ACTA MED PORT 3: 3, 1981

THE DISCRIMINANT DIAGNOSTIC POWER OF LIVER FUNCTION TESTS IN HEPATIC CIRRHOSIS

M. A. Serra, J. M. Rodrigo, J. Guix, F. Montes, A. Wassel, L. Aparisi, J. A. Olmo and M. Bixquert

Departamento de Medicina Interna. Hospital Clínico Universitário. Valência. España.

SUMMARY

We have studied the results of 10 hepatic tests with multivariate linear discriminant analysis in 44 normal subjects and 88 cirrhotic patients. The results prove that the functional tests with major diagnostic power are those that analyse the functional reserve of the liver, basically the clearance and transport maximum of bromsulphalein. Both give us a diagnostic error of 1.2% and the addition of the other tests increases only slightly the degree of discriminant power. The value of MLDA in the functional evaluation of cirrhotic patients is discussed.

Nowadays we have a large number of biological tests that tell us about the functional state of the liver. From the beginning these have been useful in the diagnosis and prognosis of hepatic diseases. No individual test, however, gives us a total picture, since the liver has multiple functions. Because of this, physicians have to make a carefully balanced evaluation of the results obtained from several tests. This global analysis is normally carried out in a subjective manner, and this tends to influence precision and reproducibility.

To date the best system providing objectivity to the complete study of the several biological values is by the use of linear discriminant analysis. ZIEVE, [1, 2] was the first who examined hepatic functional tests with this method, but nowadays these tests are no longer used. Later [RAMSOE [3]] evaluated these tests with similar statistical method, but his limited number of cases gives rise to reasonable doubt as to whether the reproducibility was sufficiently valid.

Multivariate linear discriminant analysis (MLDA) enables us to decide on the qualitative aspect — in this case healthy or diseased — and, moreover, to objectively evaluate the data and thus find a formula representing the best linear combination of values permitting the calculation of a numeric value for use in diagnosis, prognosis and treatment of a disease.

The aim of our work is the application of MLDA on values of alamime transaminase (GPT), total bilirubin (BR), alkaline phosphatase (AF), serum albumin (ALB), gammaglobulin (GG), prothrombin index (IQ), $T\frac{1}{2}$ of intravenous galactose tolerance test ($T\frac{1}{2}$ Ga) and clearance (K_1), transport maximum (Tm) and also relative storage capacity (S) of bromsulphalein obtained from large number of subjects in order to attain representative results.

Received: 27 October 1980

MATERIAL AND METHODS

This study has been performed on 44 subjects (27 males and 17 females) with a mean age of 35, having no clinical or biological symptoms of hepatic disease. We have not performed liver biopsy for ethical reasons. The cirrhotic group comprised 88 patients (40 males ond 48 females) with the anatomopathological diagnosis of hepatic cirrhosis and a mean age of 55. At the time of this study the cirrhotic patients had no symptoms of encephalopathy, hemorrhagic disease or infectious process that might have complicated their condition in a serious way.

In all cases the following tests were performed within 72 hours: plasma values of alanine transaminase (GPT), [4] total bilirubin (BR), [5] alkaline phosphatase (AF), [4] serum albumin (ALB), gammaglobulin (GG), prothrombin index (IQ), [6] $T\frac{1}{2}$ of intravenous galactose tolerance test ($T\frac{1}{2}$ Ga), [7] and clearance (K_1), [8] Transport Maximum (Tm) and relative storage capacity (S) [9] of bromsulphalein.

STATISTICAL METHODS

We have used MLDA. In short this method consists in: given two normal n-variant populations π_1 and π_2 with a common covariance matrix Σ and different mean vectors, designated by μ_1 and μ_2 an observation is classified as belonging to one or another population, based on the following rule of decision:

$$\text{if } Z(x) = x' \Sigma^{-1} (\mu_1 - \mu_2) - \frac{1}{2} (\mu_1 + \mu_2) \Sigma^{-1} (\mu_1 - \mu_2) \geqslant \log k$$

x is assigned to population π_1

$$\text{if } Z(x) = x' \Sigma^{-1} (\mu_1 - \mu_2) - \frac{1}{2} (\mu_1 + \mu_2) \Sigma^{-1} (\mu_1 - \mu_2) < \log k$$

x is assigned to population π_2.

Log k is denominated the discrimination point and k is a quantity that is defined as where p_i is the probability *a priori* of x belonging to π_1, and c (i/j) $i = 1,2$; $i \neq j$ is the cost that assigning a subject to π_i implies when really belongs to π_j. Details concerning the above method can be consulted in ANDERSON. [10]

Our method is performed by means of a stepwise discriminant analysis, which consists in increasing in one unit, at each step, the number of variables evaluated in the discrimination. The new variable is that which most decreases the probability of misclassification. Thus we endeavour with this method to discover those variables whose addition significantly improves the probabilities and can thus be considered redundant. The GARSIDE [11] algorithm is used in this procedure; other algorithms such as that of EFROYMSON [12] lead to results that are not necessarily optimal.

RESULTS

The statistical test used in this study requires that the variables be normally distributed. [10] Consequently, the distribution of variables from control and cirrhotic patients was examined separately by inspection of graphs of the cumulative data distri-

bution and the logarithms of the data. The best distribution was chosen. We have therefore used the logarithmic transformation in the values of alanine transaminase, alkaline phosphatase, bilirubin and gammaglobulins.

In table I we have set out the results following the same sequence as RAMSOE, [3] ordered in accordance with the test of least misclassification error. This table shows the mean of values, the range according standard deviation, the t-value, the discriminant point and the estimated probability of diagnostic error expressed by percentage of overlapped area. The order in the table is established from the most discriminative test. The last column shows the cumulative diagnostic error, the successive combination of tests.

Table 2 gives the best combination of one or more tests and their capacity to distinguish between the normal and cirrhotic groups independent of other combination, according to the statistical method employed. The last combination includes every test that does not evaluate the functional reserve of the liver.

Figue 1 illustrates the population of the normal subjects and cirrhotic patients based on the values of the K_1 of the bromsulphalein with their overlap, the calculation of Z for each case and the variations of log k when the quotient p_1/p_2 is 1, or as in our case in which it is 0.6. This quotient was calculated after a review of 450 cases including normal, cirrhotic and patients with other hepatic diseases. In this figure it is possible to see the minimal incidence in the discriminant point of large variation of log k.

Similarly, figure 2 shows the study of both populations based on all cases. The variation of log k in the graph shows the low incidence that the calculation of costs of misclassification have, since variations in a large interval of log k produce minimal changes in the discriminant point.

Finally figure 3 shows the situation of the two populations and their discriminatory line based on the Tm and K_1 values of bromsulphalein. The absence of false positive cases in our population can be observed.

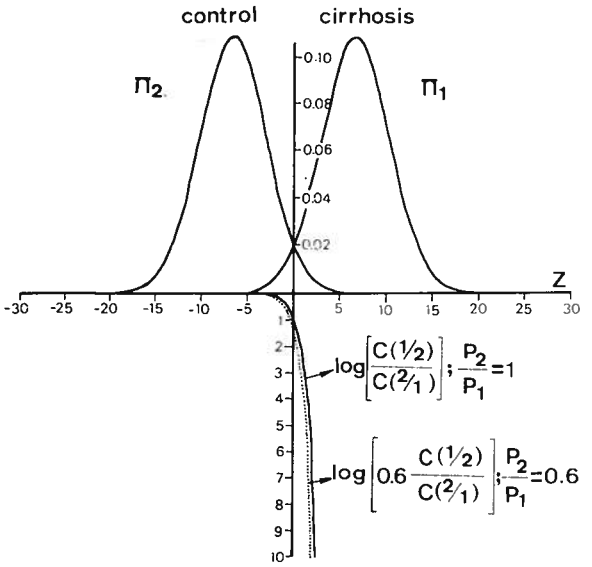

Figure 1 — *The estimated probability distribuition of Z based in K_1 values of bromsulfalein*
$Z = 13.933 - 1.55318\ K_1$

Table 1

Comparison of liver tests in control subjects and patients with cirrhosis. — K_1: clearance of bromsulphalein. Tm: transport maximum. S: relative storage capacity. BR: total bilirubin. T ½ Ga: T ½ of intravenous galactose tolerance test. AF: alkaline phosphatase. GPT: alanine transminase. IQ: prothrombin index. ALB: serum albumin. GG: serum gammaglobulin.

	CONTROL (44)		CIRRHOSIS (88)					
	Mean	Range (± S. D.)	Mean	Range (± S. D.)	t-value	Overlap point	Overlap area %	Cumulative overlap %
K_1 (%)	13.26	10.88 — 15.64	4.67	2.34 — 7.01	19.78	8.67	3.39	3.39
Tm (mg/min)	9.24	7.86 — 10.62	4.82	3.51 — 6.12	18.16	7.03	4.68	1.29
BR (mg%)	0.76	0.54 — 1.07	1.19	0.68 — 2.11	4.53	0.94	33.78	1.15
T½Ga (min)	12.90	10.9 — 15.9	29.1	19.1 — 60.2	13.94	21.00	9.89	1.06
AF (U/1)	35.51	25.6 — 48.7	47.5	31.9 — 72.8	4.07	41.1	35.35	1.03
GPT (U/1)	4.8	1.8 — 12.0	14.5	5.7 — 36.1	6.38	8.3	27.78	0.93
S (mg/mg%)	51.26	31.2 — 71.3	24.8	7.8 — 41.7	7.93	38.03	23.17	0.92
IQ (%)	99.02	95 — 113	83.26	63.7 — 102.8	5.26	91.14	31.34	0.92
ALB (g.%o)	4.05	3.55 — 4.55	3.26	2.61 — 3.87	6.99	3.65	35.90	0.92
GG (g%o)	1.23	1.06 — 1.58	2.06	1.45 — 2.95	8.70	1.59	21.08	0.92

Table 2

	DIAGNOSTIC ERROR
K_1	3.39 %
K_1 + Tm	1.29 %
K_1 + Tm + BR	1.15 %
K_1 + Tm + BR + GPT	1.05 %
K_1 + Tm + BR + AF + T½ Ga	1.03 %
K_1 + Tm + BR + GPT + T½ Ga + S	0.93 %
K_1 + Tm + BR + GPT + T½ Ga + S + AF	0.92 %
K_1 + Tm + BR + GPT + T½ Ga + S + AF + IQ	0.92 %
K_1 + Tm + BR + GPT + T½ Ga + S + AF + IQ + ALB	0.92 %
K_1 + Tm + BR + GPT + T½ Ga + S + AF + IQ + ALB + GG	0.92 %
BR + GPT + AF + IQ ALB + GG	13.55 %

The best combination of the tests with minor diagnostic error. K_1: clearance of bromsulphalein. Tm: transport maximum of bromsulphalein. S: relative storage capacity of bromsulphalein. BR: serum bilirubin. GPT: alanine transaminase. AF: alkaline phosphatase. T ½ Ga: T ½ of intravenous galactose tolerance test. IQ: prothrombin index. ALB: serum albumin. GG: serum gammaglobulins.

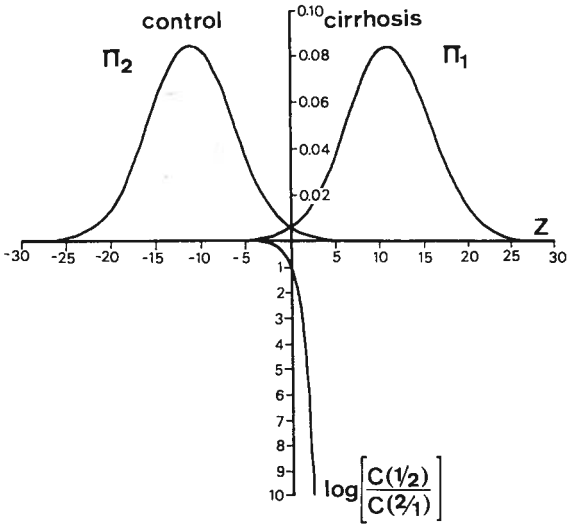

Figure 2 — *The estimated probality distribution of Z based in values of all tests: alanine transaminase (GPT), total bilirrubin (BR), alkalin phosphatase (AF), serum albumin (ALB), gammaglobulin (GG), prothrombin index (IQ), T ½ of intravenous galactose tolerance test (T ½ Ga) and clearance (K_1), transport maximum (Tm) and relative storage capacity (S) of bromsulfalein Z=0.99 log GPT+0.371 log AF-2.371 log BR-0.22 ALB10.251 log GG+0.01 IQ-0.001/T ½ Ga-1.92 Tm-1.28 K_1-0.02 S+24.73*

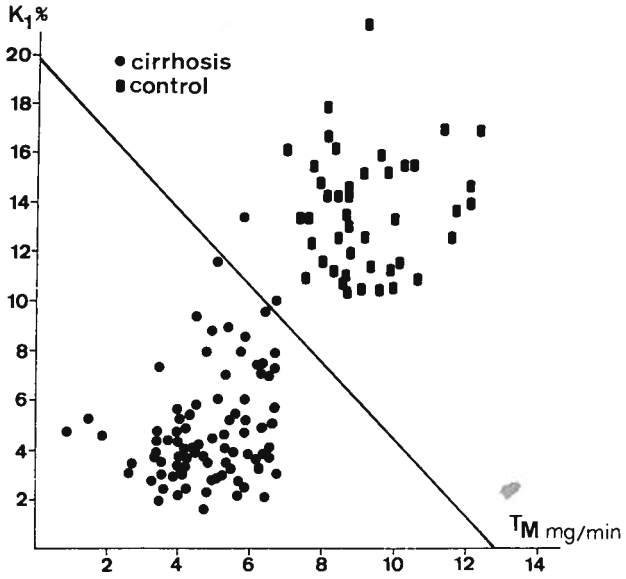

Figure 3 — *The discrimination between cirrhosis and control by two variables clearance (K_1) and transport maximun (Tm) of bromosulphalein*

DISCUSSION

The important role of p_1, p_2, c_1 and c_2 forced us to calculate these values in order to obtain the discriminant point. The difficulty, however, of performing an objective evaluation of these quantities, especially of the cost (c_1 and c_2) made us avoid the problem assuming that $c_1/c_2 = 1$ and adopting the most unfavourable position with respect to p_1 and p_2 making $p_1 = p_2 = \frac{1}{2}$ thus rendering $\log k = 0$. However, these suppositions do not qualitatively change the decisions that are taken, and ultimately the probability of misclassification as is shown in Figure 1 where the variation of log k is plotted.

MLDA, as performed by us, shows, in the first place, its usefulness in the diagnostic evaluation of biological tests, and it can always be applied to new cases if the populations are really a reflection — same variance and mean — of the universal set of the subjects who can be studied in our environment, which is difficult to affirm in a secure manner in spite of the fact that our study is larger than RAMSOE's [3] but with unavoidable differences of selection, such as age in both groups.

The results prove conclusively that the tests with greatest diagnostic or discriminant power continue to be those that estimate the functional reserve of the liver, and among them the clearance (K_1) of bromsulphalein that has an error of misclassification slightly lower than the Tm of WHEELER. [9] By our data, however, the tests that do not analyse the functional reserve of the liver, possess an error possibility of 13.5%, a value that is higher than that produced by any isolated functional test.

Our results show some differences compared with RAMSOE's [3] when we take into account the other tests, since, for instance, the intravenous galactose tolerance

test is put in fourth place according to its discriminant power, the estimated level of error of 9.9% is much lower than that obtained by RAMSOE,[3] with a similar test, galactose elimination capacity being 17.1%. The order of the other tests is also different, but we have to point out that this situation is determined by minor differences in the calculation of error of misclassification.

The use of discriminant power analysis allows us to evaluate the redundancy of the group of variables in order to give an effective diagnosis; that is to say, the combination of tests that is necessary to find the best diagnosis, and from which point onward the analysis of new biological tests does not contribute to a greater discriminant power. So we can see that the combination of functional tests of bromsulphalein, except S, in spite of possible complications, but we have not found any complications in more than 500 tests performed by us. Together with the calculation of bilirubin and the intravenous galactose tolerance test gives us a discriminant power that is scarcely improved by addition of new tests. The latter does not imply that the other tests do not give us complementary information as to the degree of cytolisis or colestasis, useful for a deeper understanding of any individual case.

Finally, we think that the use of MLDA, providing us with a method for the calculation of Z, allows an evaluation of the functional state of the liver in each subject with hepatic cirrhosis, expressed by a real number, in the mathematical sense, which is more useful than semiquantitative evaluations, such as those used by ORREGO[13] or the calculation of the diagnostic possibilities, with a dicision tree, carried out by SCHMIDT.[11] This statistical calculation also allows us to establish the cut-off point in the functional diagnosis of hepatic disease. This is a previous basis according to CONN[15] in the method of separating normal and abnormal function for a later consideration of the specificity and sensitivity of this functional diagnostic method. Thus we have chosen for our study a group of patients with a definite and totally established hepatic disease, to create a model of analysis which is an obligatory and necessary step to study its possibilities in the diagnosis of a minor hepatic disease. Undoubtedly the diagnosis in an invidual case has to consider the possibilities of misclassification.

RESUMO

Avaliou-se o resultado de 10 provas de função nepática por meio de análise discriminatória linear multivariada, em 44 indivíduos normais e 88 doentes cirróticos. Os resultados provam que os testes funcionais com maior relevância diagnóstica são aqueles que incidem sobre a reserva funcional do fígado, principalmente a clearance e o transporte máximo da bromosulftaleina. Qualquer um destes testes nos dá um erro diagnóstico de 1,2% e a adição de outras provas limita-se a aumentar ligeiramente o poder discriminatório. Discute-se ainda o valor da ADLM na avaliação funcional do doente cirrótico.

REFERENCES

1. ZIEVE L, HILL E. An evaluation of factors influencing the discriminative effectiveness of a group of liver function tests. III. Relative effectiveness of hepatic test in cirrhosis. *Gastroenterology* 1955; 28: 785-802.
2. ZIEVE L, HILL E. An evaluation of factors influencing the discriminative effectiveness of a group of liver function tests. IV Nature of the interrelationships among hepatic tests in cirrhosis. *Gastroenterology* 1955; 28: 914-926.
3. RAMSÖE K, TIGSTRUP N, WINKEL P. The redundancy of liver test in the diagnosis of cirrhosis estimated by multivariate statistics. *Scan J Clin Lab Invest* 1970; 26: 307-312.

4. PLOMTEUX G, TOULET J. L'enzimologie serique in Foie et voies biliares. Exploration functional et morphologique in pathologie hepatobiliare pp 76-114 Expansion Scientifique, Paris, 1975.
5. JENDRASSIK L, Grof P. Vereinfatche photometrische methoden zur bestimmung des blutbilirubins. *Biochem Z* 1938; 297: 81-83.
6. OWREN P A, AASK H. The control of dichumarol therapy and the quantitative determination of prothrombin and proconvertin. *Scan J Clin Lab Invest* 1951; 3: 201-204.
7. TENGSTROM B. An intravenous galactose tolerance test and its use in hepatobiliary diseases. *Act Med Scand.* 1968; 183: 31-40.
8. CAROLI J, NYS A. Epreuve de la BSP. Modification Nys-Caroli. *Rev Med Chir Mal Foie* 1956; 2: 13-28.
9. WHEELER H O, MELTZER J I, BRADLEY S. Biliary transport and hepatic storage of sulfobromophthalein sodium in the unanesthetized dog, in normal man and in patients with liver disease. *J. Clin Invest* 1960; 39: 1131--1144.
10. ANDERSON T W. An Introduction to Multivariate Statistical Analysis. Wiley & Sons, New York 1966.
11. GARSIDE M J. The best sub-set in multiple regression analysis. *Appl Stat* 1965; 14: 196-200.
12. EFROYMSON M A. Multiple regression analysis in mathematical methods for digital. Computers pp. 191-203. Wiley & Sons, New York 1960.
13. ORREGO H, KALANT H, ISRAEL Y, et al. Effect of sohrt-term therapie with propylthiouracil in patients with alcoholic liver disease. *Gastroenterology* 1979; 76: 105-115.
14. SCHMIDT E. Strategy and evaluation of enzyme determinations in serum in diseases of the liver and biliary system in Evaluation of liver of liver function. Multifaceted approach to clinical diagnosis. pp. 79-102. Urban & Schwarsenberg inc. Baltimore 1978.
15. CONN H O. Diagnostic techniques in hepatobiliary disease. *Gastroenterology.* 1978; 75: 1175-1177.

Address for reprints: *Dr. M. A. Serra*
c/Gorgos 29 — 11ª
Valência — 21
ESPAÑA