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An expert system approach for the objective interpretation of serum tumour marker levels

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Summary

The aim of our work was to study specific aspects of statistical Weinstein–Bayes’s analysis in order to find the most suitable program for presenting our results and for obtaining information which could be used as a guide in the clinical decision-making process. Our efforts resulted in a computer processing system based on modified Weinstein–Bayes receiver operating characteristics (ROC) analysis. The data analysis provides numeric values of sensitivity, specificity, positive predictive value and negative predictive value as output tumour marker databases, which would serve as graphic input. It becomes possible to plot the ROC curve as a graphical distribution of tumour marker levels. The computer program also allows the estimation of the potential utility of the serum tumour marker measured in patients with various diseases, simultaneous determination of serum tumour markers in diseased patients, and the real value of each serum tumour marker level in diseased patients.

Introduction

Physicians have an enormous range of clinical information to use as a guide in decision making. In in vitro nuclear medicine, physicians and other specialists were confronted with different laboratory conditions, various techniques and a large flow of various results on different tumour markers and hormones. Many authors have contributed to the estimation of various laboratory findings, but we wish to emphasize the importance of the Bayesian approach [1]. We use Bayes theorem in considering the relevance of diagnostic laboratory tests (especially for tumour markers), for confirming the probability of whether a patient has a disease, the probability that a treatment will alleviate symptoms etc.

We know that biological variables often show a substantial variety of values for both the diseased and nondiseased person. Thus, the values in the two groups usually overlap. The only way to compare the values of the two populations was to estimate the results on measured substances using Bayes’s formula and to plot them on a receiver operating characteristics (ROC) curve [2–4].

Materials and methods

To study specific aspects of statistical Weinstein–Bayes’s analysis to find the most suitable program for presenting our results and to obtain information which would be a guide in the clinical decision-making process, it was decided to use the modified Weinstein–Bayes ROC analysis [5].

In order to calculate the probability that a disease would give a positive test result, or calculate the probability that a disease would give a negative test result, Bayes included in his famous formula the prevalence of the disease. In many cases physicians were not able to calculate either the positive or the negative predictive value because the prevalence of the disease in the population investigated was not known. In addition, the prevalence varied from population to population, from area to area, from town to town, from clinic to clinic. Finally, to compare a group of persons with confirmed biopsies with a healthy group, estimation of prevalence was not required. Therefore, in our investigations the parameter of prevalence was not taken into consideration and the estimation of the results was simplified (Fig. 1).
**Expert system tumour markers**

**THE PROBABILITIES IN DECISION MAKING PROCESS**

<table>
<thead>
<tr>
<th>Number of patients examined</th>
<th>Diseased (D)</th>
<th>Healthy (H)</th>
<th>Positive predictive value: $\frac{TP}{TP + FP} = \frac{TP}{TP + FN}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>High values (positive results) (PR)</td>
<td>True positive results (TP)</td>
<td>False positive results (FP)</td>
<td></td>
</tr>
<tr>
<td>CUT OFF VALUE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low values (negative results) (NR)</td>
<td>False negative results (FN)</td>
<td>True negative results (TN)</td>
<td>Negative predictive value: $\frac{TN}{FN + TN} = \frac{TN}{NR}$</td>
</tr>
<tr>
<td>The primary probability</td>
<td>Sensitivity $\frac{TP}{TP + FN} = \frac{TP}{D}$</td>
<td>Specificity $\frac{TN}{TN + FP} = \frac{TN}{H}$</td>
<td>The operative characteristics on diagnostic test</td>
</tr>
</tbody>
</table>

The graphic expression on operative characteristics is the ROC curve

**Accuracy** $\frac{TP + TN}{D + H}$

---

**Tumour marker acquisition**

Serum tumour markers were determined by various techniques (such as radioimmunoassay (RIA), IRMA, EIA, FIA etc.) in patients with various diseases, at various stages of the disease and during various stages of their treatments during follow-up.

**Data analysis**

Our software first invokes GW BASIC and then our computer program for data analysis (Sava) and finally it invokes a graphics program (based on Harward’s graphic II).

The first step in our computer processing protocol (Fig. 2) is to form input tumour marker databases on serum tumour marker levels, which are then sorted by magnitude. Next the individual values (high or low) are evaluated. This is done by cut off value, calculated on the basis of the control group results and those of the benign disease group. These values are calculated by adding the double standard deviation to the mean value of the tumour marker in the control group. The cut off value accounts for over 90% of the low values in the group of healthy persons but it is still acceptable as the upper limit of normal values.

Calculating a cut off value for tumour markers is one of the most important steps in the program and in any other estimation in in vitro, or in vivo diagnostics.

The new and acceptable cut off value for each estimation of the results and methods must be evaluated.

If we have in mind the significance of the cut off value each serum tumour marker level can be estimated as a specific cut off value (Table 1). Using this specific cut off value the distribution of other results, both in the healthy group and in the diseased group can be evaluated. This

---

*Fig. 1.*

*Table 1.*

<table>
<thead>
<tr>
<th>Line</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>530</td>
<td>REM DETERMINATION OF LOCAL SENS, SPEC, POSPREDVAL, NEGPRDVAL</td>
</tr>
<tr>
<td>540</td>
<td>FOR I=1 TO NDRS</td>
</tr>
<tr>
<td>550</td>
<td>TP=I-5; FN=NDIR-TP</td>
</tr>
<tr>
<td>560</td>
<td>IF CCON(1) AND DDIS(0) THEN FP=-0;TN=NCN</td>
</tr>
<tr>
<td>570</td>
<td>IF CCON(NCON) I AND DDIS(0) THEN FP=NCN;TN=0</td>
</tr>
<tr>
<td>580</td>
<td>FOR J=1 TO NCON</td>
</tr>
<tr>
<td>590</td>
<td>IF CCON(D) AND DDIS(0) THEN FP=-1;TN=NCN-FP</td>
</tr>
<tr>
<td>600</td>
<td>IF CCON(I) AND DDIS(0) THEN FP=1;TN=NCN-FP</td>
</tr>
<tr>
<td>610</td>
<td>NEXT J</td>
</tr>
<tr>
<td>620</td>
<td>SPEC(I)=TN/NCN+SENS(I)=TP/NDIS</td>
</tr>
<tr>
<td>630</td>
<td>SPEC(I)=100<em>SPEC(I);SENS(I)=100</em>SSENS(I)</td>
</tr>
<tr>
<td>640</td>
<td>PPV(I)=TP/(TP+FP)</td>
</tr>
<tr>
<td>650</td>
<td>PPV(I)=100*PPV(I)</td>
</tr>
<tr>
<td>660</td>
<td>NPV(I)=TN/(TN+FN)</td>
</tr>
<tr>
<td>670</td>
<td>NPV(I)=100*NPV(I)</td>
</tr>
<tr>
<td>680</td>
<td>NEXT I</td>
</tr>
</tbody>
</table>

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Fig. 2. Flow chart of the computer program.

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is the key to understanding the estimation of our results. Using such a calculation (Fig. 1) four main parameters (sensitivity, specificity, positive predictive value and negative predictive value) for the cumulative results and for each serum tumour marker level can be obtained.

Results
Finally, the data analysis provides numeric values of sensitivity, specificity, positive predictive value and negative predictive value as output tumour marker databases. These parameters can serve as graphical input tumour marker databases and it becomes possible to plot the ROC curve as a graphical distribution of tumour marker levels.

Sensitivity of tumour marker values in patients with certain disease proved useful in the estimation of tumour marker utility. In addition, the sensitivity can serve as an indicator of the increased tumour marker values in the disease examined. Specificity is the indicator of the normal or not elevated tumour marker levels in healthy persons. Positive predictive value is the indicator estimating positive, i.e. elevated tumour marker levels in diseased patients. Negative predictive value is the indicator estimating negative, i.e. decreased tumour marker levels in healthy patients.

The computer program also allows estimation of the potential utility of the serum tumour marker measured in patients with various diseases (Fig. 3), simultaneous determination of serum tumour markers in diseased patients (Fig. 4); the real value of each serum tumour marker level in diseased patients (Fig. 3). Figure 5 shows the ROC curves of serum CA 19-9 in various diseases and Fig. 6 shows CA 72-4. Figure 7 shows the ROC curves for CEA, CA 19-9 and CA 72-4 in patients with colorectal cancer.
Fig. 4. ROC curves of tumour markers CEA, CA 19-9 and CA 72-4 in the group of patients at the beginning of malignant alteration in colorectal adenomas (38) with the cumulative results of the tumour marker's operational characteristics.

+—— CA 19-9, ○-○ CA 72-4, △-△ CEA.

Fig. 5. ROC curves of serum CA 19-9 in various diseases with the tested serum CA 19-9 level (35 U/ml) along with the serum CA 19-9 values in patients at the beginning of malignant alteration in colorectal adenomas or in those with benign polypoid adenomas.

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Fig. 6. ROC curves of serum CA 72-4 in various diseases with the tested serum CA 72-4 level (3.2 U/ml) along with the serum CA 72-4 values in patients at the beginning of malignant alteration in colorectal adenomas or in those with benign polyloid adenomas.

Fig. 7. ROC curves of tumour markers CEA, CA 19-9 and CA 72-4 in the group of patients with colorectal benign polyloid adenomas (66) with the cumulative results of the tumour marker's operational characteristics. +++ CA 19-9, O--O CA 72-4, △--△ CEA.
Discussion

The importance of testing the potential utility of cumulative serum tumour marker levels is well known, but it would be emphasized the testing of each serum tumour marker level by data analysis. By comparing each single newly measured tumour marker level along with the previously measured values in patients with confirmed diagnoses, four numerical parameters for each tumour marker level tested were obtained (Fig. 4). This approach would serve as a useful diagnostic tool in following up patients with various diseases. Thus new avenues for estimating the potential utility of serum tumour markers are offered. Thanks to these numerical parameters (the tumour marker operational characteristics) we can communicate in a precise way with a numeric code for every single disease or stage of the disease, as well as with various treatment codes during follow-up of the disease.

To do this we need an input database of the numerous serum tumour marker levels of patients with established diagnoses (confirmed by microscopy of tissue specimens). For such an estimation it is not enough to pool the local tumour marker databases from one Medical Centre only or from one area only. We need a European Tumour Markers Data Base Centre which would play an important role in the development of tumour marker expert systems and which would offer to all researchers in medical and research centres all over Europe a knowledge-based system (KBS) as a promising method of providing expert knowledge in clinics about tumour markers; eliminating an unnecessary workload for experts; reducing variation in quality of tumour marker reports; and assisting in the management of tumour marker databases for clinical decisions [6].

Within the scientific and technical context this cooperative action at the European level would lead to the setting up of tumour marker international subprojects which might be incorporated into the COST B2 project: Quality Assurance in Nuclear Medicine Software.

References