

IFCC Professional Scientific Exchange Programme (PSEP) Report:

INFORMATION FROM LABORATORY DATA. INTERPRETATION OF SERIAL MEASUREMENTS.

Natàlia Iglesias Canadell

Laboratoris Clínic Vall d'Hebron, Hospital Vall d'Hebron, Barcelona, Spain

Dr. Natàlia Iglesias Canadell visited the Dept. of Clinical Biochemistry, Odense University Hospital, Denmark for 4 months (April – June 2003). The topic of her training was “Information from laboratory data” (Interpretation from single and serial measurements). Her supervisor at the Odense University was Dr. Dr. Per Hyltoft Petersen.

INTRODUCTION

In daily clinical practice, physicians request laboratory tests to assist in diagnosis, to monitor a patient and to suggest or change a type of treatment. If we focus on the monitoring situation, usually, the patient has more than one result available for the same analyte, it is then common to compare the values of two consecutive measurements sampled at different times. There are some possible ways to evaluate if a difference between measurements is significant, one of them is using the Reference Change Value (RCV) proposed by Harris and Yasaka (1). This concept takes into account that the result of an individual is compared with his/her previous results in order to have a more objective interpretation of a measured difference in patient monitoring.

The formula to calculate RCV is as follows:

$$RCV = z_p \times 2^{1/2} \times (CV_A^2 + CV_I^2 + CV_P^2)^{1/2}$$

where z_p is the z-statistic, which depends on the probability selected of significance and whether the change is uni- or bi-directional; $2^{1/2}$ is a constant (it takes into account two measurements, assuming same variation for both); CV_A is the analytical variation of the method; CV_I is the within-subject biological variation and CV_P is the preanalytical variation (considered negligible if specimens are collected under standard conditions or included in CV_P).

The formula may be expressed in standard deviation (s) if the analytical and biological mean is the same:

$$RCV_s = z_p \times 2^{1/2} \times (s_A^2 + s_I^2)^{1/2}$$

If we define the standard deviation of the difference (s_D) as:

$$s_D = 2^{1/2} \times (s_A^2 + s_I^2)^{1/2}$$

then,

$$RCV_s = z_p \times s_D$$

Many authors have used RCV in monitoring situations (2-6), however, the formula commented above only takes into account the probability of false positives (FP) in the interpretation of measured differences, which is determined by the value of z_p . In clinical practice we define FP as calling a change significant when it is not. However, another probability exists, that is missing a significant change when the difference between measurements is less than the calculated RCV, which is called false negative (FN) and is represented by .

THEORY

It is assumed that an individual is in steady-state and when a measurement is performed, it has associated a random variation that depends on analytical and biological. Therefore, this measurement may be represented as a Gaussian distribution. If two serial results of an analyte are compared in an individual in steady-state, it is possible to represent the differences as a Gaussian distribution. RCV has been defined only taking into account one distribution of no change (steady state, where there are no real differences between measurements), with the mean in 0 ($\mu=0$) and standard deviation (s) depending on biological and analytical variation. However, when an individual has a pathological change, it may be represented as another Gaussian distribution where the mean has the value of the change ($\mu \neq 0$) and s is assumed the same as in steady state. In that case, two situations can be defined:

1. Compared distributions are totally separated, then, there is no doubt for a certain measured difference, if it corresponds to the distribution of change or not. Figure 1.
2. Compared distributions overlap, therefore, there is an uncertainty zone where we are less able to decide at which distribution the change corresponds. Figure 2.

In this situation if RCV is applied, Figure 3 is obtained.

As may be observed in this Figure, when RCV is calculated for a determined value of z_p (e.g., $z_p=1.96$), a probability for a FP (α) is obtained. We have to take into account that the choice of α will affect β (FN) and the statistical power to detect the change ($1-\beta$).

POWER FUNCTIONS

The probability to detect a real (or pathological) change (P_{cd}) for a selected value of RCV may be represented as a power function, using the Microsoft Excel® 2000 software package. Power functions have been widely used for error detection in Internal Quality Control (IQC) by Westgard and Groth (7). However, the probability of FN has never been investigated for RCV. Therefore, we studied a model that shows the relationship between an assumed pathological change and the probability to detect it ($1-\beta$) by using power functions. This is represented in Figure 4.

In this plot, the y-axis represents the probability of change detection (P_{cd}) and the x-axis shows possible pathological changes in a patient for an analyte, expressed in units of standard deviation of the difference (s_p). In a situation of no change, x-value is zero, and the y-intercept gives the probability for a false positive (P_{fp}). Therefore, the plot presented above would have a $P_{fp}=0.025$, for a $z_p=1.96$ because a bi-directional probability is selected (other z-statistic may be chosen resulting in different power-functions). The rest of the curve describes the continuous probability of detection (y-value) for the different changes of interest (x-value). As may be seen in the figure above, if a patient has a change of 3 (units of s_p), this has a probability of being detected of 0.85. It means that we have a probability of 0.15 of missing a significant change (FN) when the measured difference is less than the calculated RCV.

The power for detecting an increase in a change is identical to the decrease. This is represented in Figure 5.

In the Figure presented above, the RCV has a value of 1.96 for an increase (for a decrease $RCV=-1.96$), this represents that when a measured difference is the same as the calculated RCV, it will be detected in 50% of situations. It means that in 50% of times, the measured difference will be below the RCV.

CLINICAL PRACTICE

It is possible to apply these power functions to specific clinical situations. If we are monitoring serum levels of Albumin in a patient, and in the first determination has s-Albumin = 45 g/l and in a second determination after 3 months the value has changed to 39 g/l, the most probably measured difference corresponds to 6 g/l.

We may represent a power function for s-Albumin, which is calculated using a $CV_f=3.1\%$, obtained from the tables on biological variation that are available on the Internet (8). The analytical variation is $CV_A=1.6\%$, that corresponds to the desirable quality specifications based on biology ($CV_A=0.5 \times CV_f$) (9). Other quality specifications for analytical variation may be chosen, obtaining different power functions. In this example, we have selected a probability of change bi-directional, $z_p=1.96$, then, the $RCV_s = z_p \times 2^{1/2} \times (s_A^2 + s_i^2)^{1/2} = 4.2$ g/l. If we represent the power function for the corresponding $RCV_s = 4.2$ g/l, Figure 6 is obtained.

In this Figure, the vertical line represents the calculated RCV_s and the vertical dotted line represents the assumed change of 6 g/l of s-Albumin. As may be seen in this example, if only the probability of FP is taken into account (α), therefore, using the formula of RCV proposed by Harris and Yasaka (1), we would say that the expected difference of 6 g/l is significant. However, the probability to detect this change (P_{cd}) is 0.81, therefore, this

change has a probability of 0.19 to be missed (FN) when the measured difference is less than calculated RCV.

CONCLUSIONS

As we explained above, the use of power functions give us information of false positives (FP) and also false negatives (FN). This is the main difference with the RCV proposed by Harris and Yasaka, which only reflects the probability of FP.

The probability to detect a change (P_{cd}) is related with the wideness of the Gaussian distribution, which depends on biological and analytical variation and z_p . When the distributions of steady state and pathological change overlap (Figure 3), there is an uncertainty zone where we are less able to decide at which distribution a change corresponds. Therefore, using power functions we may identify the probability of false negatives, then, the probability that a change can be misclassified.

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LEGENDS TO FIGURES

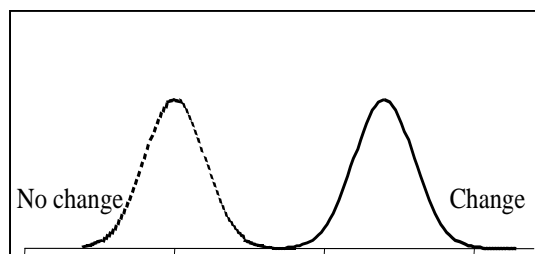


Figure 1 Comparison between two separated distributions with same standard deviation (s), one representing no change (steady state) and the other a change.

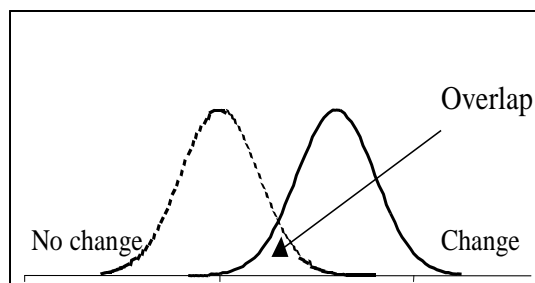


Figure 2 Comparison between two distributions with same standard deviation (s) that overlap, one represents no change and the other a smaller change than is figured.

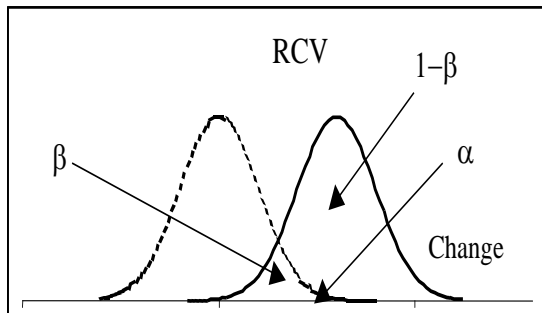
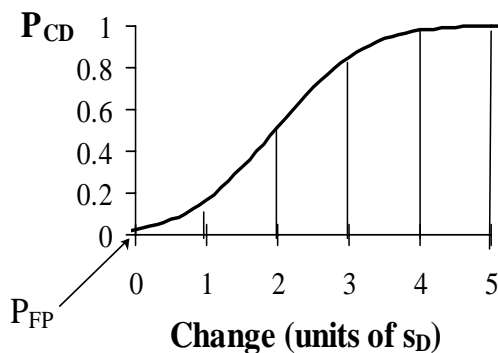
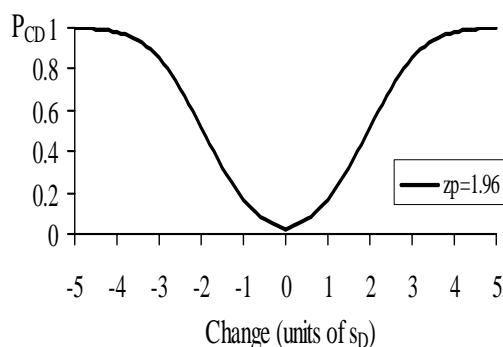


Figure 3 Illustration of the relationship between distributions, for a calculated RCV, the probability of α and the effect in β and in the probability to detect a change ($1-\beta$).



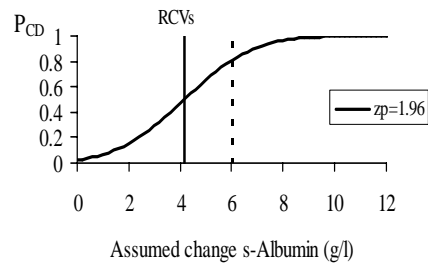
Iglesias et al. Clin Chem Lab Med 2004;42:415-22

Figure 4 Obtained power function for a $z_p=1.96$; the x-axis represents the change (from 0 to +5) and the y-axis is the probability to detect it (P_{CD}).



Iglesias et al. Clin Chem Lab Med 2004;42:415-22

Figure 5 Illustration of possible changes, increase or decrease, related to the probability of detection, for a $z_p=\pm 1.96$.



Iglesias et al. Clin Chem Lab Med 2004;42:415-22

Figure 6 Probability to detect a change of 6g/l of serum-Albumin (vertical dotted line) for RCV_s with $z_p=1.96$, $CV_A=1.6\%$ and $CV_r=3.1\%$ (vertical line).

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