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Six Sigma Metrics: A Guiding Path for Evaluating Quality Management System in a Clinical Laboratory.

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ABSTRACT

The accurate, precise and reliable laboratory results are essential for important clinical decision-making. To ensure reliability of test reports laboratories implement internal quality control (IQC) and external quality assurance schemes (EQAS). Additionally, the laboratories can imply six sigma metrics to provide a quantitative framework for objectively evaluating assay performance, optimize quality control (QC) strategies, and enhance overall quality management systems (QMS). This study aims to evaluate the analytical performance of common biochemistry analytes using six sigma metrics and to optimize QC frequency accordingly. The mail objectives is to to analyze the quality control of biochemistry analytes using the Six Sigma metric method and to plan the frequency of Internal Quality Control (IQC) according to Six Sigma analysis results. A retrospective study was conducted in the central clinical laboratory of Dr. VPMCH & RC, Nashik, using five months data of Internal quality control and External Quality Control (July–December 2023). QC data was obtained from a fully automated biochemistry analyser (Sysmex BX 3010) and EQAS reports from CMC Vellore were taken. Precision (CV %) was derived from IQC, bias (%) from External Quality Assurance Scheme (EQAS) and total allowable error (TEa) from CLIA guidelines. Sigma metrics were calculated as: σ = (TEa − Bias) / CV%. Glucose, AST, ALT, ALP, total protein, triglyceride, Bilirubin and uric acid demonstrated $\sigma > 6$. Creatinine and HDL showed σ between 3–6, indicating poor performance requiring closer QC monitoring and the need for corrective measures. Six sigma metrics are valuable tools for objectively assessing laboratory performance. They help categorize assays requiring minimal, moderate, or stringent QC interventions, ensuring accuracy, efficiency, and patient safety.

Keywords: Six Sigma, Quality management System (QMS), Sigma metrics, Quality control, Internal Quality Control (IQC), External Quality Assurance Scheme (EQAS)

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INTRODUCTION

Laboratories serve as the backbone of health care system as they provide the laboratory results necessary for assessing the patient's wellbeing. Clinician's decision making primarily depends upon the results provided by the laboratories which are fundamental to clinical decision-making. This necessitates a robust quality control programs to be run in a laboratory to ensure the accuracy and precision of the test results. So, laboratories have a stringent quality management system (QMS) which rely on both internal quality control (IQC) and external quality assurance schemes (EQAS) for continuous monitoring of performance and to ensure analytical reliability.

Quality in the clinical laboratory is defined as conformance to requirements of the end users. Quality is assessed in terms of following accuracy, precision, sensitivity and specificity. Though laboratories have their IQC and EQAS in place but lately in clinical laboratories, six sigma metrics have emerged as an objective, quantitative approach to assess analytical performance [2]. Sigma metrics integrate total allowable error (TEa), imprecision (CV%), and bias, offering a standardized tool to compare assay reliability [3].

In 1981, Dr. James O. Westgard proposed several statistical process control rules used with Levey-Jennings chart for evaluating Quality Control (QC) performance [2].

A Six Sigma assay implies 99.99966% defect-free results, equivalent to only 3.4 errors per million opportunities [4]. Tests are classified into world-class ($\sigma \geq 6$), excellent ($\sigma \geq 5$), good ($\sigma \geq 4$), marginal ($\sigma \geq 3$), and unacceptable ($\sigma < 3$). Such classification facilitates tailoring of QC strategies, avoiding both excessive false rejections and under-detection of errors [5].

This study aims to evaluate the analytical performance of common biochemistry analytes using Six Sigma metrics and to optimize QC frequency accordingly.

Aims And Objectives

Aim

To evaluate the analytical performance of common biochemistry analytes using Six Sigma metrics.

Objectives

- To analyze the quality control of biochemistry analytes using the Six Sigma metric method.
- To plan the frequency of Internal Quality Control (IQC) according to Six Sigma analysis results.

MATERIAL & METHODS

Study type- This was a Cross-sectional study.

Study design-Health care workers working at tertiary care hospital were included in this study.

Study Duration- July 2023 to December 2023.

This study was conducted at the Central Clinical Laboratory, Dr. VPMCH & RC, Nashik, after approval from the institutional ethics committee.IQC data was taken from analyzer and BIAS was calculated from EQAS reports of CMC Vellore.

We analyzed Sigma metrics of 10 parameters in biochemistry using Fully automated biochemistry analyser (Sysmex BX 3010). IQC data of 10 analytes was analysed retrospectively over a period of 5 months from July 2023 to December 2023, excluding the month of August. Two levels of QC samples (L1 and L2) were assayed before running patient samples every day. The calibration of the instruments and analytes was ensured regularly. The biochemistry analytes assessed were Glucose, AST, ALT, ALP, Creatinine, Uric acid, Bilirubin, Total protein, HDL, Triglyceride. Two levels of QC materials (L1 and L2) were assayed.

For all these parameters, imprecision was estimated using CV% which is a measure of variability of an assay and indicator of random errors. Bias however is an indicator of accuracy and systematic errors in analysis. Bias % was calculated for each parameter by using the Monthly EQAS report from CMC, Vellore [1].

Total allowable error (TEa) was taken from Clinical Laboratory Improvement Amendments (CLIA) guidelines.

Bias was calculated for each parameter as follows:

$$\frac{\text{Mean of all laboratories using same instrument and method - our mean}}{\text{Mean of all laboratories using instrument and method}} \times 100$$

Sigma metrics was calculated from CV, percentage bias, and TEa for the parameters by the following formula:

$$\Sigma(\sigma) = (TEa - bias)/CV\%$$

The minimum acceptance limit for sigma was considered to be 3 sigma level.

Coefficient of variance (CV):

$$\text{Imprecision (CV\%)} = \frac{\text{Standard deviation (SD)} \times 100}{\text{Mean}}$$

Bias: Bias is the systematic difference between the expected results obtained by the laboratory's test method and the results that would be obtained from an accepted reference method.

Total allowable error (TEa): can be defined as the total allowable difference from accepted reference value seen in the deviation of single measurement from the target value. TEa values were taken from Clinical Laboratories Improvement Act (CLIA) guidelines.

Ethical consideration- Approval to conduct the study was obtained from Institutional Ethics Committee (IEC).

Data collection tools and procedure- After IEC approval, the data was collected from Internal Quality Control in the laboratory. And BIAS was taken from EQAS reports of CMC Vellore.

Statistical analysis- The data collected was compiled using Microsoft excel and analyzed using SPSS.

RESULTS

The assay performance of any analyte can be evaluated in terms of sigma metrics with

$\sigma \geq 6$ indicating world class performance,
$\sigma \geq 5$ as excellent performance,
$\sigma \geq 4$ as good,
$\sigma \geq 3$ as marginal,
$\sigma \geq 2$ as poor and
$\sigma < 2$ as unacceptable performance [1].

In the present study we observed that parameters like Glucose, AST, ALT, ALP, total protein, triglyceride, Bilirubin and uric acid demonstrated to have sigma value of >6 indicating a very good performance of these parameters and also emphasizing that there is no need of changing the IQC protocols for the above said parameters.

Hence the only Westgard rule ($1_{3}s$) with one control measurement at two QC material levels per QC events is sufficient for maintaining the quality of reports for these analytes [2].

While for parameters like Creatinine was found to have a sigma value between 3-6, a revised protocol for QC monitoring should be designed as it shows suboptimal performance, also requiring method evaluation and corrective action, but still, it is in acceptable limits [3].

The sigma metrics value was found to be just above 3 for HDL. A very stringent internal QC has to be followed for this parameter, and the frequency of internal QC should be increased and corrective action should be taken for this parameters. AST, ALT, ALP, triglyceride, uric acid, glucose, bilirubin and total protein demonstrated sigma values > 6, indicating world-class analytical performance for level 1 and level 2 QC. (Analytical performance of routine biochemistry assays based on Six Sigma metrics for level 1QC (Table 1a). Analytical performance of routine biochemistry assays based on Six Sigma metrics for level 2.(Table 1b)The Coefficient of variation was shown to be good for all parameters suggesting high precision for analytes. (Table 2) BIAS was variable for the analytes. It denotes the accuracy of measurement it was found to be highest for HDL, total protein and for bilirubin and uric acid also was high from CMC Vellore. [Table 3]. This can be due to systemic errors in the system. The TEa for six sigma metric calculation is shown in [Table 4].

Table 1a: Analytical performance of routine biochemistry assays based on Six Sigma metrics for level 1

Level 1					
Analyte	**TEa**	**BIAS %**	**CV %**	**Sigma Value**	**Interpretation**
Glucose	10	-3.57	2.18	6.22	World-class (≥ 6σ)
AST	20	-7.35	2.37	11.54	World-class (≥ 6σ)
ALT	20	6.49	2.06	6.55	World-class (≥ 6σ)
ALP	30	-7.49	2.47	9.11	World-class (≥ 6σ)
Bilirubin	20	-17.04	3.70	10.01	World-class (≥ 6σ)
HDL	15	26.12	2.60	4.27	Acceptable (≥ 3σ)
Uric Acid	17	-20.74	2.55	14.80	World-class (≥ 6σ)
Total Protein	10	-26.04	2.17	7.39	World-class (≥ 6σ)
Triglyceride	25	-7.68	2.24	14.58	World-class (≥ 6σ)
Creatinine	15	10.89	1.26	3.26	Acceptable (≥ 3σ)

Table 1b: Analytical performance of routine biochemistry assays based on Six Sigma metrics for level 2

Level 2					
Analyte	**TEa**	**BIAS %**	**CV %**	**Sigma Value**	**Interpretation**
Glucose	10	-3.57	1.16	5.54	World-class (≥ 6σ)
AST	20	-7.35	1.32	9.58	World-class (≥ 6σ)
ALT	20	6.49	2.25	6.04	World-class (≥ 6σ)
ALP	30	-7.49	2.65	8.49	World-class (≥ 6σ)
Bilirubin	20	-17.04	2.70	13.71	World-class (≥ 6σ)
HDL	15	26.12	3.40	3.27	Acceptable (≥ 3σ)
Uric Acid	17	-20.74	3.50	10.78	World-class (≥ 6σ)
Total Protein	10	-26.04	3.27	11.02	World-class (≥ 6σ)

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Triglyceride	25	-7.68	2.48	13.17	World-class (≥ 6σ)
Creatinine	15	10.89	1.32	3.11	Acceptable (≥ 3σ)

CV% for level 1 and 2 QC

Table 2a

Level 1 CV %

Analyte	July	Sep	Oct	Nov	Dec	Mean
Glucose	2.12	2.25	2.22	2.15	2.1	2.17
AST	2.34	2.46	2.43	2.29	2.3	2.36
ALT	2.05	2.15	2.1	2	2	2.06
ALP	2.45	2.58	2.52	2.36	2.4	2.46
Bilirubin	3.7	3.9	3.78	3.5	3.6	3.70
HDL	2.1	3.1	2.6	2.6	2.6	2.60
Uric Acid	2.55	2.68	2.6	2.4	2.5	2.55
Total Protein	2.15	2.1	2.2	2.3	2.1	2.18
Triglyceride	2.25	2.35	2.32	2.1	2.2	2.24
Creatinine	1.58	1.26	1.12	1.22	1.11	1.26

Table 2 b

Level 2 CV %

Analyte	July	Sep	Oct	Nov	Dec	Mean
Glucose	1.12	1.21	1.22	1.15	1.1	1.16
AST	1.34	1.36	1.28	1.29	1.36	1.32
ALT	2.21	2.52	2.23	2.2	2.17	2.25
ALP	2.58	2.64	2.68	2.66	2.67	2.65
Bilirubin	2.7	2.6	3.01	2.2	3.01	2.70
HDL	3.4	3.26	3.5	3.04	3.78	3.40
Uric Acid	3.5	3.46	3.26	3.5	3.8	3.50
Total Protein	3.15	3.2	3.3	3.6	3.1	3.27
Triglyceride	2.35	2.53	2.42	2.62	2.5	2.48
Creatinine	1.38	1.16	1.32	1.22	1.51	1.32

Table 3:BIAS

Analyte	July	Sep	OCT	Nov	Dec	Mean
Glucose	–5.24%	–10.46%	–2.15%	1.86%	-1.86	-3.57
AST	–1.07%	–10.69%	17.80%	–21.39%	–21.39	-7.35
ALT	–5.20%	–4.11%	7.62%	–15.37%	–15.37	6.49
ALP	–17.43%	8.68%	–1.50%	–13.61%	–13.61	-7.49
Bilirubin	–8.05%	–1.41%	2.86%	–39.29%	–39.29	-17.04
HDL	–1.72%	–0.53%	2.94%	64.95%	64.95	26.12
Uric Acid	–20.65%	–19.84%	–4.90%	–29.16%	–29.16	-20.74
Total Protein	–18.87%	–14.50%	– 32.41%	–32.20%	–32.20	-26.04

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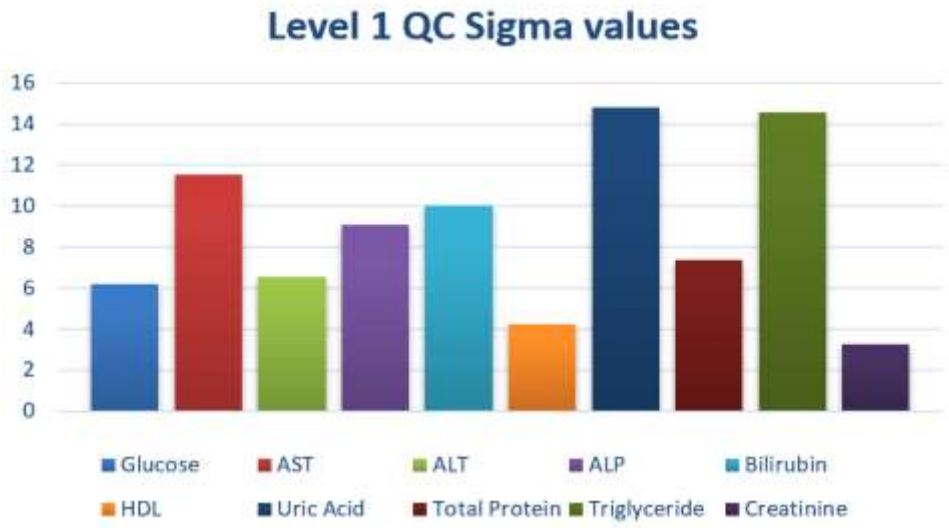
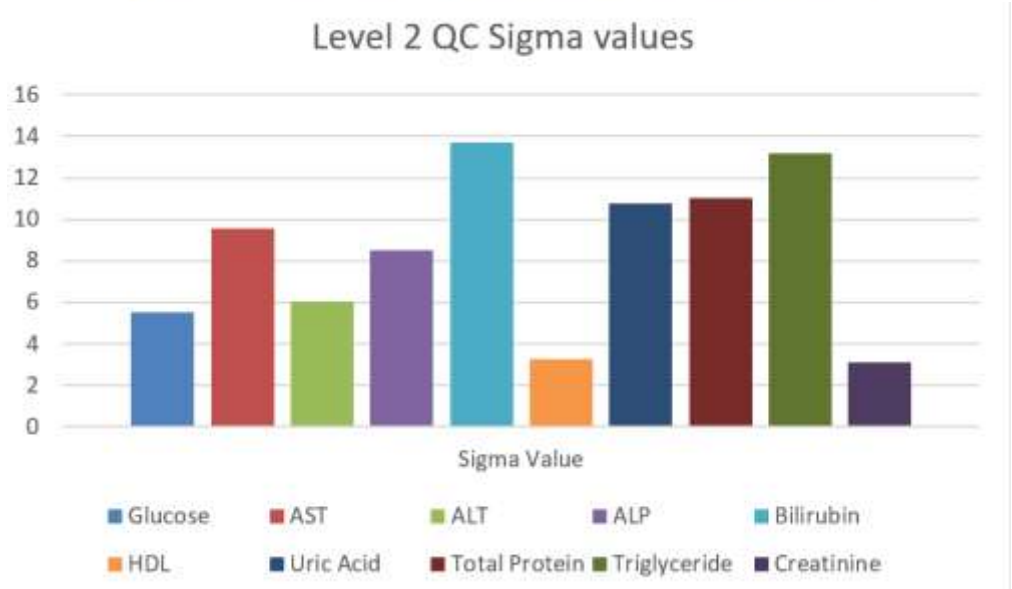
Triglyceride	–0.23%	–0.09%	–0.46%	–18.81%	–18.81	-7.68
Creatinine	–11.11%	23.87%	–5.91%	23.81%	23.81	10.89

Table 4

Analyte	TEa (%)
Glucose	**10**
AST	**20**
ALT	**20**
ALP	**30**
Bilirubin	**20**
HDL	**15**
Uric Acid	**17**
Total Protein	**10**
Triglyceride	**25**
Creatinine	**15**





DISCUSSION

The results of this study demonstrate the utility of Six Sigma metrics in objectively assessing analytical quality and guiding QC strategies. Most analytes evaluated exhibited high sigma values, indicating robust precision and minimal bias.

Most laboratories have the curated QC protocol for the levels and number of times the IQC schedules everyday based on the guidelines of various Accreditation bodies. However, as per good laboratory practice every laboratory can have an Individualized Quality Control Plan (IQCP) the protocol can modified based on Sigma values obtained from Sigma metric analysis.[4] The inclusion of sigma metrics results in the reduction of laboratory errors by maintaining six standard deviations between the parameter average and its upper and lower limits.

In a study conducted by Goel.P Et al they concluded that Sigma metrics serve as an excellent tool for performance analysis of tests performed in a clinical laboratory. However, lack of precision shown in CV% was seen for poor performers including BUN and ALT with Ca, TG and Cholesterol. Total allowable error targets in their study using Biological Variability data revealed $\sigma < 3$ for 10 parameters and using CLIA guidelines $\sigma < 3$ was seen for only 5 parameters of IQC level-2. [1] Our study showed that AST, ALT, ALP, triglyceride, creatinine, uric acid, and glucose, Bilirubin and total protein were having sigma values > 6. suggesting excellent performance. HDL and Creatinine showed $\sigma < 6$, requiring method evaluation and corrective action.

Our findings align with those of Kashyap et al., who observed $\sigma > 6$ for triglycerides and uric acid and HDL while glucose and creatinine, albumin, creatinine showed a moderate performance and had sigma values between 3-6. Which implied the requirement of improvement in quality control (QC) processes. They found sigma value of < 3 in AST, ALT, direct bilirubin, urea nitrogen, while our study demonstrated AST, ALT, ALP, triglyceride, bilirubin, uric acid, and glucose were having sigma values > 6 this difference for some analytes between our study and others can be due to the difference in Traceability calibrators used, the methodology, instrument used, quality control material used, and other preanalytical and analytical conditions.[5].

In a Pilot Study conducted by Alneil Abdallah Hamza Application of Sigma Metrics for the assessment of analytical quality in clinical biochemistry laboratories in Sudan they found that all the laboratories sigma values for the targeted parameters like glucose, urea and creatinine was unsatisfactory. And demonstrated poor performance of testing results. They suggested that these laboratories need appropriate interpretation of IQC data and a prompt corrective and preventive actions should be developed to monitor the routine performance of the testing processes. This was in concordance with our study for a parameter like HDL and creatinine showed $\sigma < 3$, requiring method evaluation and corrective action. While other parameters like AST, ALT, ALP, triglyceride, bilirubin, uric acid, and glucose and total protein were having sigma values > 6 which showed excellent performance.

Another study conducted by Kumar BV, Mohan T et.al, in this study they found that sigma metrics is a good quality tool to assess the analytical performance of a clinical chemistry laboratory, and they concluded by stating sigma metric analysis provides a benchmark for the laboratory to design a protocol for IQC, address poor assay performance, and assess the efficiency of existing laboratory processes [4].

Zhou, B., Wu, Y et.al in year 2020 in a study found out that with the analytes they assessed, five analytes with $\sigma \geq 6$ achieved world-class performance, and only the Westgard rule (13s) with one control measurement at two QC material levels per QC events, in contrast, more control rules were needed for quality assurance for five analytes with ≤ 4 σ. concluding that the Six Sigma methodology is an effective tool for evaluating the performance of biochemical analytes and is conducive to quality assurance and improvement[6].this study findings are concordant with our study.

In the study by Sharma LK et.al in 2020 they concluded that sigma metrics is a good quality tool to assess the analytical performance of a clinical chemistry laboratory and stringent internal QC rules need not be adopted for methods with sigma ≥ 6. Also, false rejections in such cases can be minimized by relaxing control limits to 13S. However, for a problem analyte with sigma metric below 3, root cause analysis should be performed along with improvement in method performance before it can be routinely used [12].

According to Westgard's recommendations, high-sigma assays require minimal QC (13s rule, two levels per event), while assays with σ < 3 demand method improvement before clinical use. Excessive QC for high-sigma assays leads to unnecessary false rejections, whereas low-sigma analytes warrant strict monitoring.[2]

Implementing Sigma metrics in non-NABL laboratories can support efficient resource allocation and continuous quality improvement, ensuring reliability and compliance with accreditation standards.

CONCLUSION

Six Sigma metrics provide a robust and quantitative framework for evaluating the analytical performance of biochemistry assays in biochemistry laboratory. In this study, most analytes achieved good performance, whereas HDL required corrective measures. We found that integration of Sigma metrics into routine QC design enhances accuracy, efficiency, and readiness for accreditation. In a way implementation of six sigma metrics helps to create a roadmap for accreditations for laboratories

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