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Use of six sigma metrics in assessing the performance of the ımmunonephometric device in C-reactive protein measurements

Sanem Karadag Gecgel[1*] and Sevim Esmedere Eren[2]

[1]Departments of Microbiology and Clinical Microbiology and [2]Department of Biochemistry, University of Health Sciences, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey

Abstract: *Background:* We carried out a study for the purpose of comparing the six sigma values of the C-reactive protein (CRP) assay measured by immunonephometry with references of different authorities' quality criterias and evaluating the performance of the devices in our laboratory. *Methods:* In our study, internal quality control data of the CRP test performed on two different Siemens BN ProSpec (Dade Behring, Derfield, IL) devices at Bursa Yuksek Ihtisas Training and Research Hospital. *Results:* According to Ricos 'desired Total allowable error (TEa) ratio'; all the sigma values of the CRP test in BN ProSpec-1 and BN ProSpec-2 nephelometry devices were calculated as> 6 σ in each of the three periods and the performance of the CRP test was notified as 'world class'. Also, the sigma value determined according to Ricos 'optimal TEa' ratio was 5.8 σ (3.90 to 8.48 σ in each period) on both devices and CRP test performance was defined as 'excellent'. Moreover, when we considered the ratio of Rilibak TEa, the mean sigma values were 3.9 σ (between 2.59 and 5.75 σ in all three periods) and the CRP test performance was identified 'good'. *Conclusion:* As a consequence, the performance of the CRP test with nephelometry was evaluated as 'good' when the Rilibak criteria with the lowest TEa values is taken into consideration. Therefore, it is necessary for the correct quality control analysis to establish the reference TEa% values of our country for the CRP test.

Keywords: Six Sigma Metrics, Quality control, C-reactive protein.

Introduction

C-reactive protein (CRP) is a plasma protein, known as acute phase reactant, which increases in levels of trauma, tissue damage, infection, surgery, cardiovascular diseases and various inflammatory diseases. CRP levels are analyzed in laboratories by using immunonephelometric method, immunoturbidimetric method and various immunological methods [1-3]. In order to determine the test results reported in the laboratory whether they are sufficient for appropriate diagnosis and treatment should be evaluated by statistical and analytical quality control of the studied system [4-5].

Six sigma is a quality control management method in which the analytical process in the laboratory is statistically analyzed, and the quality control strategies and procedures to be applied to determine the error rates in the analytical process and to be applied to the error of the error [6-7]. Standard deviation (SD), variability coefficient (CV), bias determining systematic error and total permissible error (TEa) values are used to determine the random error used in the evaluation of the control values in the analytical process [8].

For quality evaluation, six sigma is a first-class performance indicator with three sigma values being the minimum acceptable value for routine performance [9]. As a result, six sigma values indicate the test performance change more quantitatively by determining which tolerance limit of quality indicators is [10]. We aimed to compare the six sigma values of the CRP test measured by immunonephometry in our study with reference to the quality criteria of different authorities and to evaluate the performance of the devices in our laboratory.

Material and Methods

In our study, internal quality control (IQC) data of the CRP test were used in two different Siemens BN ProSpec (Dade Behring, Derfield, IL) devices in the evaluation of analytical phase performance in

the medical microbiology laboratories of Bursa Yuksek Ihtisas Training and Research Hospital. The internal quality controls that were run in three periods, February-March, May-June, July-August, 2017, were studied at two levels. Two levels (L) Siemens N / T Rheumatology ICC data of the same lot number were used per period (Table 1).

Table-1: The analytical process parameters determined in different periods according to the IQC values of the CRP test in different devices

Instruments	Period	IQC Level (L)	Lot Number	N	Reference Average	Laboratory Average	SD	CV %	Bias %
BN ProSpec-1 Nephelometry device	February- March	L1	S1-199402	30	12,7	13,16	0,83	6,32	3,62
	May- June		S1-199403	37	12,6	12,66	0,74	5,85	0,51
	July- August		S1-199404	20	12,4	12,8	0,56	4,41	3,19
	February- March	L2	S2-199599	30	53,1	52,72	2,68	5,07	0,71
	May- June		S2-199502	37	49,6	50,69	2,99	5,90	2,2
	July- August		S2-199504	20	49,5	51,55	1,84	3,57	4,13
BN ProSpec-2 Nephelometry device	February- March	L1	S1-199402	40	12,7	13,05	0,75	5,78	2,78
	May- June		S1-199402	59	12,7	12,68	0,51	4,04	0,15
	July- August		S1-199403	49	12,6	12,64	0,62	4,92	0,32
	February- March	L2	S2-199501	40	48,0	46,77	1,42	3,03	2,57
	May- June		S2-199502	59	49,6	46,61	2,03	4,36	6,02
	July- August		S2-199502	49	49,6	48,15	1,45	3,00	2,92

The CV% value indicates the repeatability between days, ie the accuracy of the test result [11]. In the study, the average of the IQC values of the two levels in each period was taken as the laboratory average value. CV (%) = (SD / lab. ($\bar{X}$)) × 100. Bias is the difference between the value obtained from the analysis of the test and the reference value, which indicates the accuracy of a test [11]. The IQC kit prospectus values were accepted as reference values in the study. Bias = average-reference mean value formula and % Bias = [√ (bias2)] / reference mean value × 100 formula.

TEa shows a conclusive rate of conclusive and precise concession that will not threaten patient safety [11]. In our study, sigma values were determined by Carmen Ricos and colleagues (Spain) using the desired, optimal TEa ratios based on biological variation and the TEa ratios referenced to Rilibak (Germany) quality criteria [12-14]. Sigma (σ) value formula is; σ = (% TEa- % Bias) /% CV.

Results

The analytical process parameters in our study; The numbers of the IQC and the two different levels of IQC which are evaluated in the BN ProSpec-1 and BN ProSpec-2 nephelometry devices for the three periods of February-March, May-June and July-August are the lot numbers, reference averages, laboratory averages, SD values, CV % values, bias% values are shown in Table 1.

In our study, we evaluated the analytical performance of the CRP test according to the different level (L) IQC results in two nephelometry devices in our hospital. For the CRP test, sigma values were determined according to different Tea % values, which were referenced to Rilibak and to the desired and optimal quality criteria based on biological variation by Carmen Ricos (Table 2). For the CRP parameter, the 'desired TEa' value and the 'optimal TEa' value, which were

determined by Carmen Ricos and colleagues based on biological variation, were accepted as 56.6% and 28.3% respectively, while the TEa value was accepted as 20.0% according to Rilibak quality criteria (Table 2). CRP test sigma values determined according to Ricos 'desired TEa' value were determined between 8.38 and 17.88 σ in each of the three periods. Mean sigma value was found to be 10.8 (> 6 σ) in the BN ProSpec-1 nephelometry device and 13.6 (> 6 σ) in the BN ProSpec-2 nephelometry device (Table 2).

Table-2: Comparison of six sigma values determined with reference to different TEa values

Instruments	Period	Ricos Sigma Value-1 *		Ricos Sigma Value-2**		Rilibak Sigma Value	
		IQC-L1	IQC-L2	IQC- L1	IQC-L2	IQC-L1	IQC-L2
BN ProSpec-1 Nephelometry device	February- March	8,38	11,01	3,90	5,44	2,59	3,80
	May- June	9,59	9,22	4,75	4,42	3,33	3,02
	July- August	12,11	14,69	5,69	6,77	3,81	4,44
BN ProSpec-2 Nephelometry device	February- March	9,32	17,81	4,42	8,48	2,98	5,75
	May- June	13,96	11,61	6,96	5,11	4,91	3,21
	July- August	11,45	17,88	5,69	8,45	4,00	5,69
Reference TEa Rates		56,6%		28,3%		20,0%	

* Sigma value determined according to 'desired TEa' ratios. ** Sigma value determined by 'Optimal TEa' ratios

The CRP test sigma values determined according to Ricos 'optimal TEa' value ranged from 3.90 to 8.48 σ in each of the three periods. The mean sigma value of the BN ProSpec-1 nephelometry device was 5.2 σ and the mean sigma value of the BN ProSpec-2 nephelometry device was 6.5 σ (> 6 σ) (Table 2). According to the Rilibak TEa value, sigma values of CRP test were determined between 2.59 and 5.75 σ in all three periods. Mean sigma value of 3.5 σ in the BN ProSpec-1 nephelometry device and 4.4 σ in the BN ProSpec-2 nephelometry device (Table 2). The multiple Westgard rules proposed in our laboratory to be applied according to the daily Levey-Jennings chart on routine are presented in Table 3 [4, 15]. The error rates that can occur in millions of estimates based on Sigma values are also presented in Table 4 [4, 16-17] to improve performance and mitigate risk, as recommended by Westgard rules.

Table-3: Multiple Westgard rules proposed to be applied according to the Levey-Jennings chart [4,15]

Analytical phase evaluation	Westgard rule
Stimulus rule	If the single control value is above 2 SD (1_{2S})
Rejecting rule (When the stimulus rule is detected)	The single control value is above 3 SD (1_{3s})
	The presence of two consecutive control values on 2 SDs on the same side of the center line (2_{2s})
	The distance between the two control values is above 4 SD (R_{4s})
	Four consecutive control values must be above 1 SD on the same side of the center line (4_{1s})
	Eight consecutive control values are below or above the average value ($8_{\bar{x}}$)

Table-4: Error risk according to Sigma values and recommended practices according to Westgard rules [4, 16-17]		
Sigma (σ)	**Error risk n / million**	**Implemented according to the value of Sigma multiple Westgard rules**
1,0	690000	Unacceptable
2,0	308000	Poor
3,0	66800	Acceptable- Multible rules $1_{3s}/2_{2s}/R_{4s}/4_{1s}/8_x$ Preferably, four controls in two runs (N=4, R=2) or Alternatively, two controls in four runs during the day (N=2, R=4)
4,0	6210	Good- Multible rules $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ Preferably, four controls in one run (N=4, R=1) or Alternatively, two controls in two runs during the day (N=2, R=2)
5,0	320	Very Good $1_{3s}/2_{2s}/R_{4s}$ - Two controls in one run (N=2, R=1)
6,0	3,4	First Quality-World Class 1_{3S} - Two levels of control at different concentrations in each run (N=2, R=1)

Discussion

The multiple Westgard rules proposed to be applied according to the Levey-Jennings chart were first presented in the 1980s. Today, it is frequently used in clinical laboratories for the detection of random and systematic errors in the analytical phase [4, 15]. Six sigma is limited to scientific work in clinical laboratories in the analytical stage [16, 18-19], although in the past it has been accepted as a statistical indicator used to identify error risk and improve quality and performance in various industrial sectors. According to Westgard, which provides both analysis methods, increasing the number of rules and control applied with six sigma increases the error detection rate and reduces false rejections [4-5] (Table 3-4).

To improve quality management in the laboratories, there are quality requirements determined by many countries and the working group, and TEa ratios determined for each parameter. According to the biological variation, there are three types of TEa formulas and ratios as the minimum, desired, optimal TEa [20]. In our study, CRP test performance of BN ProSpec-1 and BN ProSpec-2 nephelometry devices using immunoephelometry method was evaluated by sigma value determined according to TEa ratios determined by three different authorities.

All sigma values calculated for all three periods of the CRP test of BN ProSpec-1 and BN ProSpec-2 nephelometry devices were found to be >6 σ based on Ricos 'desired TEa' ratio. The performance of the CRP test determined by Ricos 'desired TEa' ratio was found to be 'first quality-world class' and it was found that the CRP test in our laboratory was studied with minimum error risk (Tab-4).

According to Ricos 'optimal TEa' ratio, the sigma value detected was 5.8 σ on average in both devices (between 3.90 and 8.48 σ in all three periods). Eight of the sigma values were >5 σ. Only the BN ProSpec-1 nephelometry device detected an IQC-L1 value <4 σ during the February-March period. The results of IQC sigma values were not found below 3 sigma values. CRP test performance was determined to be 'very good' (Table 4).

The mean of the sigma values determined according to the ratio of Rilibak TEa in our study was 3.9 σ (between 2.59 and 5.75 σ in all three periods). Only in the February-March period of both devices was the IQC-L1 value <3 σ. The CRP test performance determined by the ratio of Rilibak TEa was 'acceptable and good' (Table 4).

In the analytical evaluation of CRP immunoturbidimetric and nephelometric methods performed by Buğdaycı et al., The CV values of the BN ProSpec device were evaluated as <5% [21]. In our study, > 5% (5,07-6,32) of the 5 CV values we calculated were detected (Table 1). When CV values were >5%, sigma values were found to be 2.59-3.8 σ compared to Rilibak and 3.90-5.44 σ according to Ricos' optimal TEa (Table 2).When CV values were >5%, Rilibak sigma values were significantly lower.

When the CRP performance of both nephelometry devices was compared, the sigma values of the BN ProSpec-2 nephelometry device were found to be higher. BN ProSpec-2 nephelometry device only works with CRP parameter while BN ProSpec-1 device has different parameters. It is also possible that the workload is higher in the laboratory where the BN ProSpec-1 is located and the fewer samples are in the laboratory where the BN ProSpec-2 is located.

In our study, sigma values were used to evaluate the analytical performance. As the value of sigma increases, test compliance improves and test cost decreases [9]. When a test has a sigma value of 6, the rejection of control levels up to 3 SD limits can be reduced compared to Levey-Jennings graphs. Sigma values 3 and below, if there is no improvement after repeated internal quality control studies, adjustments are needed to improve the performance of the method [22]. For example, keeping the internal quality control materials in view of storage conditions, increasing device washing procedures, increasing the calibration frequency for inappropriate testing.

As a result of our work, we need to study the CRP test in our laboratories in the form of two controls in one day during the day when the IQC's are working in one day, in order to create the correct statistical quality procedure recommended by Westgard, based on the sigma values of the CRP test determined when Ricos quality criteria are taken into consideration. When the Ricos 'optimal TEa' values were taken into consideration, it was sufficient to apply a single quality control procedure [4-5] to evaluate the 3 quality control procedures recommended by Westgard, considering Ricos 'desired TEa' values (Table 4).

According to the sigma value determined when we refer to the Rilibak criteria, the number of CRP test IQC trials in our laboratories needs to be increased during the day and Westgard's multiple rules should be applied for evaluation (Table 4) [4-5]. There are no similar studies to compare the sigma values of the CRP test obtained in our study. For this reason, there is a need to further study the use of sigma analysis to establish the right quality control strategy in laboratories and to validate quality control procedures [9, 23].

As a result, the performance of the CRP test in our study was evaluated as 'acceptable and good' according to the sigma values determined when the Rilibak criteria including the lowest TEa values were taken into consideration. If Ricos is classified as 'first class quality' and 'very good' according to biological variation, it has been shown that the TEa ratio selection can result in different evaluations. For this reason, it is necessary for the correct quality control analysis to establish the reference TEa% values of our country jointly for the CRP test. It will help our Sigma statistical laboratories work better with our two different devices, analyzing their work and performing their corrective preventive actions. The use of sigma analysis in conjunction with Westgard multiple rules in laboratory quality control assessment is the recommended method for establishing the right quality control plan.

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*All correspondences to: Dr. Sanem Karadag Gecgel, Department of Microbiology and Clinical Microbiology, Yuksek Ihtisas Training and Research Hospital, 152 Evler, Prof. Tezok Cd. No:2, Yıldırım/Bursa, Turkey. E-mail: sanemkaradag@yahoo.com