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Short Communication

Evaluating the analytical quality control of urinary albumin measurements using sigma metrics

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ABSTRACT

Background: There is no worldwide recognized reference system and standard for urinary albumin measurement until now, so the analytical quality from different laboratories has always varied. In this study, we aimed to evaluate the analytical performance of a urinary albumin assay system using Sigma-metric, and thereby choose a suitable control rule to guarantee the analytical quality of the assays.

Method: Two levels of diluted reference material (ERM-DA47OK/IFCC) were used to calculate the biases, the coefficient of variation (CV) were calculated from six months of internal quality control measurements at two levels, and the external quality assessment standard of China for urinary albumin (30%) was used as the total allowable error(TEa).

Results: The Sigma values for quality control levels 1 and 2 were 4.28 and 6.14, leading to recommended Westgard rules of $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) and 1_{3s}(N = 2, R = 1), respectively. Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$(N = 2, R = 2) was selected for the quality control of the urinary albumin measurements, and with it, the power function graph showed a high efficacy for determining the detection errors with a probability of false rejection of 1.004% and a probability of error detection of 98.80%.

Conclusion: With a TEa of 30% recommended by the external quality assessment standard of China, Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$(N = 2, R = 2) with a high efficacy for determining the detection error is recommended for the quality control of urinary albumin measurements.

1. Introduction

Albuminuria plays an important role in the early screening of kidney damage caused by diabetes and in monitoring the progression of chronic kidney disease [1,2]. Therefore, providing reliable test results for albuminuria is necessary to satisfy clinical requirements. However, there is no existing reference analytical system and material so far [3], and its performance can vary between different detection systems and laboratories. In the questionnaire survey organized by Jinhua Center for Clinical Laboratories in 2016, < 33% of laboratories in Jinhua city performed daily quality control (QC) of urine albumin [4], and so these laboratories could not ensure that the results were reliable enough to be released. Additionally, the external quality assessment organized by the National Center for Clinical Laboratories showed that the variation was 60% for low levels of urine albumin and 45% for high levels [4,5]. Hence, it has become important to improve the quality and assessment of quality for urine albumin. QC is both external and internal, but unfortunately, both of these lack the ability to assess the exact number of defects or errors in the clinical laboratory [6].

Sigma-metric is recognized as a useful tool the QC design process in recent years. Not only does the six sigma scale allows benchmarking of method and instrument performance on a common scale, it also allows laboratories to easily visualize performance, optimize the QC rules and control the quantity of measurements, and now even arrange the frequency of QC measurements [7]. Hence, we aimed to evaluate the performance of urinary albumin measurements and to select an appropriate rule using Sigma-metric.

2. Materials and method

2.1. Materials

Urinary albumin was tested using a Dade-Behring BNII special protein analyzer. Two levels of homemade QC materials that could been kept stable more than eight months at −20 °C and whose performances had been verified in the previous study [4] were used as internal quality

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control products. ERM-DA47OK/IFCC was diluted to two concentrations of albumin: 14.88 and 148.80 mg/L. In this study, the power function graph was generated by using quality control management software, Q-Expert System (QUALAB, Shanghai, China).

2.2. Measurement performance assessment

1. Total allowable error (TEa) represents the allowable difference between the test results in the clinical laboratory and the true values. In this study the external quality assessment standard of China for urinary albumin (30%) was used as the TEa.
2. Coefficient of variation (CV) indicates the precision of the measurements. We collected the internal QC data from May 2018 to October 2018. The mean values for level 1 and level 2 were 17.2 and 150.2 mg/L, the standard deviations were 1.11 and 6.11, and the CVs were 6.47% and 4.07%, respectively.
3. Estimated bias is the systemic difference between the test results in the clinical laboratory and the true values. It can be obtained by measuring the quantity value of one or more reference materials several times under repeatability conditions [8]. In this study, two levels of diluted ERM-DA47OK/IFCC were tested three times, respectively, and biases were calculated. Bias = |theoretical value − test value|/ theoretical value.
4. Sigma value = (TEa − bias)/CV.
5. Quality goal index (QGI) is used to find the reason for the detection error in measurements with a Sigma value < 5 [9]: QGI = bias/(1.5 × CV). When QGI < 0.8, this suggests that the precision should be improved; when 0.8 < QGI < 1.2, this suggests that both the precision and trueness should be improved; and when QGI > 1.2, this suggests that we should pay more attention to the trueness.
6. The probability of false rejection (Pfr) is the probability of rejecting a quality control rule that should be accepted.
7. The probability of error detection (Ped) is the probability that the quality control rule checks out the correct rejections.

3. Results

For the two levels of diluted ERM-DA47OK/IFCC, the test mean ± SD value was 14.54 ± 1.20 mg/L for the low one, 156.25 ± 5.48 mg/L for the high one. The biases were −2.28% and 5.01%, respectively. These two biases were used to calculate sigma values of quality control level 1 and level 2, respectively. The Sigma value for QC level 2 was 6.14, and the recommended Westgard rule was 1_{3s}(N = 2, R = 1). However, there was a lower Sigma value 4.28 for level 1, thus Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) was recommended (Fig. 1). The QGI for QC level 1 was 0.23.

Fig. 2 showed the power function graph of Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) for urinary albumin QC level 1: the Ped was 98.80% and the Pfr was 1.004%.

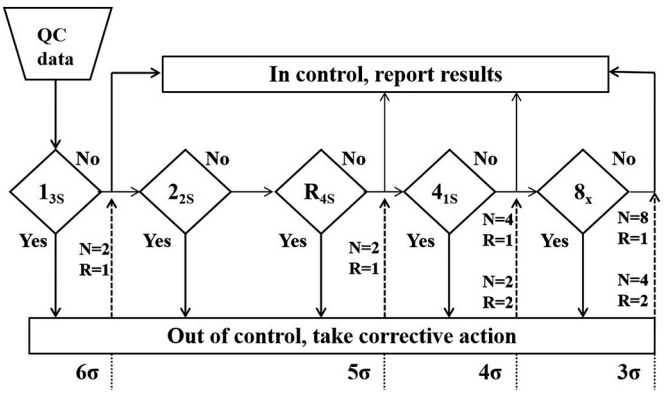


Fig. 1. Power function graph for level 1 of quality control with a $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ rule.

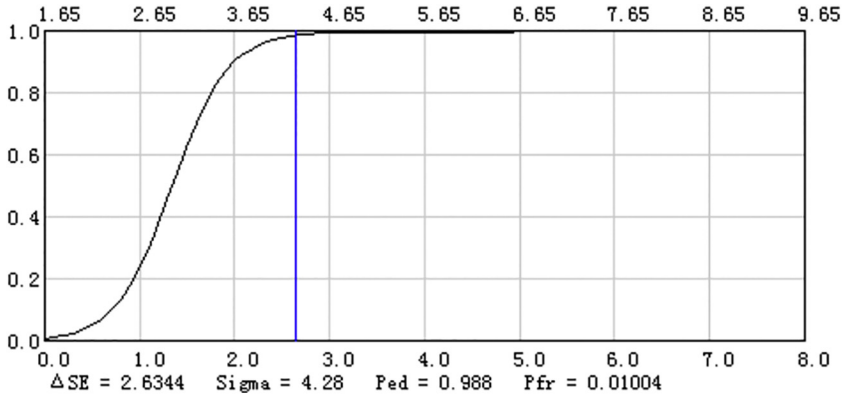
4. Discussion

The matrix of internal quality control materials should be the same as the patients' samples [10]. However, there are no commercial QC materials for urinary albumin whose matrix is identical to the samples so far. Therefore, in this study, two levels of homemade QC material that could been kept stable for more than eight months at −20 °C and whose performance had been verified in the previous study [4] were used to possibly reduce the matrix effect. For external QC, the bias is calculated based on the mean of all of the laboratories, so it can not represent the exact difference between the true value and the result in laboratories. ERM-DA470K/IFCC is a candidate reference material for urinary albumin, and most clinical analytical systems are calibrated to be traceable to it [3]. Hence, two levels of diluted ERM-DA470K/IFCC were used to calculate biases in this study.

According to the results, to improve the ability to determine the defects or detection errors of the analytical system and assure that the results were reliable enough to be released, more attention should be paid to the level of the quality control which was closer to the medical decision point. Although the values of urine albumin in some diabetic patients are very high, the values of urine albumin of most patients are in low levels. The median value of type 2 diabetic patients is 11 mg/g in the study of Tomohito Gohda [11]. Most results are closer to the level 1 which is close to clinical interpretation level. Therefore, laboratories should not loosen restriction on the clinical interpretation level. Hence, Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) was selected as the control rule for urinary albumin detection with this analytical system. The power function graph of Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) for QC level 1 showed error detection would be approximately 98.80% with only a Pfr of approximately 1.004%. Furthermore, QC level 2 with a Sigma-metric of 6.14 would have even higher error detection capability. In addition, the QGI for level 1 was 0.23, which suggests that it is necessary to improve the precision of the urinary albumin measurements.

Many laboratories design the internal QC for urinary albumin measurements according to the guidelines of national accreditation bodies [10]. For example, we used rule $1_{3s}/2_{2s}/R_{4s}/10_x$ (N = 2, R = 1) to monitor the quality of urine albumin measurements as other items in the laboratory before. After Sigma-metric assessment, Westgard rule $1_{3s}/2_{2s}/R_{4s}/4_{1s}$ (N = 2, R = 2) was used (once in the morning, once in the afternoon). Although it increased the number of QC test and the frequency of outliers, the new Westgard rule could monitor the quality of measurements again after a long run of the machine from 7:30 am. In addition, the QC measurement in the afternoon and the rule 4_{1s} could find out the defects which might be missed by previous rules. Therefore, the results could be more reliable to be released, the clinicians could make a more accurate assessment of the patients' condition, and the patients could get a more accurate treatment plan.

It is worth mentioning that Sigma-metric depends directly on the selected TEa, so it is important to identify the most appropriate performance specifications. According to the minimum global consensus for TEa determined by Ricos and several Spanish EQA programs, the TEa of urine albumin is 38% [12]. With a TEa of 38% sigma values for level 1 and level 2 are 5.52 and 8.11, respectively. In addition, in AACC Annual Meeting of Atlanta in 2015 [13], Dr. Miller indicated a TEa of < 25% as reasonable for the bias and CV error components (assuming a CV of 6% or less and a bias between methods of < 13%). In this case, with a TEa of 25% the sigma values for level 1 and level 2 are 3.51 and 4.91, respectively. However, Dr. Miller also indicated that the median differences was approximate 40% in the comparison between a routine measurement procedures for urine albumin and isotope dilution tandem mass spectrometry, interquartile minimum to maximum differences between methods of approximately 60%. The bias between



Ped: Probability of error detection; Pfr: probability of false rejection

Fig. 2. Westgard sigma rules for two levels of controls.

methods were so large that the tighter TEa might not be appropriate for the laboratories at present. Additionally, in this study homemade control was used. However, it is hard to produce the control which has the same values as before, this limits the reproducibility of the study.

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Declaration of Competing Interest

No authors declared any potential conflicts of interest.

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