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Original Article

Biochemistry Section

Application of Sigma Metrics for Evaluating the Analytical Performance of Thyroid Profile and Cortisol in Clinical Biochemistry Laboratory

SMITA NATVARBHAI VASAVA[1], ROSHNI GOKALDAS SADARIA[2]

ABSTRACT

Introduction: Now-a-days quality is the key aspect of clinical laboratory services. The six sigma metrics is an important quality measurement method for evaluating the performance of the clinical laboratory.

Aim: To assess the analytical performance of clinical biochemistry laboratory by utilising thyroid profile and cortisol parameters from Internal Quality Control (IQC) data and to calculate sigma values.

Materials and Methods: Study was conducted at Clinical Biochemistry Laboratory, Dhiraj General Hospital, Piparia, Gujarat, India. Retrospectively, IQC data of thyroid profile and cortisol were utilised for six subsequent months (July to December 2019). Coefficient of Variation (CV%) and bias were calculated from IQC data, from that the sigma values were calculated. The sigma values <3, >3 and >6 were indicated by poor performance procedure, good performance and world class performance, respectively.

Results: The sigma values were estimated by calculating mean of six months. The mean sigma value of Thyroid Stimulating Hormone (TSH) and Cortisol were >3 for six months which indicated the good performance. However, sigma value of Triiodothyronine (T3), Tetraiodothyronine (T4) were found to be <3 which indicated poor performance.

Conclusion: Six sigma methodology applications for thyroid profile and cortisol was evaluated, it was generally found as good. While T3 and T4 parameters showed low sigma values which requires detailed root cause analysis of analytical process. With the help of six sigma methodology, in clinical biochemistry laboratories, an appropriate Quality Control (QC) programming should be done for each parameter. To maintain six sigma levels is challenging to quality management personnel of laboratory, but it will be helpful to improve quality level in the clinical laboratories.

Keywords: Internal quality control, Serum cortisol, Six sigma, Thyroid function tests

INTRODUCTION

Six sigma management methodology come to attention publically because it is a system that integrates with accurate evaluation, problem-solving, and process improvement [1]. The laboratory process is divided into three phases; pre-analytical, analytical and post-analytical, in clinical medical laboratories. Errors that appear in each stages ultimately affect the test results and therefore for each stage, the magnitude of total error should be calculated. It has been found that most commonly errors occur at the pre-analytical phase [2]. The six sigma is quality control methodology which detect defect rate of 3.4 defects per million opportunities. Six sigma was initially developed by Bill Smith of Motorola in 1986 for eradicating defects in manufacturing. This defect is explained to be a process or product which fails to meet customers' requirements and expectations. The six sigma improvement model, Define, Measure, Analyse, Improve, and Control (DMAIC) specifies the sequence of steps for understanding and improving a process are: a) defining the project goals and customer (internal and external) requirements; b) measures the process for determination of current performance; c) analysing and determining the root causes of relevant defects; d) improving the process with elimination of defect root causes, and e) controls the subsequent future performance of process [3]. In clinical laboratories, six sigma deliver the manner to make lesser mistakes in all processes by removing errors before they come into sight.

In the present study, the CV% and bias were derived from IQC data of T3, T4, TSH and cortisol parameters and sigma values were calculated by which the analytical performance of clinical biochemistry laboratory was evaluated in Central Clinical Biochemistry laboratory, Dhiraj General Hospital, Gujarat, India.

MATERIALS AND METHODS

The present retrospective cross-sectional study was conducted at Central Clinical Biochemistry Laboratory of Dhiraj General Hospital, Piparia, Gujarat, India. Approval for the study was obtained from Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC/ON/MEDI/RP/20125, dated 14/12/2020). IQC data of thyroid profile and cortisol were obtained from Maglumi 800 Chemiluminescence Immunoassay Analyser (CLIA) retrospectively from July 2019 to December 2019. The following serum immunoassay parameters were included: T3, T4, TSH and cortisol. [Table/Fig-1] shows, unit of measurement, normal range of parameters and IQC range of T3, T4, TSH and cortisol.

Parameter	Unit	Normal range	IQC range
T3	ng/mL	0.79-1.58	4.0-7.44
T4	ug/dL	4-11	9.7-16.3
TSH	uIU/mL	0.39-5.0	2.32-4.32
Cortisol	ug/dL	8-10 AM: 8-25 4-6 PM :1-17 Midnight: 1-5	8.2-13.8

[Table/Fig-1]: Unit of measurement, normal range and IQC range of T3, T4, TSH and cortisol.
Total triiodothyronine (T3), Thyroxine (T4); Thyroid-stimulating hormone (TSH); IQC: Internal quality control

IQC level of QC materials were given with kit and analysed every alternate day regularly. All QC materials were ready to use and given with kit. QC values were taken according to the reference method and Maglumi 800 Immunoassay Analyser was calibrated regularly.

The CV is a standardised measure of dispersion of a probability distribution or frequency distribution which is often expressed as a percentage. Analytical method and analyser have a good performance if the CV% value is ≤5% while CV% values ≥10% suggests that analytical method and analyser have an inadequate performance [2]. First mean and SD were calculated and from that CV% was calculated from IQC data of T3, T4, TSH and cortisol with the formula CV%=(SD/Mean)×100. CV% is defined as the degree of precision.

First mean and SD were calculated and from that CV% was calculated from IQC data over the six months. Bias measures, how far was your observed value from a target value. Calculation of bias% was done by the following formula as {(lab Mean of IQC data-target mean of IQC data)/(target mean of IQC data)}×100. Percent bias values of each parameter were calculated from July to December 2019.

Total Allowable error (TEa) values of T3, T4, TSH and cortisol were obtained from the Clinical Laboratories Improvement Act (CLIA) guidelines [4] and Nar R and Emekli DI study [2]. The sigma metrics was calculated for various parameters by the following equation: Sigma metrics (σ)=(TEa%-bias%)/CV% [5], where, TEa and bias are an indicator of systematic errors, whereas CV% is an indicator of random errors. Sigma metrics involve simple and minimal calculations. All that is necessary is to decide the quality goals and calculate the method's imprecision and bias levels as one would ordinarily do in method validation studies [6]. In the present study, the sigma values <3, ≥3 to 6 and >6 were considered as a poor performance procedure, good performance and world class performance, respectively.

STATISTICAL ANALYSIS

Mean and Standard Deviation (SD) values, CV%, bias% and six sigma values were calculated by following formulations. All calculations were done in the spread sheet; MS excel of Windows 6. The sigma metrics was calculated for various parameters by the following equation: Sigma metrics (σ)=(TEa%-bias%)/CV% [5], where, TEa and bias are an indicator of systematic errors, whereas CV% is an indicator of random errors.

RESULTS

The target mean, laboratory mean and the calculated SD of the IQC data for various parameters in clinical biochemistry laboratory is shown in [Table/Fig-2].

The CV% values of IQC were found <5 for the parameters T3, Cortisol. While CV% of IQC were found between 5 to 10 for T4 in month November 2019. Total allowable error, bias and CV% values of the IQC for each parameter is shown in [Table/Fig-3].

The sigma values for cortisol were found to be 6.02 in month of September 2019. But, several parameters had sigma values less than 3 (<3): T3 (July to December 2019); T4 (July to December 2019); TSH (November 2019). Cumulative sigma metrics of last six months (July-December 2019) for TSH and cortisol was found to be more than 3 (except in November 2019). Complete sigma metrics for thyroid profile and cortisol are shown in [Table/Fig-4,5].

DISCUSSION

The six sigma methodology permits the clinical laboratories to evaluate the effectiveness of their ongoing quality control processes [7]. Six sigma is a procedure of detecting errors used for the purpose of improvement under the roof of total quality management [8]. The sigma metrics reveals whether bias, imprecision, or both are contributing to a lower sigma metric for an assay or analyser currently in use. This valuable information was used for the evaluation of the associated processes which can be thoroughly used for improvements to reduce bias or imprecision which ultimately improve the quality and subsequently reducing laboratory costs [9].

Parameter	Target Mean	IQC											
		July		August		September		October		November		December	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T3	5.72 ng/mL	5.78	0.14	5.25	0.22	5.18	0.12	5.11	0.12	4.55	0.12	4.67	0.18
T4	13 ug/dL	11.26	0.12	10.91	0.31	10.85	0.28	11.68	0.12	12.67	1.41	12.67	0.35
TSH	3.32 ulU/mL	2.89	0.13	2.90	0.09	3.1	0.14	3.01	0.19	3.11	0.29	2.95	0.11
Cortisol	11 ug/dL	10.08	0.36	10.92	0.29	10.46	0.27	10.08	0.39	9.84	0.42	11.1	0.45

[Table/Fig-2]: Target mean, laboratory mean and Standard Deviation (SD) values of each parameter.

Parameter	TEa (%)	IQC											
		July		August		September		October		November		December	
		CV%	Bias%	CV%	Bias%	CV%	Bias%	CV%	Bias%	CV%	Bias%	CV%	Bias%
T3	6.8	2.42	4.78	4.19	4.25	2.32	4.18	2.35	4.11	2.64	3.55	3.85	3.43
T4	10.4	1.07	10.26	2.84	9.91	2.58	9.30	1.03	10.68	9.6	12.3	2.76	9.0
TSH	23.7	4.50	1.89	3.10	1.90	4.52	2.1	6.31	2.01	9.32	2.11	3.73	1.97
Cortisol	25	3.57	9.08	2.66	9.92	2.58	9.46	3.87	9.08	4.27	8.84	4.05	10.19

[Table/Fig-3]: Total allowable error (TEa), bias and CV% values of internal quality.

Parameter	July	August	September	October	November	December	Cumulative sigma metrics
	IQC Sigma (σ) value	IQC Sigma (σ) value	IQC Sigma (σ) value	IQC Sigma (σ) value	IQC Sigma (σ) value	IQC Sigma (σ) value	
T3	0.83	0.61	1.13	1.14	1.23	0.88	0.97
T4	0.13	0.17	0.21	1.07	0.07	0.51	0.36
TSH	4.85	7.03	4.78	3.44	2.32	5.83	4.71
Cortisol	4.46	5.67	6.02	4.11	3.78	3.66	4.61

[Table/Fig-4]: The sigma metrics month-wise and cumulative sigma metrics for each parameter.

Sigma metrics	July	August	September	October	November	December
Group 1 (<3)	T3, T4	T3, T4	T3, T4	T3, T4	T3, T4, TSH	T3, T4
Group 2 (3-6)	TSH, Cortisol	Cortisol	TSH	TSH, Cortisol	Cortisol	TSH, Cortisol
Group 3 (>6)	-	TSH	Cortisol	-	-	-

[Table/Fig-5]: Sigma metrics performance groups for each parameter.

Sigma metrics were computed using the data obtained from the measurement of QC materials to be used as quality indicators that represent the balance between quality requirements (TEa) and test variation (bias and CV). Thus, six sigma focuses on gathering data for analysis, which is used for Quality Assurance (QA). Laboratory errors thus can be reduced by maintaining ±6 SD between the mean value and the range [10].

A six-month CV is considered the representative of true test variation because many different laboratory technicians will perform

QC measurements, and significant events, such as calibration or manufacturer maintenances will occur in that time frame. Unfortunately, there are currently no guidelines published regarding the sigma metric calculation. The variables that affect such a comparison include, the heterogeneous nature of data collection, the differences in methodologies, different IQC materials, different proficiency testing bodies giving bias and the time interval upon which sigma metrics is calculated, study period with cumulative bias and different environmental conditions in addition to the different analytical or clinical benchmarks that are chosen for evaluation of TEa. It also would be preferable to assess bias against a reference method or material [10]. It is important that an analytical procedure achieves a good sigma level if a high reliability is to be attached to the results [11].

In the present study, CV% values of IQC were found less than 5 for T3 and Cortisol. While CV% values of IQC were found between 5 to 10 for T4 in month November, 2019, respectively. The reasons for variability of CV may be errors due to instability of the IQC or calibrator material during transport or storage and sample handling of laboratory technicians. For better CV, it is necessary to identify a protocol for transportation, preparation and aliquoting the IQC and calibrator material to prevent differences between laboratory technicians during assay.

The mean sigma values were found to be more than 3 for TSH and Cortisol. So, for theses parameters, more elaborate QC strategies are required. The sigma values were <3 for T3 (July to December 2019); T4 (July to December 2019); TSH (November 2019). The mean sigma values of T3 and T4 were less than 3 (Sigma <3). So, for these parameters, the frequency of IQC should be increased and corrective action should be undertaken for these parameters. In our laboratory calibrations of parameters with poor sigma performance are more frequently performed now and the number of daily IQC has been increased.

In a study performed by Nar R and Emekli DI, concluded that sigma value of TSH was >6 for both QC for three months. The sigma value mean of three months for TSH was found to be 13, 06/16, 13 for first and second level. So the study suggests that TSH had world class performance for both QC levels [2].

In the study conducted by Gulbahar O et al., demonstrated that according to six sigma value, there was world class performance for TSH in both instruments [12]. There was differences in six sigma values may be due to type of immunoassay analyser used, IQC material or pre-analytical and post-analytical conditions. In the present study, only one instrument was available for immunoassay measurement. So, inter-instrument variation could not be used for comparison.

The six-sigma methodology is an effective method for the evaluation of analytical stage, the quality measurement of the laboratory tests and the optimisation of quality control rules according to sigma values. IQC practices should be specific to the test and they should be generated in accordance with the sigma values of each test [2].

Limitation(s)

Limitation of the present study was, only one IQC level material was available with kit (either normal or abnormal level control). Multilevel IQC materials, upgraded analysers and better methodologies may help in reducing the errors and improve the sigma values in the laboratory. Along with analytical process, pre-analytical and post-analytical processes should be performed for evaluation of general performance of clinical laboratory.

CONCLUSION(S)

The analytical performance of our laboratory according to six sigma methodology, it was good for cortisol and TSH. But unsatisfactory value for T3 and T4 which shows instability and low consistency of results being delivered which require detailed root cause assessment of analytical process. Quality is ongoing process, so, quality personnel of the laboratory should not stop by generating CV% and Bias% of the any analyte but also monitor sigma matrix regularly to give world class quality of laboratory work. Evaluation of overall performance of clinical laboratory should done with analytical process as well as pre-analytical and post-analytical processes.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry, Smt. BK Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India.
2. Associate Professor, Department of Biochemistry, Smt. BK Shah Medical Institute and Research Centre, Sumandeep Vidyapeeth Deemed to be University, Piparia, Vadodara, Gujarat, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Roshni Gokaldas Sadaria,
C-204, Lilleria Avenue, Sama-Savali Road, Vadodara-390024, Gujarat, India.
E-mail: drroshnijasani@gmail.com

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