MULTIVARIATE ANALYSIS USING A LINEAR DISCRIMINANT FUNCTION FOR PREDICTING THE PROGNOSIS OF CONGESTIVE HEART FAILURE

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Some of cases of congestive heart failure (CHF) are intractable or refractory and respond poorly to conventional treatment. We have examined factors which may influence the clinical course and prognosis. The subjects were 114 hospitalized patients with CHF. Of these, 77 had a good response to treatment and were classified as the curative group (Group C) while the remaining 37 who were difficult to treat, including those with poor prognosis, were designated the refractory group (Group R). Of the various clinical background factors including the findings of laboratory and other examinations, the following 8 variables made a significant contribution to differentiation between the 2 groups: 1) heart rate (X_1), 2) hemoglobin content (X_2), 3) serum K (X_3), 4) serum total protein (X_4), 5) A/G (X_5), 6) BUN (X_6), 7) grade of hepatomegaly (X_7), and 8) number of previous CHF episodes (X_8). The linear discriminant function represented by the following equation using these 8 variables showed an excellent result in differentiating the 2 groups.

$$Y = -9.64 - 0.0686X_1 + 0.345X_2 + 1.351X_3 + 1.513X_4 + 1.988X_5 - 0.0876X_6 - 0.792X_7 - 0.737X_8$$

When Y value is over 0, Group C is judged. When Y value is under 0, group R is judged.

We concluded that the discriminant equation covering these 8 factors is a useful means of predicting the prognosis in CHF and the response to treatment.

Key Words:

Congestive heart failure
Multivariate analysis
Discriminant function
Prognosis
Clinical course

CONGESTIVE heart failure (CHF), which results from various heart diseases, is common and its course and prognosis are influenced by many factors.¹⁻⁷ Although there are general guidelines for treatment, the individual response is variable.

In this study, we have examined some clinical background factors at the start of treatment to

(Received January 27, 1981; accepted September 19, 1981)

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TABLE I UNDERLYING DISEASE

Underly. disease	C group	R group
MVD	34 (44.1)	4 (10.8)
AVD	3 (3.9)	4 (10.8)
CVD	7 (9.1)	9 (24.4)
HHD	12 (15.6)	2 (5.4)
IHD	17 (22.1)	5 (13.5)
ICM		3 (8.1)
Constrict. pericard.		1 (2.7)
Cor pulm.	2 (2.6)	6 (16.2)
Miscellan.	2 (2.6)	3 (8.1)
Total	77 (100)	37 (100)

MVD: mitral valvular disease
 AVD: aortic valvular disease
 CVD: combined valvular disease
 IHD: ischemic heart disease
 HHD: hypertensive heart disease
 ICM: idiopathic cardiomyopathy

assess their effect on prognosis and on the response to treatment. The patients were classified into a curative group (Group C) and a refractory group (Group R). It was thought that individual factors might be mutually correlated or have to be weighted differently. In this context, we performed multivariate analysis to characterize a possible difference between the 2 groups.

MATERIALS AND METHODS

The subjects of the study were 114 hospitalized patients with CHF treated during the 10 years from 1969 to 1979, after the exclusion of patients meeting the following criteria: 1) those who had been treated elsewhere before admission, 2) those who died within a very short period, 3) those whose records were not well-documented and 4) those whose case cards were filled in incompletely or erroneously. Table I indicates the underlying diseases of 114 subjects. There were 38 patients with mitral valvular disease (MVD), 7 with aortic valvular disease (AVD), 16 with combined valvular disease (CVD), 14 with hypertensive heart disease (HHD), 22 with ischemic heart disease (IHD), 3 with idiopathic cardiomyopathy (ICM), 8 with cor pulmonale, 2 with infective endocarditis, and one of each with constrictive pericarditis, aortitis syndrome, ventricular septal defect and hyperthyroidism. The age distribution shown in Table II indicates that 28 patients were younger than 40 years, 46 were aged between 40 and 59

TABLE II AGE DISTRIBUTION OF THE MATERIALS

	Age			Mean $\pm$ SD
	≤ 39	40 ~ 59	60 $\leq$	
C group	17 (22.0)	31 (40.3)	29 (37.7)	53.9 $\pm$ 15.5
R group	11 (29.7)	15 (40.6)	11 (29.7)	50.1 $\pm$ 15.5

(): %

years, and 40 were older than 60 years.

Among the background factors affecting the prognosis, the following 27 items which could be represented quantitatively were selected: 1) age, 2) sex, 3) presumed duration from the onset of the underlying disease, 4) incidence of previous episodes of heart failure, 5) complications, 6) infection, 7) grade of functional capacity according to New York Heart Association (NYHA) criteria, 8) heart rate (HR), 9) cardiothoracic ratio (CTR), 10) systolic blood pressure (SBP), 11) diastolic blood pressure (DBP), 12) retinal changes, 13) grade of hepatomegaly, 14) red blood cell count (RBC), 15) hemoglobin content (Hb), 16) serum Na, 17) serum K, 18) serum Cl, 19) serum total protein (TP), 20) serum albumin (Alb.), 21) A/G, 22) thymol turbidity test (TTT), 23) SGOT, 24) SGPT, 25) serum total bilirubin (TB), 26) PSP (15-minute value), and 27) BUN. Discriminant analysis was then performed to ascertain which of these had a true effect.

The classification of patients into Group C and Group R was based on the following criteria:

Group C: The symptoms of heart failure improved smoothly in response to therapy.

Group R: (1) Although appropriate therapeutic measures were taken, the symptoms did not improve within 2 weeks of the start of therapy.

(2) The therapeutic effect was unstable and improvement was not sustained.

(3) The prognosis was so poor that death ensued.

The statistical significance of the linear discriminant coefficient derived from discriminant analysis was evaluated to select factors thought to be important for differentiation and to see whether simple discriminant function existed among these variables. On the basis of the func-

TABLE III SIGNIFICANCE OF COEFFICIENT OF LINEAR DISCRIMINANT FUNCTION (P: 27)

Item	Fo value	Item	Fo value	Item	Fo value
Age	1.50	Serum K	3.30 ^Δ	BUN	4.94*
Sex	2.73	Serum Cl	0.08	PSP	0.11
Heart rate	3.08 ^Δ	TP	9.46**	Hepatomegaly	7.99**
CTR	0.34	Albumin	5.33*	NYHA	0.02
Systolic BP	0.77	A / G	7.47**	Eye ground	0.17
Diastolic BP	0.40	S-GOT	0.39	Complication	0.26
RBC	0.52	S-GPT	1.29	Duration of underly, d.	0.09
Hb	3.03 ^Δ	Total bilirubin	0.09	Incidence of CHF	15.11**
Serum Na	1.02	TTT	1.39	Infection	0.28

Δ, *, **: statistically significant ($p < 0.1, 0.05, 0.01$ respectively)

TABLE IV SIGNIFICANCE OF COEFFICIENT OF LINEAR DISCRIMINANT FUNCTION (P: 8)

Item	Fo value	Item	Fo value
Heart rate	6.93 ^{XX}	A / G	3.32 ^Δ
Hb	4.14 ^X	BUN	5.09 ^X
Serum K	5.11 ^X	Hepatomegaly	11.47 ^{XX}
TP	10.48 ^{XX}	Incidence of CHF	25.75 ^{XX}

Δ, X, XX: significant ($p < 0.1, 0.05, 0.01$ respectively)

tion obtained, the subjects were classified into 2 groups.

RESULTS

Significance Determination of the Linear Discriminant Coefficients of Individual Variables

Table III shows the statistical analysis of the linear discriminant coefficients of the 27 variables. The coefficients of HR, Hb and serum K were significant at a level of 10%, those of Alb. and BUN at 5%, and those of TP, A/G, grade of hepatomegaly and incidence of previous CHF episodes at 1%. Among these 9 factors, 8 factors except serum albumin were selected as having a significant effect on the clinical course and prognosis of CHF.

Significance Determination of the Linear Discriminant Coefficients of the 8 Variables

Table IV presents the analytical results of the 8 factors. All showed significance at a level of 1 to 10%.

Significance Determination of the Coefficients of These 8 Variables Plus One of the Others

To assess the reliability of the 8 factors as variables, each of the other 18 was added to

them and a similar analysis covering 10 factors was carried out. Table V shows that none of the additional factors except age showed a significance and we concluded that they made no appreciable contribution to the differentiation of the 2 groups.

Linear Discriminant Function

Table VI shows the coefficients of the 8 variables and the constant. An equation to obtain a discriminant function is formed as follows:

$$Y = -9.64 - 0.0686X_1 + 0.345X_2 + 1.351X_3 + 1.513X_4 + 1.988X_5 - 0.0876X_6 - 0.792X_7 - 0.737X_8$$

A discriminant function "Y" can be obtained by multiplying each variable by a related coefficient " $X_1 - X_8$ ", summing the products of multiplication and, finally, adding the constant to the sum. The equation is designed to serve as a criterion for differentiating between the 2 groups depending on whether the final product of the calculation or the discriminant function is plus or minus, as shown below.

$$Y > 0 \dots \dots \dots \text{Group C}$$

$$Y < 0 \dots \dots \dots \text{Group R}$$

TABLE V SIGNIFICANCE OF ADDITION OF THE REMAINING ITEMS TO 8 ITEMS

Item	Fo value	Item	Fo value
Age	2.71	S-GPT	0.82
Sex	0.86	Total bilirubin	0.16
CTR	0.09	TTT	0.31
Systolic BP	0.45	PSP	0.04
Diastolic BP	0.56	NYHA	0.16
RBC	0.53	Eye ground	1.65
Serum Na	0.10	Complication	2.90 ^Δ
Serum Cl	0.09	Duration of underlying dis.	0.45
Alb.	5.63 [×]	Infection	1.46
S-GOT	0.13		

×: $p < 0.05$ Δ: $p < 0.1$

TABLE VI THE COEFFICIENT OF 8 ITEMS AND THE CONSTANT

Item	Coefficient
Heart rate	-0.0686
Hb	+0.345
Serum K	+1.351
TP	+1.513
A/G	+1.988
BUN	-0.876
Hepatomegaly	-0.792
Incidence of CHF	-0.737
Constant	-9.64

Fig.1. Histogram of score obtained by discriminant function.

Ten of the 77 patients (13.0%) belonging to Group C in the original classification fell into Group R while 4 of the 37 patients (10.8%) belonging originally to Group R fell into Group C. Accordingly, the probability of erroneous classification was 23.8%.

Relative Frequency of Discriminant Score

Figure 1 illustrates the relative frequencies of the discriminant scores computed from linear discriminant functions in individual cases. They indicate the extent of agreement between the classification based on the linear discriminant function and that based on clinical evaluation. The two classifications were in close agreement and the correct discrimination rate was 87.7% when calculated by the following formula:

$$(67 + 33) / 114 \times 100 = 87.7$$

DISCUSSION

Congestive heart failure is a syndrome caused by underlying diseases and its clinical course, prognosis and response to treatment differ among individual patients.¹⁰⁻¹⁸ The difference is attributable to variable factors including data from laboratory and other examinations.

In this study, we placed the CHF cases associated with different underlying diseases into 2 groups, curative and refractory groups, to see which factors influenced the clinical course and prognosis of CHF. Of the clinical findings at the commencement of treatment, 27 items which could be represented quantitatively were selected. We performed the statistical analysis of the linear discriminant coefficients of the 27 variables. As

a result, 8 of these variables were selected as items made a significant contribution to differentiation between the 2 groups. Simple analysis using a single variable may fail to exclude an apparent influence. On the other hand, it may be unjustifiable to use individual factors separately because clinical manifestations are frequently influenced by complicated mutual relation among them.

According to the discriminant function theory, a distribution overlap in the analysis for differentiation between 2 groups using a unitary variable is so wide that a satisfactory result will not be found. In contrast, a linear combination of multiple variables may reduce the overlap. Because of the usefulness of multivariate analysis, it is often utilized for diagnostic purposes and especially for differential diagnosis.

Some authors^{8,9} have already reported on its use in the diagnosis and prognosis of heart disease. We found no reports of this analytical technique in the study of CHF, possibly because the clinical course and prognosis are different from underlying diseases and are affected by many background factors.

We selected those factors which contributed to differentiation between Groups C and R, and the linear discriminant coefficient of each factor was obtained and its statistical significance measured. The results suggested that the following 8 factors have a great influence on the clinical course and play an important role in differentiating between the 2 groups: 1) number of CHF episodes, 2) HR, 3) grade of hepatomegaly, 4) Hb, 5) serum K, 6) TP, 7) A/G and 8) BUN.

Congestive heart failure represents the final clinical expression of deteriorating cardiac function. The clinical manifestations of congestive heart failure are principally related to resultant dysfunction of vital organs other than the heart, such as lungs, kidneys and liver. The clinical course and prognosis are influenced by extracardiac factors. Systemic venous congestion results in hepatomegaly in CHF. Hypoproteinemia and reduced serum albumin content are expected in advanced CHF.³ Hypoproteinemia may reflex hepatic congestion and dysfunction. Blood urea nitrogen may be elevated indicating reduced renal blood flow based on the cardiac dysfunction, especially on lowered cardiac output.¹ Electrolytes are dependent upon duration and severity of CHF. Hypopotassemia is frequently observed in advanced CHF.^{1,13,16} Heart rate may reflect reduced cardiac reserve.

As mentioned above, it is suggested that these variables selected in this study may be reliable as influencing factors on the clinical course and prognosis in CHF. The proper medication of CHF is based on a firm knowledge of the pathophysiology of advanced heart failure and contributory extracardiac factors.

When the discriminant equation covering these 8 variables was used, the accuracy of differentiation was 87.7% and the rate of mistaken differentiation was 23.8%. Both specificity and sensitivity of this equation were excellent.

The clinical background factors were reviewed in erroneously differentiated patients. Most of 10 patients who were erroneously classified in Group R instead of Group C mostly had acquired valvular disease of moderate severity. The values of individual items were abnormal and there were frequent episodes of CHF and marked hepatomegaly. These 2 variables seemed to contribute strongly to the production of minus functions indicative of Group R and there may be a high risk of transferring these cases from Group C to Group R without proper treatment.

Of the 4 patients who were classified under Group C instead of Group R, 3 had ICM as the underlying disease and one had CVD. Since ICM itself is difficult to treat perhaps it should be regarded as being clinicopathologically different from other heart diseases. Usually, heart failure in these patients responds poorly to digitalis and, in addition, there is particularly prone to toxic manifestation of digitalis therapy which did occur in 2 of the 3 patients. Therefore, CHF caused by ICM should be evaluated separately from other types of left sided heart failure and the 3 patients should have been excluded from the study.

We have confirmed that this discriminant function can be applied clinically as a predictive index for ascertaining the clinical course and prognosis of CHF, with exception of special group mentioned above.

Acknowledgement

We are very grateful to Professor Dr. Akira Kitabatake, Department of Medical Statistics, for his helpful advice and to Mr. Yoshimasa Ishii, Department of Statistical Analysis of Tanabe Seiyaku Co., Ltd., for his cooperation concerning discriminant analysis.

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