Research Article

# Integration of Patient-Based Real-Time Quality Control with Conventional Internal Quality Control: Improved Error Detection and Cost-Benefit Analysis in a Clinical Laboratory

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**Keywords**

Patient-Based Real-Time Quality Control (PBRTQC), Internal Quality Control (IQC), Moving Average (MA), Error Detection, Sigma Metrics, Bias Detection, Truncation Limits, Average number of patients data required for error detection (ANPed), Clinical Biochemistry, Laboratory Quality Management, Cost-Benefit Analysis, Risk Management, Clinical Laboratory Improvement Amendments (CLIA)

**Abstract**

**Background:** Internal Quality control (IQC) is essential as it ensures analytical accuracy. However, IQC may have certain limitations, for example, it may miss intermittent or matrix-related errors. Patient-Based Real-Time Quality Control (PBRTQC) can overcome this limitation by continuously monitoring the patient data and also aids in early detection of shifts. Hence, integration of PBRTQC with IQC enhances the error detection and the cost efficiency in clinical laboratories.

**Aim:** To study the effect of integrating Patient-Based Real-time Quality Control with Conventional Quality Control for improved detection of errors, cost benefit and risk-based cost benefits.

**Methods:** Four parameters, creatinine, urea, Aspartate Transaminase (AST), and Thyroid Stimulating Hormone (TSH), were selected based on low sigma value and high monthly sample load. Historical patient data was collected from the laboratory information system. Data was divided into training and validation sets. Truncation limits were calculated using the interquartile range method. Simple Moving Average (SMA) was calculated for various block sizes. Control limits were set using the maximum/minimum of the moving average or percentiles. A bias simulation study was performed by introducing bias from -50% to +50% to plot bias detection curves and determine the optimum block size and ANPed. Optimized PBRTQC parameters were validated. The optimized algorithm was applied to daily patient data and integrated with IQC. Moving average alarm rate and percentage increase in error detection were calculated. Potential cost-benefit and risk-based benefits were determined.

**Results:** optimum block size and (ANPed) at TEa was 50 for creatinine (161), 25 for urea (207), 50 for AST (22), and 25 for TSH (68). The MA alarm percentage remained below 1% for all analytes. Integration improved error detection by 28.57% for creatinine, 25% for urea, and 20% for TSH. Net cost benefit demonstrated total savings of 426.92 through QC reductions (264.56) and avoided reanalysis costs (162.36).

**Conclusion**: PBRTQC integration with IQC significantly improves error detection for low sigma performance assays, is cost-effective and provides a strong risk-based cost-benefit advantage.

## Introduction

Quality control (QC) represents a fundamental component of the laboratory quality management system and is essential for maintaining analytical accuracy and reliability. Within this framework, Internal Quality Control (IQC) serves as a core element that provides daily, routine monitoring of analytical performance, ensuring that patient results are valid and reliable before release [1]. Despite its importance, IQC alone does not always guarantee consistent analytical reliability. Several well-recognised limitations exist. First, because IQC is performed at intervals, it cannot detect analytical errors that occur between two QC events. Second, matrix effects hidden interferences within control materials can cause non-commutability, meaning that control samples may not accurately reflect patient specimens. Third, some assays lack stable, commutable control materials, limiting their monitoring effectiveness. Finally, methods with sigma metrics below 4 are inherently more prone to analytical error, and conventional IQC strategies may not provide sufficient assurance of quality in such cases [2,3].

To address these gaps, many laboratories are now incorporating Patient-Based Real-Time Quality Control (PBRTQC) systems. PBRTQC is a modern adaptation of the classical "Average of Normals" (AON) concept introduced by Hoffman and Waid. By applying advanced statistical algorithms to aggregated patient data, PBRTQC enables continuous, real-time monitoring of analytical performance. This approach not only complements traditional IQC but also provides coverage across the pre-analytical, analytical, and post-analytical phases, making it a more comprehensive quality safeguard [4–6].

PBRTQC is particularly useful for analytes that exhibit low biological variation (CVg) compared with analytical variation (CVa), which is typical of tests with lower sigma performance [7,8]. However, successful implementation requires carefulunderstanding of the laboratory's patient population, including age, sex distribution, and the types of clinical services provided. When tuned to these characteristics, PBRTQC can detect even subtle shifts in analytical performance that may otherwise go unnoticed.

The statistical foundation of PBRTQC includes several critical elements: algorithms for calculating continuous or moving patient means, determination of block size, setting truncation limits to exclude physiological outliers, and defining control limits for identifying and validating potential analytical issues. When combined, these features establish PBRTQC as a robust, data-driven tool for continuous quality monitoring in modern clinical laboratories.

This study aimed to implement a PBRTQC protocol using the moving average algorithm for four key analytes and integrate it with existing IQC procedures, and evaluate its performance in improving error detection and cost effectiveness.

## Materials and methods

### Study Design and Setting

This study was conducted in the Department of Biochemistry, JIPMER, Puducherry. Institutional ethical approval was obtained (JIP/IEC-OS/2023/053) with a waiver of consent.

### Analyte Selection and Data Collection

Four analytes creatinine, urea, AST, and TSH - were selected based on a sigma value <4, AST (sigma 4.39) was included as a comparator to help determine whether the benefits of PBRTQC integration are specific to low-sigma assays or represent a more general effect that might also benefit higher performing assays and high monthly sample volume to ensure robust data analysis. Five months of historical patient data were collected from the Laboratory Information System (LIS). Data was divided into a training set (≥60%) for parameter optimisation and a validation set (remainder) for testing, as detailed in Table 1.

**Table 1:** Characteristics and data distribution of analytes selected for PBRTQC implementation.

| Analyte | Sigma value | Sample load per month | Total Data Points | Training Set (%) | Validation Set (%) |
|---|---|---|---|---|---|
| Creatinine (mg/dL) | 3.47 | 8966 | 34,768 | 60% | 40% |
| Urea (mg/dL) | 3.10 | 8860 | 49,056 | 60% | 40% |
| AST (IU/L) | 4.39 | 6288 | 35,153 | 60% | 40% |
| TSH (µIU/mL) | 3.34 | 3825 | 13,207 | 69% | 31% |

*AST: aspartate transaminase, TSH: thyroid-stimulating hormone*

### PBRTQC Parameter Optimization

The process to establish the PBRTQC protocol involved three systematic steps:

Truncation Limit Setting: The interquartile range (IQR) method was used to remove extreme outliers, thereby reducing skewness and stabilising the moving average calculation, The limits were calculated as: Lower Truncation Limit (LTL) = Q1 - 1.5*IQR Upper Truncation Limit (UTL) = Q3 + 1.5*IQR Moving Average and Control Limit Calculation: A Simple Moving Average (SMA) algorithm was applied: SMA = ($x_1$ + $x_2$ + … + $x_n$) / n Control limits (CLs) were set using one of two methods, chosen based on which gave a lower false alarm rate:

Method 1: The maximum and minimum of the moving average for UCL and LCL.

Method 2: The 99.95 percentile and 0.05 percentile for UCL and LCL.

**Bias Simulation for Block Size Selection Introduction of bias**
Different sets of bias were introduced, ranging from –50% to +50% in 10% increments, to fully characterise the bias detectioncurve across small, moderate, and large biases. In addition to this full range, bias equivalent to the CLIA-total allowable error (TEa) was specifically introduced, as the optimal block size and ANPed were determined at this clinically relevant threshold. Baseline phase: The first block of data was kept for unbiased reference. Moving average calculation: MA was calculated for the biased data set with different block sizes (10, 25, 50, 75, 100). Control limit breach: The first data point breaching UCL or LCL was identified. ANPed calculation: The average number of patient data points from bias introduction to control limit breach was recorded as ANPed. Optimal block selection: A bias detection curve (ANPed vs. Bias) was plotted. The optimal block size was selected from this curve.

**Validation of Optimised Parameters**
The optimised PBRTQC settings derived from the training dataset were applied to the independent validation dataset. A systematic bias equivalent to the total allowable error (TEa) from CLIA guidelines was intentionally introduced into the validation dataset to simulate analytical bias. The moving average (MA) was recalculated using the optimised block size. The point at which the MA value breached the pre-established control limits was recorded, thereby validating the error detection capability of the model.

**Error Rate and Cost-Benefit Analysis**
The MA alarm rate was calculated as (Number of Alarms / Total MA Data Points) × 100. The percentage improvement in error detection was calculated as (Errors detected by PBRTQC / Total Errors) × 100. A cost-benefit analysis was performed using a laboratory billing system to determine the costs of IQC runs and reagent consumption per test.

**Risk-Based Cost-Benefit Analysis**
The integrated implementation of PBRTQC and IQC performed a risk-based cost-benefit analysis. Benefits were mapped across four risk categories: patient safety, regulatory compliance, operational failure, and financial loss. Data sources were cross-referenced to validate each benefit.

## Results

**Optimised PBRTQC Parameters**
The optimised PBRTQC parameters for each analyte, derived from bias simulation studies, are shown in Table 2. For creatinine, urea and TSH, the lower truncation limits were not applicable due to negative values. Block size and ANPed were derived from the bias detection curve for each analyte. When bias equal to the total allowable error (TEa) was introduced, the average number of patient data points required for error detection (ANPed) was 161 for creatinine, 207 for urea, 22 for AST, and 68 for TSH.

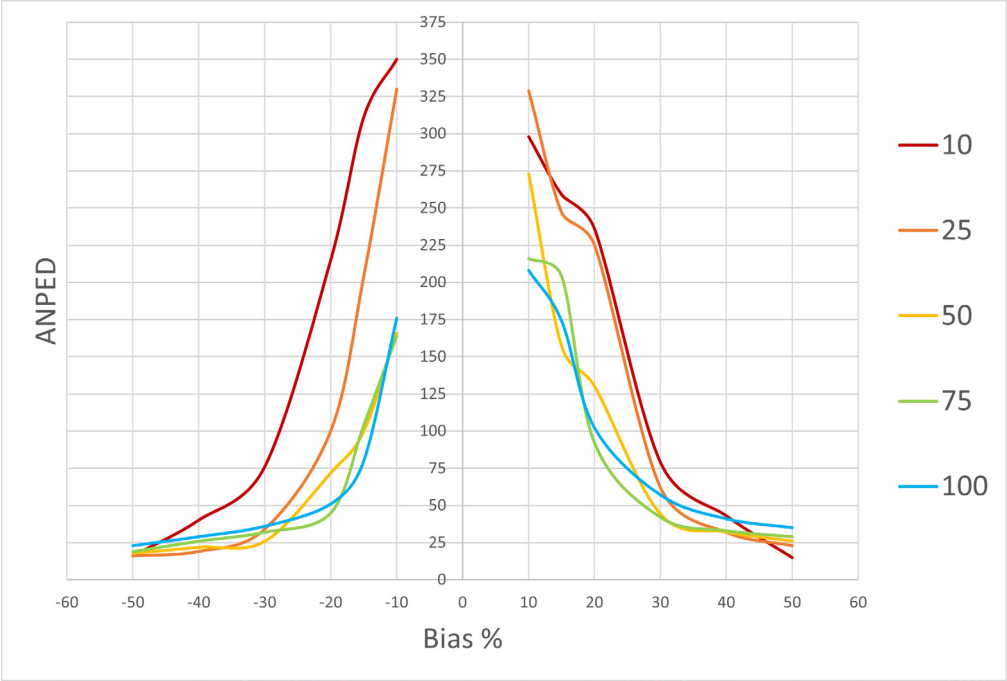
**Table 2:** Optimised PBRTQC parameters for creatinine, urea, AST, and TSH.

| Analyte | Truncation limit | Control limit | TEa (%) | Block size | ANPed at TEa |
|---|---|---|---|---|---|
| Creatinine | UTL= 1.6 LTL= NA | UCL= 0.96 LCL= 0.59 | ±15% | 50 | 161 |
| Urea | UTL= 51 LTL= NA | UCL= 28.7 LCL= 15.9 | ±9% | 25 | 207 |
| AST | UTL= 36 LTL= 12 | UCL= 26.2 LCL= 18.8 | ±20% | 50 | 22 |
| TSH | UTL= 7.8 LTL= NA | UCL= 3.7 LCL= 1.7 | ±20% | 25 | 68 |

*UTL: upper truncation limit, LTL: lower truncation limit. UCL: upper control limit, LCL: lower control limit. TEa: total error allowable, obtained from CLIA guidelines. ANPed: average number of patient data required for error detection. Block size and ANPed were obtained from bias detection curves.*

**Bias Detection and Validation for Creatinine**
Bias detection curves were obtained by performing the bias simulation study on creatinine data. Larger biases required fewer patient data points for detection. Smaller block sizes led to falsealarms due to lower ANPeds, while larger block sizes delayed bias detection. Block sizes of 25 and 50 showed optimal performance Figure 1.

**Figure 1:** Bias detection curve for Creatinine.

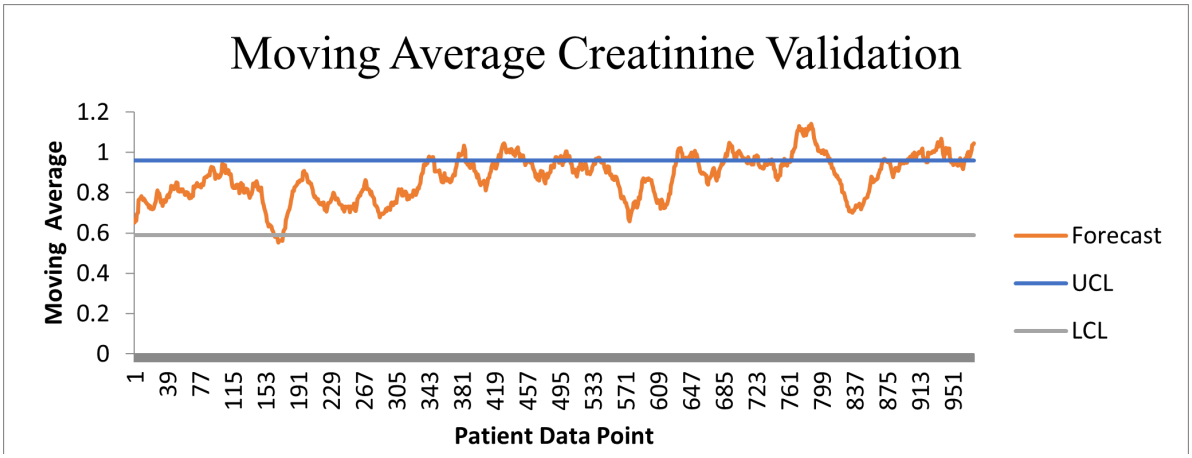



*The curve shows Average Number of Patient data points required for error detection (ANPed) across varying levels of introduced systematic bias for different block sizes (10, 25, 50, 75, 100). The optimal block size of 50 was selected for its balanced performance.*

**Validation of the moving average algorithm for Creatinine**

Average technique successfully detected the bias, as indicated by The optimised settings were validated on the validation dataset. A the breach of control limits Figure 2. bias equivalent to CLIA TEa was introduced. The moving

**Figure 2:** Optimised PBRTQC parameters validation for creatinine.




**The moving average (Forecast) breaches the upper control limit (UCL) shortly after the introduction of a systematic bias equivalent to the total allowable error (TEa), confirming successful error detection. Block size = 50. **

*Bias detection curves and validation charts for urea, AST, and TSH are provided in the Supplementary Material (Figures S1-S6).*

**Live Implementation and Alarm Analysis**

The optimised moving average algorithm was applied to daily patient data forcreatinine, urea, and AST from January to March 2025, and for TSH during February and March 2025. MA alarms triggered when control limits were breached. Alarms were investigated with reanalysis of stable period patient samples.

**Table 3:** MA alarm investigations, root causes and corrective actions.

| Analyte | Number of MA alarms generated | IQC performed (Passed/failed) | Check whether the patient was having really high / low values | Probable Cause for alarm | Corrective and Preventive Action |
|---|---|---|---|---|---|
| Creatinine (mg/dl) | UCL breach = 2 LCL breach = 3 | Passed 3 times | High value = 1 time<br>Low value = 2 times | Unclean wash nozzle leading to accumulation of debris in cuvettes<br><br>Calibration not done after reagent lot change | The wash nozzle was cleaned and installed back.<br>Monthly maintenance is to be done regularly.<br><br>Calibration to be performed after every reagent lot change |
| Urea (mg/dl) | UCL breach = 4 LCL breach = 2 | Passed 4 times | High value = 3 times<br>Low value = 1 time | On-board reagent deterioration<br><br>Unclean wash nozzle leading to accumulation of debris in cuvettes | Regular calibration should be done.<br><br>The wash nozzle was cleaned and installed back |
| AST (IU/L) | UCL breach = 1 LCL breach = 1 | Passed 2 times | High value = 1 time<br>Low value = 1 time | Patients were having pathologically high and low values | |
| TSH (µIU/mL) | UCL breach = 3 LCL breach = 1 | Passed 3 times | High value =1 time<br>Low value = 1 time | Pipetting error | Pipette calibration should be done |

**Moving average alarm rate**

Across 20143 creatinine, 22667 urea, 13776 AST and 5920 TSH moving average data points, the MA alarm percentage remainedless than 1% for all four analytes, indicating the obtained MA parameters for PBRTQC are producing less false alarm rates.

**Table 4:** The number of MA data points, total alarms generated, and MA alarm rates for each analyte.

| Analyte | Number of MA data points | Total alarms generated | MA alarm rate (%) |
|---|---|---|---|
| Creatinine (mg/dL) | 20143 | 5 | 0.0248 |
| Urea (mg/dL) | 22667 | 6 | 0.0267 |
| AST (IU/L) | 13776 | 2 | 0.0145 |
| TSH (µIU/mL) | 5920 | 4 | 0.0675 |

**Percentage increase in error detection after PBRTQC and IQC integration**

IQC and PBRTQC data were collected over three months (January 2025 to March 2025) for creatinine, urea, and AST, and for TSH during February 2025 and March 2025. The percentage improvement in error detection was calculated for the integration of IQC and PBRTQC.

**Table 5:** shows PBRTQC integration improved error detection for Creatinine (28.57%), Urea (25%), and TSH (20%), Consistent with its role as a comparator, AST the only analyte with a sigma value above 4 showed no improvement in error detection with PBRTQC integration.

| Analyte | No of errors detected | No of errors detected | No of errors detected | % increase in error detection after IQC-PBRTQC integration |
|---|---|---|---|---|
| Analyte | IQC | PBRTQC | Total | % increase in error detection after IQC-PBRTQC integration |
| Creatinine | 5 | 2 | 7 | 28.57% |
| Urea | 6 | 2 | 8 | 25% |
| AST | 3 | 0 | 3 | 0% |
| TSH | 4 | 1 | 5 | 20% |

*Both PBRTQC alarms for creatinine and urea, and one alarm for TSH, were exclusive error detections occurring between scheduled IQC runs, confirmed by reanalysis of stable-period samples. These represent errors that would have remained undetected until the next IQC run. AST: aspartate transaminase, TSH: thyroid-stimulating hormone*

**Cost-Benefit Analysis**

The scheduled IQC frequency remained unchanged. The reported cost savings reflect the unscheduled IQC runs that would havebeen required to detect errors occurring between scheduled QC intervals in the absence of PBRTQC. The integration model yielded a net saving of INR 426.92 from avoided IQC runs and reanalysis costs.

**Table 6:** Potential Cost-benefit analysis of PBRTQC implementation**.**

| Analysis Type | Creatinine | Urea | TSH | Total |
|---|---|---|---|---|
| Errors detected by PBRTQC | 2 | 2 | 1 | 5 |
| Cost per IQC run (INR) | 15.90 | 26.38 | 180.00 | |
| IQC savings (INR) | 31.80 | 52.76 | 180.00 | 264.56 |
| Cost per reanalysis (INR) | 9.10 | 22.08 | 100.00 | |
| Reanalysis savings (INR) | 18.20 | 44.16 | 100.00 | 162.36 |
| Total savings (INR) | 50.00 | 96.92 | 280.00 | 426.92 |

*Savings represent the unscheduled IQC runs that would have been needed to detect errors occurring between scheduled QC intervals. IQC savings = Number of errors detected by PBRTQC × Cost per IQC run Reanalysis savings = Number of errors detected by PBRTQC × Cost per reanalysis Total savings = IQC savings + Reanalysis savings*

**Risk-based Cost-benefit advantage**

Table 7 demonstrates the synergistic benefits of integrating PBRTQC with conventional IQC across four risk domains. Key findings include a 20–28.6% improvement in error detection (enhancing patient safety), compliance with CLIA/ISO 15189 through continuous monitoring, proactive identification of operational failures (e.g., reagent deterioration), and net cost savings of 426.92 (Table 6). Data sources are cross-referenced to validate each benefit.

**Table 7:** Risk-based Cost-benefit advantage.

| Risk category | Key benefit of PBRTQC | Supporting data from the study |
|---|---|---|
| Patient safety | 20 to 28.6% faster error detection rate vs IQC alone | Table 5 (% increase in error detection) |
| Regulatory compliance | Continuous monitoring meets CLIA/ ISO 15189 | Table 2 (ANPed calculation at bias equal to TEa as per CLIA guidelines) |
| Operational failure | Early detection of errors (reagent/calibration issues) | Table 3 (alarm and root cause analysis) |
| Financial loss | Saves IQC material and avoids reanalysis | Table 6 (net cost benefit) |

*CLIA: clinical laboratory improvement amendments, IQC: internal quality control, ISO:International organization for standardization*

## Discussion

The implementation of Patient-Based Real-Time Quality Control (PBRTQC) in our clinical biochemistry laboratory using Microsoft Excel was guided by three key prerequisites: (1) prioritizing analytes with lower sigma values, as these parameters are inherently more error-prone and thus require heightened monitoring; (2) accommodating the laboratory's high monthly sample volume; and (3) leveraging robust historical datasets to ensure methodologically sound parameter optimization.

### Parameter Selection and Data Robustness

We prioritised analytes with lower sigma values because they are more susceptible to analytical errors, making their continuous monitoring crucial for quality assurance. The use of historical data allowed us to simulate realistic lab conditions, ensuring that the PBRTQC settings derived from this training dataset were robust and practical for actual use.

An essential step in the PBRTQC setup was outlier handling. We adopted an interquartile range (IQR)-based truncation approach to eliminate outliers, thereby reducing skewness of the dataset. This helped reduce the influence of extreme values and ultimately decreased several false alarms. Although winsorization could be a more effective technique, leading to earlier error detection, as highlighted by Badrick et al [9]. Our IQR method still produced satisfactory results.

### Control Limit Optimisation

With the help of real historical data, tight control limits were established, which proved to be critical for early error detection. Tightening the limits and reducing false alarms was found to be done using a percentile of daily extremes (specifically the 0.05 and 99.95 percentiles), which was more effective, and this particular approach was very consistent with the findings from the work of Van Rossum [2,10]. Optimal block size was determined with the bias simulation study using the bias detection curves and the average number of patient data points required for error detection (ANPed). Early error detection was observed with the smaller block sizes, which in turn led to an increase in the rate of false alarms, pointing towards the need for balance.

### Alarm Management Strategy

Establishing a particular alarm management strategy was done after selecting the optimal Moving Average (MA) parameters. According to our findings, individual pathological findings oranalytical errors have shown a significant proportion of alarms. This validated the practice of reviewing patient results before the alarm [9].

In our laboratory, upon each PBRTQC alarm, stable-period patient samples were immediately reanalysed. If bias was confirmed, IQC was performed immediately for double-confirmation and root cause analysis. If reanalysis showed no bias, IQC was performed at its scheduled interval, with subsequent reanalysis confirming the values reflected true pathological highs or lows. This two-step verification protocol aligns with recommendations as suggested by Badrick et al. [9,11].

In our study, alarm fatigue was not observed with the frequency of alarms; instead, the number of alarms was seen to remain manageable.

### Validation, practical impact, and cost benefit

Since AST demonstrated relatively better sigma performance compared to the other three analytes, it showed fewer MA alarms. Consistently, the absence of benefit for AST supports the specificity of our observations and suggests that PBRTQC integration yields maximum value for assays with sigma values below the commonly accepted threshold for acceptable performance.

For validation, we introduced bias equivalent to the total allowable error (TEa), as recommended by the IFCC working group on PBRTQC [12]. The optimized settings successfully detected this bias, confirming their reliability. Our previous sigma matrix evaluations, conducted using CLIA guidelines, were consistent with the TEa values used in this study [13].

The clinical utility of ANPed as a performance metric must be interpreted in the context of the laboratory's sample volume. A higher ANPed does not necessarily equate to delayed error detection if daily sample throughput is proportionally high, as demonstrated with urea in this study. This reinforces the importance of laboratory-specific parameter optimisation rather than the adoption of generic block sizes.

The integration of PBRTQC with IQC improved error detection for low-sigma analytes while also demonstrating cost benefits. PBRTQC complements IQC by providing an additional layer of continuous error detection during intervals between scheduled QC runs. The cost savings reported reflect the unscheduled IQC runs avoided - those that would have been required to detect

theseerrors without PBRTQC - demonstrating a cost-benefit advantage without altering the existing QC schedule. By enabling earlier detection of analytical errors, this integrated approach reduces patient risk by preventing the release of erroneous results that could lead to misdiagnosis.
Furthermore, our study bridges regulatory and quality management frameworks: validation against CLIA's TEa meets analytical requirements, while the risk-based approach aligns with ISO 15189 goals [14,15].

**Conclusion**
The study demonstrated that Patient-Based Real-Time Quality Control (PBRTQC) can be effectively implemented using simple tools like Excel to monitor laboratory analytes, especially with low sigma performance. By optimising block sizes, control limits, and truncation methods, PBRTQC successfully detected analytical errors early with minimal false alarms. Integration with traditional IQC further strengthened error detection, improving overall laboratory quality and patient safety cost-effectively and practically. This integrated approach provides a strong risk-based cost-benefit advantage, enhancing compliance with international standards while proactively mitigating patient risk through continuous quality monitoring.

**Limitations**
In this study, a limited number of analytes were evaluated for PBRTQC procedures.
Simple Moving Average (SMA) was used; employing an Exponentially Weighted Moving Average (EWMA) could have been more effective.
Paediatric creatinine patient data were not excluded, which may have influenced the results due to physiologically lower creatinine values in children.
A limitation of this study is that the error events detected by IQC and PBRTQC were not mutually exclusive, precluding formal statistical comparison. The findings are therefore presented as descriptive improvements.

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**Author Statements**
**Credit Author Statement**
We'd like to clarify how each author contributed to this work:
**Mudasir Bashir Dandroo:** Was responsible for the core ideas, performing the analysis, working with the data, writing the first draft, and creating the figures.
Dr Devanatha Desikan V: Assisted in data collection, contributed to cost benefit analysis, provided valuable suggestions during study design and offered overall study oversight.
**Dr Ramesh R:** Provided the initial concept and designed the study, provided guidance, oversight throughout the project, resources, and thoroughly reviewed and edited the manuscript
As the corresponding author, I confirm that this accurately reflects our contributions.

**Declaration of Competing Interests**
The authors declare that there is no conflict of interest.

**Ethical Approval**
Our study used existing, anonymised lab data. The **Ethics Committee at JIPMER, Puducherry,** reviewed and approved this project (Ref: JIP/IEC-OS/2023/053). Because the data was historical and anonymous, the committee waived the requirement for individual patient consent.

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**Data Availability Statement**
The anonymised patient data that support the findings of this study are available from the corresponding author, upon reasonable request and with permission from the Institutional Ethics Committee of JIPMER.

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## Supplementary files

**PBRTQC performance characteristics – Urea**

For urea same methodology which was employed for creatinine was used for urea, to obtain optimum truncation limits, control limits and block size and ANPed were calculated by performing a bias simulation study and plotting bias detection curves.

**Table 1:** Shows the PBRTQC performance characteristics for urea, including truncation limits, control limits, TEa, block size, and ANPed.

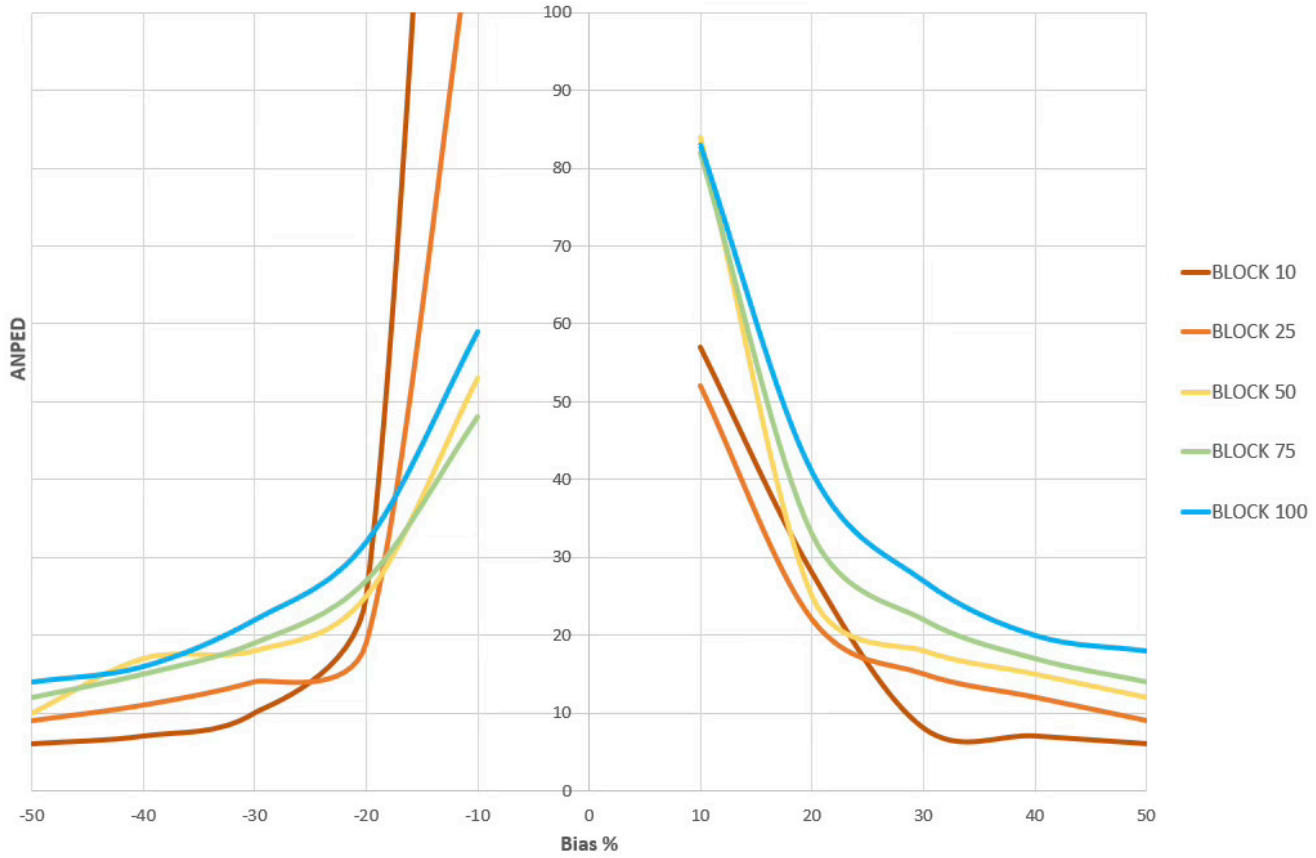
| Analyte | Truncation limit | Calculation algorithm | Control limit | Tea (%) | Block size* | ANPed* At TEa |
|---|---|---|---|---|---|---|
| Urea | UTL= 51<br>LTL= NA | SMA | UCL= 28.7<br>LCL= 15.9 | ±9% | 25 | 207 |

*UTL: upper truncation limit, LTL: lower truncation limit. UCL: upper control limit, LCL (lower control limit). TEa: total error allowable, it was obtained from the CLIA guidelines. ANPed: average number of patient data required for error detection*
**Block size and ANPed were obtained from bias detection curves*

**Bias detection curves were obtained by performing the bias simulation study on urea**

Larger biases required fewer patient data points for detection. Smaller block sizes (e.g., 10) led to false alarms due to lower ANPeds, while larger block sizes (75-100) delayed bias detection due to higher ANPeds requirements. Block size of 25 with ANPed 207 at error equal to TEa showed optimal performance.

**Figure 1A:** Optimizing PBRTQC Using Bias Detection Curves.

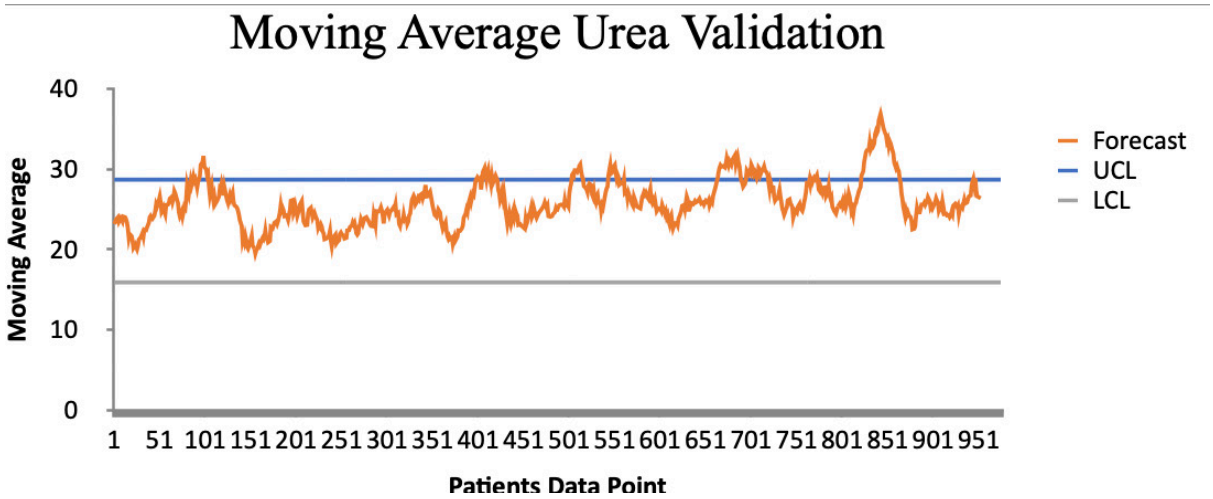



*This figure compares urea PBRTQC protocols using the mean of the most recent 10, 25, 50, 75, and 100 patient results. It shows the average number of patient samples required to detect an error (ANPed) across varying systematic bias levels (-50% to +50%), enabling direct comparison to identify the most effective error detection protocol.*

**Validation of derived optimized parameter settings on the validation data set**

Optimized PBRTQC settings were derived from a urea training dataset and applied to a 1,000-point validation dataset with simulated analytical bias (TEa). The moving average (MA) technique detected the bias via a control limit breach.

**Figure 1B:** Shows the moving average (red line) breaches upper control limit, shortly after the introduction of systematic bias equivalent to total allowable error, indicating the successful detection of bias, Block used to calculate moving average was kept equal to 25.




**PBRTQC performance characteristics - AST**

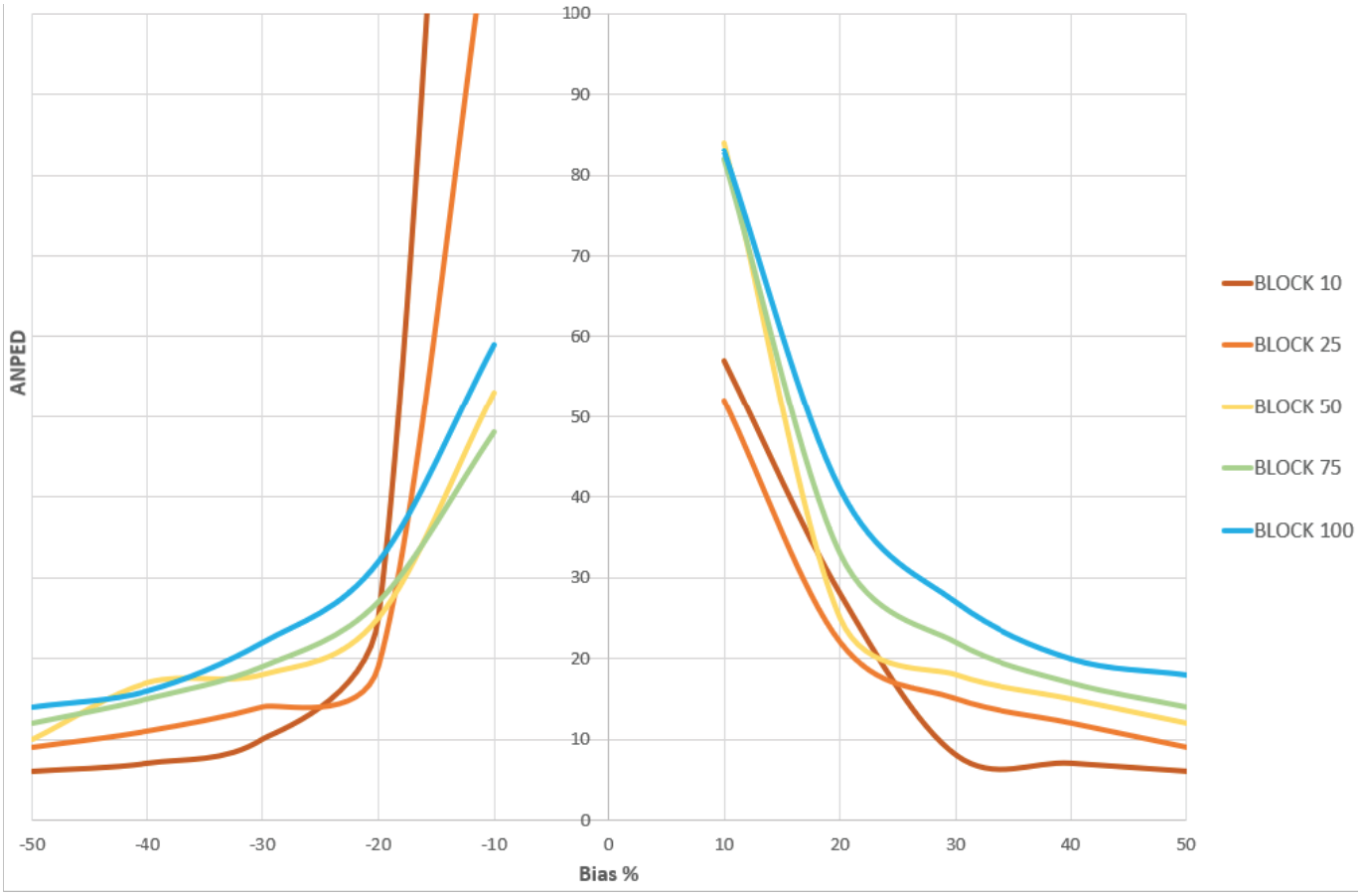
Similar methodology was used to AST, to obtain optimum truncation limits, control limits and block size and ANPed were calculated by performing a bias simulation study and plotting bias detection curves.

**Table 2:** shows the PBRTQC performance characteristics for AST, including truncation limits, control limits, TEa, block size, and ANPed.

| Analyte | Truncation limit | Calculation algorithm | Control limit | TEa (%) | Block size* | ANPed* At TEa |
|---|---|---|---|---|---|---|
| AST | UTL= 36 LTL= 12 | SMA | UCL= 26.2 LCL= 18.8 | ±20% | 50 | 22 |

*UTL: upper truncation limit, LTL: lower truncation limit. SMA: simple moving average UCL: upper control limit, LCL (lower control limit). TEa: total error allowable, it was obtained from the CLIA guidelines. ANPed: average number of patient data required for error detection*
**Block size and ANPed were obtained from bias detection curves*

**Figure 2A:** Optimizing PBRTQC Using Bias Detection Curves.




*This figure compares AST PBRTQC protocols using the mean of the most recent 10, 25, 50, 75, and 100 patient results. It shows the average number of patient samples required to detect an error (ANPed) across varying systematic bias levels (-50% to +50%), enabling direct comparison to identify the most effective error detection protocol*

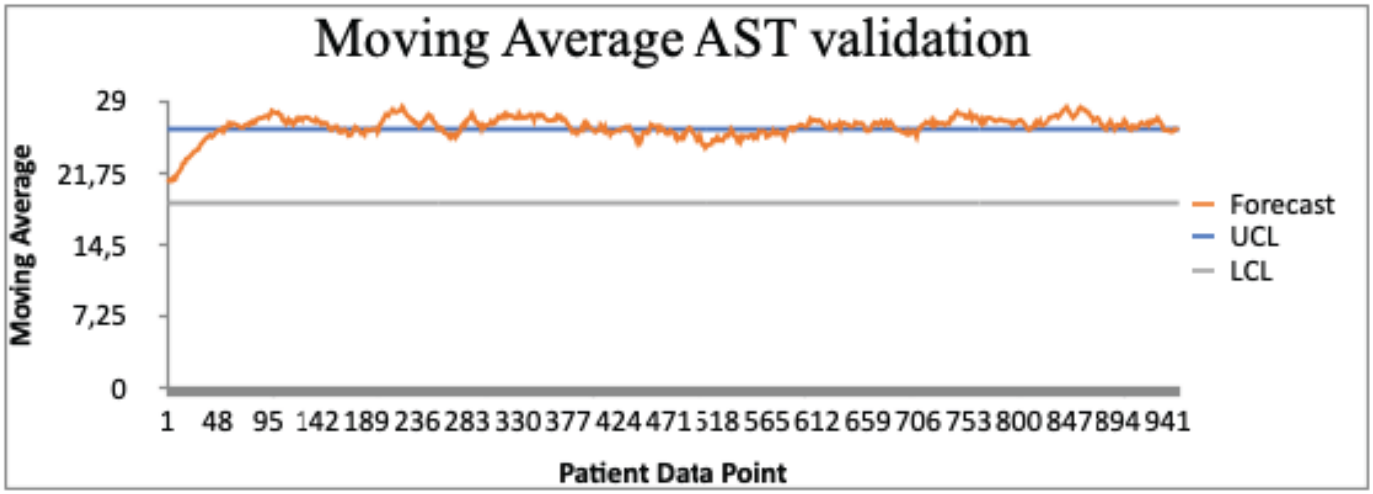
**Bias detection curves were obtained by performing the bias simulation study on AST**

larger biases required fewer patient data points for detection. Smaller block sizes (e.g., 10) led to false alarms due to lower ANPeds, while larger block sizes (75-100) delayed bias detection due to higher ANPeds requirements. Block sizes of 50 with ANPed 22 at error equal to TEa showed optimal performance.

**Validation of derived optimized parameter settings on the validation data set**

Optimized PBRTQC settings were derived from a urea training dataset and applied to a 1,000-point validation dataset with simulated analytical bias (TEa). The moving average (MA) technique detected the bias via a control limit breach.

**Figure 2B:** Shows the moving average (red line) breaches upper control limit, shortly after the introduction of systematic bias equivalent to total allowable error, indicating the successful detection of bias Block used to calculate moving average was kept equal to 50.




**PBRTQC performance characteristics**

Similar methodology as described above was used for TSH, to obtain optimum truncation limits, control limits and block size and ANPed were calculated by performing a bias simulation study and plotting bias detection curves.

**Table 3:** PBRTQC performance characteristics for TSH, including truncation limits, control limits, TEa, block size, and ANPed.

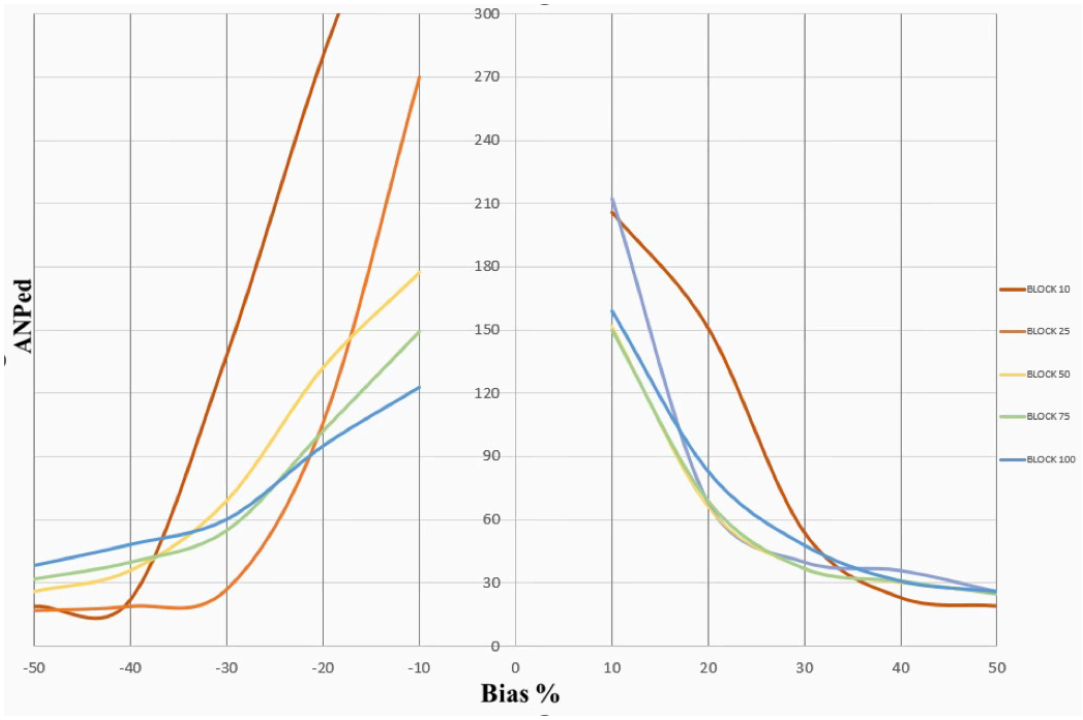
| Analyte | Truncation limit | Calculation algorithm | Control limit | TEa (%) | Block size* | ANPed* At TEa |
|---|---|---|---|---|---|---|
| TSH | UTL= 7.8 LTL= NA | SMA | UCL= 3.7 LCL= 1.7 | ±20% | 25 | 68 |

*UTL: upper truncation limit, LTL: lower truncation limit. SMA: simple moving average UCL: upper control limit, LCL (lower control limit). TEa: total error allowable, it was obtained from the CLIA guidelines. ANPed: average number of patient data required for error detection*
**Block size and ANPed were obtained from bias detection curves*

**Bias detection curves were obtained by performing the bias simulation study on TSH**

larger bias percentages required fewer patient data points for detection. Smaller block sizes (e.g., 10) led to false alarms due to lower ANPeds, while larger block sizes (75-100) delayed bias detection due to higher ANPeds requirements. Block sizes of 25 with ANPed 68 at error equal to TEa performed best.

**Figure 3A:** Represents Optimization of PBRTQC Using Bias Detection Curves: This figure compares urea PBRTQC protocols using the mean of the most recent 10, 25, 50, 75, and 100 patient results.




*It shows the average number of patient samples required to detect an error (ANPed) across varying systematic bias levels (-50% to +50%), enabling direct comparison to identify the most effective error detection protocol.*

**Validation of derived optimized parameter settings on validation data set**

Optimized PBRTQC settings were derived from a urea training dataset and applied to a 1,000-point validation dataset with simulated analytical bias (TEa). The moving average (MA) technique detected the bias via a control limit breach.

**Figure 3B:** Shows the moving average (red line) breaches upper control limit, shortly after the introduction of systematic bias equivalent to total allowable error, indicating the successful detection of bias Block used to calculate moving average was kept equal to 25.