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A Retrospective Study to Evaluate the Quality Assurance of Thyroid Profile In A Tertiary Care Clinical Biochemistry Laboratory

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Abstract

Background: The Six Sigma methodology has become a standard in quality assessment and management, widely adopted in various industries since the mid-1980s. This methodology is applicable wherever the outcome of a process needs measurement. One area where Sigma metrics find utility is in laboratory services, particularly in evaluating the quality assurance of biochemical parameters. **Aims:** This study aimed to measure and analyze the sigma metrics of thyroid hormones T3, T4, and TSH within the framework of NABL accreditation (National Accreditation Board for Testing and Calibration Laboratories). **Materials & Methods:** The study was designed as a retrospective observational study, utilizing quality control data from the Clinical Biochemistry section spanning from January 2021 to December 2021 retrieved from laboratory records. The data considered included Bio-Rad Lyphochek Immunoassay Internal Quality Control (IQC) Control and Bio-Rad External Quality Assurance Scheme (EQAS) Immunoassay monthly program data. Calculations for Coefficient of variation (CV %), Bias %, and Total Error allowable (TEa) were made to derive the sigma metric. The formula used for sigma calculation was Sigma $\Sigma(\sigma)$ = (TEa% - Bias%) / CV%, while the Quality Goal Index (QGI) ratio was determined using the formula QGI = Bias / 1.5CV. **Results:** The results categorized the assay performance based on sigma levels: >6 denoted world-class performance, 5-6 indicated excellence, 4-5 represented good performance, 3-4 was deemed acceptable, and 2-3 signified poor performance. All analytes demonstrated sigma levels below 6 (2.61-5.85) varying from poor to excellent and the QGI was below 0.8, indicating a need to enhance the precision of assays. **Conclusion:** The Six Sigma metric analysis serves as a benchmark tool that can aid laboratories in enhancing assay performance, formulating protocols for Inter-

nal Quality Control (IQC), and evaluating existing laboratory procedures.

Keywords: Six sigma; Quality Goal Index; Internal Quality Control

Introduction

Six Sigma methodology is an evolution in quality assessment and management that has been widely implemented in business and industry since the mid-1980s[1]. It can be applied whenever an outcome of a process needs to be measured. The Six Sigma approach has been utilized in hospital quality administration since 1999[2]. The general application steps are to "define, measure, analyze, improve, and control" as depicted in Figure 1[3]. Six Sigma metrics can be effectively used in laboratory services evaluate the quality the assurance of biochemical parameters[4].

The Six Sigma Quality Management System is tailored to meet the quality standards necessary for the specific purpose of a test. The allowable total error is the most relevant measure for determining this quality requirement. Calculating the sigma metric serves as an effective predictor of risk in an analytical testing process and helps in selecting the appropriate statistical quality control (SQC) procedure to detect clinically significant errors. For laboratory purposes estimates of sigma at medical decision levels are useful[5]. Thyroid profile in clinical laboratories serve as markers for thyroid function, essential for diagnosing conditions viz., hyperthyroidism, hypothyroidism, autoimmune disorders and multiple endocrine neoplasia. Given their critical role, it's imperative to assess their analytical performance with precision and accuracy[6]. The objective of this study was to evaluate the sigma metrics of thyroid hormones- T3, T4, and TSH within the framework of NABL (National Accreditation Board for Testing and Calibration Laboratories) accreditation at a rural tertiary healthcare center and teaching hospital.

Methodology

- Design of study – Retrospective observational study
- Internal Quality Control data was obtained from Vitros ECi Enhanced Chemiluminescence Immunoassay Analyser retrospectively. Quality control data from the Clinical Biochemistry section for the serum immunoassay parameters T3, T4 and TSH from Jan 2021 to Dec 2021 was retrieved from the from the laboratory records. Bio-Rad Lyphochek Immunoassay Internal Quality Control (IQC) Control for two levels (Level I & II) as mentioned in Table 1 and Bio-Rad External Quality Assurance Scheme (EQAS) Immunoassay monthly program data were considered.

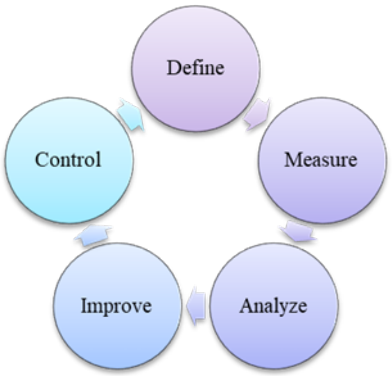

Fig 1. Steps in Six Sigma methodology

Calculations of Coefficient of variation (CV %), Bias % and Total Error allowable (TEa) were considered for sigma metric[7,8].

The TEa was derived from the Federal Register. Clinical Laboratory Improvement Amendments of 1988 (CLIA) amended in 2019[9].

Bias= [Our lab EQAS result–peer group mean (using the same instrument and method)] / Peer group mean (using the same instrument and method) X 100 %

CV was calculated from the Laboratory mean and Lab standard deviation obtained from the IQC data over the preceding months

CV%= (Standard deviation /Laboratory mean) X 100 %

For each analyte of thyroid profile, sigma metric was calculated using the formula:

Sigma $\Sigma(\sigma)$=(TEa%−Bias%)/CV%

Quality Goal Index (QGI) ratio was calculated using the following formula and interpreted as shown in Table 2

QGI = Bias/1.5CV

Statistical analysis

Data was tabulated and entered in Microsoft excel. The sigma metrics were calculated using the formulas stated in methodology. Mean and Standard Deviation (SD) were computed, along with CV%, bias%, and six sigma values, using specific formulas. These calculations were performed using MS Excel on a Windows 10 spreadsheet application.

Results

The results for the sigma metrics of thyroid hormones T3, T4, and TSH in the Clinical Chemistry laboratory are shown in Table 3.

T3 assay: The Coefficient of Variation (%CV) for T3 Level I is 4.45 and for Level II is 9.95. The Bias % for Level I is 3.94, whereas for Level II, it is significantly higher at 30. The Total Error allowable (TEa) CLIA is 5.85 for Level I and

Table 1. Unitof measurement, normal range and IQC range of T3, T4 and TSH

Analyte	Unit of measurement	Biological Reference Interval	IQC range	
			Level I	Level II
T3 Total	ng/mL	New Born: 1.0- 7.0 ng/mL < 1 year: 1.0- 2.4 ng/mL < 10 years: 0.9-2.4 ng/mL Adults: 0.7-2.0 ng/mL > 60 years: 0.4-1.8 ng/mL	1.31-1.89	3.01-4.31
T4 Total	μg/dL	New Born: 11.8- 22.6 μg/dL <1 Year: 7.8- 16.5 μg/dL < 10 years: 6.4-13.3 μg/dL Adults: 4.5-11.0 μg/dL >60 years: 5.0-10.0 μg/dL	4.01-5.87	8.68-12.4
TSH	μIU/mL	New Born: 1.0- 39 μIU/mL <2 to 20 weeks: 1.7- 9.1 μIU/mL< 20 years: 0.7-6.4μIU/mL Adults: 0.4- 4.2 μIU/mL> 60 years: 0.5-8.9 μIU/mL	0.174-0.306	3.61-5.20

Table 3. Six Sigma metrics for thyroid profile

Parameter	% CV		Bias %	TEa CLIA	Sigma		QGI		Problem
	Level I	Level II			Level I	Level II	Level I	Level II	
T3	4.45	9.95	3.94	30	5.85	2.61	0.6	0.3	Imprecision
T4	5.05	5.03	4.59	20	3.05	3.06	0.6	0.6	Imprecision
TSH	5.18	3.51	2.35	20	3.4	5.02	0.3	0.4	Imprecision

Table 2. Criteria for interpreting QualityGoal Index ratio (QGI)

QGI	Problem
<0.8	Imprecision
0.8-1.2	Both Imprecision and Inaccuracy
>1.2	Inaccuracy

drops to 2.61 for Level II. The calculated Sigma values are 0.6 for Level I and 0.3 for Level II, indicating a decrease in precision from Level I to Level II. Similarly, the Quality Goal Index (QGI) also drops from 0.6 in Level I to 0.3 in Level II. These results highlight a significant problem of imprecision, especially notable in Level II where the sigma is lower and the Bias % is higher, suggesting a need for improvements in assay performance and quality control measures.

T4 assay: The Coefficient of Variation (%CV) for T4 at Level I is 5.05 and at Level II is 5.03. The Bias % for Level I is 4.59, whereas for Level II, it increases to 20. The Total Error allowable (TEa) CLIA is 3.05 for Level I and slightly higher at 3.06 for Level II. The Sigma values remain constant at 0.6 for both Level I and Level II, indicating consistent precision across the two levels. Similarly, the Quality Goal Index (QGI) remains constant at 0.6 for both levels as well. However, the problem of imprecision is observed in both Level I and Level II, highlighting the need for improved precision in assay performance and quality control measures across the board.

TSH assay: The Coefficient of Variation (%CV) for TSH at Level I is 5.18, while at Level II, it decreases to 3.51. The Bias % for Level I is 2.35, but it significantly increases to 20 for Level II. The Total Error allowable (TEa) CLIA is 3.4 for Level I and higher at 5.02 for Level II. The Sigma values show a decrease, with Level I having a Sigma of 0.3 and Level II at 0.4. Similarly, the Quality Goal Index (QGI) decreases from 0.3 at Level I to 0.4 at Level II. The problem of imprecision is notably observed in Level II, where the Bias % is higher, and Sigma is lower, indicating the need for enhanced precision and quality control measures, especially in Level II assays.

Overall, the sigma metrics indicate varying levels of precision and accuracy in the assays for T3, T4, and TSH, with notable issues of imprecision observed in certain levels of each hormone. These results highlight the need for improvements in assay performance and quality control measures to ensure accurate and reliable thyroid hormone measurements in the Clinical Chemistry laboratory.

Discussion

In order to enhance the process and mitigate the identified imprecision in thyroid hormones assays, a series of strategic steps were implemented. Firstly, a thorough analysis was conducted to pinpoint the root causes contributing to the imprecision. This entailed scrutinizing factors such as instrument calibration, the quality of reagents, operator techniques, and environmental conditions to identify potential sources of variation as shown in Figure 2 Cause-effect chart (Fish-bone diagram) for the low sigma value of the analytes**.**

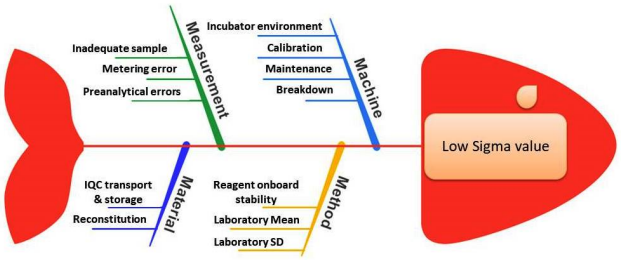

Fig 2. Cause-effect chart (Fish-bone diagram) for possible causes for low sigma value

The root cause analysis revealed incubator environment fluctuations and instrument breakdown during the days prior to EQAS run. The corrective action involved the service engineer attending to the call onsite and repairing the instrument during breakdown. To address the temperature fluctuations the air conditioner was replaced and additional air conditioner installed to maintain the required ambient temperature. The DMAIC road map [D- Define, M-Measure, A-Analyze, I-Improve, C-Control] was applied in our study for poor assay performance analyte T3 as shown in Figure 3.

In a study by Liu Y et al, the utilization of sigma metrics, Quality Goal Index (QGI) analysis, and Root Cause Analysis (RCA) proved to be an effective assessment system for evaluating the analytical performance of endocrine analytes[4]. The findings in our study are also congruent with this in context to thyroid hormone assays.

In Vasava S N et al's study, the average sigma value for Thyroid Stimulating Hormone (TSH) and Cortisol remained above 3 for six months, indicating satisfactory performance. Conversely, the sigma values for Triiodothyronine (T3) and Tetraiodothyronine (T4) were below 3, indicating subpar

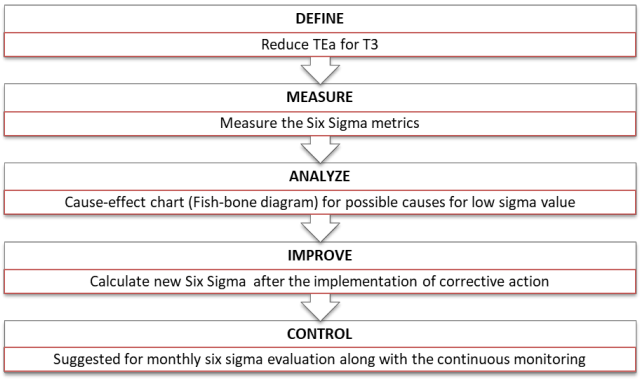

Fig 3. DMAIC road map for improving the low sigma values of T3 assay

performance[10]. Similarly in our study, we encountered low sigma values for T3 only analyte which performed <3 sigma metrics. In a pilot study investigation utilizing Six Sigma metrics to assess the Randox International Quality Assessment Scheme within a clinical biochemistry laboratory conducted by Yadav N et al, it was observed that their Sigma metrics for thyroid profile fell below three sigmas. These initial results underscore the necessity for a comprehensive evaluation, and we advocate for the integration of Sigma metrics in quality assurance protocols, prioritizing the welfare of patients[11].

Gulbahar O et al, conducted a study using the Roche Cobas e 602 autoanalyzer, comparing the two-level Internal Quality Control (IQC) sigma values of Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3), and Free Thyroxine (FT4) with two immunoassay analyzers. Upon calculating the sigma values, it was determined that TSH exhibited a 'World-class' performance while FT4 showed an 'unacceptable' performance in both analyzers. For FT3, the results were 'unacceptable' and 'good' for the two levels of IQC in the first analyzer and the second level of the second analyzer, respectively[12]. In a study by Wadhwa N et al, Gamma-glutamyl transferase (GGT) Level (L) 2 exhibited the highest sigma value of 13.22. Total bilirubin demonstrated the highest sigma values at both control levels, with 7.15 at L1 and 9.49 at L2, respectively. A sigma value of $\geq$4 was noted across all control levels for anti-TPO, CK-MB, potassium, PSA, and TSH. However, alpha-feto protein (AFP) at L1 and Troponin I at L2 had sigma values of $\leq$3. For the remaining analytes, sigma values were consistently $\leq$3. Notably, applying suggested rules led to a significant improvement in sigma for L1 of AFP, increasing from 2.5 to 9.3[13].

Sigma metric values play a crucial role in establishing the acceptability criteria for Internal Quality Control (IQC) and in designing and implementing effective control strategies based on sigma values[14]. The laboratories' quality objective is the allowable total error (TEa), which signifies the level of variation necessary to detect a clinically significant decision limit for subsequent actions such as investigations or treatment. The combined effect of overall imprecision and inaccuracy in analyzing a specific analyte in a patient sample should not surpass this total allowable error (TEa) threshold. Guidelines from the Clinical Laboratory Improvement Amendments (CLIA) are utilized to determine the TEa limit for different parameters[15]. The Quality Goal Index (QGI) ratios observed for thyroid analytes in our investigation indicate potential issues related to imprecision (QGI <0.8). Therefore, it is essential to adhere to a highly rigorous Internal Quality Control (IQC) protocol, increase the frequency of IQC measures, and implement corrective actions for these parameters as suggested by Westgard et al. in 2006[16].

Here are simplified guidelines for selecting appropriate Westgard rules and IQC levels: For biochemical parameters with a Sigma Scale of 6 or higher (indicating excellent performance), use one level of QC per day (alternating levels between days) and apply the 1-3 s Westgard rule independently. For Sigma Scales between 4 and 6 (indicating good/acceptable performance), use two levels of control once daily and apply the 1-3 s, 2-2 s, R4 s Westgard multirules. For Sigma Scales between 3 and 4 (indicating poor performance), use two levels of controls twice daily and follow the 1-3 s, 2-2 s, R4s, and 4-1 s Westgard's multirules. If the Sigma Scale is less than 3 (indicating a problematic analyte), conduct a root cause analysis, improve method performance, and address issues before routinely using the method[16].

Furthermore, it is crucial to provide comprehensive training and education to laboratory personnel involved in conducting the assays. This training should cover aspects such as proper sample handling techniques, adherence to assay protocols, troubleshooting procedures, and effective data interpretation to minimize errors and improve overall assay performance.

Continuous monitoring of assay performance is paramount and can be achieved by establishing a system for ongoing evaluation using internal quality control (IQC) samples and participating in external quality assurance programs (EQAS). Monitoring key metrics such as %CV, Bias %, TEa CLIA, Sigma, and QGI on a regular basis allows for the timely detection of any deviations from acceptable performance standards, enabling prompt corrective actions to be taken.

Conclusion

Six sigma metric analyses is a benchmark which can be used to help laboratories improve their assay performance, develop protocols for IQC and evaluate current laboratory procedures. However, the findings underscores the unlikelihood of a universal TEa goals model capable of encompassing all methods and clinical applications, advocating for an appraisal checklist to facilitate standardized evaluation of current and

forthcoming publications on biological variation data. Efforts should also be directed towards process optimization by identifying and addressing bottlenecks or inefficiencies in the assay workflow. This may involve streamlining procedures, optimizing reagent volumes, and incorporating automation technologies where feasible to enhance efficiency and reduce variability.

Regular data analysis is essential to identify trends, patterns, and areas for improvement. Statistical tools and techniques should be employed to analyze assay data comprehensively, providing valuable insights and facilitating informed decision-making for implementing corrective actions and process enhancements. Lastly, maintaining detailed documentation of all assay procedures, quality control measures, and corrective actions taken is imperative. This documentation ensures traceability, facilitates audit processes, and ensures compliance with regulatory requirements, thereby reinforcing the reliability and validity of the assay results.

Authors' contributions

HR, SKN and PK participated in the process of the initial writing of the manuscript, its revision, presentation of the idea and initial design, and collection and analysis of data. All participated in review of manuscript, data analysis and revision of the manuscript. Moreover, all authors accept the responsibility for the accuracy and correctness of the contents of the present manuscript and approve the final version of the manuscript.

Ethical considerations

This study was conducted based on the principles of the Declaration of Helsinki. Before the study, the approval of the Institutional Ethics Committee of Sri Devaraj Urs Medical College (No. DMC/KLR/IEC/106/2022-23 Dt. 27.05.2022) was obtained.

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