Biochemical and haematological indicators of excessive alcohol consumption*

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SUMMARY Discriminant function analysis was used to determine the optimum combination of haematological and biochemical tests which gave the best discrimination between hospital patients with high and low alcohol intakes. We studied 265 patients with alcohol-related disease, 133 gastroenterology outpatients drinking less than 20 g of alcohol per day, and 104 patients with a variety of non-alcoholic liver disease. Values of mean cell volume (MCV), serum bilirubin, aspartate transaminase, serum alkaline phosphatase (AP) and γ glutamyl transferase (γGT), serum albumin, serum globulin, and uric acid were determined in each patient. The best discrimination between the three groups of patients was provided by a combination of mean corpuscular volume, log_{10} γGT, and log_{10} serum alkaline phosphatase. In women, 92% of the high alcohol group, 100% of the low alcohol group, and 87% of the non-alcoholic liver disease were correctly allocated by the discriminant analysis. The corresponding figures for the men were 80%, 100%, and 71%. Thus, over 80% of patients with excessive alcohol intake were correctly allocated by the use of three simple laboratory tests.

Alcohol consumption in the United Kingdom has been increasing rapidly with an accompanying rise in the prevalence of alcohol-related diseases. As recognition of these patients is often difficult, there is a need for simple laboratory investigations to help identify those patients whose illness is associated with excessive alcohol intake.

The most widely used tests for this purpose are standard liver function tests, γ glutamyl transferase (γGT), and mean cell volume (MCV) as measured using an electronic cell counter. Although γGT is a sensitive indicator of excessive alcohol intake, it is also raised in a variety of non-alcoholic liver diseases.1 We have found mean cell volume to be raised in approximately 80% of hospital patients with excessive alcohol consumption.2 However, this test is also non-specific and it is difficult to assess the significance of small increases in mean cell volume.

In order to overcome some of the disadvantages of these tests when used individually, we have attempted to determine the optimum combination of tests which gives the best discrimination between hospital patients with high and low alcohol intakes. The method chosen was discriminant function analysis,3 which is particularly suited to the analysis of continuous variables such as the results of biochemical tests. This technique has been successfully used in situations such as the differential diagnosis of hypercalcaemia4 and the differentiation of iron deficiency from thalassaemia trait.5

Methods

The data required for the initial analysis (study A) was obtained from the first complete set of laboratory tests of 373 patients who were seen at Northwick Park Hospital between 1973 and 1978. These patients were made up of the following three groups:

1 HIGH ALCOHOL INTAKE GROUP 219 patients (146 men and 73 women—mean age 50-9 years).

These patients had been drinking more than 80 g alcohol per day for at least one year. Most were steady rather than 'spree' drinkers and all were thought to be actively drinking until shortly before presentation. Details of their main clinical features are given in

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Received for publication 1 June 1981
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Table 1  Mode of presentation of patients with high alcohol intakes

<table>
<thead>
<tr>
<th></th>
<th>Men (n = 178)</th>
<th>Women (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study A (mo.)</td>
<td>Study B (mo.)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>40</td>
<td>15</td>
</tr>
<tr>
<td>Known excessive alcohol intake*</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Overt liver disease*</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Other†</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>146</td>
<td>32</td>
</tr>
</tbody>
</table>

*Including 50 patients seen at a psychiatric clinic.
†Including chest infections, collapse, hypertension, trauma etc.

Table 1, and, where possible, the evidence of excessive alcohol intake was corroborated by close relatives or friends. The majority were inpatients under the care of the gastroenterology unit, and 50 were referred as outpatients to one psychiatrist for treatment of excessive drinking. Serum vitamin B₁₂ was above the lower limit of the normal range in all patients with macrocytosis.

2  LOW ALCOHOL INTAKE GROUP  84 new patients (41 men and 43 women—mean age 43.5 years)

These patients were referred to the gastroenterology outpatient clinic and their alcohol intake was prospectively assessed as being less than 20 g/day. Diagnoses are given in Table 2, and no patient had liver disease, haematological disorder, or malabsorption. Approximately 60% had non-ulcer dyspepsia, irritable bowel syndrome, or anxiety symptoms, and 20% had uncomplicated peptic ulcer or diverticular disease.

3  NON-ALCOHOLIC LIVER DISEASE GROUP  70 patients (35 men and 35 women—mean age 55.3 years)

These patients with a variety of non-alcoholic liver diseases, were drinking less than 20 g alcohol per day. Final diagnoses are given in Table 2 and liver histology or laparotomy findings were available for all patients.

LABORATORY INVESTIGATIONS

Blood counts were performed within 24 hours of presentation, using the same Coulter Counter Model S set so that the haematocrit excluded trapped plasma. The reference range for mean cell volume was 80 to 92 fl and liver function tests were performed using standard laboratory techniques. Serum γ glutamyl transferase (γGT) was measured at 37 °C by the method of Rosalki et al. Values for mean cell volume, serum bilirubin, aspartate transaminase, γGT, serum alkaline phosphatase, serum albumin, and globulin and uric acid were recorded for each patient and the information entered onto a computer.

DISCRIMINANT ANALYSIS

A stepwise discriminant analysis was performed using the BMDP7M programme of the University of California (version of 10 June 1965, Health Sciences Computing Facility, UCLA). This programme performs a multiple group discriminant analysis. The variables used in computing the linear classification functions are chosen in a stepwise manner. At each step the variable adding most to the separation of the groups is entered until group separation ceases to improve. A classification table is computed, and a plot made of two discriminant functions to give an optimal two-dimensional picture of the separation of the groups.

PROSPECTIVE STUDY

After the result of the initial 373 patients had been calculated, another 129 patients (study B) were studied to determine if the discriminant functions derived from the original data base would give similar results in a prospective study. Details of the patients are given in Tables 1 and 2.

Results

STUDY A

Initial analysis indicated that a combination of mean cell volume, log γGT, and serum alkaline phosphatase gave the best discrimination between high and low alcohol groups. Gammaglutamyl transferase was superior to aspartate transaminase for this purpose, and the addition of any of the remaining variables did not significantly improve the results. As mean cell volume and γGT values tended to be higher in the women with excessive alcohol consumption as compared with their
male counterparts, the results were calculated for the two sexes separately.

In addition to determining the optimum combination of variables to separate the three groups, the BMD07M programme also classified cases into one of the three groups on the basis of squared distances from the group means. The number of cases classified into the three groups and the actual groups from which they were derived are shown in Table 3.

In women, 95% of the high alcohol group, 100% of the low alcohol group, and 77% of the non-alcoholic liver disease group were correctly allocated by this method. The corresponding figures for the men were 83%, 100%, and 63%.

**STUDY B**

The results of the prospective study (Table 4) were very similar to the initial study with regard to the high and low alcohol groups. However, 40% of the men with non-alcoholic liver disease were incorrectly classified into the high alcohol group. Logarithmic transformation of the serum alkaline phosphatase values as well as yGT reduced this false positive rate to 20%, with no significant change in the results in the other groups. Logarithmic transformation was then performed on the alkaline phosphatase values in study A so that overall results could be obtained.

**OVERALL RESULTS**

Studies A and B were combined and discriminant functions recalculated using mean cell volume, log yGT, and log alkaline phosphatase. Table 5 gives the classification table obtained for the entire 502 patients.

Figures 1 and 2 show the plots of the first and second discriminant functions and illustrate the better separation of the groups in women. The mean values for each of the three groups are shown, as well as circles representing those areas in which 90% of the patients in each group might be expected to fall.

The co-ordinates of any new patient can be calculated from the equations given below, and a classification obtained by plotting on either Figs 1 or 2. Exact probabilities of an individual belonging to a particular group cannot be obtained, as this would involve making the assumption that the data conform to a multivariate normal distribution, which is unlikely to be the case.

**Women**

1st discriminant function = (0.141 × MCV) + (0.86 × log10 γGT) − (4.22 × log10 AP) − 10.09

2nd discriminant function = −(0.036 × MCV) − (1.60 × log10 γGT) − (2.03 × log10 AP) + 8.6

**Men**

1st discriminant function = (0.127 × MCV) + (1.025 × log10 γGT) − (3.84 × log10 AP) − 9.84

2nd discriminant function = −(0.008 × MCV) − (1.59 × log10 γGT) − (2.58 × log10 AP) + 6.43

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### Table 3

**Discriminant function analysis using MCV, log serum γGT and serum AP in initial group of 373 patients (study A)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Men (n = 222)</th>
<th>Group</th>
<th>Women (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group (no. (%)</td>
<td></td>
<td>Group (no. (%)</td>
</tr>
<tr>
<td></td>
<td>1 2 3</td>
<td></td>
<td>1 2 3</td>
</tr>
<tr>
<td>1 High alcohol intake (n = 146)</td>
<td>121(83) 23(16) 2(1)</td>
<td>1 High alcohol intake (n = 73)</td>
<td>69(95) 4(5) 0</td>
</tr>
<tr>
<td>2 Low alcohol intake (n = 41)</td>
<td>0(0) 41(100) 0(0)</td>
<td>2 Low alcohol intake (n = 43)</td>
<td>0(0) 43(100) 0(0)</td>
</tr>
<tr>
<td>3 Non-alcoholic liver disease (n = 35)</td>
<td>5(14) 8(23) 22(63)</td>
<td>3 Non-alcoholic liver disease (n = 35)</td>
<td>1(3) 7(20) 27(77)</td>
</tr>
</tbody>
</table>

### Table 4

**Discriminant function analysis using MCV, log serum γGT, and serum AP in 129 patients (study B)**

<table>
<thead>
<tr>
<th>Group</th>
<th>Men (n = 62)</th>
<th>Group (no. (%)</th>
<th>Women (n = 67)</th>
<th>Group (no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group (no. (%)</td>
<td></td>
<td>Group (no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 2 3</td>
<td></td>
<td>1 2 3</td>
<td></td>
</tr>
<tr>
<td>1 High alcohol intake (n = 32)</td>
<td>27(84) 5(16) 0(0)</td>
<td>1 High alcohol intake (n = 14)</td>
<td>13(93) 1(7) 0(0)</td>
<td></td>
</tr>
<tr>
<td>2 Low alcohol intake (n = 20)</td>
<td>0(0) 20(100) 0(0)</td>
<td>2 Low alcohol intake (n = 29)</td>
<td>0(0) 29(100) 0(0)</td>
<td></td>
</tr>
<tr>
<td>3 Non-alcoholic liver disease (n = 10)</td>
<td>4(40) 0 6(60)</td>
<td>3 Non-alcoholic liver disease (n = 24)</td>
<td>1(4) 2(8) 21(88)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5

**Discriminant function analysis using MCV, log serum γGT, and log serum AP for all 502 patients.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Men (n = 284)</th>
<th>Group (no. (%)</th>
<th>Women (n = 218)</th>
<th>Group (no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group (no. (%)</td>
<td></td>
<td>Group (no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 2 3</td>
<td></td>
<td>1 2 3</td>
<td></td>
</tr>
<tr>
<td>1 High alcohol intake (n = 178)</td>
<td>143(80) 27(15) 8(5)</td>
<td>1 High alcohol intake (n = 87)</td>
<td>80(92) 6(7) 1(1)</td>
<td></td>
</tr>
<tr>
<td>2 Low alcohol intake (n = 61)</td>
<td>0(0) 61(100) 0(0)</td>
<td>2 Low alcohol intake (n = 72)</td>
<td>0(0) 72(100) 0(0)</td>
<td></td>
</tr>
<tr>
<td>3 Non-alcoholic liver disease (n = 45)</td>
<td>6(13) 7(16) 32(71)</td>
<td>3 Non-alcoholic liver disease (n = 59)</td>
<td>2(3) 6(10) 51(87)</td>
<td></td>
</tr>
</tbody>
</table>
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Discussion

Our study shows that a combination of three simple laboratory tests will identify between 80 and 92% of hospital patients with alcoholic-related disease who are actively drinking more than 80 g alcohol per day. In addition, all of the low alcohol intake group and over 70% of the non-alcoholic liver disease group were correctly allocated by this discriminant analysis. These results are a considerable improvement over any of the three tests when considered individually.

The basis of the discrimination is that the heavy drinkers tend to have a raised mean cell volume, a high γGT, but only a slightly raised serum alkaline phosphatase. In contrast, the mean cell volume in non-alcoholic liver disease is normal and alkaline phosphatase levels high.

There have been several recent reports of the relationship of various laboratory tests to alcohol intake in individuals attending health-examination centres.9-11 These workers all found an increased prevalence of abnormal γGT, mean cell volume, and aspartate transaminase results with increasing alcohol intake. However, these studies do not indicate how these test results should be combined to identify subjects with an excessive alcohol intake.

The use of mathematical and computer-assisted procedures in the diagnosis of liver disease has been reviewed by Goldberg and Ellis.12 Previous studies using discriminant analysis13 17 have included relatively small numbers of patients with alcoholic liver disease. Solberg et al.14 found, when attempting to distinguish between alcoholic cirrhosis and four other groups of liver diseases, that the 17 patients with alcoholic cirrhosis were often misclassified. Goldberg and Ellis15 used discriminant analysis with 13 laboratory tests and 14 diagnostic categories. One of these categories was alcoholic liver disease, but only 24 out of 59 of this group were correctly allocated. The probable reason for our greater success in distinguishing patients with alcohol-related disease was the use of mean cell volume as well as liver function tests.

Liver histology was available in 75% of our high alcohol intake group, of whom 24% had alcoholic cirrhosis. However, this analysis does not distinguish between patients with alcoholic cirrhosis, non-cirrhotic alcoholic liver disease, and those heavy drinkers with no histological evidence of liver disease.

All of the classifications that were made using discriminant analysis were made on the basis of the laboratory results at presentation. We have observed that repeating the tests at a later stage of the illness resulted in the correct classification being made in some patients with non-alcoholic liver disease who were initially misclassified. Repeating the analysis was also useful in some of the high alcohol group who continued to drink, but, in those who became abstinent, the abnormal tests returned towards normal levels.

The finding that a higher proportion of the female ‘drinkers’ were correctly allocated by this method was because there were more abnormal test results among the women. This gives support to the clinical impression that women are more susceptible than men to a variety of alcohol-related diseases.18 19 The greater diagnostic accuracy in the women is particularly useful, as these patients are often reluctant to admit to an
excessive alcohol intake.

Although we have not used these discriminant functions on data obtained from other laboratories, it is hoped that our approach may prove useful to other centres using similar analytical techniques. However, it should not be assumed that the same results would be obtained from heavy drinkers in the community, as our data base was derived from hospital patients who might be more susceptible to the toxic effects of alcohol.

We thank the Departments of Clinical Chemistry and Haematology for measurements and assistance. We also thank Dr H Hershon for permission to study patients under his care. D M Chalmers held a Medical Research Council Training Fellowship.

References
