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ORIGINAL STUDY

Sigma-Metric Analysis to Evaluate Quality Management of Analytical Processes Using RCA and QGI in a Clinical Biochemistry Laboratory, South India

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Abstract

Introduction: **This study aimed to identify laboratory errors at the earliest through Sigma-metric analysis and to evaluate quality management of analytical processes.**

Methods: **Sigma-metrics and Quality Goal Index (QGI) were calculated by harvesting the IQC and EQC data of an accredited laboratory for 31 biochemical parameters run on Roche Cobas6000 and e411. Those with Sigma $\leq$ 2 were further analysed by applying the various Westgard rules, as suggested**

Results: **Nearly 13 chemistry analytes showed world-class performance with Sigma >6 and most of the immunoassay parameters showed marginal performance with sigma >2 $\leq$ 6. Sodium, Chloride, Total T4, Beta-HCG and TSH were found to have Sigma <2 indicating unacceptable performance. A significant improvement was observed in the Sigma-metrics analysis after performing the root cause analysis**

Conclusion: **Sigma-metric analyses the quality management of various analytical processes in biochemistry. The poor assay performance will be picked up by the Root cause analysis and Quality Goal Indices calculation. With the help of RCA and QGI, we plan to increase the resource management by decreasing the frequency of QC runs.**

Keywords: Allowable total error, Quality control, Quality goal indices, Root cause analysis, Sigma-metrics, Total quality management

1. Introduction

Total Quality Management System(QMS) in the laboratories world-wide targets at the appropriate collection, analysis, and delivery of accurate and timely reports to the right person [1]. Laboratory is a dynamic area where errors can occur due to various reasons such as personnel, instruments, reagents, calibrators and QC materials used. Nearly 70% of patient-related decisions in hospitals are based on laboratory results. The estimated error-rates in the three different phases are 30–75%(pre-analytical), 4–30%(analytical) and 9–55%(post-analytical) respectively [2]. Quality Control(QC) is the foundation for ensuring accuracy(Bias%) and precision(CV%) of the analytical process and helps in the detection of immediate errors during the analytical process in the laboratory. It involves the assay of Internal Quality Control(IQC) and External Quality Control(EQC). The IQC ensures continuous monitoring of the analytical systems on a daily basis [Precision-CV%] and assures that the patient

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reports released everyday are reliable and valid while the EQC analyzes and reports a control material given by an external agency once a month and assures the laboratory of its accuracy [Bias%] [3]. Dr. James O. Westgard proposed several control rules and the use of different graphical charts in the year 1981 to evaluate the QC performance [4]. Neither IQC nor EQC can be used for assessing the exact number of errors in the laboratory and hence the need for our study, as employing sigma-metrics provides a quantitative framework for assessing process performance and creates a scientific basis for designing an appropriate QC strategy [4]. A widely-accepted QMS was initially used as the product of innovation at General-Electric and Motorola company and was never a part of healthcare industries until the early 2000's [5,6]. Six-Sigma quantifies the performance of processes as a rate of Defects-Per-Million Opportunities (DPMO). As noted from history, the goal of Six-Sigma is to reduce all variations in a given process and improve performance thus achieving both quality and efficiency. The entire analysis concentrates on regulating the process to six Standard Deviations (6 SD's). A process that is six-sigma compliant will produce only 3.4 DPMO. It can be inferred that as sigma increases, the consistency and steadiness of the test improve, thereby reducing the operating costs [5–8].

As the laboratory was NABL accredited by the Quality Council of India, the staff-members actively captured all the details as per the requirements of the accreditation body. However, there were still errors which could not be picked up at the earliest. Hence, the present study aimed to take the quality of the lab to the next level by performing a sigma-metric analysis. The analysis would give scope for improvement as a thorough Root Cause Analysis (RCA) and Quality Goal Index (QGI) calculation was planned for those analytes with an unacceptable performance (Sigma<2). Most laboratories that use sigma-metrics for evaluation of QC performance have done the same for either Clinical Chemistry (CC) or Immunoassay (IA) parameters separately, however, the present study aimed to measure the sigma-metrics for both at the same time and also used it as a continuous monitoring tool for rectifying errors regularly.

2. Methods

The study was conducted in a NABL accredited Clinical Biochemistry laboratory of a tertiary care teaching hospital in South India. The IQC data of 31 analytes were collected retrospectively for a period of 10 months from May-2020 to February-2021. This was followed by collecting data from March to September-2021 prospectively only for those parameters which showed Sigma<2 during the earlier mentioned period (Sigma metric analysis was performed for all parameters, but only those parameters with Sigma<2 are depicted here in further analysis). The Ethical Clearance to collect the data was obtained from the Institutional Ethical Board, with letter number - IEC/210421/24NCT/2021–22. The Mean, SD, and coefficient of variation (CV%) from the 10 months' IQC data was obtained from Infinity-Software and Bias% from the last 10 months EQC data was obtained from the BIORAD-EQAS program. The Sigma values(σ) were calculated from the Total Allowable Error (TEa) obtained for acceptable performance from the CLIA guidelines [9] and using the CV% and Bias% as per the below formula:

$$\text{Sigma values}(\sigma) = (\text{TEa} - \text{Bias}\%)/\text{CV}\%$$

TEa = Values obtained as per Clinical Laboratory Improvement Amendments(CLIA) guidelines [9].

Bias=(mean of all laboratories using the same instrument and method–lab's mean)/mean of all laboratories using the same instrument and method) X 100%.

Following the calculation of Sigma, the analytes shall be grouped based on their values as follows [10]:

1. Sigma≥6 = Analytes with World-class performance
2. Sigma≥3 < 6 = Analytes showing excellent to marginal performance.
3. Sigma≥2 < 3 = Analytes showing poor performance.
4. Sigma<2 = Analytes with unacceptable performance.

The QGI and RCA were performed to identify the causes for poor and unacceptable performance and the number of QC runs were determined accordingly. The QGI can be calculated using the formula Bias%/ CV%. It helped in determining the cause for lower sigma-metrics and thereby improve the choice of quality control. A value < 0.8 indicated that imprecision, whereas a value > 1.2 indicated inaccuracy [13].

2.1. Instruments, IQC and EQC used for analysis

The instruments used for the analysis were the Integrated analyzer Roche Cobas6000 (c501+e601+

electrolytes) and Roche Cobas-e411(only IA) respectively. The IQC for CC and IA analysis were procured from BIORAD (Hercules, California 94547 USA) laboratories, Inc. The IQC used was Lyphochek Assayed Chemistry Control (c-310-5) with Lot no. 26450 and Lyphochek Immunoassay Plus Control (370) with Lot nos.40370 & 40380 (40370 - May 2020 to11/09/2020 and 40380–12/09/2020to30/09/2021) respectively. The Standard Operating Procedure for the IQC plan in the present laboratory was as follows: Two levels (L1+L2) of CC and IA-IQC (L1+L2/L2+L3/L1+L3) for all analytes were run early in the morning before running patient samples every day. Two levels IQC for Renal Function tests (Glucose, Urea, Creatinine, Uric acid, Electrolytes) and Liver Function Tests (Total and Direct Bilirubin, Total Protein, Albumin, AST, ALT and ALP) were run once in 8hrs respectively. Another level of IA-IQC (L1/L2/L3) was run after 8 h for only thyroid function tests. Westgard-rules were applied for the interpretation of the IQC results. The rules 1_{3s}, 2_{2s}, R_{4s}, $4_{1s,}$ and 10X rules were considered as rejection, and 1_{2s} was considered as a warning rule for the respective run. The laboratory of this tertiary-care hospital was registered with the yearly BIORAD-EQAS PROGRAM for CC and IA(Monthly program) analytes for both instruments respectively.

2.2. Statistical analysis

Data collected were entered in MS Excel 2010. Descriptive analysis measures like Mean,SD and CV % were obtained from the IQC data. Bias%, Sigma and QGI values was calculated using the formulas as described in the methodology section. The TEa values were as per the CLIA guidelines.

3. Results

A total of 31 analytes run on two different instruments were selected for analyzing the Sigma-metrics. About 26 analytes (22-CC and 04-IA) were run on Roche Cobas 6000 and about 05-IA analytes were run on Roche Cobas e411.

The descriptive statistics of the CC and IA, IQC and EQC run on Roche Cobas 6000 and E411 of various analytes such as Mean, SD, CV%, and Bias% are depicted in Tables 1 and 3. The TEa, Sigma-value, and QGI are depicted in Tables 2 and 4. The results after the RCA and QGI analysis are as depicted in Tables 6-8 respectively.

4. Discussion

"Quality is everyone's job" was how Dr. James O Westgard, described Quality management(QM) in clinical laboratories. In healthcare institutions, every patient visiting the hospital needs to be clinically examined, diagnosed and treated with best options available, ensuring patient safety and highest possible quality. Often based on the laboratory test, another procedure may be required immediately, just-in-time for diagnosis and treatment. Hence the delivery of healthcare stresses upon the highest level of quality and the most advanced QMS to be in place.

Six-Sigma incorporates robust techniques such as Define-Measure-Analyze-Improve-Control and RCA to find and eliminate defects and variations within a process. It also offers an unbiased evaluation of analytical methods and instrumentation along with a judicious plan needed for active implementation [8]. In the present scenario, most of the laboratories worldwide design their IQC protocol based on the standard guidelines of the respective countries. It includes the number of times and number of levels the IQC is scheduled per day depending on the number of patient samples received in a laboratory [15,16]. In India, The NABL 112 (National Accreditation Board for Testing and Calibration Laboratories) guidelines are followed which suggests two levels of IQC to be run before running the patient's samples and then subsequently one level IQC once in every 8 h which ensures quality in the laboratories. However, good laboratory practice requires every individual laboratory to design its own customized Individualized Quality Control Plan. It is a protocol based on Sigma-values obtained from analysis that ensures the reduction of laboratory errors by maintaining six SD's between the parameter average and its upper and lower limits [11].

4.1. Statement of principal findings

1. Out of twenty two parameters run on C501, nine of them have shown world-class performance with $\sigma > 6$ in both level CC analytes (Amylase, AST, HDL-Cholesterol, Creatine Kinase, Creatinine, LDH, Magnesium, Triglycerides and Uric acid) and nearly five parameters have a $\sigma > 6$ in one level CC analytes {Iron (L1), ALP, ALT, Total Bilirubin and Potassium (L2)}. Only two analytes Sodium and Chloride were found to have a $\sigma < 2$ indicating an

Table 1. Descriptive statistics of the Clinical Chemistry parameters IQC and EQC (Roche Cobas 6000).

Sl No.	Analytes	Mean		SD		CV%		Bias%
		Level 1	Level 2	Level 1	Level 2	Level 1	Level 2	EQC
1.	Albumin (g/dL)	4.25	2.88	0.10	0.08	2.27	2.74	0.169
2.	Alkaline Phosphatase (U/L)	96.83	385.18	4.75	16.44	4.90	4.27	1.87
3.	ALT(ALAT/GPT) [U/L]	25.23	89.7	0.89	2.07	3.54	2.31	0.04
4.	Amylase (U/L)	80.44	371.23	1.84	6.44	2.29	1.73	0.046
5.	AST/GOT (U/L)	38.26	207.95	1.12	4.16	2.93	2	0.12
6.	Bilirubin, Total (mg/dL)	0.88	4.09	0.04	0.12	4.92	2.93	0.385
7.	Calcium (mg/dL)	9.57	12.23	0.18	0.22	1.84	1.81	0.39
8.	Chloride (mEq/L)	110.19	86.47	3.21	2.02	2.91	2.34	0.91
9.	Cholesterol, HDL (mg/dL)	65.38	23.62	1.85	0.63	2.83	2.69	0.5
10.	Cholesterol, Total (mg/dL)	24.58	95.32	4.28	1.96	1.77	2.06	2.43
11.	Creatinine kinase (U/L)	135.88	425.7	3.1	7.55	2.28	1.77	1.03
12.	Creatinine (mg/dL)	1.9	5.14	0.04	0.13	2.23	2.45	1.5
13.	Glucose (mg/dL)	80.16	274.16	1.8	5.61	2.24	2.05	2.71
14.	Iron (mg/dL)	245.36	69.07	5.57	2.44	2.27	3.54	1.68
15.	LDH (U/L)	176.49	366.2	3.66	7.17	2.08	1.96	1.37
16.	Magnesium (mg/dL)	2.08	4.38	0.08	0.14	3.91	3.14	0.53
17.	Phosphorus (mg/dL)	3.47	7.3	0.07	0.13	2.16	1.81	0.08
18.	Potassium (mEq/L)	4.03	6.26	0.08	0.09	1.89	1.42	1.27
19.	Protein, Total (g/dL)	6.35	4.18	0.14	0.09	2.14	2.24	1.19
20.	Sodium (mEq/L)	145.35	123.39	1.86	1.6	1.28	1.29	1.66
21.	Triglycerides (mg/dL)	196.4	96.86	4.31	2.62	2.19	2.7	0.59
22.	Uric Acid (mg/dL)	4.61	9.74	0.12	0.25	2.65	2.52	0.65

Table 2. Descriptive statistics of the Immunoassay parameters IQC and EQC (Roche Cobas 6000 & e411).

Analytes	Mean			SD			CV%			Bias%
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	EQC
Roche Cobas 6000										
Cortisol (μg/dL)										
Lot no.: 40370	2.85	17.9	26.64	0.14	1	1.65	4.89	5.58	6.18	4.28
Lot no.: 40380	3.66	15.67	25.14	0.23	0.97	1.22	6.34	6.2	4.84	4.28
Total T3 (μg/mL)										
Lot no: 40370	0.94	2.07	3.2	0.04	0.06	0.09	4.58	2.88	2.9	1.13
Lot no: 40380	0.86	2.25	3.33	0.04	0.08	0.13	4.1	3.48	3.75	1.13
Total T4 (μg/dL)										
Lot no: 40370	4.61	10.81	14.19	0.11	0.31	0.57	2.43	3.03	4.01	5.3
Lot no: 40380	6.43	10.8	14.24	0.44	0.61	0.93	6.84	5.65	6.5	5.3
TSH (μIU/mL)										
Lot no: 40370	0.5	5.85	39.74	0.01	0.14	1.3	1.85	2.48	3.29	0.06
Lot no: 40380	0.53	6.19	33.64	0.02	0.2	1.33	2.86	3.29	3.95	0.06
Roche Cobas e411										
hCG (mIU/mL)										
Lot no.: 40370	3.01	19.07	138.3	0.17	0.96	7.13	5.51	5.02	5.16	3.99
Lot no.: 40380	5.53	19.92	152.28	0.27	0.72	6.99	4.93	3.63	4.56	3.99
Total T3 (ng/mL)										
Lot no: 40370	0.99	2.13	3.43	0.05	0.23	0.3	4.82	10.93	8.67	0.24
Lot no: 40380	0.84	2.27	3.4	0.06	0.15	0.25	6.83	6.41	7.22	0.24
Free T4 (ng/dL)										
Lot no: 40370	0.83	2.54	5.11	0.025	0.1	0.22	3.1	4.1	4.22	1
Lot no: 40380	1.11	2.62	4.93	0.06	0.15	0.34	5.31	5.56	6.81	1
Total T4 (μg/dL)										
Lot no: 40370	4.39	9.57	1349	0.21	0.85	1.36	4.83	8.87	8.87	1.71
Lot no: 40380	6.31	10.45	14.29	0.29	0.48	0.75	4.58	4.63	5.23	1.71
TSH (μIU/mL)										
Lot no: 40370	0.47	5.6	37.34	0.02	0.25	1.49	3.75	4.45	3.98	4.13
Lot no: 40380	0.52	6.26	34.16	0.02	0.16	1.09	2.9	2.54	3.2	4.13

Table 3. TEa, Sigma metrics and QGI of clinical chemistry parameters.

Analytes	TEa		Sigma		QGI		Remarks
	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2	
Amylase (U/L)	30	30	13.08	17.31	0.02	0.03	–
Creatinine kinase (U/L)	30	30	12.71	16.37	0.45	0.58	–
Triglycerides (mg/dL)	25	25	11.15	9.04	0.27	0.22	–
Cholesterol,HDL(mg/dL)	30	30	10.42	10.97	0.00	0.00	–
LDH (U/L)	20	20	8.96	9.51	0.66	0.69	–
Creatinine(mg/dL)	15	15	6.39	5.34	0.71	0.59	–
AST/SGOT (U/L)	20	20	6.78	9.94	0.04	0.06	–
ALT/SGPT) [U/L]	20	20	5.64	8.64	0.01	0.02	–
Iron (mg/dL)	20	20	8.07	5.18	0.74	0.47	–
Magnesium (mg/dL)	25	25	6.26	7.79	0.14	0.17	–
Potassium (mEq/L)	12.41	7.99	5.89	7.85	0.64	0.88	–
Uric Acid (mg/dL)	17	17	6.17	6.49	0.25	0.26	–
Alkaline Phosphatase	30	30	5.74	6.59	0.38	0.44	–
Bilirubin, Total (mg/dL)	20	20	3.99	6.69	1.34	2.25	–
Calcium (mg/dL)	10.46	8.19	6.20	4.93	0.06	0.06	–
Phosphorus (mg/dL)	10	10	4.59	5.48	0.03	0.04	–
Cholesterol, Total(mg/dL)	10	10	4.28	3.67	0.03	0.03	–
Albumin (g/dL)	10	10	4.33	3.59	0.74	0.62	–
Protein, Total (g/dL)	10	10	4.12	3.93	0.56	0.53	–
Glucose (mg/dL)	10	10	3.25	3.56	1.21	1.29	–
Chloride (mEq/L)	5	5	1.41	1.75	0.31	0.39	**Imprecision**
Sodium (mEq/L)	2.752	3.242	0.85	0.85	1.30	1.29	**Inaccuracy**

Table 4. TEa, Sigma and QGI of Immunoassay parameters.

Analytes	TEa			Sigma			QGI			Remarks
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	
Roche Cobas 6000										
Total T4 (μg/dL)										
Lot no: 40370	20	20	20	6.05	4.85	3.67	2.18	1.75	1.32	–
Lot no: 40380	20	20	20	2.15	2.60	2.26	0.77	0.94	0.82	–
Cortisol(μg/dL)										
Lot no.: 40370	25	25	25	4.24	3.71	3.35	0.88	0.77	0.69	–
Lot no.: 40380	25	25	25	3.27	3.34	4.28	0.68	0.69	0.88	–
TSH (μIU/mL)										
Lot no: 40370	6	7.18	9.89	3.21	2.87	2.99	0.03	0.02	0.02	–
Lot no: 40380	11.32	9.69	11.86	3.94	2.93	2.99	0.02	0.02	0.02	–
Total T3 (μg/mL)										
Lot no: 40370	12.74	8.69	8.44	2.53	2.63	2.52	0.25	0.39	0.39	–
Lot no: 40380	13.95	10.67	11.71	3.13	2.74	2.82	0.28	0.32	0.30	–
Roche Cobas e411										
Total T4 (μg/dL)										
Lot no: 40370	20	20	20	3.79	2.06	1.81	0.35	0.19	0.17	**Imprecision**
Lot no: 40380	20	20	20	3.99	3.95	3.50	0.37	0.37	0.33	–
Total T3 (ng/mL)										
Lot no: 40370	15.15	32.39	26.24	3.09	2.94	3.00	0.05	0.02	0.03	–
Lot no: 40380	21.43	19.82	22.06	3.10	3.05	3.02	0.04	0.04	0.03	–
Free T4 (ng/dL)										
Lot no: 40370	9.04	11.81	12.92	2.59	2.64	2.82	0.32	0.24	0.24	–
Lot no: 40380	16.22	17.18	20.69	2.87	2.91	2.89	0.19	0.18	0.15	–
Beta hCG (mIU/mL)										
Lot no.: 40370	16.94	15.1	15.47	2.35	2.21	2.22	0.72	0.79	0.77	–
Lot no.: 40380	14.65	10.84	13.77	2.16	1.89	2.14	0.81	1.10	0.88	**Imprecision and Inaccuracy**
TSH (μIU/mL)										
Lot no: 40370	12.76	13.32	11.97	2.05	2.07	1.97	0.98	0.93	1.04	**Imprecision and Inaccuracy**
Lot no: 40380	11.58	7.66	9.57	2.57	1.39	1.70	1.42	1.63	1.29	**Inaccuracy**

Table 5. Sigma metric tools for QC design and frequency [13].

Sl. No	Sigma Metric	Control Rule	QC frequency
1	$\sigma \geq 6$	1_{3s}, N = 2	1 per 1000 patient samples
2	$\sigma \geq 5 < 6$	$1_{3s}/2_{2s}/R_{4s}$, N = 2	1 per 450 patient samples
3	$\sigma \geq 4 < 5$	$1_{3s}/2_{2s}/R_{4s}/4_{1s}$, N = 4	1 per 200 patient samples
4	$\sigma \geq 3 < 4$	All Westgard rules as above including 10X, N = 6	1 per 45 patient samples
5	$\sigma < 3$	Maximum Westgard rules, N = 6	1 per 10 patient samples

unacceptable performance and QGI<0.8 indicating an imprecision in IQC for over 10 months as depicted in Table 2 respectively.

2. Of the four IA analytes assayed on E601, only one analyte, Total T4 (L1 QC Lot No.40370) has a $\sigma > 6$ indicating world-class performance. Most of the other analytes show good to poor performance as depicted in Table 4 respectively. However, none of the analytes have shown unacceptable performance.
3. Of the five IA analytes analyzed on E411, almost all the analytes have yielded a Sigma of 2–4 indicating a marginal to poor performance. None of the analytes show world-class performance. Beta HCG (L2,40380), Total T4 (L3,40370), TSH (L2&3, 40370&40380) showed a $\sigma < 2$ indicating unacceptable performance. The QGI calculated for the same indicates Imprecision (QGI<0.8) for Total T4, whereas Imprecision and Inaccuracy (QGI = 0.8–1.2) for Beta HCG and TSH.
4. A repeat analysis (Tables 7 and 8) of the sigma-metrics from March to September 2021, after performing a thorough RCA and application of suggested Westgard rules and other Corrective action and Preventive action(CAPA) indicated an improvement for those analytes which had shown poor to unacceptable performance

4.2. Strengths

1. Sigma metric analysis was performed for both CC and IA parameters. It involves a retrospective analysis of all parameters followed by RCA&CAPA for analytes showing $\sigma < 2$ followed by a prospective analysis of those parameters with $\sigma < 2$ (follow up done).
2. Assessment of quality was based on both IQC and EQC performance, which in itself is a big step towards Quality Improvement in Medical Laboratories.

4.3. Limitations

1. CLIA guidelines were used as observed in previous studies. This does not have a Bias% defined for most of the IA parameters and a few CC analytes. This was a major limitation of this study and could be overcome by the use of Desirable Biological Variations for the analysis.

4.4. Interpretation within the context of the wider literature

1. **C 501:** The IQC rules followed for the analytes with $\sigma > 6$ can be relaxed i.e. only one 3_s or even a wider control limit can be used for these analytes. If we translate this sigma metric to the frequency of quality control run, then a minimum of 1000 patient samples can be run between each quality control run (Table 5). The probability of false rejection will be greatly reduced which will ultimately lead to reduced reagent consumption, save time and labor. Only Sodium and Chloride among the CC analytes were having an unacceptable performance. The same has been observed in previous studies conducted by Bhavna Singh et al. & Sunil Kumar Nanda et al. [3,12,16,17] An RCA performed for the same indicated that the Roche Cobas6000 Integrated analyzer was installed in April-2019 in the present laboratory. The IQC was reviewed daily by using Westgard Multi-rule Chart (as described above). A daily ISE maintenance was performed as suggested by the company service engineer. Approximately 6000 tests were run per month for electrolytes from May-2019 onwards. The Sodium, Potassium, Chloride, and Reference electrodes were replaced during preventive maintenance done in June 2020. The operator's manual for Roche Cobas 6000 indicates that the electrodes for Sodium, Potassium, and Chloride needs to be changed once in 2 months or at the end of 2000 tests performed and the Reference Electrode needs to be changed once in 6 months or at the end of 10,000 tests. However, the electrodes were replaced only in Feb 2021 as the IQC for both the parameters were well within range and the LJ-chart review every month showed the CV% to be well within the acceptable monthly peer-group CV% and no issues noted in EQAS performance too. Nonetheless, from the end of January 2021, there were repeated IQC issues for electrolytes and the CV% for Chloride was more

than the acceptable monthly peer-group CV%. The role of sigma-metrics is that it takes into account TEa which is very low for Sodium (around 4 mmol/L) and Chloride (5%) indicating the critical nature of these analytes. A repeat analysis as depicted in Table 8 shows the improvement in the Sigma-value for both Sodium and Chloride, however, Sodium still shows an unacceptable performance with Sigma <2.

2. **E601 -** An RCA for poor performance indicated that initially when the instrument was installed in April 2019, one level IQC was run every day for all IA parameters before running the patient samples. $1_{2s}/1_{3s}/2_{2s}$ were the only Westgard Multi-rules followed in the laboratory. R_{4s}, 4_{1s} or 10 X rules were not followed for IA parameters. Liquid Flow Cleaning was performed on e601 once in 15 days and daily maintenance was performed as per the instructions given. The calibrations were performed on new reagent lots and whenever IQC outlier was observed or when the monthly LJ-chart review revealed an unacceptable CV%. Another reason for low performance could be the personnel handling the instrument and IQC preparation. Though trained well, some still do not show the dedication required to maintain quality. An outlier was often missed by some technologists either out of sheer laziness, lack of interest, trainee technologists who were unaware of the correct IQC rules to be followed or due to a high load of patient samples. The IQC outlier was often troubleshooted by the consultant biochemists posted in the laboratory. All the results were withheld until the IQC was systematically corrected by troubleshooting and then patient samples were rerun before the release of final reports. During the process the technicians were educated on the effect of their negligence on patient management.
3. **E411** – An RCA of the above revealed that the Roche Cobase411 instrument was installed in 2014 and repeated gripper issues since beginning of 2019 resulted in instrument breakdown at various intervals. Though regular yearly preventive maintenance was performed by the service engineers and daily maintenance was done by the technicians, wear and tear of the instrument was noted by repeated breakdowns as documented in the Equipment Breakdown Register. A request for a new instrument was placed in December-2019 and due to the pandemic and nationwide lockdown, there was delay in installing and validating the new equipment. The probable reasons why most of the parameters show a poor to marginal performance with some showing unacceptable performance may be due to: 1) Data input from both old and new instruments 2) Reduction in the sensitivity of the old instrument to pick up errors 3) Monthly LJ-chart review of the parameters showing an acceptable CV% 4) An improper IQC schedule (before Nov-2020).

4.5. Implications for policy, practice and research

1. **C501-** Stringent maintenance of the ISE module along with the change of electrodes as suggested by the manufacturer could help us prevent releasing any false reports to the patient. Hence what could be missed during IQC review through monthly LJ plots such as the above systemic errors could have been picked up earlier if Sigma-metrics analyses were performed. Unacceptable Sigma Scores for Sodium allowed us to further think on documenting achievable goals specific to the analyzer used and the analyte being tested.
2. **E601 -** A significant improvement in Sigma-metric analysis was observed (Table 8), as guidelines were followed and both senior and trainee technologists were re-trained in preparation and run of IQC.
3. **E411** – An improvement in the Total T4, Beta-HCG, and TSH was noted with T4 and TSH showing a good to excellent performance while Beta-HCG showed only a marginal improvement (Table 8).

James O. Westgard describes certain good practice guidelines that can be followed by everyone in the laboratory [4]. They include the following: 1) Use of 2SD control limits for all analytes not advisable, 2) Use of same control rules for all tests is not sensible, 3) Selecting an IQC procedure for individual tests based on the Sigma-value(CV%, Bias % & TEa) will be better, 4) Minimizing the false rejections to maximize response to real problems when they occur, 5) Building in the error detection is necessary to detect medically important errors by a selection of appropriate control rules and numbers of control measurements and last but not the least, 6) Complement the IQC procedure with an appropriate Total Quality Control strategy [4].

Table 6. Comparison of the Sigma metric analysis of the present study with previous studies.

		Bhavna Singh et al. [12]		Sunil Nanda et al. [3]	Kirankumar P. Chauhan et al. [14]		Kumar BV et al. [11]		Bingfei Zhou et al. [13]		Study by present group of authors				
Year of study		**2011**		**2013**	**2017**		**2018**		**2019**		**2020–21**				
Total analytes		15		13	12		16		19		31 (22 + 09)				
Clinical chemistry/ Immunoassay		Clinical chemistry		Clinical chemistry	Clinical chemistry		Clinical chemistry		Clinical chemistry		Clinical Chemistry & Immunoassay				
Study period		6 months		6 months	12 months		12 months		6 months		10 months				
Instrument used		Olympus biochemistry analyser		Cobas integra auto-analyser	Cobas integra 400 plus auto-analyser		VITROS 4600		AU 5800 P1 & P2 module + ISE module		Roche Cobas 6000 (C501 + E601) & Roche Cobas e411				
Total instrument		1		1	**2**		1		**2**		**2**				
IQC material		RANDOX		BIORAD	RANDOX		BIORAD		BIORAD		BIORAD				
QC level		2		2	2		2		2		2 level for chemistry & 3levels for Immunoassay				
EQAS		RANDOX		CMC	BIORAD		BIORAD		NCCL of China		BIORAD				
Tea Guidelines followed		CLIA		CLIA	CLIA		CLIA		CLIA		CLIA				
Six sigma (σ)		L1	L2	L1 and L2	L1	L2	L1	L2	L1	L2	C501 (Chem)		E601 + E411 (Immunoassay)		
											L1	L2	L1	L2	L3
World class performance	σ ≥ 6	05	04	04	04 04	06 05	04	04	06 06	07 07	10	13	01	–	–
Excellent performance	σ ≥ 5 to < 6	01	01	02	01 –	03 02	01	03	03 02	– 03	04	03	–	–	–
Good performance	σ ≥ 4 to < 5	–	02	01	05 06	01 03	03	01	02 02	05 01	04	–	01	01	01
Marginal performance	σ ≥ 3 to < 4	06	03	02	– –	– –	03	04	03 02	03 02	02	04	08	04	05
Poor performance	σ ≥ 2 to < 3	02	04	03	02 01	02 02	02	01	05 03	04 03	–	–	08	10	09
Unacceptable performance	σ < 2	01	01	01	– 01	– –	03	03	– 01	– –	02	02	–	03	03
Analyte showing unacceptable performance		Sodium		Chloride	Urea		Total Cholesterol, Albumin and Potassium		Phosphorus		Sodium & Chloride		Level 2 Beta HCG, Level 3 T4, Total and Level 2 & 3 TSH		
% of parameters showing world class performance		26.67%		30.77%	33.33%	50% 41.67%	25%		P1 31.58% P2 31.58%	P1 36.84% P2 36.84%	45.45%	59.01%	E601 11.11% E411 -	–	–
% of parameters showing unacceptable performance		6.67%		7.7%	8.33%	-	18.75%		–	–	9.09%		-	E411 33.33%	E411 33.33%

Table 7. Descriptive statistics of all analytes which were followed up from March 2021 to Sept 2021.

Analytes	Mean			SD			CV%			Bias%
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	EQC
Roche Cobas 6000										
Chloride mmol/L	105.01	85.76	–	1.95	1.54	–	1.86	1.80	–	1.24
Sodium mmol/L	145.83	125.87	–	1.76	1.88	–	1.21	1.49	–	1.44
Total T4 μg/dL (e601)	6.06	9.90	13.30	0.26	0.46	0.53	4.24	4.62	3.97	1.72
Total T4 μg/dL (e411)	6.38	10.67	14.72	0.21	0.35	0.47	3.43	3.27	3.18	5.69
TSH μIU/mL (e411)	0.53	6.02	32.88	0.02	0.17	1.01	3.16	2.82	3.08	2.44
Beta HCG mIU/mL (e411)	5.37	19.73	153.87	0.25	0.96	6.35	4.63	4.85	4.13	3.39

Table 8. TEa, Sigma and QGI of all analytes followed up after Root Cause Analysis and Corrective Action and Preventive Action from Mar 2021 to Sept 2021.

Analytes	TEa			Sigma			QGI			Remarks
	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	Level 1	Level 2	Level 3	
Chloride mmol/L	5	5	–	2.02	2.09	–	–	–	–	–
Sodium mmol/L	2.75	3.17	–	1.08	1.16	–	1.19	0.97	–	**Inaccuracy**
Total T4 μg/dL (e601)	20	20	20	4.31	3.96	4.60	–	–	–	–
Total T4 μg/dL (e411)	20	20	20	4.17	4.38	4.5	–	–	–	–
TSH μIU/mL (e411)	15.09	8.47	9.21	4.00	2.14	2.20	–	–	–	–
Beta HCG mIU/mL (e411)	13.97	14.60	12.38	2.29	2.31	2.18	–	–	–	–

5. Conclusion

The current study has shown World-class performance for most of the CC analytes and marginal to poor performance of IA analytes. As pointed out in the discussion, the laboratory has identified several issues that need to be sorted out to have an excellent to world-class performance for all analytes and the same when addressed have shown improved performance. The issues identified during RCA proved to be invaluable. A commitment to perform sigma-metrics once in 6 months was planned along with training and education of technicians and making Quality everyone's job. Sigma-metrics will augment resource management as it involves a more holistic approach by decreasing the frequency of QC runs. This would be beneficial to the entire patient population, laboratory-personnel and the treating physicians as patients receive high-quality reports from well-maintained laboratories and this helps the clinician to use discretion while treating the patient appropriately with less burden on further investigations.

Author contribution

Conceptualising the Idea, Writing up of the article and correction of the finalised manuscript: Sathish Raju Nilakantam. Conceptualising the Idea, Design of the work, Writing up of the article, Collection of the data, Statistical analysis, Formatting and correction of the whole manuscript: Kusuma K S. Conceptualising the Idea, Correction of the whole manuscript with suggestions for further analysis and corrections done at various stages of the study with contribution of methodological expertise: Akila Prashant. Conceptualising the Idea and providing guidance at crucial stages while doing the study & review of the final manuscript: Melanahalli Dayananda. Conceptualising the Idea and providing guidance at crucial stages while doing the study& review of the final manuscript: Suma Maduvanahalli Nataraj. Collection of the data, Statistical analysis, Writing up of the article at preliminary stages: Namratha G D.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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