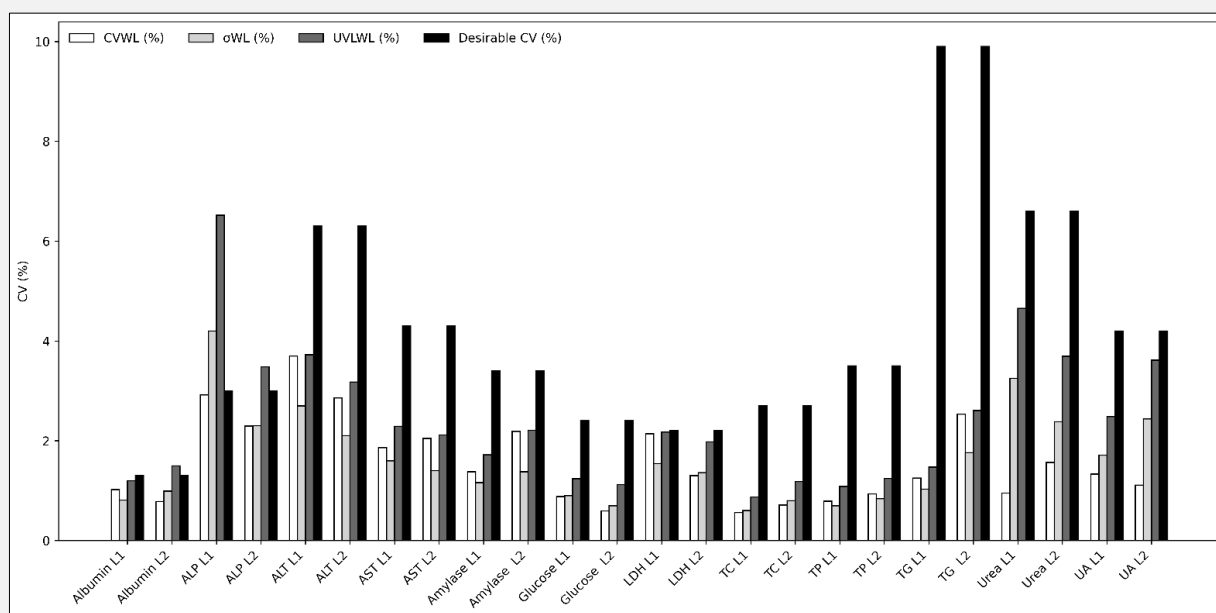


Figure 1. Comparison of within-laboratory imprecision (CVWL), manufacturer-claimed within-laboratory precision (σ WL), upper verification limits (UVLWL), and desirable analytical performance specifications for imprecision (Desirable CV) derived from biological variation for the evaluated analytes at two quality control levels.

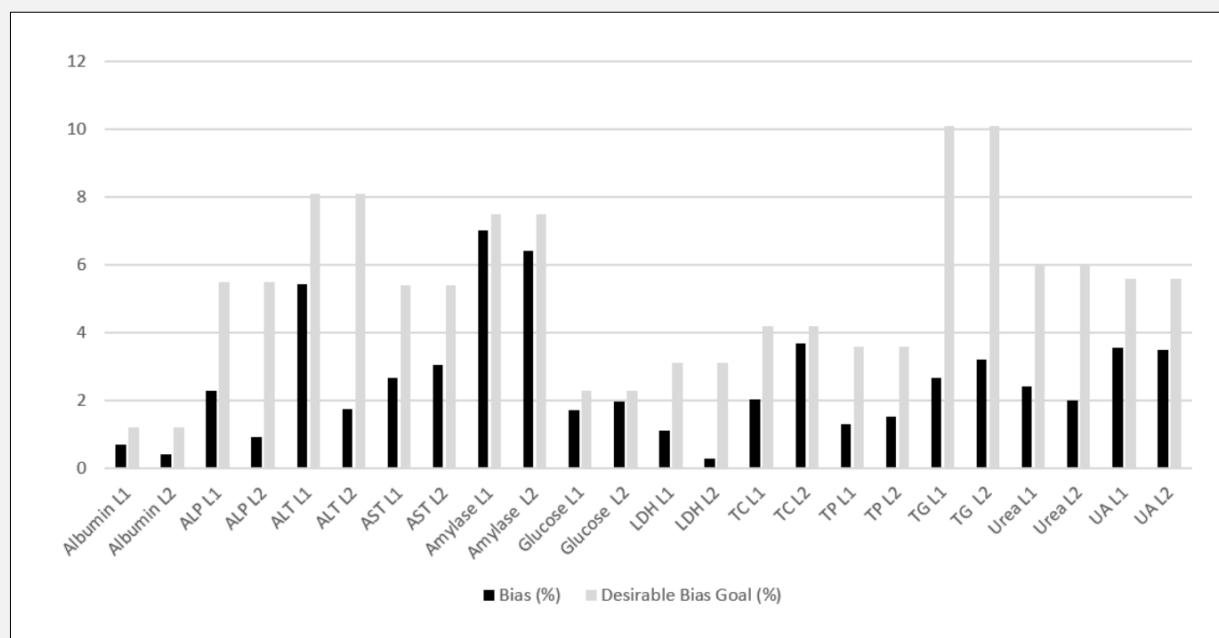


Figure 2. Comparison of observed bias (%) values with biological variation-based desirable bias specifications for each analyte and quality control level.

could provide a practical preliminary estimate of the MU until sufficient long-term QC data were available [29]. In the present study, expanded MU estimated from EP15-A3 verification data demonstrated that all analytes except albumin fulfilled the corresponding MAU specifications. These findings suggest that verification-derived precision data may provide a practical approach for preliminary MU estimation during method verification and may facilitate implementation of ISO/TS 20914 in routine laboratories.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the verification process was conducted in a single laboratory using a single Beckman Coulter AU680 analyzer; therefore, the results may not be directly generalizable to other laboratories, analytical platforms, reagent lots, calibration systems, or operating conditions. Second, this study used commercially available QC materials rather than patient samples. Although this approach is consistent with the CLSI EP15-A3 protocol, differences in matrix composition and commutability between QC materials and patient samples may have influenced the estimated bias values. Third, the evaluation was limited to two QC levels, representing clinically relevant low and high concentrations, and the full analytical measurement range was not evaluated. Fourth, this study focused primarily on precision and trueness verification according to the CLSI EP15-A3 guideline, together with TAE and MU assessment, and did not include the evaluation of other analytical performance characteristics, such as linearity, carryover, limit of detection (LoD), or interference studies. Furthermore, no external validation was performed; therefore, the reproducibility of the findings across different laboratory settings could not be assessed. Finally, when interpreting the results, the relatively limited number of observations inherent to the CLSI EP15-A3 5×5 design should be considered, because this statistical procedure may be associated with an increased risk of false rejection. Despite these limitations, this study provides practical evidence to support the analytical performance of the evaluated methods and demonstrates the applicability of APS based on BV using CLSI EP15-A3 in routine clinical laboratories.

CONCLUSION

In conclusion, all evaluated routine biochemical tests demonstrated acceptable analytical performance according to the verification criteria defined in the CLSI EP15-A3 guidelines. Beyond conventional precision and trueness assessments, the integration of APS based on the BV and TAE approach provides a more comprehensive and clinically meaningful evaluation of analytical quality. These findings indicate that the Beckman Coulter AU680 analyzer can provide analytically reli-

able results under routine laboratory conditions and can contribute to quality assurance and accreditation processes conducted in accordance with ISO 15189:2022. Furthermore, incorporating BV-based performance specifications and TAE evaluation into routine method verification studies represents a practical approach for laboratories seeking to demonstrate analytical competence using objective quality indicators. Future studies involving patient samples and multicenter designs will contribute to the validation of these findings in different laboratory settings and enhance the generalizability of the results.

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Declaration of Generative AI in Scientific Writing

Paperpal (a generative AI-assisted language editing tool) was used solely for language editing to improve the grammar, clarity, and readability of the manuscript. The authors reviewed and approved all revisions and take full responsibility for the content of the manuscript.

Declaration of Interest:

There are no conflicts of interest for any author. All authors have read and approved the manuscript.

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