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Effect of room-temperature storage duration of assayed serum control on total bilirubin quality control

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Abstract

Internal quality control is an important process to ensure the quality of laboratory test results. Assayed serum control monitors examination accuracy and precision; however, room-temperature storage may affect analyte stability. This study aimed to determine how room-temperature storage duration affects the reliability of total bilirubin quality control. This experimental study used repeated measurements of normal and pathological serum samples at 0, 4, and 8 hours of storage. We evaluated results using the coefficient of variation (CV), bias, total error (TE), Levey-Jennings charts, and Westgard rules. Data were analyzed using Repeated Measures ANOVA. Results showed that storage duration significantly affected total bilirubin at the normal level ($p=0.009$) and the pathological level ($p<0.001$). All CV values met the acceptance criteria (<5%), and TE values remained below TEa. Levey-Jennings evaluation showed that quality control results remained within control limits at the normal level but were rejected (out of control) at the pathological level from 4 hours onward. Despite this loss of statistical control, total error remained below the allowable total error (TEa) threshold at both levels throughout the 8 hours, indicating that Westgard control status and total error assess different, complementary aspects of analytical quality. Storage duration affected total bilirubin quality control reliability, particularly at the pathological level, and acceptable storage duration should be judged by control level and QC criteria rather than a single uniform time limit.

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1. Introduction

Clinical laboratory testing underpins most medical decision-making, with an estimated 70–75% of diagnoses relying on laboratory data (Chaudhry et al., 2023). Because laboratory quality depends on how well testing processes meet established standards (International Organization for Standardization, 2022), quality assurance across the pre-analytical, analytical, and post-analytical phases is essential to safeguarding patient care. Although analytical-phase errors account for a comparatively small share (10–15%) of total laboratory errors relative to pre- and post-analytical errors, monitoring at this stage remains indispensable for confirming that instruments, reagents, and methods perform according to specification (Akhmad et al., 2025).

Internal quality control, implemented through statistical monitoring of control materials, is the primary mechanism for verifying analytical reliability and detecting systematic or random error before releasing patient results (Naphade et al., 2023; World Health Organization, 2011). Reliability refers to the consistency and stability of a measurement method in producing dependable, reproducible results

(Subhaktiyasa, 2024). Assayed serum control materials are widely used for this purpose because they carry manufacturer-assigned target values and span clinically relevant concentration ranges, allowing comprehensive evaluation of method performance (World Health Organization, 2011). However, quality control validity depends on control material stability; environmental factors such as ambient temperature and storage duration can alter control matrix composition and compromise result validity (Hartadi & Sudarma, 2025; Maulidiyanti et al., 2021; Pramesti et al., 2024).

Total bilirubin is among the analytes most susceptible to environmental degradation, as it is both photosensitive and thermolabile (Vachali et al., 2025). Reported stability findings for bilirubin under room-temperature storage are inconsistent: some studies report significant change within 4 hours (Kughapriya & Elanchezhian, 2019), others report marked decline without light protection (Akhmad et al., 2025), while manufacturer specifications and other reports describe stability extending to 8 hours or longer (Roche, 2024; Vachali et al., 2025). Most prior studies on bilirubin stability have examined patient serum specimens rather than commercial control materials, leaving limited evidence on how reconstituted assayed serum controls behave under repeated room-temperature handling and how this affects quality control reliability over time. This gap is particularly relevant to routine laboratory practice, where a reconstituted control material is often used repeatedly over several hours rather than discarded after a single measurement. The present study addresses this gap by evaluating the effect of room-temperature storage duration on the reliability of total bilirubin quality control using a reconstituted commercial assayed serum control subjected to repeated handling, in contrast to the single-measurement conditions typically examined in patient-specimen stability studies. This approach reflects a practical laboratory scenario and provides evidence on whether prolonged room-temperature storage of a repeatedly handled, reconstituted control material compromises the reliability of total bilirubin quality control.

This gap has direct practical relevance at the Clinical Pathology Laboratory of GMIM Bethesda General Hospital, Tomohon, where quality control for high-frequency analytes follows a fixed daily schedule. In contrast, control testing for lower-frequency parameters, such as total bilirubin, is often performed conditionally, only when a clinician requests it. This practice can result in the same reconstituted control aliquot being reused and re-tested at different time points throughout the day. A usage pattern that differs from the closed, single-use storage conditions typically evaluated in manufacturer stability claims and prior stability studies. Control material left at room temperature for prolonged periods is prone to quality deterioration (Ramdan & Aryani, 2023), which may cause quality control values to fall outside acceptable control limits and require repeat testing with fresh control material (Gruber et al., 2024). Therefore, the duration of control material exposure to room temperature must be carefully monitored to ensure accurate quality control results.

Given variability in reported bilirubin stability findings and the discrepancy between controlled stability testing and actual laboratory practice, this study evaluated how room-temperature storage duration affects the reliability of total bilirubin quality control. By assessing a realistic pattern of repeated aliquot use rather than single-use closed storage, this study offers evidence directly applicable to laboratory decision-making on control material handling. The objective of this study was to determine the effect of storage duration (0, 4, and 8 hours) of assayed serum control at room temperature on the reliability of total bilirubin quality control at the Clinical Pathology Laboratory of GMIM Bethesda General Hospital, Tomohon.

2. Method

2.1 Research Design and Participants

This study used a laboratory-based quantitative experimental design with a repeated comparative measures approach. The same assayed serum control samples were examined repeatedly under three room-temperature storage conditions: immediate testing (0 hours, serving as the control condition), 4 hours of storage, and 8 hours of storage. This design allowed direct comparison of total bilirubin quality control results across storage durations and enabled inferential analysis of storage duration's effect on quality control reliability. The study population comprised all assayed serum control material used for daily internal quality control monitoring of total bilirubin testing at the study site, consisting of two concentration levels (normal and pathological), with 20 vials available for each level. One vial from each control level was selected, reconstituted with 5 mL of distilled water, and divided into 20 aliquots of 250 µL each. The aliquots were stored frozen until use and then analyzed at 0, 4, and 8 hours of room-temperature storage, with each aliquot measured repeatedly at each time point. Thus, we obtained 20 replicate experimental units

for each control level. We based the sample size on the recommendation to collect a minimum of 20 measurements to establish reliable statistical targets for quality control evaluation (World Health Organization, 2011). Inclusion criteria required control material from the same lot number and within the manufacturer's expiration date; material from a different lot number or past its expiration date was excluded. This study was conducted over two months (May–June 2026) at the Clinical Pathology Laboratory of GMIM Bethesda General Hospital, Tomohon.

2.2 Instruments and Data Collection

Total bilirubin concentration was measured using a Cobas C 311 chemistry analyzer, following the diazo method (Roche, 2025). The assayed serum control material used was PreciControl ClinChem Multi (PCCM), comprising a normal level (PCCM1) and a pathological level (PCCM2), reconstituted according to the manufacturer's instructions (Roche, 2024). Data collection proceeded in two stages: a preliminary period and a control period. In the preliminary period, each control level was measured 20 times on the same day immediately after reconstitution, to establish the mean and standard deviation used for control limit calculation (mean ± 3 SD). In the control period, on each of 20 separate testing days, one fresh aliquot per control level was thawed and measured at three time points—0 hours (baseline), 4 hours, and 8 hours—after storage at room temperature (20–25 °C) with protection from light using aluminum foil. This procedure was repeated daily for 20 days using a new aliquot each day, resulting in 20 independent measurement cycles at 0, 4, and 8 hours for each control level and 120 measurements across the two control levels. The same operator performed all measurements following the hospital's standard operating procedure for the Cobas C 311 analyzer. The operator monitored ambient temperature with a room thermometer and logged all instrument activity in a daily equipment log.

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2.3 Data Analysis

Data analysis used both descriptive and inferential methods. Descriptive statistics characterized the data for each storage duration and control level, including central tendency, variability, and data visualization (Subhaktiyasa et al., 2025). We calculated bias as the percentage deviation of the measured mean from the control material's assigned target value, and total error using the following formula**:** $TE = bias + z \times CV\%$ (Milinkovic et al., 2018). Calculated TE% values were compared against a total allowable error (TEa) of 26.94% for total bilirubin (Ricos et al., 2014). We used mean and SD values from the preliminary period as reference values to construct Levey-Jennings charts for the control period, then evaluated them against Westgard multirule criteria to identify random or systematic error. For inferential analysis, we first assessed data normality using the Shapiro-Wilk test. Because the repeated-measures design compared the same control material across three storage time points, we used repeated-measures analysis of variance (ANOVA) for normally distributed data. A significance threshold of $p < 0.05$ was used to determine whether storage duration had a significant effect on total bilirubin results. Where a significant overall effect was found, pairwise post hoc comparisons were performed to identify which storage-duration pairs differed significantly. All statistical analyses were performed using SPSS.

2.4 Ethical Considerations

This study received ethical approval from the Health Research Ethics Committee of STIKES Wira Medika Bali, with approval number 814/E1.STIKESWIKA/EC/VI/2026. This study did not involve human or animal subjects; the study object was a commercial assayed serum control material, and therefore posed no biological or ethical risk to research participants. All procedures for handling, storage, and testing of the control material followed standard laboratory operating procedures and applicable research ethics guidelines, and data were reported objectively.

3. Results and Discussion

3.1 Results

The study material consisted of assayed serum controls at normal and pathological levels, each measured at three storage durations (0, 4, and 8 hours), yielding 120 total measurements. Table 1 presents the sample distribution.

Table 1. Sample distribution by control level and storage duration

Control Level	Aliquots (n)	Storage duration	Measurements (n)
Normal (PCCM1)	20	T_0 (0 h)	20
		T_1 (4 h)	20
		T_2 (8 h)	20
Pathological (PCCM2)	20	T_0 (0 h)	20
		T_1 (4 h)	20
		T_2 (8 h)	20

Table 2. Descriptive quality control statistics by control level and storage duration

Control level	Storage duration	*Mean* (mg/dL)	SD	CV (%)	Bias (%)	TE (%)
Normal (PCCM1)	T_0 (0 h)	0.87	0.035	3.993	0.64	8.63
	T_1 (4 h)	0.85	0.035	4.114	-0.87	9.10
	T_2 (8 h)	0.85	0.030	3.554	-1.05	8.15
Pathological (PCCM2)	T_0 (0 h)	3.29	0.090	2.745	-0.80	6.29
	T_1 (4 h)	3.28	0.090	2.745	-1.33	6.82
	T_2 (8 h)	3.22	0.071	2.216	-2.98	7.41

Mean total bilirubin concentration declined progressively with storage duration at both control levels. At the normal level, the mean concentration decreased from 0.87 mg/dL (T_0) to 0.85 mg/dL (T_1) and remained at 0.85 mg/dL (T_2). At the pathological level, the mean concentration decreased from 3.29 mg/dL (T_0) to 3.28 mg/dL (T_1) and further to 3.22 mg/dL (T_2), representing a comparatively larger absolute decline. CV values remained below 5% for both control levels across all storage durations, meeting the acceptance criterion. Bias shifted from slightly positive to increasingly negative with longer storage, more markedly at the pathological level. TE values ranged from 8–9% (normal level) and 6–7.4% (pathological level), remaining well below the total allowable error threshold of 26.94%.

Table 3. Preliminary-period quality control reference values

Control Level	*Mean*	SD	-1SD	-2SD	-3SD	+1SD	+2SD	+3SD
Normal (PCCM1)	0.86	0.034	0.83	0.79	0.76	0.89	0.93	0.96
Pathological (PCCM2)	3.32	0.115	3.21	3.10	2.98	3.44	3.56	3.67

Table 3 shows the quality control results obtained during the preliminary period. The normal-level control had a mean total bilirubin concentration of 0.86 mg/dL and an SD of 0.034 mg/dL, with observed values ranging from 0.83 to 0.96 mg/dL. The pathological-level control had a mean concentration of 3.32 mg/dL and an SD of 0.115 mg/dL, with observed values ranging from 3.21 to 3.67 mg/dL. We used the mean and SD from the preliminary period as baseline parameters for subsequent quality control monitoring and plotted them on Levey–Jennings charts (Figure 1 and Figure 2).

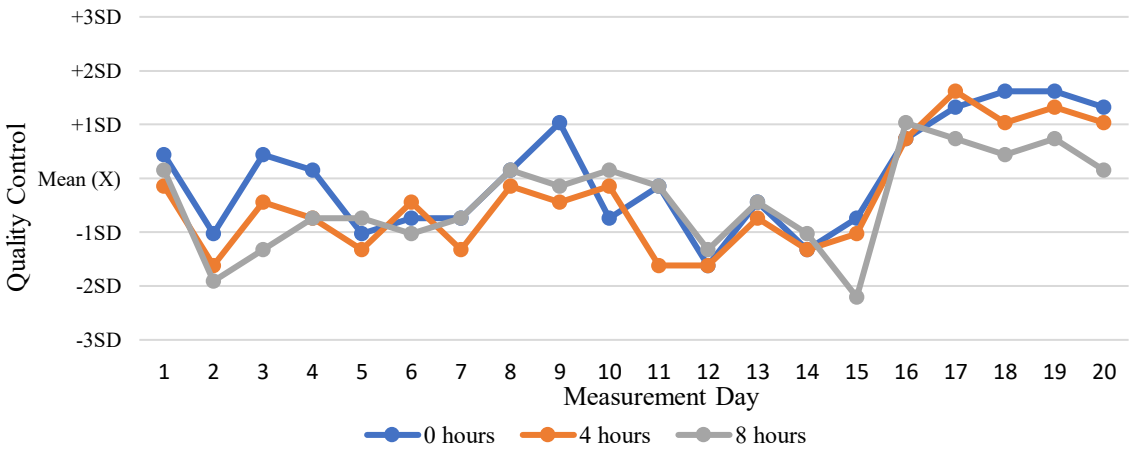


Figure 1. Levey–Jennings Chart: Normal-Level Control

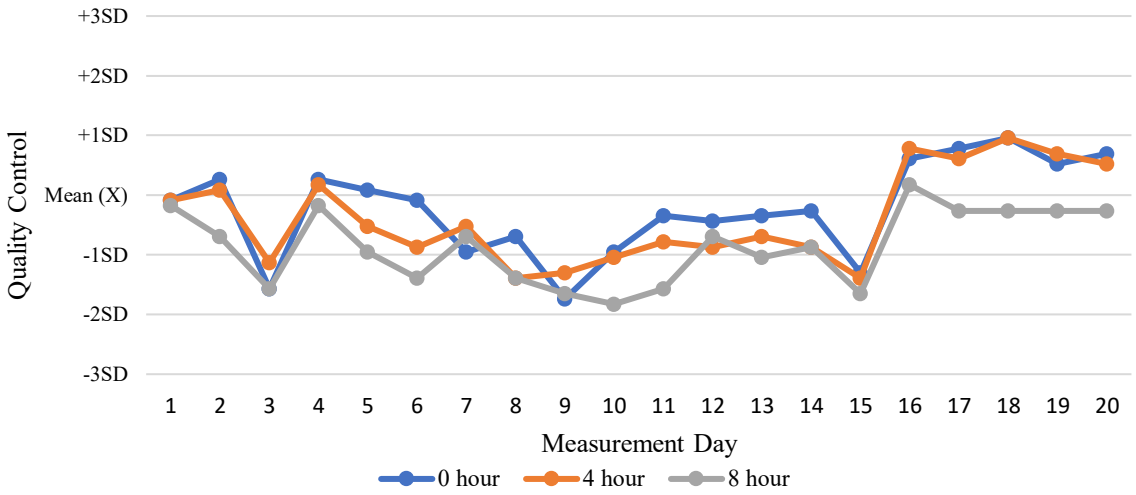


Figure 2. Levey–Jennings Chart: Pathological-Level Control

At the normal level, results at 0 and 4 hours showed no Westgard rule violations and were classified as in control. At 8 hours, one data point exceeded the −2SD limit (rule 1-2s), interpreted as a warning rather than rejection, so results remained in control. At the pathological level, only the 0-hour measurements were in control; at 4 hours, a 10x rule violation occurred (11 consecutive points below the mean); at 8 hours, both the 10x rule (15 consecutive points below the mean) and the 4-1s rule were violated, indicating out-of-control status. We conducted inferential statistical analyses to assess the effect of storage duration on total bilirubin levels and determine when significant changes emerged, as shown in Tables 4 and 5. Shapiro-Wilk testing confirmed normal distribution for all groups ($p > 0.05$ in all cases), justifying the use of parametric tests.

Table 4. Repeated measures ANOVA results

Control level	F	Sig.
Normal	5.336	0.009
Pathological	26.606	<0.001

Table 4 shows that storage duration had a statistically significant effect on total bilirubin levels at both the normal control level ($p = 0.009$) and the pathological control level ($p < 0.001$).

Table 5. Pairwise comparisons (post hoc)

Comparison	Normal level Sig.	Pathological level Sig.
0 h vs 4 h	0.014	0.076
0 h vs 8 h	0.046	<0.001
4 h vs 8 h	1.000	<0.001

According to Table 5, at the normal level, significant differences emerged by 4 hours, with no further significant change between 4 and 8 hours. At the pathological level, no significant difference was found between 0 and 4 hours, but significant differences emerged between 0 and 8 hours and between 4 and 8 hours.

3.2 Discussion

The progressive decline in total bilirubin concentration at both control levels, more pronounced at the pathological level, may reflect oxidative degradation of bilirubin to biliverdin, in which the methene bridge of the bilirubin tetrapyrrole ring is cleaved by reaction with molecular oxygen (Ruiz et al., 2021). Because the diazo method used in this study quantifies bilirubin through the intensity of the azo-bilirubin complex formed during the reaction, any reduction in intact bilirubin available for this reaction due to prior oxidation manifests as a lower measured concentration (Roche, 2024; Damayanthi et al., 2018). This degradation is cumulative: the longer the control material remains at room temperature, and the more

frequently the same aliquot is opened for repeated measurement, the greater its cumulative exposure to atmospheric oxygen.

This pattern aligns with Hussien et al. (2013), who reported declining bilirubin concentrations in plasma stored at room temperature, and with Kughapriya and Elanchezhian (2019), who identified meaningful bilirubin change beginning at 4 hours of storage without light exposure**,** closely matching the timing observed here. By contrast, reported that bilirubin remained stable at 33 °C for up to 2 hours under light protection before declining sharply by 24 hours, likely attributable to the lower storage temperature range (20–25 °C) used here. Akhmad et al. (2025) reported bilirubin losses of up to 59% without light protection; the considerably smaller decline observed in the present study, approximately 1–3% at both control levels over 8 hours, suggests that the consistent light protection applied in this study likely limited degradation predominantly to thermal oxidation. Conversely, Sofronescu et al. (2012) and Kift et al. (2015) reported no significant change up to 8 hours, and Vachali et al. (2025) reported stability up to 72 hours, findings that diverge more substantially from those of the present study.

These discrepancies likely reflect differences in sample matrix, handling protocol, and instrument sensitivity across studies. Unlike prior studies that typically used human serum specimens in closed, undisturbed containers, this study used a lyophilized commercial control material reconstituted and repeatedly opened for measurement at each time point**,** conditions that more closely mirror everyday laboratory practice. The lyophilization process, which alters the control material matrix, may lead to commutability issues and differences in measurement results compared with human serum (Vesper et al., 2007). Repeated aliquot opening increases oxygen exposure at each sampling event, and the high analytical precision of the Cobas C 311 may have detected subtle concentration changes that lower-precision instruments in earlier studies could not resolve. This distinction represents a meaningful contribution of the present study: it evaluates control material stability under a laboratory-use scenario designed to approximate repeated handling of reconstituted control material, rather than the single-use closed-storage conditions typically assessed in manufacturer validation and prior stability research. Laboratories should therefore consider independently verifying manufacturer stability claims under their own actual usage patterns, particularly for analytes such as bilirubin that are prone to oxidative degradation.

CV values below 5% across all groups indicate that measurement precision remained acceptable throughout the storage period, meeting both WHO criteria and the 7% threshold specified in Indonesian Ministry of Health Regulation No. 43 of 2013. The progressive negative shift in bias with increasing storage duration**,** more pronounced at the pathological level**,** indicates an emerging systematic error; however, because the total allowable error for bilirubin is comparatively wide (reflecting high biological variability of the analyte), the resulting TE values remained substantially below the 26.94% threshold (Ricos et al., 2014) despite this systematic drift. This suggests that although a measurable directional error was present, overall analytical performance still met quality requirements.

This finding is consistent with Rahmani et al. (2024), who reported that consistent instrument performance and appropriate methodology sustain long-term bilirubin quality control, and with Iacovetti et al. (2025), who similarly reported increasing bias with longer control material storage. By contrast, Sari et al. (2023) reported TE values exceeding acceptable limits, attributable to deliberate light exposure in their protocol**,** a condition avoided in this study through consistent light protection. These comparisons suggest that the acceptable precision and total error observed here reflect the combined effect of calibrated instrumentation, consistent control material lot use, monitored ambient temperature (20–25 °C), and light protection.

A key interpretive contribution of this study is that quality-control reliability cannot be judged from bias alone: a negative bias shift might initially suggest declining quality, yet when considered with CV and TE, overall analytical performance remains acceptable. Combining precision, accuracy, and total error into a single evaluative framework thus provides a more complete and clinically meaningful assessment. Although total error remained within the predefined allowable limit (TEa) for all storage durations, Westgard monitoring indicated a loss of statistical control at the pathological level beginning at 4 hours. Thus, 8-hour storage of assayed serum control should not be interpreted as universally acceptable across control levels; instead, continued use beyond 4 hours should be evaluated by control level and QC criteria, with total error monitored routinely as a primary indicator of analytical adequacy.

The contrast between the normal and pathological control levels remaining in control throughout at the normal level (aside from a single warning-level violation at 8 hours) versus repeated out-of-control violations at the pathological level from 4 hours onward indicates that pathological-level control material

is more vulnerable to storage-related degradation. This is consistent with the Gaussian principle underlying Levey-Jennings monitoring, whereby a stable analytical system produces measurements normally distributed around the target mean (World Health Organization, 2011), and reflects the established sensitivity of Levey-Jennings charts in visually detecting systematic shifts and trends (Karkalousos & Evangelopoulos, 2011). One factor contributing to such systematic errors is suboptimal storage conditions (Mutie et al., 2023).

This finding parallels Ramdan and Aryani (2023), who similarly observed declining control material quality with increasing storage duration. Although the manufacturer's kit insert specifies bilirubin stability up to 8 hours (Roche, 2025), the present results suggest that at higher analyte concentrations, systematic deviation from target values may emerge earlier than the labeled stability window suggests, consistent with Ramdan and Aryani's (2023) finding that a different commercial control material's glucose stability lasted only 6 hours in practice, considerably shorter than manufacturer claims. The greater sensitivity to degradation at the pathological level likely reflects the larger absolute pool of bilirubin molecules available for oxidative breakdown at higher starting concentrations (Ahmad et al., 2013), compounded by daily fluctuations in ambient temperature and the frequency of aliquot opening. These findings suggest that laboratories should apply heightened caution when reusing pathological-level control material beyond the earliest signs of instability, rather than relying uniformly on manufacturer-stated stability windows across concentration levels.

The repeated measures confirm that storage duration significantly affects total bilirubin concentration at both control levels. However, the pattern of significance differed: at the normal level, a significant difference emerged as early as 4 hours with no further change by 8 hours, whereas at the pathological level, significance was only reached by 8 hours. This divergence likely reflects the underlying degradation dynamics. At the normal level, the smaller absolute change was detected early because low measurement variability gives the statistical test high sensitivity to small shifts, with the most labile bilirubin fraction apparently degrading early and the remainder stabilizing thereafter. At the pathological level, larger absolute variability at 4 hours delayed statistical significance, but the cumulative decline by 8 hours became large enough to reach significance, suggesting a non-linear, progressive oxidation process that accelerates between 4 and 8 hours.

The statistical test results showing a significant effect of storage duration on bilirubin levels are consistent with Lestari et al. (2022), who reported that storage duration and temperature variation significantly affect analyte stability in control materials generally, and more specifically with Sari et al. (2023), who attributed declining bilirubin concentration to progressive molecular degradation during storage. The earlier onset of significant change at 4 hours for the normal level is also consistent with Kughapriya and Elanchezhian (2019). The apparent discrepancy between the pairwise comparison result at 4 hours (not significant) and the Westgard 10x violation already observed at the same time point for the pathological level is explained by the differing analytical logic: statistical testing evaluates average differences between time points, whereas Westgard rules assess the pattern of individual data points relative to the target mean, making them more sensitive to consistent directional drift even before it becomes significant in an averaged comparison. Because both methods converged in flagging the pathological level as increasingly unreliable, this agreement reinforces the conclusion that pathological-level control material is more vulnerable to storage-related instability than normal-level material.

As Pramesti et al. (2024) noted, statistical tests can be highly sensitive to small variations that may not carry clinical importance—an interpretive principle directly relevant to the differing patterns observed between the two control levels in this study. Taken together, these findings highlight the importance of considering statistical significance alongside clinical acceptability when evaluating QC stability. Therefore, assess QC stability using multiple complementary indicators rather than relying on statistical significance alone.

4. Conclusion

This study shows that room-temperature storage duration significantly affects assayed serum control total bilirubin concentration and quality control reliability. Total bilirubin levels declined progressively at both normal and pathological concentrations, with reliability more compromised at the pathological level. Coefficient of variation values remained below 5% and total error remained well within the allowable total error threshold at both levels across all storage durations; however, Westgard monitoring identified a loss of statistical control at the pathological level starting at 4 hours, compared to only a

warning-level deviation at the normal level after 8 hours. Acceptable storage duration should therefore be determined according to control level and interpreted jointly using both Westgard control status and total error, rather than a single uniform time limit. This study is limited by its focus on a single analyte, controlled laboratory conditions that may not reflect field variability in temperature and light exposure, observation restricted to 8 hours at 4-hour intervals, and its focus on control material rather than patient specimens; future research should examine longer storage intervals, varying temperature conditions, additional analytes, and alternative control materials and instruments to strengthen the generalizability of these findings.

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Conflict of Interest

The authors declare no conflict of interest.

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