Chest Radiography compared to Laboratory Markers in the Detection of Alcoholic Liver Disease

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The diagnosis of alcoholism is frequently missed because an adequate history of alcohol consumption is often not taken[1] or the true facts may have been concealed. Numerous physiological, clinical, psychological, behavioural and laboratory criteria have been suggested as aids to the diagnosis of alcoholism. Even carefully designed questionnaires may detect fewer than half of those individuals already known to be alcoholic[2]. In clinical practice recognition of problem drinkers is often dependent upon the use of haematological and biochemical markers, the most useful being the red cell mean corpuscular volume (MCV) and the serum gamma-glutamyltranspeptidase (GGT)[3]. However, these laboratory indices have certain limitations as screening tests.

Two recent studies have reported that the presence of fractures on a routine chest radiograph is a characteristic finding in patients who abuse alcohol[4,5]. We were interested to examine the sensitivity and specificity of this finding (thoracic fractures) in comparison with standard laboratory tests, in the detection of patients with alcoholic liver disease.

Patients and Methods

This study included all patients on a single medical firm over a five-year period who had undergone liver biopsy during the investigation of hepatomegaly, jaundice or abnormal liver function, and in whom a routine chest radiograph had been performed within three months of biopsy. Clinical and laboratory data were available on 166 patients who had undergone liver biopsy. However, in six patients no chest radiograph was available, and this report is confined to results on the remaining 160 patients.

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Alcoholic Liver Disease. Seventy-four patients had a final diagnosis of alcoholic liver disease (ALD) on the basis of compatible liver biopsy, together with a history of prolonged (more than 12 months) excessive alcohol consumption (over 80g/day for males and 40g/day for females). The ALD group consisted of 52 males (mean age 54 years) and 22 females (mean age 56 years). Cirrhosis was present in 45 per cent of those with ALD.

Non-Alcoholic Liver Disease. Of the patients, 86 had non-alcoholic liver disease (NALD), including autoimmune, metastatic and granulomatous disorders, and acute or chronic hepatitis. The NALD group comprised 41 males (mean age 50 years) and 45 females (mean age 53 years). Cirrhosis was present in 20 per cent of those with NALD.

Controls. Ninety-five out-patients presenting to a gastroenterology clinic with a variety of gastrointestinal complaints, and who were drinking less than 20g alcohol per day, served as controls (C). The group comprised 44 males (mean age 47 years) and 51 females (mean age 52 years). The majority had functional bowel disturbance. Other diagnoses included peptic ulcer, oesophagitis, diverticular disease and gallstones.

Investigations

For the liver disease groups the laboratory data analysed was that which was obtained immediately before the admission on which liver biopsy was performed. For control subjects laboratory data and chest radiographs were obtained at the same out-patient visit. The MCV was measured electronically on a Coulter Counter. Liver function tests were performed in the routine laboratory, using standard automated techniques.

Each chest radiograph was reviewed by two trained radiologists (who were unaware of the relevant clinical, laboratory or liver biopsy findings). The presence of rib

Table 1. Sensitivity and specificity of laboratory tests and chest radiograph fractures in the detection of ALD.

	AP >110 iu/litre	ALT >50 iu/litre	GGT >65 iu/litre	MCV >98 fl	Any fracture on chest radiograph	Bilat. and/or multiple fractures
Sensitivity %	50	43	89	60	27	15
Specificity %	66	74	72	97	97	99

or other fractures was agreed by both observers. In the light of the clinical classification radiological findings were then analysed into alcoholic liver disease (ALD), non-alcoholic liver disease (NALD) and control (C) groups, and compared with laboratory findings.

Analysis

For the assessment of the sensitivity (the proportion of patients with alcoholic liver disease who have an abnormal result) and the specificity (the proportion of patients who do not have alcoholic liver disease with a normal result) of laboratory tests in the detection of alcoholic liver disease, arbitrary cut-off points for abnormal values were used (Table 1).

To examine whether a combination of variables (laboratory results and radiological findings) could distinguish between patient categories we used discriminant analysis[6]. This method finds the linear function of the variables which best discriminates between groups. In the simplest case (comparison of two groups) all individuals with high values of the discriminant function (calculated from the measured values of the variables used) are allocated to one group, while individuals with low values are in the other. The best function will be that which allocates most individuals to the correct groups. With more than two groups more discriminant functions are used (the number of functions being the number of groups minus one). We wished to make the discriminant contain as few variables as possible to simplify measurement and calculation, so used a stepwise approach in which variables are added one by one until discrimination ceases to improve. Stepwise linear discriminant analysis was performed using the SPSS programme of North Western University (version 7 of June 1977) by the University of London Computer Centre[7].

Results

Table 2 shows laboratory and chest radiograph findings in each of the three groups separately for males and females.

Laboratory values were similar for males and females in C, and for males and females in NALD, but GGT and MCV tended to be more severely deranged for females with ALD than for males. There was a striking increase in the prevalence of fractures in both males and females with ALD (27 per cent overall), compared with non-alcoholic

Table 2. Laboratory data (mean ± SD) and chest radiograph findings in C, ALD and NALD. M = male, F = female. CXR = chest radiograph.

		Controls (C) (n = 95)	Alcoholic Liver Disease (ALD) (n = 74)	Non-Alcoholic Liver Disease (NALD) (n = 86)
Sex distribution	M	44	52	41
	F	51	22	45
Age (years)	M	47 ± SD 16	54 ± SD 14	50 ± SD 19
	F	52 ± SD 19	56 ± SD 9	53 ± SD 15
Alkaline phosphatase (AP iu/litre) (20–100)*	M	56 ± SD 18	143 ± SD 116	200 ± SD 191
	F	67 ± SD 66	168 ± SD 122	256 ± SD 217
ALT iu/litre (<35)*	M	19 ± SD 11	61 ± SD 62	147 ± SD 239
	F	18 ± SD 18	70 ± SD 68	103 ± SD 138
GGT iu/litre (<50)*	M	25 ± SD 14	188 ± SD 124	170 ± SD 141
	F	33 ± SD 109	387 ± SD 232	174 ± SD 136
MCV fl (80–92)*	M	89 ± SD 5	100 ± SD 8	87 ± SD 8
	F	88 ± SD 6	104 ± SD 11	89 ± SD 6
Any fracture on CXR	M	4.6%	28.9%	0%
	F	5.9%	22.7%	2.2%
Bilat./multiple fractures on CXR	M	2.3%	13.5%	0%
	F	2.0%	18.2%	0%

*Normal values.

controls (C) (5.3 per cent), or patients with NALD (1.2 per cent). More patients with ALD had bilateral and/or multiple (>2) fractures on chest radiographs (15 per cent) than had patients in group C (2.1 per cent), or the NALD group (0 per cent).

Table 1 shows the sensitivity and specificity table constructed to compare the usefulness, in the detection of alcoholic liver disease, of fractures visible on the chest radiograph (any fracture, or the presence of bilateral and/or multiple (>2) fractures) with laboratory data, using arbitrary upper limits of normal as cut-off points.

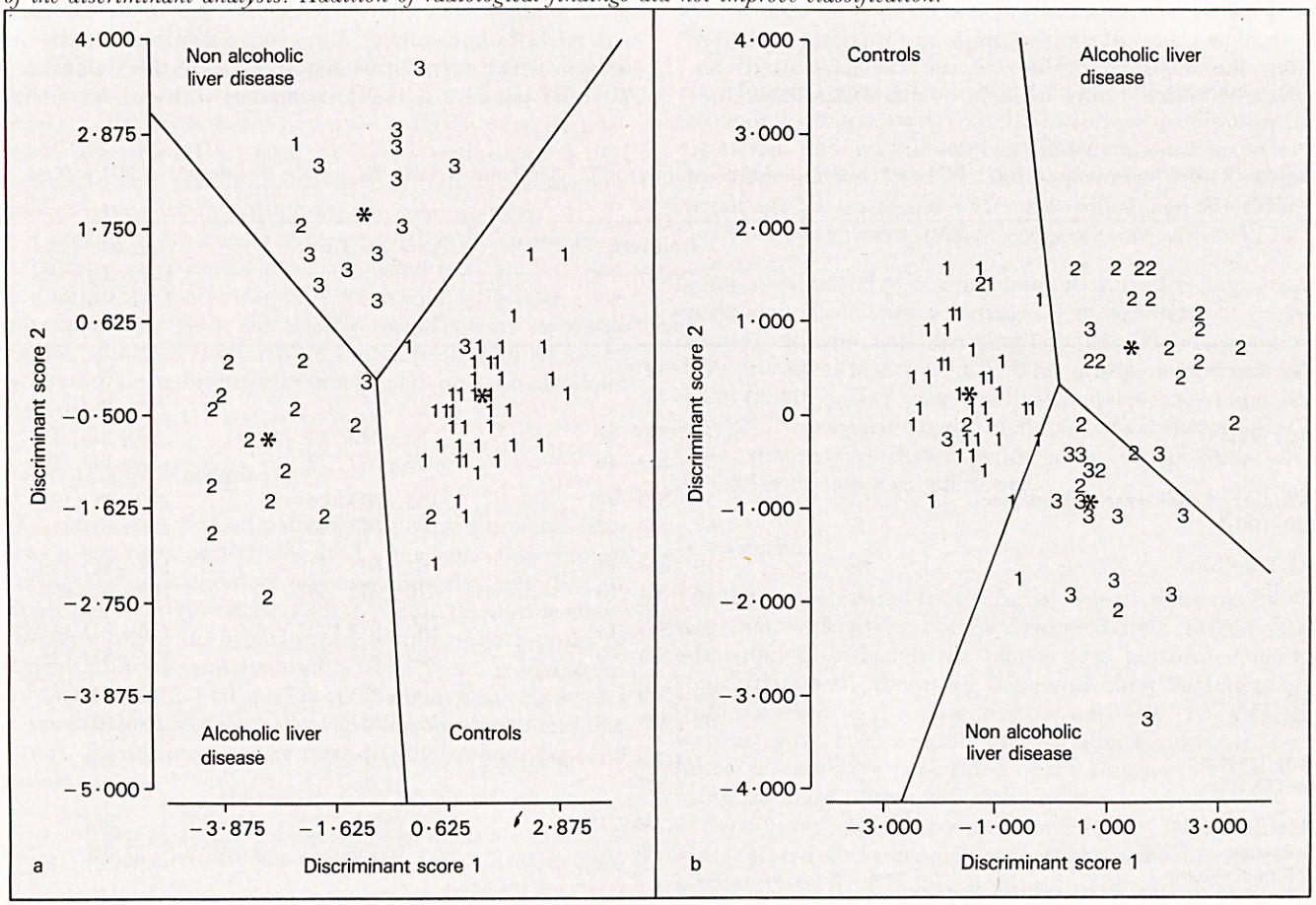
All the laboratory markers examined were more sensitive indicators of ALD than fractures, but fractures were the most specific marker of ALD, with a specificity of 99 per cent for the criterion of bilateral and/or multiple (>2) fractures. When the criteria were widened to include any fracture observed on the chest radiograph, the specificity decreased to 97 per cent, but sensitivity improved from 15 per cent to 27 per cent.

Discriminant function analysis was performed after log transformation to normalise the biochemical data. Initial analysis showed that the optimum combination of variables which gave the best discrimination between ALD, NALD and C was MCV, $\log_{10}$ AP and $\log_{10}$ GGT. The addition of further variables (including information from the chest radiograph) did not significantly improve the results. Using these variables, the discriminant analysis programme classified cases from each of the three groups separately by sex (Fig. 1a,b). In the figures the position of each point shows the values of the two discriminant functions (since three groups are compared). The lines dividing the figure show the three groups into which individuals are classified by the discriminant analysis, while the numerical code (1 = C, 2 = ALD, 3 = NALD) indicates the group to which individuals actually belong. Although most subjects were correctly classified, some were located quite close to the centre of other groups and thus would have been misclassified. For the women in this study 87 per cent ALD, 98 per cent C and 87 per cent NALD were correctly allocated, while for the men 74 per cent ALD, 94 per cent C and 77 per cent NALD were classified correctly.

Discussion

In view of the growing prevalence of alcohol-related disorders and the recognition that they are under-diagnosed, there has been much interest in the application of

Fig. 1. *Discriminant function analysis for (a) females and (b) males showing separation between controls (1), alcoholic liver disease (2) and non-alcoholic liver disease (3) on the basis of MCV, $\log_{10}$ AP and $\log_{10}$ GGT. Each point represents two discriminant functions for each subject, and * is the centroid for each group. The territorial map shows classification into three groups on the basis of the discriminant analysis. Addition of radiological findings did not improve classification.*



simple tests to detect excessive drinking and alcohol-related disease[2-5, 8-14]. Assessments of the efficacy of various screening tests have given conflicting results, in part because of the problems involved in defining alcoholism. Moreover, the validity of data on alcohol consumption against which such tests are usually gauged is dependent on the subject's accuracy of recall, which is of uncertain reliability and unverifiable. It is also difficult to evaluate different screening procedures when the populations which have been examined—company directors and alcohol production workers[8], psychiatric in-patients[9], or, as in the present study, patients with biopsy-proven alcoholic liver disease—are not strictly comparable, and may differ in their accuracy of recall, or susceptibility to the metabolic effects of alcohol.

The reported sensitivity and specificity for structured questionnaires varies widely from one study to another [2, 9-11, 15]. Some are dependent on interviewing skills, and all rely heavily on the co-operation and integrity of the patient. Laboratory measurements have been more widely used, in particular the serum gamma-glutamyl-transpeptidase (GGT), and the red cell mean corpuscular volume (MCV). Again, different studies have reached widely differing conclusions as regards the accuracy of these tests in the detection of heavy drinkers. The sensitivity reported for an elevated GGT ranges from 33 per cent[9] to 88 per cent[12], with specificities around 85 per cent[8,9]. For an elevated MCV the range is even wider, with sensitivities varying between 2 per cent[9] and 89 per cent[13], and specificities of the order of 95 per cent[8,9].

The alcoholic group in this study differed from those in most other reports in that they were defined, in part, on the basis of objective criteria. The patients were drawn from a single medical firm at St George's Hospital over a five-year period. The composition of the group with non-alcoholic liver disease (and hence the specificity of laboratory tests and radiological findings, and the results of discriminant analysis in the diagnosis of alcoholic liver disease) might well have differed from that seen in specialist referral centres with a bias towards specific forms of liver disease. In our patients all four laboratory markers proved to be more sensitive indicators of ALD than the chest radiograph, but fractures were the most specific marker of ALD.

Single tests are unreliable in the detection of problem drinkers or patients with alcohol-related disease, as laboratory variables are all non-specific (they may be raised by concomitant drug therapy[16] or in non-alcoholic liver diseases), and may revert to normal during periods of abstinence[12]. It is difficult to assess the significance of small changes, and arbitrary cut-off limits above the normal range are usually chosen in defining sensitivity and specificity. At the levels chosen MCV (60 per cent), AP (50 per cent) and ALT (43 per cent) had rather low sensitivity, while GGT, although sensitive (89 per cent), was not a very powerful screening test because of low specificity (false positives). The MCV was, however, a very specific (97 per cent) indicator of ALD.

Discriminant analysis showed that the combination of the three most sensitive laboratory tests (MCV, GGT, AP) provided optimum separation between patient groups. Between 74 per cent and 87 per cent of patients with ALD were correctly classified. Chalmers *et al.*[14], who used the same variables, achieved greater accuracy in classifying alcoholics, but selected patients who were thought to have been actively drinking shortly before presentation. Interestingly, they also demonstrated that alcohol-related disease is more readily identified by laboratory tests in women than in men.

Chest radiography had a lower predictive value than laboratory tests, and did not improve diagnostic accuracy when added to MCV, AP and GGT in a discriminant analysis (Fig. 1a, b). In view of its low sensitivity in the detection of ALD it is thus of little value as a screening test. Nevertheless, it should be remembered that among alcoholics there is an increased prevalence of respiratory disorders[17], and chest radiology is a readily available and frequently performed examination. Moreover, abnormal laboratory tests may only be present when subjects are actively drinking[12], whereas rib fractures usually persist indefinitely. The presence of fractures on a chest radiograph is a very specific marker of ALD. This finding should not be overlooked, as it may result in the serendipitous detection of occult alcoholism and associated liver disease.

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