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Original Article

First assessment the analytical quality specification in Clinical Chemistry laboratory, using Sigma scale and EQA/PT in Iran: a pilot study

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ABSTRACT

Background: To assess the analytical performance of quality trough external quality assesses and internal quality program data on sigma scale.
Method and material: Imprecision was determined from the cumulative Levey-jenning SD over the 6 month, bias was calculated from the external quality records, Finally, analytical sigma metric estimates were calculated for each Analytes by the following equation: sigma metric: (TEa – Bias)/CV. All function and statistical analysis were done in our Private laboratories.
Result: The sigma value >6 was observed for most analytes. Some of analytes have poor sigma metric <3 such as Creatinine and ALP in normal level and Calcium in pathologic level. Glucose, Urea, Uric Acid, Calcium, Phosphorous, total bilirubin, in normal levels and Urea, Creatinine, total and direct bilirubin in pathologic level have intermediate sigma metric 4-6.
Conclusion: Chemistry tests are not commodities. Quality varies significantly from manufactures to manufactures and method to method. The sigma-assessment from multiple EQA/IQC programs provides more insight into the performance of methods and quality. Laboratory seeking optimal quality program would do well to consult this data as part of their decision-working process.

Key Worlds: Sigma scale, quality control, EQA, proficiency test, clinical laboratory.

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INTRODUCTION

Clinical laboratories are particularly important discipline among healthcare services, because physicians make their decisions mostly in accordance with laboratory results (1). Also in life, there is continuous fluctuation of the components in biological fluids. The biological variation (BV) of analytes is of three types, namely, variation over the life span, cyclical variation and random variation. The latter causes subtle variation around the setting point of each individual which is responsible for the within-subject or intra-individual BV, while the overall variation is responsible for the between-subject or inter-individual BV. The BV and the analytical variation both affect the test result, but while the latter can be minimized, minimization of the former is not possible. Hence it is important to ensure that the analytical variation is kept minimized and does not contribute significant additional variation to that contributes by the BV (2). To achieve this goal, the laboratory must carry out quality control. The term "quality control" (QC) has been introduced in the clinical laboratory setting many decades ago, and refers to the statistical quality control that is commonly used in laboratories to monitor the routine performance of testing processes, detect possible errors, and correct problems before test results are reported. The analytical quality still remains the primary issue, because none of the other laboratory quality characteristics matter unless analytical quality is achieved (3).

A more modern assessment of quality can be attained through the use of the Sigma scale. Sigma scale combine, bias, imprecision, and the allowable total error and convert that into an overall assessment of the analytical quality of the test. The concepts of Six Sigma have been around industry and healthcare for decades (4). Sigma scale is easily interpreted and appreciated by laboratories and can be calculated for both qualitative and quantitative assays. In industries outside of healthcare, quality is assessed on the sigma scale with criterion of 3 as the minimum allowable sigma for routine performance and a sigma of 6 being the global for world-class quality (5).

Responsibility for assessment of quality assurance is shared by a number of interested parties; Laboratory personnel, legislative agencies, accreditation bodies, metrologists, and organizers of External Quality assessment (EQA) scheme or proficiency testing scheme. External Quality Assessment (EQA) and Proficiency Testing (PT) are valuable tools in the quality improvement process. They provide objective evidence of laboratory competence for customers, accrediting bodies, and regulatory agencies, and serve as a unique source of information that is not obtainable in other ways. In particular, internal quality control (IQC) and external quality assessment (EQA) programs are used to evaluate and continuously improve analytical quality. Currently, the terms External Quality Assessment (EQA) and Proficiency Testing (PT) are used interchangeably as valuable tools in the quality improvement process of clinical laboratory services (6).

The aim of present study was to: (i) undertaken to evaluate the quality of the analytical performance of clinical chemistry laboratory, (ii) study sigma metric of clinical chemistry analytes and plan the quality control strategy, (iii) calculate the total error in our laboratory and compare it whit that of biological variation guidelines (also commonly known as "Ricos goals").

MATERIAL AND METHODS

Instrument and materials: Data from the general chemistry analytes were analyzed over a period of 6 month from May 2016 to November 2016. The analytes assessed were Glucose, Urea, Creatinine, Uric acid, Triglyceride, Cholesterol, HDL, LDL, AST, ALT, ALP, GGT, Calcium, Phosphorous, total bilirubin, direct bilirubin using commercial available kit and running on Hitachi/917 (Roche, Germany) aoutoanalyzer. Internal Quality Control (IQC) was done according to westgard recommendation (7) and both normal and pathologic control materials were obtained from Roche, Germany, as well as SERO, Norway. The control SERO complies whit the direction set by the ISO 15189. Its value is traceable to international certified reference material: CRSE/IFCC, SRM927 c, SRM 909b, ERM-DA470, ERM-DA455, BRM 97/662, RMW 1066, and BCR470 (Seronorm human and human high were Traceable control material with target value for reference method). We used this control material as third party control. Validation of quality control of our lab was done by calculating 6 month mean from the data of EQAP (External Quality Program) provided by Iranian Association of Clinical Laboratory Doctors to establish the Bias for each Analytes.

Before beginning this study, aoutoanalyzer in all tests was assigned based on the target value of reference method that insert in control SERO. This was done by applying the equation of the regression linear.

Analytical Methods: Imprecision was determined from the cumulative Levey-jenning SD over the 6 month by using IQC according to westgard

recommendation , and CV% was calculated at the level of the instrument group mean (CV: Cumulative SD × 100/Laboratory mean). Bias was determined from EQA/PT records using the following formula:

(Mean of all laboratories using same instrument and method- Our mean)/ mean of all laboratories using same instrument and method) × 100. However, as we will see, ultimately the calculation of bias became irrelevant to the study. Total Error%: 1.9 CV%+ Bias % (7).

Biological variation (also commonly known as "Ricos goals") performance specifications were used as the basis for analytical performance specifications (Table1) (8).

Finally, analytical sigma metric estimates were calculated for each analytes by the following equation: sigma metric: (TEa – Bias)/CV (9). All function and statistical analysis were done in our private Laboratories.

RESULTS

Table 1 showed the Target Value and acceptable range of traceable Seronorm control (as a third party control with target value for reference methods of all analytes), laboratory men and the calculated Cumulative SD value in 6 month of the two normal and pathologic levels quality controls that run in our laboratory for different parameter. As the table show, all means of analytes were near to target value of reference method that use as third party control. However, in beginning some analytes such as Calcium, total bilirubin, Creatinine has impaired result.

Bias was calculated from data of EQAP provided by Iranian Association of Clinical Laboratory Doctors. This result is tabled in table 2; also calculated bias from EQAP was compared with difference the mean of Levey-jenning chart and target value for reference method of SERO control. Table 3 highlights TE (Total Error), TEa (Allowable Total Error), average of bias, coefficient of variation (CV) and sigma value of the two quality control levels for the different parameters. According to table 3, all TE are less than TEa that indicate high quality of internal quality management and good stability in laboratory system. The sigma value >6 was observed for most analytes. As the table show, most of analytes have sigma metric >6 such as AST, ALT, GGT in both normal and pathologic levels. In the other hand, some of analytes have poor sigma metric <3 such as Creatinine and ALP in normal level and Calcium in pathologic level. Glucose, Urea, Uric Acid, Calcium, Phosphorous, total bilirubin, in normal levels and Urea, Creatinine, total and direct bilirubin in pathologic level have intermediate sigma metric 4-6.

DISCUSSION

The quality control panel of clinical chemistry laboratory is divided into two IQC and EQA programs and measurement of laboratory analytical errors fall into two main categories, systematic error and random error. IQC is run daily and shows the imprecision, repeatability and random error of results by the standard westgard rules (10). Repeatability and precision are dependent on many factors such as instrument, reagent, samples, personnel, temperature and etc..., and usually determine by random errors.

Bias is the systematic difference between the expected results obtained by the laboratory's test method and the results that would be obtained from accepted reference method or reference materials. The reference methods may be a consensus reference like an EQA program or an inter-laboratory peer comparison program (11). Calculation of bias and trueness is an important factor in quality control of quantitative methods. To obtain of this aim, EQA programs have significant roles in both harmonization and standardization of laboratory results and calculation of bias. The role of EQA is to provide the reliable information that allows laboratories to assess and monitor the quality status of internal procedure and processes, suitability of the diagnostic system, accountability and competence of the staff. Furthermore, it cannot forget the central role recognized to EQA to define measurement uncertainly and bias of laboratories results. According to the definitive of ISO/REMCO N1129, commutability and tractability are the most important sample features that used in External quality program, because matrix effect of non-commutable and non-traceable can be interference with results and therefore mean of all laboratories are depended on methods and instruments (12).

Sigma metrics as performance indicator allows analyzing internal quality and external quality program in a flexible manner according to analytes performance, thus avoids repeated testing of IQC in a period when the system was performing stably, consequently minimizes un-necessary cost expenditure and man-hours wastage. Attainment of six sigma is envisaged as the gold standard for defining world class measure of quality, Adopting a Six Sigma quality control program enable the laboratory to have a standardize method to quantify laboratory quality and improved laboratory

efficiencies by eliminating redundant procedures (13).

In this study, we aimed to evaluate the analytical quality performance of clinical chemistry laboratory whit calculate the sigma metric in our laboratory. Assay above six sigma are all considered identical in performance and would share the same recommendation for QC design. Assay in the five sigma value are all considered excellent and, for the most part, receive the same recommendation for QC. According to the results, we have sigma value <3 for Creatinine and ALP in normal level. For less than 3 sigma value, method performance must be improved before the method can be used for routine production. For a method with sigma below 3 calls for improvement in the methods as quality of test cannot be assured even after repeated QC runs. For ALP, increased imprecision caused the paired sigma metric however bias is well. Creatinine results indicated the poor repeatability and trueness in internal and external quality programs. For Creatinine, we adjusted the instrument by linear regression according to rate blanked and compensated methods to increase the trueness and for increase the precision, commercial kit were changed. This function have effective role to improve sigma metric of Creatinine up to 4, however this functions has done after the end of this study. We have obtained sigma value 3 for Pho, Total bilirubin. For a 3 sigma process, use a multi rule procedure with number of QC of 6 or 8 have to be used. We have obtained sigma value 4 for Glucose, Urea, and Ca. For a 4 sigma process, use 2.5 SD control, limits or a multi rule procedure with number of QC of 4 have to be used. We have obtained sigma value 5 for U.A and direct bilirubin. For a 5 sigma process, use 3.0 SD control limit with number of QC of 2 have to be used. We obtained sigma >6 for most analytes in both normal and pathologic levels. For a 6 sigma process, use 3.5 SD control limit with number of QC of 2 (number of controls to be run per day) have to be used.

There is a "big data" benefit of comparing the results period of 6 months EQA/IQC. On an by analyzing the bias of method groups and standard deviation of IQC and calculating sigma metric based on that data, there is consensus among the EQA/IQC programs about the quality of analytical performance.

CONCLUSION

Finally, in modern assessment of quality program, westgard multi rules have not a good performance and efficacy in error detection and quality management, therefore quality manager shod be select suitable quality rules of control processes according to sigma metric. The six sigma motive is to minimize both variance and control processes to guarantee compliance with the critical specification. Method decision chart, Sigma SQC selection graph and Chart of operating specifications (POC) are new methods and effective system for managing analytical quality and useful metric to assess laboratory quality. Each and every laboratory must measure the CV and bias and calculate the total error and sigma metric for all analytes and design effective quality control panel to increase performance of quality.

Limitation: Since each study of sigma metric, the instrument and method group SDs include both between laboratory and within laboratory variations, and thus may be too pessimistic in their estimation of performance. Furthermore, these sigma metric projections may be impacted by matrix effect, since most EQA programs do not provide commutable specimens. Thus, it, may be that no patients, there is no analytical challenge. This is not just a problem facing this study, but a problem facing EQA programs in general.

Conflict of interest: The authors declare that no conflict of interests existed in the organization, results, presentation and the finance of the research article.

Table 1: Comparison of acceptable range and laboratory mean with cumulative SD for a period of 6 month.

Parameter	Normal Level			Pathologic Level		
	acceptable range	Lab mean	SD	acceptable range	Lab mean	SD
Glucose (mg/dL)	77 ± 5	78	1	183 ± 12	185	1.1
Urea (mg/dL)	27 ± 2	29	0.9	77 ± 5	78	2.1
Creatinine (mg/dL)	0.89 ± 0.06	0.9	0.02	2.86 ± 0.18	2.80	0.04
Uric Acid (mg/dL)	5.01 ± 0.32	5.0	0.09	11.5 ± 0.7	11.2	0.2
Triglyceride (mg/dL)	84 ± 5	88	2.8	386 ± 26	380	5
Cholesterol(mg/dL)	153 ± 10	155	1.8	235 ± 15	241	2
HDL (mg/dL)	34 ± 3	33	0.8	54 ± 6	55	0.8
LDL (mg/dL)	106 ± 9	107	1	147 ± 13	144	2
AST(IU/L)	46 ± 4	46	0.7	232 ± 19	230	2
ALT (IU/L)	42 ± 3	43	0.8	150 ± 12	145	2
ALP (IU/L)	88 ± 9	90	3	271 ± 27	265	4
GGT (IU/L)	42 ±4	43	1.1	150 ± 12	149	2.8
Ca (mg/dL)	9.3 ± 0.3	9.2	0.1	12.7 ± 0.4	12.8	0.2
Pho (mg/dL)	3.1 ± 0.17	3.12	0.08	9.02 ± 0.49	9.0	0.1
total bilirubin (mg/dL)	0.74 ± 0.08	0.76	0.05	4.19 ± 0.46	4.21	0.25
direct bilirubin (mg/dL)	0.32 ± 0.04	0.31	0.02	0.81 ± 0.09	0.77	0.06

Table2: Percentage bias calculated from EQAP results for a period of 6 months.

Parameter	Set 1	Set 2	Set 3	Set 4	Set 5	Set 6	Average
Glucose	1.0	1.9	1.9	0.9	1.1	1.8	1.1
Urea	1.0	2.3	0.8	1.8	2.1	1.2	1.15
Creatinine	3.2	1.3	2.5	3.0	2.1	1.9	2.3
Uric Acid	0.9	1.2	1.6	1.1	2.0	1.5	1.3
Triglyceride	3.3	1.9	1.8	2.6	1.5	2.8	2.3
Cholesterol	1.5	1.7	2.1	1.8	1.9	1.5	1.7
HDL	0.9	1.1	1.0	1.2	0.8	1.2	1.03
LDL	1.3	1.2	1.9	1.3	2.2	1.9	1.6
AST	2.2	2.1	2.8	2.0	3.1	2.7	2.4
ALT	1.9	3.1	2.2	1.7	2.1	2.4	2.2
ALP	3.3	2.5	2.9	1.8	3.0	2.1	2.6
GGT	3.1	3.2	1.9	3.0	2.5	2.1	2.6
Ca	1.0	1.2	1.1	1.2	1.0	1.1	1.2
Pho	2.3	3.1	1.9	2.7	2.1	1.9	2.3
total bilirubin	4.1	3.9	5.5	4.8	5.3	3.7	4.5
direct bilirubin	8.3	7.9	9.1	7.7	6.9	8.1	8

Table3: Average of calculated bias%, TE%, CV% and sigma values for a period of 6 months.

Parameter	TEa (%)	Average of TE%	Average Bias	Normal Level		Pathologic Level	
				CV%	Sigma	CV%	Sigma
Glucose	6.9	4.3	1.4	1.2	4.5	0.5	11.0
Urea	15.5	7.9	1.15	3.1	4.6	2.6	5.3
Creatinine	8.8	6.4	2.3	2.2	2.9	1.4	4.6
Uric Acid	11.9	4.7	1.3	1.8	5.8	1.7	6.2
Triglyceride	25.9	8.1	2.3	3.1	7.6	1.3	18
Cholesterol	9.01	3.7	1.7	1.1	6.6	0.8	9.1
HDL	11.6	5.5	1.03	2.4	11.1	1.4	10.8
LDL	11.9	3.3	1.6	0.9	11.4	1.3	7.9
AST	16.6	5.2	2.4	1.5	9.4	0.8	17.7
ALT	27.4	5.6	2.2	1.8	14	1.3	19
ALP	12.04	8.8	2.6	3.3	2.8	1.5	6.2
GGT	22.1	7.3	2.6	2.5	7.8	1.8	10.8
Ca	6.1	3.9	1.2	1	4.9	1.5	3.2
Pho	10.1	7	2.3	2.5	3.1	1.1	7
total bilirubin	26.9	16.8	4.5	6.5	3.4	5.9	3.7
direct bilirubin	44.5	20	8	6.4	5.7	7.7	4.7

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