# Assessment of Sigma Metric Results of Serum Parameters of Liver and Kidney Function Tested by Automated Chemistry Analyzer in Medical City Hospital

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## ABSTRACT:

**BACKGROUND:**

A major goal of quality assurance is the minimization of error rates in order to augment patient safety, six sigma or sigma metrics were used to assess the analytical quality of automated clinical chemistry, six sigma metrics is used in combination with total allowable error, method imprecision and bias. The goal is to achieve the highest possible sigma scale within the acceptable limits of total allowable error.

**OBJECTIVE :**

For assessment of sigma metrics results of serum parameters of liver and kidney function test tested by automated chemistry analyzer in Medical City Hospital.

**METHODS**:

In the current study, internal quality control (IQC) and external quality assessment (EQA) data were analyzed for the period from May 2017 to July 2017 using chemistry auto analyzer (Siemens Dimension RxL Max) at the Teaching Laboratories of the Medical City Hospital. Mean, standard deviation, coefficient of variation %, bias %, total error and sigma metrics were calculated for serum urea, creatinine, total serum bilirubin(TSB), alkaline phosphatase (ALP), aspartate aminotransferase(AST) and alanine aminotransferase (ALT).

**RESULTS**:

Excellent sigma values (≥6) were elicited for TSB (14) and AST (7.7), Satisfactory sigma values (≥3) were elicited for ALT (6) and ALP (4.6), while serum urea and creatinine performed poorly (2.5), (2.8) respectively on the sigma scale.

**CONCLUSION:**

Total serum bilirubin was the best performer on six sigma scale, for AST, ALT and ALP the sigma results was accepted. While serum urea and creatinine had poor performance, so there is need for improvement of their methods which should be controlled with greater attention to ensure quality.


**KEYWORDS:** chemistry analyzer, sigma metrics.

## INTRODUCTION:

Quality Control defined as overall system of actions whose purpose is to control the quality of a product or service so that it meets the needs of customers. The aim is to offer quality that is acceptable, adequate, dependable and economic [(1)].

The purpose of a clinical laboratory test is to assess the pathophysiologic condition of an individual patients to support with diagnosis, to observe or monitor therapy, or to assess risk for a disease or for progression of a disease. To have value for clinical conclusion creating, an individual laboratory test result must have total error small enough to reflect the biological condition being assessed [(2)] .

There are mainly two type of Quality Control:(1) Internal quality control (IQC) and (2) External quality control (EQC). IQC is a process that periodically examine a measurement procedure to confirm that it is performing according to pre-established specifications [(2)].

External Quality Control (EQC) determines all Statistical Quality Control (SQC) methods which are performed periodically (i.e. every month, every two months, twice a year) by the laboratory personnel with the involvement of an external center (referral laboratory, scientific associations, diagnostic industry etc.). It checks primarily the

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accuracy of the laboratory‘s analytical methods [3].

Sigma metrics is a management approach that seeks to increase the quality of process outputs by identifying and removing the causes of defects or error and reducing variability in manufacturing and business processes. The idea of the sigma metrics highlights a relationship between the numbers of product defects, wasted operating costs and levels of customer satisfaction. It can be established that as sigma increases, the reliability and steadiness of the test improves, so reducing the operating costs. The sigma scale is easily understood and appreciated by laboratories. Sigma values can be calculated for both qualitative and quantitative assays [4].

Six Sigma emphases on controlling a process to 6 SDs, which parallels to 3.4 DPM opportunities. Attainment of Six Sigma quality is considered to be a standard of excellence. Performance at the 3 sigma level is revealed the minimum acceptable quality for a production process. In simpler terms, a higher sigma metric means the systematic error that must be detected to ensure accurate results by the use of statistical QC is large and should be more easily identified. A lower sigma metric means QC must detect smaller systematic errors, which is more difficult [5].

The present-day healthcare services are only effective at 3 sigma’s and in some cases 4 sigma levels that translate roughly into 66,807 and 6,210 DPM opportunities respectively (Table 1) [6].

**Table 1: Level of sigma performance and corresponding Defect Per Million opportunities [6]**

| sigma level | DPMO |
|---|---|
| 6 | 3.4 |
| 5 | 233 |
| 4 | 6.210 |
| 3 | 66.807 |
| 2 | 308.537 |
| 1 | 690.000 |

Sigma metrics methodology first approved by Motorola at 1986, Motorola was really impacted by the quality improvements in foreign products. Under the guidance and support of Bob Galvin, the immediate origin of Six Sigma can be drawn to its early roots at Motorola and specifically to Bill Smith (1929 - 1993), Bill Smith was an employee of Motorola and a Vice President and Quality Manager of Land based Mobile Product Sector [7].

The important principle of the latent defect theory is that variation in industrial processes is the main offender for defects, and eradicating variation will help eliminate defects, which will in turn eliminate the wastes associated with defects, saving money and increasing customer satisfaction, variation is measured in terms of sigma values or thresholds, the threshold determined by Smith and agreed to by Motorola is 3.4 defects per million opportunities (3.4 DPMO), which is derived from sigma shifts from specifications. Motorola adopted the concepts and went on to win the first ever Malcolm Baldrige Excellence Award in 1988, just two years after Bill Smith’s introduction of Six sigma [7].

In health care systems the first application describing sigma metrics in a healthcare laboratory was available by Nevalainen et al in the year 2000. This application focused on pre analytical and post analytical processes [8]. The acceptance of Six sigma principles as a methodology to quality management in health care has grown in the last 10 years. In 2000, there were one article published describing specifically the application Six sigma, according to a PubMed search utilizing the phrase “six-sigma, sigma metrics, laboratory.” This number has risen to 105 articles published in 2016/2017 [9].

The aim of the study is to assess sigma metrics results of serum urea, creatinine, total serum bilirubin, aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase tested by automated chemistry analyzer in Medical City hospitals in Iraq.

## MATERIALS AND METHODS:

### Study design

Sigma metrics estimation was done by using the auto analyzer Dimension RxL Max Integrated Chemistry System from Siemens Healthcare Diagnostics at the Teaching Laboratories of the Medical City Hospital.

Estimation of sigma metrics according to Westgard by the following steps

1. Define goals for intended use (TE a),
2.Validate method performance (CV%, bias %),
3.Sigma calculation,
4.Select Westgard rule.

**Total allowable error (TEa)**

Westgard was the first to introduce the idea of total error in 1974, Total Allowable Error (TEa), total analytic error (TAE) or Allowable Total Error (ATE) defined as an analytical quality requirement that sets a limit for both the imprecision (random error) and inaccuracy or bias (systematic error) that are tolerable in a single measurement or single test result to assure clinical usefulness.

Total allowable error was obtained according to Ricos specification (2014) update, shown in (Table 2) [10].

**Table 2: Desirable specifications for total error, imprecision, and bias [10]**

| Parameter | Imprecision I(%) | Bias B(%) | (TE a)% |
|---|---|---|---|
| Urea | 6.15 | 5.51 | 15.66 |
| Creatinine | 3 | 3.9 7 | 8.92 |
| TSB | 11.9 | 11.42 | 31.06 |
| ALP | 3.2 | 6.40 | 11.68 |
| ALT | 9 | 11.42 | 26.27 |
| AST | 5.95 | 5.37 | 15.19 |

Calculate the analyzer's observed total error TE(obs)%, using measured CV% and measured bias%, according to the following formula:

TE (obs)% = 2CV% + Bias%

Compare measured TEobs % to TEa %. If TEobs% < TEa % (or very close to it), then the quality requirement is met and instrument is considered suitable for measurement of that analyte.

**Internal quality control material**

For internal quality control, we used Human Assayed Multi-sera provided from RANDOX Laboratories.

**External quality control material**

For external quality assessment, we used The RIQAS General Clinical Chemistry EQA program provided from RANDOX Laboratories. RIQAS is the largest international EQA scheme in the world.

**Measurements of analytes**

All the biochemical parameters were analyzed on automated analyzers (Siemens Dimension RxL Max) from May-July 2017 using International Federation of Clinical Chemistry and Laboratory Medicine standard (IFCC) methods. Prior to analysis, manufacturer instructions were followed regarding calibration, maintenance and controls.

**Estimation of coefficient of variation (CV%)**

The Coefficient of Variation (CV%) is the ratio of the standard deviation to the mean and is expressed as a percentage [11]. The CV% allows us to make easier comparisons of the overall precision.

CV%= (SD/mean) x 100%

At first, we use the manufacturer given values of the internal QC materials, this is because the manufacturer range is wide, after 20 readings from (22 May-18 June 2017) the calculated mean, SD and range were obtained, then the calculated range was used (19 June-24 July 2017) Quality Control material was analyzed daily for 20 days and plotted as the Y axis, because assuming a Gaussian or normal distribution, it would be expected that about 68% of the points fall within the mean ± 1 SD, 95% within the mean ± 2 SD.

The results are plotted on Levey Jennings chart for both normal (level 2) and pathological (level 3) for each analyte (Serum urea, Creatinine, TSB, ALP, AST and ALT) and using the calculated range (Table 2) as lower and upper limits.

• Levey-Jennings chart used to evaluate run quality
• looking for systematic error and random error
• Westgard rules applied to evaluate the quality of analytical runs
• At the end of the 20 days, mean, SD and CV% were calculated.
• CV% for level 2 and level 3 were calculated for each analyte, then the mean of both readings was used and compared with desirable specifications for imprecision.

**Estimation of bias**

Bias was assessed utilizing EQAS (RIQAS) data as % deviation from the consensus mean of the participating labs. EQAS provides a means of measuring the analytical performance of a laboratory compared to other laboratories utilizing the same methods and instruments.

Proficiency Testing (PT) Provider used was RANDOX International External Quality Assessment Scheme (RIQAS) which is the

largest international EQA scheme in the world. It is used by more than 40,000 laboratory participants in 124 countries.

**Estimation of sigma metrics**

Sigma metric were calculated from CV, percentage bias and total allowable error for the parameters by the following formula [12]:

Sigma-metric = (TE a% – Bia%)/CV %, Figure 1.

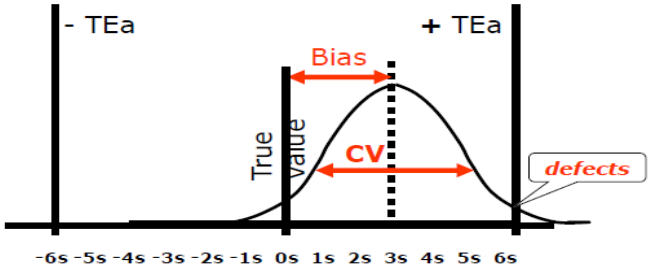


**Figure 1: Relationship of imprecision (CV %), inaccuracy (bias %) and allowable total error (TEa %) in predicting defects [12].**

The Six Sigma scale typically runs from zero to six, but a process can actually exceed six sigma's, if variability is sufficiently low as to decrease the defect rate.

In industries outside of healthcare, 3 sigma's 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.

**Westgard rule selection**

The Sigma Metrics formula's was presumed that every Westgard rule has its own Sigma value [13].

• 6-sigma quality needs only a single control rule, $1_{3s}$, with 2 control measurements in each run one on each level of control. The notation N=2 R=1 indicates that 2 control measurements are needed in a single run

• 5-sigma quality requires 3 rules, $1_{3s}/2_{2s}/R_{4s}$, with 2 control measurements in each run (N=2, R=1).

• 4-sigma quality requires addition of a 4th rule and implementation of a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ multirule, preferably with 4 control measurements in each run (N=4, R=1), or alternatively, 2 control measurements in each of 2 runs (N=2, R=2).

• <4-sigma quality requires a multirule procedure that includes the 10x rule, which can be applied with 4 control measurements in each of 2 runs (N=4, R=2) or alternatively with 2 control measurements in each of 4 runs (N=2, R=4).

**Statistical analysis**

Calculation of mean, SD, CV, TE and sigma metrics was done by using Microsoft excel 2010, Statistical analysis for plotting of Levey Jennings chart was done by using Microsoft excel 2010.

**RESULTS:**

We have analyzed 6 analytes over a period of 2 Months (22 May-24 July 2017) and assessed for sigma metrics. In order to calculate sigma, calculated mean, standard deviation (SD) (Table 3), coefficient of variation (CV%), bias % and (TEa)%(Table4) have been calculated. Standard deviation measures 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 standardization 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.

Precision is closeness of agreement between independent, repeated results obtained from the same sample under specific conditions. Lesser the CV%, better is the precision.

**Table 3: Calculated and Manufacturer range, Mean, SD for L2, L3 QC material.**

| | Serum Urea | Creatinine | TSB | ALP | ALT | AST |
|---|---|---|---|---|---|---|
| Manufacturer range level 2 | 36.20-49.00 | 1.16-1.76 | 1.25-1.91 | 131.00-177.00 | 33.00-49.00 | 43.00-65.00 |
| Calculated range level 2 | 39.87-46.23 | 1.26- 1.56 | 1.34- 1.70 | 139.69-165.91 | 33.65-42.35 | 45.72-59.88 |
| Manufacturer Mean ±SD L2 | 42.60±2.13 | 1.46±0.10 | 1.58± 0.11 | 154.00±7.67 | 41.00±2.67 | 54.00± 3.67 |
| Calculated Mean ±SD L2 | 43.05±1.06 | 1.41±0.05 | 1.52± 0.06 | 152.80±4.37 | 38.00±1.45 | 52.80±2.36 |
| Manufacturer range level 3 | 96.90-131.20 | 3.64- 5.44 | 3.86-5.92 | 225.00-305.00 | 119.00-179.00 | 156.00-232.00 |
| Calculated range level 3 | 102.40-124.48 | 4.06-4.72 | 4.09-5.29 | 228.81-263.79 | 128.94-140.46 | 183.42-202.08 |
| Manufacturer Mean ±SD L3 | 114.05±5.72 | 4.54±0.30 | 4.89±0.34 | 265.00±13.33 | 149.00±10.00 | 194.00±12.67 |
| Calculated Mean ±SD L3 | 113.44±3.68 | 4.39±0.11 | 4.69±0.20 | 246.30±5.83 | 134.70±1.92 | 192.75±3.11 |

Bias was calculated as the average of % deviation of 2 samples of Proficiency testing /month according to RIQAS.

The lowest total CV% has been obtained for AST (2.227) and TSB (2.469) which is below the optimum (I)% followed by serum urea (6.0666) and ALP (3.007) and ALT (4.986) which are below the desirable (I)% while creatinine (3.0417) which are below the minimum. For bias all the analytes which is below the optimum (I)%. For total error, we have obtained the total error for TSB (1.438), ALP (3.714) and AST (2.454) and ALT (7.072) which is below the optimum, then serum urea (12.933), creatinine (6.4), Which are below the desirable (TEa)%. For sigma metrics, in our study TSB has the highest sigma value (14) followed by AST (7.7), ALT (6), ALP (4.6) Creatinine (2.8) and lastly serum urea (2.5). Calculated and manufacturer range, mean, SD for L2, L3 QC materials were shown in Table 3, CV, bias, total error and sigma metrics for renal and liver enzymes with the allowable limits Table 4.

**Table 4: CV%, bias%, total error and sigma metrics for kidney and liver function test with the allowable limits.**

| | Serum Urea | Creatinine | TSB | ALP | ALT | AST |
|---|---|---|---|---|---|---|
| CV% for QC level2 | 4.930 | 4.570 | 2.070 | 3.050 | 6.760 | 1.810 |
| CV% for QC level 3 | 7.200 | 1.510 | 2.870 | 2.960 | 3.210 | 2.650 |
| Total CV% | 6.067 | 3.042 | 2.469 | 3.007 | 4.986 | 2.227 |
| Minimum (I)% | 9.230 | 4.500 | 17.850 | 4.800 | 13.500 | 8.930 |
| desirable(I)% | 6.150 | 3.000 | 11.900 | 3.200 | 9.000 | 5.950 |
| optimum(I)% | 3.080 | 1.500 | 5.950 | 1.600 | 4.500 | 2.980 |
| Bias% | 0.800 | 0.300 | -3.500 | -2.300 | -2.900 | -2.000 |
| Minimum (B)% | 8.270 | 5.950 | 17.130 | 9.600 | 17.140 | 8.060 |
| Desirable(B)% | 5.510 | 3.970 | 11.420 | 6.400 | 11.420 | 5.370 |
| Optimum(B)% | 2.760 | 1.980 | 5.710 | 3.200 | 5.710 | 2.690 |
| Total error | 12.933 | 6.400 | 1.438 | 3.714 | 7.072 | 2.454 |
| Minimum(TEa)% | 23.49 | 13.38 | 46.59 | 17.52 | 39.41 | 22.79 |
| Desirable(TEa)% | 15.66 | 8.92 | 31.06 | 11.68 | 26.27 | 15.19 |
| Optimum(TEa)% | 7.83 | 4.46 | 15.53 | 5.84 | 13.14 | 7.60 |
| Sigma metric | 2.5 | 2.8 | 14 | 4.6 | 6 | 7.7 |

## DISCUSSION:

A good laboratory preparation needs that laboratories design their quality control (QC) procedures to assure that informed patient results meet the quality necessary for their intended use [14]. The Sigma metrics is based on the statistical conception: laboratory errors can be reduced by maintaining 6 standard deviations between the parameter average and its upper and lower limits.

The six-sigma idea sustains 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 reducing the operating costs [15].

When the method quality objectives are set at six-sigma, stringent internal quality control rules are mandatory. Though, false rejections rate should also be kept in care which can be minimized by relaxing control limits up to 3 SD. On other hand, if method is performing at sigma level below 3, it will require to appliance a newer and better method because quality of the test cannot be assured even after multiple quality control cycles [16].

Sigma values are useful for controlling quality control strategy design. For a high sigma process, it is relatively easy for the laboratory to design a quality control procedure, to detect any out-of-control condition that could pose an important risk of producing undependable results. A relatively large out-of-control condition would have to occur before there would be much chances of producing results that contained errors that exceeded the TEa specification and it is easy to design quality control procedures that can detect large out-of-control conditions. The sigma metrics values are useful in setting the internal QC acceptability criteria [17].

The performance of the analyte can change over time for a variety of reasons (e.g., reagent lot to lot variation). Periodic calculation of sigma metrics is suitable to determine if assay quality has been maintained, has decreased, or has improved. Sigma metrics thus represent another quality assurance tool to be monitored periodically to evaluate changes in assay quality.

In industries outside healthcare, three stigmas' is considered the minimal acceptable performance for a process. When performance falls below three sigmas', the process is considered to be essentially unstable and unacceptable [18].

In healthcare, the sigma metrics used for Westgard rule selection. So, in our study the rule is,

• For TSB and AST(sigma>6) its excellent tests, so evaluate with 2 QC/day and $1_{3s}$ rule,

• For ALT and ALP (sigma >3), use multi rules with 2 levels of QC/day,
• For serum urea and Creatinine (sigma<3), use max QC, 3 levels, 3 times a day.

Consider testing samples in duplicate. Total quality management works on plan, do, check and act rules whereas sigma metrics works on define, measure, analyze, improve, control [(19)].

When process performance is confirmed against Westgard rules or any other quality criteria for acceptability of control data, probability for rejection and probability of error detection are of principal importance. The term probability of false rejection (Pfr) is used to describe a situation where there are no analytical errors present except for the inherent imprecision or random error of the method. Probability of error detection (Ped) is the term used to describe where an analytical error occurs in addition to the inherent random error. For achievement of world class quality, it is desirable to have a high probability of error detection and a low probability of false rejection [(20)].

Despite there is violation of Westgard rules but these could be a false rejection results as much as these values are below the TEa, and this can be confirmed by using a software for calculation of Pfr and Ped.

The main limitations of our study for assessment of sigma metrics are:

• The bias that is estimated as %deviation from the EQAS is based on peer group consensus mean rather than an accuracy based program,
• The lack of knowledge about the corresponding Pfr and Ped for the different analytes due to lack of appropriate software as a result of financial constraints.
• The sigma metric results are widely variable due to lot to lot variation, environmental factors and depend on which specification is used (Ricos or CLIA).

## CONCLUSION:

Sigma metric was excellent for TSB and AST (>6), sigma metric was desirable for ALT and ALP (>3), so need application of multi rules. Sigma metric was poor for serum urea and creatinine (<3) so need improvement of quality control methods.

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