The interaction of the sample and the SCE buffer alone can produce considerable change in absorbance at 340 nm: sera showed an apparent enzyme activity equivalent to 2 to 20 U/L 2 min after mixing, and 1 to 11 U/L 6 min after. Heparinized plasma samples showed activity equivalent to 170 to 530 U/L at 2 min, which decreased to 0 to 70 U/L at 6 min. EDTA-treated plasma samples showed stable activity equivalent to -3 to +2 U/L in the interval 2 to 6 min.

Evidently heparinized plasma is not the most suitable sample for determination of CK with the SCE buffer and short pre-incubation times. Indeed, some heparinized plasma specimens produced an immediate visible, increasing opalescence in the SCE buffer. The absorbance changes produced when serum is added to the SCE buffer are not negligible if one is examining samples with low enzyme activity.

The SCE took great pains to standardize and optimize the CK substrate. Attention should be given to changes in absorbance produced not only by the substrate, but also by the buffer, when performing determinations of CK and AK.

References


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Selecting a Diagnostic Study’s Cutoff Value by Using Its Receiver Operating Characteristic Curve

To the Editor:

The receiver operating characteristic (ROC) curve is an interesting and useful way to predict the performance characteristics of a diagnostic laboratory or clinical study. The method for graphing the curve has not yet been standardized in the medical literature, however. In a recent article in this journal (1) the “false positive rate (%)” was used as the x-axis and “true positive rate (%)” as the y-axis for the Cartesian coordinate system. If the x and y axes are respectively the “true negative rate”—that is, specificity—and “true positive rate”—that is, sensitivity—then simple formulas can be used to identify the rectangular coordinates corresponding to the optimal diagnostic cutoff value for the study.

The first formula allows the users of a study to identify the diagnostic cutoff value appropriate for the disease prevalence in the population being sampled. If the utility matrix for the diagnostic decision can be constructed, the second formula indicates the diagnostic cutoff value that will maximize the diagnostic utility. Both formulas can be applied to populations or to individuals.

1. Selection of the cutoff value to minimize the diagnostic misclassification rate. Let Prev = prevalence of the disease in the patient population, TNR = true negative rate (%), TPR = true positive rate (%), and Xc = cutoff value for the study.

Then the misclassification rate = Prev (1 - TPR) + (1 - Prev) (1 - TNR). Minimizing this function at Xc,

\[
\frac{d \text{misclassification rate}}{d \text{TNR}} = \frac{d \text{TPR}}{d \text{TNR}} \left| X_c = 0 \right.
\]

Therefore, the diagnostic misclassification rate is minimized at the point on the ROC curve with a slope of (Prev - 1)/Prev. The cutoff value for the study is the value corresponding to that coordinate.

2. Selection of the cutoff value to maximize the diagnostic utility. Let UTN = utility of a true negative diagnosis, UTP = utility of a true positive diagnosis, UFN = utility of a false negative diagnosis, and UFP = utility of a false positive diagnosis.

Then the expected utility = Prev(TPR UPF + (1 - TPR) UFP) + (1 - Prev) [(1 - TNR) UFP + (TNR) UFN]. Minimizing this function at Xc,

\[
\frac{d \text{expected utility}}{d \text{TNR}} = \frac{\text{Prev} \left[ \frac{d \text{TPR}}{d \text{TNR}} \text{UTP} - \frac{d \text{TPR}}{d \text{TNR}} \text{UFP} \right] + (1 - \text{Prev}) \left[ -\text{UFP} + \text{UFN} \right]}{d \text{TNR}} \left| X_c = 0 \right.
\]

Therefore, the diagnostic utility is maximized at the point on the ROC curve with a slope [(Prev - 1)/Prev] [(UTN - UFP)/(UTP - UFN)].

In practice, the optimal ROC coordinate can be easily identified graphically. A line with the slope equal to that calculated from the appropriate formula will be tangent to the ROC curve at the optimal coordinate. Hence, if a family of lines with that slope are drawn, the one that is tangent to the ROC curve passes through the optimal coordinate. This graphical technique can also be applied to ROC curves that are step functions or that are noncontinuous.

For example, consider the analysis of the performance of serum myoglobin concentration as a marker of acute myocardial infarction in the paper by Robertson and Zweig (1). When the ROC curve is redrawn with the axes suggested in the present communication, it is the left-to-right mirror image of their Figure 3. Using a prevalence of 0.5 for myocardial infarction among patients admitted to a coronary care unit, one finds the ROC coordinate associated with the minimum diagnostic misclassification rate has a tangent line with slope −1 (i.e., [0.5 - 1/0.5]) pass through it. This happens at (TPR = 0.96, TNR = 0.84), which corresponds to a diagnostic cutoff value of 100 µg/L.

Reference


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This letter was referred to the authors of ref. 1, who respond as follows:

To the Editor:

The Letter by Noe describes a legitimate and useful approach to choosing decision levels (cutoff values). However, several important points should be made about this. First, we think that his formula 1 should be avoided. Although relatively easy to apply, it ignores the importance of weighting the cost or negative value of diagnostic misclassifications. On the other hand, this cost is appropriately considered in formula 2. Several other authors (1–4) have discussed this method of choosing the optimal decision level, using terms such as “consequences,” “cost,” “value,” or “benefit” to describe the significance of each decision or diagnosis. They have considered significance to the patient, to the physician, to both, or over-

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