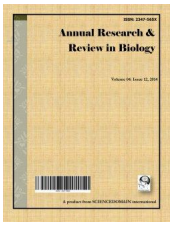

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Sigma Metrics of Biochemical Parameters in a Tertiary Care Hospital in Coastal Karnataka

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Authors' contributions

This work was carried out in collaboration between both authors. Author UA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AP managed the analyses of the study and managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Six sigma is a process of quality measurement and improvement program used in industries. Sigma metrics can be used effectively in laboratory services as total testing process has multiple steps and error can occur anywhere. The present study was undertaken to evaluate the quality of the analytical performance of clinical chemistry laboratory by calculating sigma metrics.
Methods: The study was conducted in the clinical biochemistry laboratory of Karwar Institute of Medical Sciences, Karwar. Sigma metrics of 15 parameters with automated chemistry analyzer, transasia XL 640, electrolytes with Roche electrolyte analyzer and thyroid hormones with Maglumi were analyzed.
Results: Sigma values <3 for Urea, ALT, BD, BT, Ca, creatinine (L1) and urea, AST, BD (L2), sodium, potassium and T4 were observed. Sigma lies between 3-6 for Glucose, AST, cholesterol, uric acid, total protein (L1) and ALT, cholesterol, BT, calcium, creatinine and glucose (L2), chloride, T3,TSH.Sigma was more than 6 for Triglyceride, ALP, HDL, albumin (L1) and TG, uric acid, ALP, HDL, albumin, total protein (L2).

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Conclusion: Sigma metrics helps to assess analytical methodologies and augment laboratory performance. It acts as a guide for planning quality control strategy. It can be a self assessment tool regarding the functioning of clinical laboratory.

Keywords: Bias; CV%; total allowable error; sigma.

1. INTRODUCTION

Accurate test results are very important in healthcare system since physician's decisions mostly rely on the laboratory results. The evaluation of laboratory performance is critical to maintain accurate laboratory results. Six sigma is the latest version of Total Quality Management. It is Quantitative goal for process performance.

The Sigma scale is easily interpreted and appreciated by laboratories. Sigma values can be calculated for both qualitative and quantitative assays. The Sigma scale provides guidelines for assay improvement and monitoring.

Six Sigma methodology represents an evolution in quality assessment and management that has been implemented widely in business and industry since the mid-1980s. Six Sigma methodology was developed to reduce the cost of products, eliminate defects, and decrease variability in processing. It consists of five steps: define, measure, analyze, improve, and control (DMAIC) [1-3]. These steps are universal and could be applied to all sectors of industry, business, and healthcare.

Total testing process involves three phases namely, pre-analytical, analytical and post-analytical.

The errors can occur in any of the above mentioned steps. To overcome the serious errors originating in clinical laboratories, a new perspective and approach seem to be essential. All laboratory procedures are prone to errors because in many tests, the rate of human intervention is higher than expected. It appears that the best solution for analyzing problems in clinical laboratories is the application of Six Sigma methodology. The sigma value indicates how often errors are likely to occur; the higher the sigma value, the less likely it is that the laboratory reports defects or false test results.

There are a few studies done on sigma metrics in laboratory medicine on clinical chemistry analytes [4-7]. There are a few studies done on sigma metrics of electrolytes and thyroid hormones in laboratory medicine [8-11].

Study by Singh et al reported satisfactory sigma values (>6) for creatinine, triglycerides, SGOT, CPK-Total and Amylase. Blood urea performed poorly on the sigma scale with sigma <3(4). Nanda and Colleagues reported that, for total bilirubin, uric acid, SGOT, SGPT and ALP, the sigma values were found to be more than 6. For parameters – glucose, Creatinine, triglycerides, urea, the sigma values were found to be between 3 to 6. For parameters – total protein, albumin, cholesterol and chloride, the sigma values were found to be less than 3(5).

A recent study by Iqbal reported that sigma levels were found acceptable (≥3) for glucose (L2), cholesterol, triglyceride, HDL, direct bilirubin and creatinine at both levels of control. For rest of the analytes sigma metrics was found <3. The study concluded that analytes with the sigma value <3 required strict monitoring and modification in quality control procedure. In this study application of sigma rules provided us the practical solution for improved and focused design of QC procedure [12].

However there is pausity of literature in this area.

1.1 Objectives

(i) Study sigma metrics of clinical chemistry analytes, electrolytes and thyroid hormones.
(ii) Calculate our total allowable error for the above mentioned parameters and compare it with that of CLIA guidelines.
(iii) Calculate z score for clinical chemistry analytes, electrolytes and thyroid hormones using internal quality control data.

2. METHODOLOGY

The study was conducted in the clinical biochemistry laboratory of Karwar Institute of Medical Sciences, Karwar. This is a 400 bedded, tertiary care center in which department of biochemistry was newly established. Aim of our study was to measure the sigma metrics of our laboratory and to assess the errors associated with it. We analyzed sigma metrics of 15

parameters with automated chemistry analyzer, XL 640.

The study protocol was approved by institutional human ethnics committee.

Internal quality control (IQC) data of 15 analytes were analyzed retrospectively over a period of 6 months from March 2015 to August 2015 with XL 640. Both normal (L1) and pathological (L2) levels of QC materials were assayed before commencing reporting of patient samples every day. The instruments were calibrated regularly. The analytes assessed were glucose, urea, creatinine, uric acid, total bilirubin, direct bilirubin, total protein, albumin, SGOT, SGPT, ALP, Total cholesterol, triglycerides, HDL and Calcium.

Internal quality control (IQC) data of electrolytes were analyzed retrospectively with Roche electrolyte analyzer that works on the principle of indirect ion selective electrodes. Pathological (L2) levels of QC materials were assayed before commencing reporting of patient samples every day. Internal quality control data of thyroid hormones, T3, T4 and TSH were analyzed retrospectively with Maglumi hormone analyzer that works on the principle of chemiluminescence.

Sigma values are calculated using the following formula;

- $\Sigma (\sigma) = (TEa - bias) / CV\%$
- Total allowable error (TEa): It is the total allowable difference from accepted reference value seen in the deviation of single measurement from the target value. TE_a values of various parameters were taken from Clinical Laboratories Improvement Act (CLIA) guidelines [13].
- *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. Bias was derived as follows;

  Bias (%) = (Mean of all labs with same instrument & method –our mean / Mean of all labs with same instrument & method) x100

CV% is the analytical coefficient of variation of the test method. Coefficient of variance (CV) were calculated as follows;

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

- TEa observed in our assay was calculated using the formula,

  TEa observed = bias + %CVx 2

2.1 Statistical Analysis

Microsoft Excel was used for mean, SD, CV and bias calculation.

3. RESULTS

CV%, bias, sigma values, TEa and Z scores were calculated for clinical chemistry analytes, electrolytes and thyroid hormones and represented in the Tables 1-7. Precision of our clinical chemistry analytical method was excellent for all parameters (<5%) except for ALT, direct bilirubin and calcium (Table 1). Sigma values of TB, DB, ALT and calcium showed poor performance (sigma < 3) (Table 2). However observed total allowable error was lesser for majority of the analytes except total bilirubin, calcium, creatinine, urea (Table 2). Precision was good for sodium and chloride (<5%) (Table 3), however CV for potassium was also acceptable (<10%). T3 and TSH had acceptable CV and sigma score (Table 5). Summary of sigma scores and Z-scores for chemistry analytes, electrolytes and hormones are represented in Tables 6 and 7.

Table 1. TEa, bias and CV% of clinical chemistry analytes

	TEa – CLIA	Bias	CV%-L1	CV%-L2
ALB	10	2.81	1.15	0.511
ALP	30	6.12	1.84	1.75
ALT	20	10.22	7.62	2.83
AST	20	5.59	3.11	4.87
TB	20	12.09	3.125	1.47
DB	20	12.59	28	3.33
CA	11	4.69	7.71	1.62
CHOL	10	2.69	1.5	2.1
CREAT	15	8.81	8.2	1.77
GLU	10	3	1.25	2.12
HDL	30	3.08	1.76	1.19
TP	10	0.51	1.68	1.299
TG	25	2.25	2.23	1.28
UA	17	5.02	3.25	0.45
UREA	10	3.01	2.75	4.45

Table 2. Sigma values, Z score and TEa of chemistry analytes

	Sigma –L1	Sigma -L2	Z –score	TEa of our lab	
				L1	L2
ALB	6.25	14.07	1.2	5.11	3.83
ALP	12.98	13.64	3.6	25.46	15.88
ALT	1.28	3.46	2.1	9.8	9.62
AST	4.63	2.96	1.9	11.81	15.33
TB	2.53	5.38	2.9	68.59	19.25
DB	0.26	2.22	1.2	18.34	15.03
CA	0.82	3.89	0.9	20.11	7.93
CHOL	4.87	3.48	1.7	5.69	6.89
CREAT	0.75	3.5	2.0	25.01	12.35
GLU	5.6	3.3	1.5	5.5	7.24
HDL	15.73	23.3	2.0	6.6	5.46
TP	5.65	7.3	0.4	6.71	4.81
TG	10.2	17.8	1.0	3.87	3.11
UA	3.63	26.6	2.0	11.52	5.92
UREA	2.54	1.57	0.5	8.51	11.91

Table 3. CV%, bias and TEa (different guidelines) for electrolytes

	%CV	Bias	TEa-CLIA	TEa- RCPA	TEa-RILIBAK
Sodium	3.2	0.57	2.85	5	2
Potassium	6.13	2.22	12	8	5
Chloride	1.2	1.24	5	8	3

Table 4. Sigma values for electrolytes as per defined guidelines, Z score and Tea

	Sigma CLIA	Sigma RCPA	Sigma RILIBAK	Z score	Observed TEa
Sodium	0.71	1.38	0.45	-0.178	6.97
Potassium	1.6	0.94	0.45	0.355	14.46
Chloride	3.13	5.68	1.47	0.99	3.64

Table 5. CV%, bias, sigma values and Z score of thyroid hormones

Hormones	CV%	Bias	Sigma	Z score
T3	3.6	2.09	3.01	0.59
T4	17.38	24.02	0.979	1.82
TSH	9.4	6.96	3.32	0.79

Table 6. Summary of sigma metrics of all biochemical parameters

Sigma metrics	Chemistry analytes		Electrolytes	Hormones
	L1	L2		
<3	Urea, ALT, BD, BT, Ca, Creatinine	Urea, AST, BD	Sodium, potassium	T4
3-6	Glucose, AST, cholesterol, uric acid, total protein	ALT, cholesterol, BT, calcium, creatinine, glucose	Chloride	T3, TSH
>6	Triglyceride, ALP, HDL, albumin	TG, uric acid, ALP, HDL, albumin, total protein	-	-

Table 7. Summary of Z scores for all biochemical parameters

Grading	Range	Z scores		
		Chemistry analytes	Electrolytes	Hormone
Excellent	0-1	CA, TP, TG, urea	Sodium, potassium, chloride	T3, TSH
Acceptable	1-2	Albumin, ALT, AST, DB, TC, Creat, glucose, HDL, UA	-	T4
Not acceptable	>3	ALP, TB	-	

4. DISCUSSION

Sigma metrics of chemistry analytes assessed for sigma metrics, suggest an acceptable performance for majority of the parameters except TB, DB, ALT and Calcium (Tables 1, 2). Similar studies were done by Bhavna sing et al, Sunil Nanda et al, Nitinkumar et al. [4-6]. Variations in sigma values between our study and others can be attributed to the difference in the instrument used, quality control material used and other pre & post analytical conditions. In order to calculate sigma, we have calculated mean, standard deviation (sd), coefficient of variation (cv) and bias. SD quantifies how close numerical values are in relation to each other. Since SD typically increases as the concentration of analyte increases, CV can be regarded as statistical analyzer. Since CV is the ratio of two, it cancels that effect. CV is therefore standardiztion of the SD that allows comparison of variability estimates regardless of analyte concentration. CV is dimensionless and does not vary with changes in measurement units.CVs of 5% or less generally denotes a good method performance, whereas CVs of 10% and higher implies unsatisfactory performance. We have obtained higher CV(>5%) for SGPT, creatinine, calcium and direct bilirubin in L1. CV is correlated to precision. Precision is closeness of agreement between independent, repeated results obtained from the same sample under specific conditions. Lesser the CV, better is the precision. This suggests that precision is low for above mentioned parameters. However our CV% is acceptable for all analytes for level 2 IQC.

Bias is the difference between the measured result and actual value. It is used to describe the inaccuracy of the method. In our study we have obtained a higher bias value for SGPT, creatinine, BD & BT. Lower the bias more is the accuracy. This suggests the chances of inaccuracy in the methods for measurement of above mentioned analytes which need evaluation.

The Six Sigma scale typically runs from zero to six, but a process can actually exceed Six Sigma, if variability is sufficiently low as to decrease the defect rate. In industries outside healthcare, 3 Sigma is considered the minimal acceptable performance for a process. When performance falls below 3 Sigma, the process is considered to be essentially unstable and unacceptable [14]. Sigma values <3 for Urea, ALT, BD, BT, Ca (L1) and Glucose, urea, AST, BD (L2) were obtained.

Sigma values <3 for Urea, ALT, BD, BT, Ca and creatinine (L1) and urea, AST, BD (L2) were obtained. A very stringent internal QC has to be followed for these parameters, and the frequency of internal QC (n) should be increased and corrective action should be taken for these parameters.

Sigma value between 3-6 were obtained for Glucose, AST, cholesterol, uric acid, total protein (L1) and ALT, cholesterol, BT, calcium, creatinine and glucose (L2). For a 3 sigma process, use a multi rule procedure with number of QC of 6 or 8 have to be used. For a 4 sigma process, use 2.5 SD control, limits or a multi rule procedure with n=4 have to be used. For a 5 sigma process, use 3.0 SD control limits with n=2 have to be used. For a 6 sigma process (or higher), use 3.5 SD control limits with N (number of controls to be run per day)=2 have to be used. That is QC should be run at higher frequency need to be run for analytes attaining sigma between 4-5 and 3-4 respectively.

Sigma was more than 6 for Triglyceride, ALP, HDL, albumin (L1) and TG, uric acid, ALP, HDL, albumin, total protein (L2).However Z score was not acceptable for ALP(>3). Less stringent QC rules can be followed in this case. In such cases, false rejections can be minimized by relaxing control limits up to 3 s [15].

Functioning at the 3-sigma level is regarded as the minimum acceptable level of quality. The six sigma idea asserts an association between the numbers of product defects, wasted operating costs and levels of customer satisfaction. It can be inferred that as sigma increases, the consistency and steadiness of the test improves,

thereby reducing the operating costs. As sigma increases, the consistency, reliability, steadiness and overall performance of the test improves, thereby decreasing the operating costs [16].

CV% was less than 5 for sodium and chloride whereas less than 10 for potassium (Table 2).

Total allowable error (TEa) values vary in different guidelines. As per rules, observed TEa must be lesser than that by guidelines or close to it. However our TEa is greater than that by taken guidelines for sodium and potassium suggesting a need to re-evaluate methodology and instrument (Table 2). But there are several guidelines which have higher TEa [17] which implies that we cannot conclude just based on TEa.

TEa is less for electrolytes suggesting the criticality of the analytes and also it suggests a stringent quality control. As sigma depends on TEa, its value also varies.

In our study, sigma value for both sodium and potassium were less than 3 as per all the three guidelines. Only chloride has sigma value in acceptable range (Table 4). The reason for this being calculation of sigma based on TEa which is different in different guidelines. Sigma calculated by using RCPA guidelines is highest whereas that with RILIBAK is lowest for all the parameters.

The parameters which demonstrated wide variation in the sigma values for both the levels of QC should be evaluated with discretion. The methodology should be re -evaluated. There is also a need to strictly follow Westgaurd multi rules as well as increase the number of QC runs so as to abolish this discrepancy. It is of utmost important to practice stringent maintenance of ISE unit to alleviate inaccuracies resulting in poor performance of ISE module.

There is another school of thought which opines that sigma value for a particular parameter also depends on its biological variation. For example, high biological variation parameter such as triglyceride measured by any instrument will give acceptable sigma level. While electrolytes like sodium and potassium which are having low biological variation would give low results even if we perform well in our internal quality control.

Parameters can get affected by many other factors. Stored vials of control material can have changes related to environmental factors. Different sensor systems react differently toward various matrices of quality-control materials.

Higher CV% was observed for T4 whereas lower CV for T3 and TSH.As CV is correlated to precision. Lesser the CV, better is the precision. This suggests that precision is high for T3 and TSH.In our study we have obtained low bias values for T3 and TSH. This suggests that the methods for measurement of above mentioned analytes are accurate. But high bias value for T4 suggests that its measurement method needs an evaluation.

We have sigma values <3 for T4 whereas just above 3 for T3 and TSH. It implies that procedures for T3 and TSH are in minimal acceptable standards whereas that for T4 needs a serious evaluation. However based on z-scores, our results are excellent for T3 and TSH, acceptable for T4.But this is not sufficient in health care sector as a single error may take a life. We need to achieve good results with regard to sigma metrics.

For less than 3 sigma that is for T4 method performance must be improved before the method can be used for routine production [1]. Sigma below 3 calls for improvement in the method as quality of the test cannot be assured even after repeated QC runs [15]. Upgraded analyzers and better methodologies may help in achieving sigma values. For less than 3 sigma, method performance must be improved before the method can be used for routine production [1]. For a method with sigma below 3 calls for improvement in the method as quality of the test cannot be assured even after repeated QC runs [15]. Thus sigma metrics values are useful in setting the internal QC acceptability criteria.

To achieve 3 sigma, usually only obvious changes and corrections are required.To achieve 4 sigma, processes must also be improved .To achieve 5 sigma, the design of the processes must be improved. To achieve 6 sigma, requires rigorous tools and a design for perfection.

5. CONCLUSION

To conclude, majority of our biochemical analytes had an acceptable sigma values. Even though some parameters possessed low sigma values, CV% was in acceptable range. We can say that if we apply sigma for parameters with narrow biological variation (like electrolytes) which have narrow allowable total error, then chances of low sigma value increases. Sigma

value is inherently dependent on TEa definition given by various guidelines. In spite of getting acceptable CV our sigma values were not satisfactory. It is important to see that we don't apply any stringent criteria in laboratory which can cause unnecessary wastage of time, resources, manpower and cause false rejections. Upgraded analyzers and better methodologies may help in achieving sigma values.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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