Left Ventricular Function and Hypertrophy in Cardiomyopathy with Depressed Ejection Fraction


SUMMARY
Left ventricular (LV) function and hypertrophy, assessed during cardiac catheterization by quantitative biplane angiocardiography, were related to postcatheterization course in 36 patients found to have cardiomyopathy with depressed ejection fraction (EF). EF ranged from 0.09 to 0.41, LV mass (M) from 99 to 317 g/m², LV end-diastolic volume (V) from 104 to 347 ml/m², and ratio of M/V from 0.66 to 1.63. In this study, EF was used as an index of LV function; M/V ratio was considered to represent a relative degree of LV hypertrophy. Postcatheterization survival rates (PCSR) for all patients at 12, 24, and 36 months were 68.8 ± 7.8%, 49.9 ± 9.2%, and 32.8 ± 10.2%. The 36-month PCSR was significantly higher for patients (N = 15) with EF ≥ 0.20 (75.1 ± 14.5%) than for those (N = 21) with EF < 0.20 (0%) (P < 0.01). The 36-month PCSR was also significantly higher for patients (N = 19) with M/V ratio ≥ 0.90 (53.6 ± 14.8%) than for those (N = 17) with M/V ratio < 0.90 (12.4 ± 10.4%) (P < 0.05). M/V ratio appeared to influence survival at least in part independently of EF. For patients with EF ≥ 0.20 M/V ratio ≥ 0.90 was associated with a higher 36-month PCSR (100%) than was M/V ratio < 0.90 (25.0 ± 6.5%). Likewise, for patients with EF < 0.20, M/V ratio ≥ 0.90 was associated with a higher 24-month PCSR (65.1 ± 16.8%) than was M/V ratio < 0.90 (6.8 ± 9.1%); but at 36 months, PCSR was < 10% for both subgroups.

Patients (N = 16) with mitral regurgitation (MR) > 0.70 liters/min/m² had a mean value for V (212.9 ± 74.1 ml/m²) significantly larger than for those (N = 20) without MR or with MR < 0.70 liters/min/m² (168.8 ± 40.7 ml/m²) (P = 0.0278). Although this suggests that dilatation of the mitral valve annulus contributed to the development of the regurgitation, the large overlap in V values implies that additional mechanisms played a role.

This study describes quantitatively a spectrum of hemodynamic abnormalities in patients who had cardiomyopathy with depressed EF, and demonstrates that the present series of patients had a high postcatheterization mortality rate. Both EF and M/V ratio were of prognostic value and thus appear to be useful indices for classifying such patients.

Additional Indexing Words:
Mitral regurgitation  Ventricular mass  Myocardial disease  Ventricular volume

The term cardiomyopathy is widely used to indicate the presence of a disorder of cardiac muscle for which known secondary causes of myocardial disease (e.g. coronary artery, valvular, congenital disease) are not responsible. Although many classifications of cardiomyopathy have been proposed, none is entirely satisfactory.1–6 Goodwin has recently developed a useful classification, in which he regards the cardiomyopathies to be of two main types: congestive and hypertrophic.5,6 He considers the congestive type to be characterized by depressed systolic ventricular function (e.g. ejection fraction) and increased left ventricular end-diastolic volume. In contrast, systolic ventricular function is preserved and chamber

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dilatation is usually absent in the hypertrophic type (called idiopathic hypertrophic subaortic stenosis in this country). Left ventricular hypertrophy (with or without outflow tract obstruction) is a characteristic finding, and ventricular compliance is thought to be reduced.

A study of left ventricular function and hypertrophy in patients who have cardiomyopathy with depressed ejection fraction offers an opportunity to examine the in vivo characteristics of poorly contracting cardiac muscle essentially unaffected by secondary causes of myocardial disease. The prognostic importance of the degree of impairment in left ventricular function (as described by ejection fraction) and of the degree of left ventricular hypertrophy has not been demonstrated in man. In the present study, left ventricular chamber size, function, and mass were determined by quantitative angiocardiography in 36 patients found to have cardiomyopathy with depressed ejection fraction. Left ventricular function and hypertrophy were related to the postcatheterization clinical course of the patients.

Methods

The records of patients who had biplane angiocardiography at the University of Alabama Hospital or the Birmingham VA Hospital during a 56-month period were reviewed. Thirty-six patients were found to have both: (1) a diagnosis of cardiomyopathy with depressed ejection fraction and (2) a technically satisfactory angiocardiographic study in which it was possible to quantitate left ventricular volumes and mass. The criterion for the diagnosis of cardiomyopathy was the presence of an ejection fraction < 0.50 for which there was no apparent etiology after review of the patient's clinical and cardiac catheterization data. Except for instances mentioned in the Results section, none of the patients had evidence of the following causes of myocardial disease: coronary artery disease, primary valvular disease, hypertension, congenital heart disease, anemia, or altered thyroid function.

Right and left heart catheterization was performed to define cardiac anatomy and function. Pressures were recorded through a fluid-filled catheter system by an Electronics for Medicine oscillographic recorder. Cardiac output was measured by the Fick oxygen method. Biplane left ventriculography was performed at a filming rate of 6 or 12 frames/sec following the injection of contrast material into the left atrium or left ventricle. Films exposed during a premature ventricular contraction and the beat following were excluded from analysis. Ventricular volumes were determined by the Dodge area-length method.7 Regurgitant flow, determined by multiplying heart rate by the regurgitant stroke volume (obtained by subtracting forward stroke volume as measured by the Fick technic from the total angiographic left ventricular stroke volume), was expressed in liters/min/m².8 Ejection fraction was defined as the ratio of angiographic stroke volume to end-diastolic volume. Left ventricular mass was estimated from left ventricular wall thickness and chamber dimensions as previously described.9 The thickness of the right atrial wall was assessed with the tip of a right heart catheter during fluoroscopy. Patients considered to have pericardial effusion were excluded from the study. Coronary arteriography was performed by either the Sones' or Judkins' technic.

The follow-up status of the patients was determined during a 1-month survey period either during a clinic visit or by a questionnaire sent to the patient. For patients alive at the time of the survey, survival duration was taken to the first day of the survey period. For patients who were dead at the time of survey, the primary physician was contacted to identify the probable cause of death. The interval between the day of the last catheterization included in this study and the first day of the survey period was 9 months.

Survival rate estimates and standard errors were computed using the life tables and formulas described by Cutler and Ederer.10 P values that refer to differences in survival rates were calculated using Student's t test.

Results

Data obtained at the time of cardiac catheterization are recorded in table 1. The patients, 23 males and 13 females, varied in age from 18 to 66 years, and had a mean age of 46 years. All patients described abnormal exertional dyspnea at the time of catheterization. Thirty-four patients admitted to paroxysmal nocturnal dyspnea sometime prior to catheterization. The interval between the onset of dyspnea and the time of catheterization varied from 1 month to 17 years. Episodes of chest pain consistent with the diagnosis of angina pectoris were described by five patients (nos. 17, 32, 33, 34, 36). Coronary arteriograms were within normal limits in these patients.

A history of excessive ethanol ingestion was obtained from five patients (nos. 24, 25, 31, 34, 36). All patients denied having had acute rheumatic fever. A history of mild hypertension was given by three patients (nos. 5, 7, 18). None of the patients demonstrated arterial hypertension, nor were any being treated for this disorder. Dyspnea began in the postpartum period for two patients (nos. 16, 22). No patient had a documented familial cardiomyopathy. Five patients had diabetes mellitus (nos. 5, 15, 27, 28, 36) but only one of them was receiving medication for it. Apical systolic murmurs were audible in 25 patients and a ventricular gallop sound was heard in 33. All patients were receiving a digitals preparation at the time of catheterization except for patient no. 35. Likewise, all but three patients (nos. 22, 30, 32) were taking a diuretic.
### Clinical and Laboratory Data for 36 Patients

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<th>Murmur*</th>
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#### M/V < 0.90

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<td>116/10</td>
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#### M/V ≥ 0.90

Abbreviations: AED = abnormal exertional dyspnea; CI = cardiac index; EDV = end-diastolic volume; LV = left ventricular; NM = not measured; M/V = mass/end-diastolic volume; PND = paroxysmal nocturnal dyspnea; RF = regurgitant flow; Ss = ventricular gallop sound; E = expired; S = survival continues; + = under coronary arteriograms = study performed; – (under coronary arteriograms) = study not performed.

*Apical systolic murmur.

#### Findings at Catheterization

Left ventricular end-diastolic pressure ranged from 3 to 35 mm Hg, and exceeded 12 mm Hg in 24 patients. Cardiac index (Fick method) varied from 0.92 to 4.12 liters/min/m² and was < 2.50 liters/min/m² in 19 patients.

Left ventricular end-diastolic volume (range 104–347 ml/m²) and mass (range 99–317 g/m²) values are shown in figure 1. End-diastolic volume was > 110 ml/m² in 35 patients; mass exceeded 124 g/m² in 31 patients (both values are 2 sd above normal).11 Values for ejection fraction (range 0.09–0.41) and the ratio of mass to end-diastolic volume (M/V) (range 0.66–1.63) are displayed in figure 2.

Measurable mitral regurgitation (mean 1.06 liters/min/m², range 0.36–2.48) was exhibited by 23 patients, and it exceeded 0.70 liters/min/m² in 16
patients. Regurgitant flow exceeded forward flow in four patients. End-diastolic volume is related to the presence or absence of mitral regurgitation (>0.70 liters/min/m²) in figure 3. Patients (N = 16) with mitral regurgitation had a mean end-diastolic volume (212.9 ± 74.1) significantly larger than the value (168.8 ± 40.7) for those (N = 20) without regurgitation (P= 0.0278). For patients with mitral regurgitation of > 0.70 liters/min/m², the mean end-diastolic volume for those (N = 8) with M/V ratio greater than 0.90 was not significantly different from the mean value for those (N = 8) with M/V ratio less than 0.90 (P > 0.5).

Coronary arteriograms were obtained in 15 patients and were within normal limits. One patient (no. 8), 18 years of age, whose symptoms began shortly after an influenza illness, was found to have a 2:1 left-to-right shunt. Autopsy revealed an anomalous pulmonary vein emptying into the superior vena cava in addition to inflammatory changes of the myocardium.

Findings at Follow-up

Follow-up data are recorded in table 1. All patients were traced. Nineteen patients had expired, with a mean postcatheterization survival duration of 12 months (range 1 week–33 months).
Left ventricular mass and end-diastolic volume values for the 36 patients. The continuous line separates patients with a mass/volume ratio > 0.90 from those with a ratio < 0.90. Dashed lines at lower left indicate normal limits of mass and volume (2SD above mean normal).11 EF = ejection fraction.

For the 17 patients who were alive at follow-up, mean survival duration was 26 months (range 9–61 months). Seven of the 17 surviving patients had symptomatically improved since catheterization. All deaths were thought to be related to cardiac disease. Five patients had postmortem examinations. Inflammatory changes of the myocardium were present in three patients (nos. 8, 9, 12) and nonspecific interstitial fibrosis of the myocardium was observed in the two others (nos. 4, 20). In these five patients the mitral valve apparatus was normal on gross inspection.

Relation of Ejection Fraction and M/V Ratio to Survival following Catheterization

Postcatheterization survival rates (mean and se) for all patients at 12, 24, and 36 months were 68.8 ± 7.8%, 49.9 ± 9.3%, and 32.8 ± 10.2%, respectively.

Ejection fraction is related to postcatheterization survival in figure 4A. The 36-month postcatheterization survival rate (PCSR) was significantly higher for patients with EF > 0.20 (75.1 ± 14.5%) than for those with EF < 0.20 (0%) (P < 0.01). Ejection fraction of 0.20 was arbitrarily selected as a dividing point because it was a simple number which separated the patients into two nearly equal groups.

The M/V ratio is related to postcatheterization survival in figure 4B. The 36-month PCSR was significantly higher with M/V ratio > 0.90 (53.6 ± 14.8%) than with M/V ratio < 0.90 (12.4 ± 10.4%) (P < 0.05). M/V ratio of 0.90 was selected as a dividing point empirically. The M/V ratio was also compared to EF values above and below 0.20, as shown in figure 5A and B. For patients with EF above 0.20, M/V ratio > 0.90 was associated with a higher 36-month PCSR (100%) than M/V ratio less than 0.90 (25.0 ± 6.5%). For patients with EF < 0.20, M/V ratio > 0.90 was associated with a higher 24-month PCSR (65.1 ± 16.8%) than M/V ratio < 0.90 (6.8 ± 9.1%); but at 36 months, PCSR was < 10% for both subgroups.

The interval between the onset of dyspnea and the time of catheterization is related to the M/V ratio in figure 6. Patients (N = 17) with M/V ratio < 0.90 had dyspnea of shorter duration (median 7 months) than those (N = 19) with M/V ratio > 0.90 (median 48 months).

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Figure 3

Left ventricular end-diastolic volume values and the presence or absence of mitral regurgitation of greater than 0.70 liters/min/m². The bars designate mean values ± 1SD. M/V = mass/volume ratio.

In figure 7, the M/V ratio is related to postcatheterization survival for patients in whom dyspnea began within the year prior to catheterization.

Postcatheterization survival rates for patients subdivided according to mass/volume ratio (0.90). (A) Patients with ejection fraction > 0.20. (B) Patients with ejection fraction < 0.20. See figure 4 for explanation of figures in parentheses.

(A) Life table analysis of survival for patients subdivided by ejection fraction (0.20). (B) Survival rates for patients subdivided as to mass/volume ratio (0.90). The figures in parentheses next to each point indicate the number of patients for the interval in the following categories: alive at beginning of interval; expired during interval; not yet reached next interval.

Discussion

This study has demonstrated that both left ventricular function and hypertrophy are important in determining postcatheterization survival in cardiomyopathy patients with depressed ejection fraction. In addition, it demonstrates that the present series of cardiomyopathy patients had a high mortality rate following catheterization.

Ejection Fraction

In this study left ventricular function was expressed in terms of the ejection fraction, an index of myocardial function described by Miller, Kirklin, and Swan in 1965. Because of the small number of patients and the relatively short follow-up period, postcatheterization survival was only related to ejection fraction values above and below 0.20. Nevertheless, the group of patients with an ejection fraction < 0.20 had a significantly higher 36-month postcatheterization mortality rate than the group with ejection fraction > 0.20. With a large number
The duration of dyspnea prior to catheterization is related to mass/volume ratio values above or below 0.90. The bars indicate median values.

of patients it would be possible to compare postcatheterization survival to specific ejection fraction values. It seems reasonable to expect that such a study might demonstrate that, in general, the lower the value for ejection fraction the poorer the prognosis.

Few available studies compare ejection fraction to postcatheterization survival. Hugenholtz evaluated a series of patients with congenital heart disease and implied that those with ejection fraction <0.20 had a high mortality rate. Goodwin studied a group of cardiomyopathy patients and found that patients who later died had a significantly larger mean value for end-diastolic volume than did those who lived. Although details were not given, "the ejection fraction was slightly lower in those patients with the worst prognosis."

There are a number of ways in which a depressed ejection fraction might be related to postcatheterization mortality. Progression of the disease process could result in further depression of ejection fraction. At some point cardiac output would become inadequate to sustain life. Even if ejection fraction remained stable following catheterization, it can be expected that the lower the ejection fraction the greater the amount of myocardial disease and hence the greater the risk of a catastrophic cardiac arrhythmia. By definition, the lower the ejection fraction the larger is the fraction of residual ventricular volume present. It is logical to think that the larger the residual fraction, the greater the likelihood of cavitary thrombus formation. Recent evidence has indicated that in cardiomyopathy patients the right as well as the left ventricle may empty poorly, even in the absence of pulmonary artery hypertension. Thus emboli to the pulmonary as well as systemic circulation might occur.

Unfortunately, it was usually not possible to determine the exact mechanism of death. Of the 19
patients who were dead at the time of follow-up, seven had expired while in our hospitals. Two additional patients were dead upon arrival at our emergency rooms. For the patients expiring in our hospitals, death was associated with a clinically low output state. Two patients were suspected of having digitalis toxicity at the time of their death. Pulmonary emboli were found in three of the five patients having postmortem examination. One patient had a large embolus in the left main pulmonary artery.

It is possible that the ejection fraction might improve following catheterization if the disease process subsides. Ejection fraction values presumably reflect the amount of myocardial disease present but they do not indicate the degree of compensatory ventricular hypertrophy or the likelihood of subsequent improvement in ventricular function. A recent report has described a series of patients with peripartum cardiomyopathy, some of whom had clinical improvement with return of heart size to normal following initial evaluation. It is likely that the ejection fraction increased in the patients whose heart size returned to normal. In our study, seven patients alive at follow-up were symptomatically improved. It would be of interest to know if their ejection fractions had increased after catheterization, but these data are not available.

It should be noted that the majority of ejection fraction values were < 0.30, that all patients described abnormal exertional dyspnea, and that 34 patients had experienced paroxysmal nocturnal dyspnea. The absence of asymptomatic cardiomyopathy patients probably reflects the fact that during the study period few asymptomatic patients of any type had left heart catheterization with quantitative angiography. It is likely that some patients with cardiomyopathy with depressed ejection fraction are not symptommatic. Indeed, we have since the study period evaluated an asymptomatic cardiomyopathy patient with ejection fraction of 0.15. Furthermore, several additional patients recently evaluated for chest pain did not complain of dyspnea and had normal coronary angiograms and ejection fractions in the 0.30–0.49 range. Thus the patients in this study are only representative of cardiomyopathy patients with depressed ejection fraction who also describe abnormal exertional dyspnea.

**Mass/Volume Ratio**

The degree of left ventricular hypertrophy in this study was expressed as the ratio of left ventricular mass to end-diastolic volume (M/V). This is essentially a new index, although wall thickness, chamber dimensions, and pressure have previously been related and expressed as wall stress. Grant has used the terms eccentric and concentric hypertrophy to describe the relation of wall thickness to chamber size for various cardiac conditions. A ventricle with eccentric hypertrophy was considered to be a magnified image of the normal ventricle, and was associated with valvular regurgitation or myocardial disease. Magnifying the image of the normal left ventricle would result in maintenance of the M/V ratio. The mean normal value for this ratio is 1.31, calculated from the data of Kennedy et al.

In the present study the 36-month postcatheterization survival rate was significantly higher for patients with M/V ratio > 0.90 as compared to those with M/V ratio < 0.90, suggesting that hypertrophy of the ventricular wall appropriate to the degree of dilatation was an important compensatory mechanism. Hood has shown that peak systolic wall stress is usually maintained within a fairly narrow range for various cardiac states, and has suggested that this reflects the adequacy of ventricular hypertrophy. Wall stress is proportional to chamber radius and pressure and inversely proportional to wall thickness. Since systolic ventricular pressures were within a fairly narrow range for patients in this study, the relation of chamber radius to wall thickness would be of paramount importance in determining systolic wall stress. The M/V ratio reflects the inverse relation of chamber radius to wall thickness at end-diastole. Although it would be desirable to determine values for peak systolic wall stress, the necessary data were not always available, usually because of the slow filming rates or because of difficulty in ascertaining wall thickness during systole. Nevertheless, for patients in this study, an M/V ratio < 0.99 may have been associated with abnormally high peak systolic wall stress values.

It should be noted that M/V ratio < 0.90 was associated with a low postcatheterization survival rate whether ejection fraction was above or below 0.20. That is, for patients with ejection fraction above 0.20, those with M/V ratio < 0.90 had a lower 36-month postcatheterization survival rate than those with M/V ratio > 0.90. Likewise, for patients with ejection fraction below 0.20, those with M/V ratio < 0.90 had a lower 24-month postcatheterization survival rate than those with...
M/V ratio > 0.90; but at 36 months survival rates were < 10% for both subgroups. This finding suggests that the degree of hypertrophy influenced survival, at least in part, independently of the level of ventricular function as expressed by ejection fraction.

The finding of a longer duration of dyspnea prior to catheterization for patients with M/V ratio > 0.90 compared to those with M/V ratio < 0.90 is additional but circumstantial evidence that adequate hypertrophy is necessary for survival. This evidence requires the assumption that patients with M/V ratio > 0.90 maintained a ratio > 0.90 during the entire course of their symptomatic illness. The finding of a short duration of dyspnea prior to catheterization for patients with M/V ratio < 0.90 (median 7 months) indicates that inadequate hypertrophy relative to volume was present early in the course of the symptomatic illness for the majority of this group of patients. Thus, the data concerning the duration of dyspnea prior to catheterization suggest that compensation in terms of hypertrophy occurred during the early stages of the disease process, and that the adequacy of the compensation characterized the course of the illness. To further explore this concept, the M/V ratio was related to postcatheterization survival for patients with dyspnea beginning <1 year prior to catheterization. Although the number of patients was small, those with M/V ratio > 0.90 had a higher 24-month PCSR than those with M/V ratio < 0.90.

It is possible that in some patients the M/V ratio might change from < 0.90 to > 0.90 or vice versa. For example, in some patients with M/V ratio < 0.90 hypertrophy might subsequently occur in a more appropriate manner. Although we have no M/V ratio data following catheterization, the fact that to date no patient with M/V ratio < 0.90 has survived beyond 18 months following catheterization suggests that adequate hypertrophy did not subsequently develop. Likewise, one might expect that patients with a long symptomatic illness associated with M/V ratio > 0.90 might decompensate and develop a ratio < 0.90. This may have occurred in three patients with dyspnea beginning over 3 years prior to catheterization (3%, 6, and 8 years).

Knowledge of the type of disease process present in the patients would be of great interest. We were unable to ascertain the exact cause of the disease, even in those hearts subjected to gross and microscopic examination. Many of the patients appeared to have had an illness that would be compatible clinically with viral myocarditis. Viral studies, however, were not performed. Three of the five patients at autopsy had inflammatory changes of the myocardium. In one of these patients (no. 8), an anomalous pulmonary vein was discovered as an incidental finding. Five patients gave a history of excessive ethanol ingestion, which may have been the cause of the cardiac problem. It is conceivable that some patients had coronary artery disease that was not suspected clinically. Coronary arteriograms were within normal limits in the 15 patients in whom they were obtained. Postmortem examination in five additional patients revealed vessels which were either normal or which contained an occasional insignificant atheromatous plaque. Thus essentially normal coronary arteries were demonstrated in 20 of the 36 patients.

**Mitrail Regurgitation**

Patients with mitral regurgitation >0.7 liters/min/m² had a significantly larger mean value for end-diastolic volume as compared to those without regurgitation (or a regurgitation volume <0.7 liters/min/m²). This suggests that dilatation of the mitral valve annulus contributed to the development of the regurgitation. However, the large overlap in end-diastolic volume values for the two groups implies that additional mechanisms may have played a role. One obvious mechanism would be dysfunction of the papillary muscles and of the contiguous left ventricular wall. Dilatation may alter the position of the papillary muscles and their axes of tension, as recently discussed by Perloff and Roberts. In addition, some of the dilatation could be the result of volume overload in a diseased heart. It is possible that some of the patients not studied at autopsy had rheumatic deformity of the valve leaflets or of the chordae tendineae, even though none gave a history of having had rheumatic fever and no patient had calcification of the mitral valve at fluoroscopy. Finally, coronary artery disease may have been an etiologic factor in those patients in whom it was not ruled out.

It should be mentioned that, in the presence of mitral regurgitation, it is sometimes difficult to determine whether the problem is cardiomyopathy with secondary mitral regurgitation or primary mitral valve disease with secondary impairment of left ventricular function. The past medical history of a patient is often helpful in making such a distinction. However, short of direct examination of the mitral valve at surgery or autopsy, we know of...
no definitive means for distinguishing the two entities. Although a criterion for the maximal regurgitant flow compatible with the diagnosis of cardiomyopathy was not established, none of the patients had regurgitant flow exceeding 2.5 liters/min/m\(^2\). In addition, dilatation appeared to be excessive when compared to the amount of regurgitation since, for the 23 patients with measurable mitral regurgitation, the mean regurgitant flow was 1.07 liters/min/m\(^2\) and the mean end-diastolic volume was 194 ml/m\(^2\) (mean normal for end-diastolic volume is 70 ml/m\(^2\)).

In conclusion, this study describes quantitatively a spectrum of hemodynamic abnormalities present in patients who had cardiomyopathy with depressed ejection fraction, and demonstrates that the present series of patients had a high mortality rate following catheterization. Since the ejection fraction and the M/V ratio were of prognostic value, they appear to be useful indices for classifying such patients.

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