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Abstract

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COMPARATIVE DIAGNOSIS OF ALCOHOLIC LIVER DISEASES BY MULTIVARIATE AND HISTOLOGICAL ANALYSIS

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Abstract. Sixty-seven cases of alcoholic liver disease were histologically classified into 4 groups: alcoholic liver cirrhosis (ALC), alcoholic hepatitis (AH), alcoholic liver fibrosis (ALF) and alcoholic fatty liver (AFL). They were statistically reclassified by the likelihood method using age, total alcohol intake, hepatomegaly and 12 liver function tests. A score table for likely diagnosis was constructed from the incidences of each range. The cases were re-evaluated using the score table, with an overall correct diagnosis rate of 73 %. The best combination of 5 parameters included the indocyanine green plasma disappearance rate, total alcohol intake, cholesterol, choline esterase and glutamic oxaloacetic transaminase/glutamic pyruvic transaminase ratio. A correct diagnosis rate of 75 % was attained using these 5 parameters, and 94 % of patients were correctly diagnosed by the first or the second likelihood diagnosis. Differential diagnosis of alcoholic liver diseases was easily and confidently obtained with the likelihood score table.

Key words : alcoholic liver diseases, multivariate analysis, liver function tests.

A correlation between histological findings and liver function tests in the diagnosis of alcoholic liver diseases has not been eastablished (1, 2). Likelihood diagnosis (LDx), utilizing symptom constellations, has been applied to the diagnosis and location of apoplexy (3) and head injury (4). Recently, this approach has been applied to differential diagnosis of liver diseases (5-7). We have tailored this approach to alcoholic liver diseases. Cases classified histologically were reclassified by the likelihood method using 15 parameters.

MATERIALS AND METHODS

One hundred forty-two patients were classified as habitual drinkers (8) with liver injury; all presented histories of daily consumption of more than 90 ml ethanol equivalents (540 ml sake) per day for over 5 years. These cases were selected from 666 liver disease cases diagnosed by peritoneoscopy and histological examination in the 5 year period from January, 1976 to December, 1980. Fifty eight cases were excluded because of: positive HBs antigen (17 cases), history of blood transfusion (16 cases), and history of hepatitis or jaundice (25 cases). An additional 17 cases were eliminated as the main pathological findings were other than alcoholic

liver injury: chronic active hepatitis (7), primary liver cancer (3), acute hepatitis (3), chronic persisteht hepatitis (2) and other causes (2). The remaining 67 cases were classified histologically into 4 groups according to the diagnostic criteria for alcoholic liver injury as delineated by the Japanese study group on "Alcohol and The Liver" (8). There were 37 cases of alcoholic liver cirrhosis (ALC), 14 cases of alcoholic hepatitis (AH), 7 cases of alcoholic fatty liver (AFL) and 9 cases of alcoholic liver fibrosis (ALF).

Fifteen variables were obtained on admission and were used for the LDx: age, total alcohol intake, liver extent caudal from the right costal margin, total bilirubin (mg/dl), glutamic oxaloacetic transaminase (GOT; IU/l), glutamic pyruvic transaminase (GPT; IU/l), GOT/GPT ratio, alkaline phosphatase (ALP; Bessey Lawry u.), r-glutamyltranspeptidase (r-GTP; mU/ml), indocyanine green plasma disappearance rate (KICG), cholesterol (mg/dl), choline esterase (CHE; delta pH), zinc sulfate turbidity test (ZTT; Kunkel u.), r-globulin (%) and serum iron (ug/dl). LDx was calculated by a microcomputer (SORD M223 Mark III, Tokyo). The program for calculation was made by T. Itoshima. The parameters were analyzed by forward selection and backward elimination (7).

RESULTS

Construction of score table. The distribution of the parameters was established (Table 1). As an example, the distribution of KICG is presented in Fig. 1. KICG values were demarcated into 3 groups by the values 0.11 and 0.17, 0.17 being the lowest limit of the normal range and 0.11 distinguishing liver cirrhosis from chronic hepatitis (9). The incidence (P) of each range was calculated for each of the 4 alcoholic liver diseases. The incidence was converted to the diagnosis score (S) by the following formula (10): $S = 10 \times (\log P + 1)$. For example, in ALC the incidence of KICG over 0.17 was 3 % with a score of -5, and the incidence of

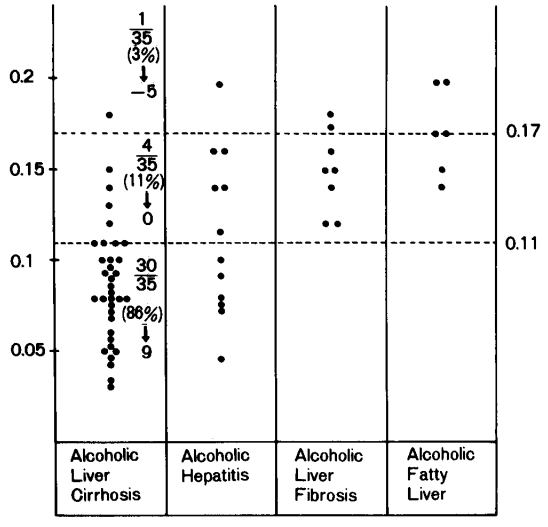

Fig. 1. KICG values and their distribution among alcoholic liver diseases.

TABLE 1. SCORE TABLE FOR DIFFERENTIAL DIAGNOSIS OF ALCOHOL LIVER DISEASES

Item	Range	Alcoholic Liver Cirrhosis	Alcoholic Hepatitis	Alcoholic Liver Fibrosis	Alcoholic Fatty Liver
Age (years old)	<40	1 (14%)	6 (36)	7 (56)	8 (57)
	<50	6 (38)	5 (29)	3 (22)	1 (14)
	50≦	7 (49)	6 (36)	3 (22)	5 (29)
Total alcohol intake (kg)	< 500	−3 (5)	3 (21)	3 (22)	6 (43)
	<1000	6 (41)	5 (29)	8 (67)	5 (29)
	1000≦	7 (54)	7 (50)	0 (11)	5 (29)
Hepatomegaly (finger breadth)	n. p	3 (22)	6 (36)	0 (11)	8 (57)
	<1.5	1 (14)	6 (36)	5 (33)	1 (14)
	2.0≦	8 (65)	5 (29)	7 (56)	5 (29)
T-Bil (mg/dl)	<1.05	6 (38)	6 (43)	8 (66)	6 (43)
	<2.05	7 (49)	5 (29)	3 (22)	6 (43)
	2.05≦	1 (14)	5 (29)	0 (11)	1 (14)
GOT (IU/L)	≦ 40	3 (19)	−2 (7)	5 (33)	5 (29)
	≦150	8 (58)	8 (57)	7 (56)	6 (43)
	150<	3 (22)	6 (36)	0 (11)	5 (29)
GPT (IU/L)	< 40	5 (33)	−2 (7)	7 (55)	−10 (0)
	≦150	6 (44)	8 (64)	5 (33)	9 (71)
	150<	3 (22)	5 (29)	0 (11)	5 (29)
GOT/GPT	<1.0	5 (31)	6 (43)	5 (33)	9 (71)
	<1.7	7 (47)	3 (21)	0 (11)	−10 (0)
	1.7≦	3 (22)	6 (36)	7 (56)	5 (29)
ALP (B. L)	≦2.8	7 (47)	6 (43)	10(100)	9 (71)
	≦4.0	6 (36)	7 (50)	−10 (0)	5 (29)
	4.0<	2 (17)	−2 (7)	−10 (0)	−10 (0)
r-GTP (mU/ml)	≦ 40	5 (33)	4 (23)	5 (33)	2 (17)
	2≦200	7 (53)	6 (38)	3 (22)	7 (50)
	200<	1 (14)	6 (38)	6 (44)	5 (33)
CHE (⊿pH)	<0.5	6 (36)	4 (23)	−10 (0)	−10 ((0)
	<0.8	8 (58)	6 (38)	3 (22)	5 (29)
	0.8≦	−2 (6)	6 (38)	9 (78)	9 (71)
Cholesterol (mg/dl)	≦130	5 (31)	−1 (8)	−10 (0)	1 (14)
	≦220	8 (64)	9 (77)	9 (89)	6 (43)
	220<	−2 (6)	2 (15)	0 (11)	6 (43)
r-Glob (%)	≦18	0 (11)	6 (38)	9 (89)	9 (71)
	≦24	5 (30)	7 (46)	0 (11)	5 (29)
	24<	8 (59)	2 (15)	−10 (0)	−10 (0)
ZTT (KU)	< 8	1 (14)	7 (50)	9 (89)	9 (71)
	<14	7 (51)	6 (43)	0 (11)	5 (29)
	14≦	5 (35)	−2 (7)	−10 (0)	−10 (0)
KICG	≦0.11	9 (86)	7 (50)	−10 (0)	−10 (0)
	<0.17	0 (11)	6 (42)	9 (33)	5 (33)
	0.17≦	−5 (3)	−1 (8)	4 (67)	8 (67)
Fe (μg/dl)	≦ 70	3 (19)	−1 (8)	5 (29)	−10 (0)
	≦150	5 (35)	5 (33)	5 (29)	6 (40)
	150<	7 (45)	8 (58)	6 (43)	8 (60)

( ) : Incidence of parameters in each range

TABLE 2. DEMONSTRATION OF SCORE TABLE USE

		Alcoholic Liver Cirrhosis	Alcoholic Hepatitis	Alcoholic Liver Fibrosis	Alcoholic Fatty Liver
KICG	≦0.11	9	7	−10	−10
	<0.17	0	6	9	5
	0.17≦	−5	−1	4	8
Total alcohol intake	<500	−3	3	3	6
	<1000	−6	5	8	5
	1000≦	7	7	0	5
Cholesterol	≦130	5	−1	−10	1
	≦220	8	9	9	6
	220<	−2	2	0	6
CHE	<0.5	6	4	−10	−10
	<0.8	8	6	3	5
	0.8≦	−2	6	9	9
GOT/GPT	<1.0	5	6	5	9
	<1.7	7	3	0	−10
	1.7≦	3	6	7	5
Total		39	32	2	−4

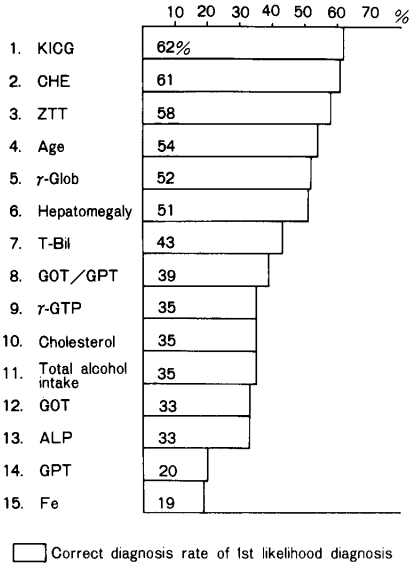

Fig. 2. Correct diagnosis rate of alcoholic liver diseases by a single parameter.

KICG less than 0.11 was 86 % with a score of 9. Likewise, a score was derived for all of the variables (Table 1).

How to use the score table. The table is simple to use. Summation of the diagnosis scores (S) of a number of parameters will present a differential diagnosis. For example, in a case with KICG 0.08, total alcohol intake 1,100 kg ethanol, cholesterol 150 mg/dl, CHE 0.6 delta pH, and GOT/GPT 1.5 (Table 2), the sum of the score was greatest in ALC; that is the first LDx and the second was AH. In this manner, the 67 cases were reclassified, and the correct diagnosis rate of the LDx method was investigated.

Correct diagnosis rate by individual variables. The most valuable parameter was KICG, with a 62 % correct diagnosis rate (Fig. 2). The correct diagnosis rate of r-GTP, which is believed to be closely related to alcohol consumption (11, 12), and that of total alcohol intake were low. Two parameters, serum iron and GPT, produced negative correlations.

Correct diagnosis rate using all parameters. The correct diagnosis rate was highest for AH (75 %), lowest for ALF (67 %), and 73 % overall (Table 3). Either the first or the second diagnosis was correct in 100 % of patients with ALF and AFL, and in 94 % overall.

Selection of discriminative combinations. Forward selection is a stepwise procedure which adds a parameter to the previously most valuable combination resulting in an improved diagnosis rate (Fig. 3). A correct diagnosis rate of 75 % was attained with the combination of KICG, total alcohol intake, cholesterol, CHE and GOT/GPT. Additional parameters had little effect on this rate. The maximal

TABLE 3. CORRECT DIAGNOSIS RATES FOR ALCOHOLIC LIVER DISEASES

	number of cases	Correct diagnosis rate of 1st likelihood diagnosis		Correct diagnosis rate of 1st or 2nd likelihood diagnosis	
		15 parameters	5 parameters	15 parameters	5 parameters
Alcoholic Liver Cirrhosis	37	27.5 Cases (74%)	30.5 (82)	34 (92)	34 (92)
Alcoholic Hepatitis	14	10.5 (75)	7 (50))	13 (93)	11 (79)
Alcoholic Liver Fibrosis	9	6 (67)	7 (78)	9 (100)	9 (100)
Alcoholic Fatty Liver	7	5 (71)	5.5 (79)	7 (100)	7 (100)
Total	67	49 (73)	50 (75)	63 (94)	61 (91)

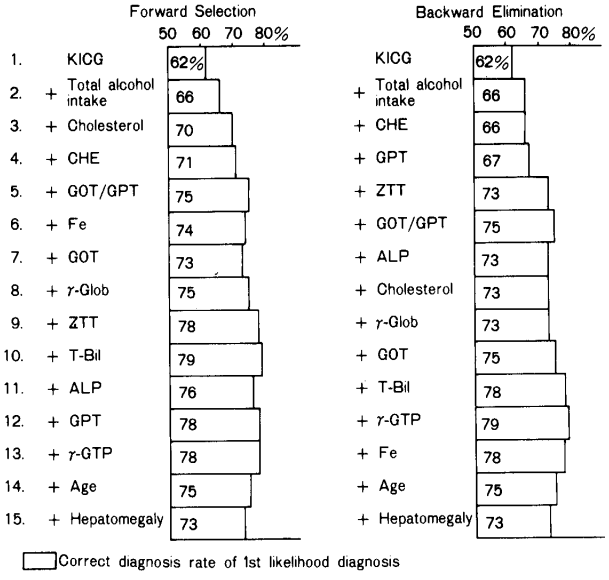

Fig. 3. Correct diagnosis rate of alcoholic liver diseases by the most discriminative combinations.

rate of 79 % required 10 variables.

Backward elimination is a stepwise removal of the least valuable parameter to retain the most effective combination. The highest correct diagnosis rate (79 %) was achieved by excluding 4 parameters; hepatomegaly, age, serum iron and r-GTP. Thereafter, the correct diagnosis rate decreased as the number of parameters was decreased. The single most informative variable was KICG, which coincided with the results of forward selection.

The best combination of 5 parameters was KICG, total alcohol intake, cholesterol, CHE and GOT/GPT as derived by forward selection. Only KICG, total alcohol intake, and CHE were so ranked by backward elimination. By both the forward selection and backward elimination procedures, total alcohol intake, cholesterol, and GOT/GPT were found to be useful, though they were weak discriminators as single parameters. The overall correct diagnosis rate (75 %) with the 5 member group selected in forward selection was greater than that obtained using all parameters (Table 3). This difference was statistically insignificant.

DISCUSSION

Histological studies are necessary to establish a differential diagnosis of alcoholic liver injury. However, liver biopsy is sometimes contraindicated. Therefore, the type of injury is often derived from patient histories and clinical and laboratory findings. Statistical evaluation of liver diseases using discriminant functions has been confirmed by histological findings (2, 13, 14). However, this process requires

access to a computer and appropriate programs (2). In contrast, the LDx, using the score table herein, does not require any equipment (6, 7).

Habitual drinkers with liver injury, who were previously categorized into 4 groups, were reclassified by the likelihood method using 15 parameters. These included 12 routine liver function tests, age, alcohol intake, and hepatomegaly. The correct diagnosis rate (Table 3) of the first LDx was 73 % and either the first or the second diagnosis was correct in 94 %; a rate accurate enough to be used in daily clinical practice in contrast to 62 % by discriminant function (2). Moreover, the likelihood method can designate the two classifications to differentiate.

The parameters which present significant discriminative ability, KICG, CHE, and ZTT reflect the progress of chronic liver diseases. These were valuable in differentiating ALC, AH, ALF, and AFL, which differ in severity. In contrast, the correct diagnosis rates of r-GTP and GOT/GPT were low, although they are known to be closely related to alcohol drinking and alcoholic liver injury (11-15). This may be explained by the fact that r-GTP and GOT/GPT are elevated in every alcoholic liver disease regardless of severity or progress.

Valuable combinations of variables were selected to improve diagnostic rates (2, 7). Both stepwise selection and elimination designated KICG as the most valuable informant (Fig. 3); this supported the reliability of the procedures. The best combination of 5 included KICG, total alcohol intake, cholesterol, CHE, and GOT/GPT. Total alcohol intake and GOT/GPT were not strong individual discriminators (Fig. 2), but became useful in combinations. Total alcohol intake and GOT/GPT may represent different aspects of injury from those denoted by KICG. The most informative combination is probably achieved by combining variables which represent different aspects of alcoholic liver injuries. The present computer diagnosis using multivariate analysis provided objective parameter selection important for differentiation of alcoholic liver diseases.

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