

Screening of pulmonary hypertension in chronic obstructive pulmonary disease and silicosis by discriminant functions

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ABSTRACT: The aim of our prospective multicentric study was to develop a screening method for pulmonary hypertension in patients with chronic lung diseases. We investigated 710 patients in 10 hospitals: 315 males and 109 females with chronic obstructive pulmonary disease, and 286 males with silicosis. Manifest pulmonary hypertension was defined as pulmonary artery pressure > 20 mmHg (2.7 kPa) at rest. The multivariate statistical method used was a stepwise discriminant analysis.

In males with chronic obstructive pulmonary disease, the diameter of the right descending pulmonary artery, forced expiratory volume in one second (FEV_1) arterial oxygen tension (P_{aO_2}) at rest, and age turned out to be relevant for discrimination of groups with and without manifest pulmonary hypertension. For females the FEV_1/FVC (forced vital capacity) ratio replaced the absolute value of FEV_1 in the calculated discriminant function. In females, sensitivity and specificity were below 80%. In males, both were distinctly above 80%. In silicosis, the diameter of the right descending pulmonary artery was much less important, since it could frequently not be measured precisely. In these cases, precision of the prediction of about 80% could only be obtained by combined evaluation of spirometry, P_{aO_2} during exercise, and body plethysmography.

The calculated discriminant functions are appropriate for screening patients with risk of pulmonary hypertension. For different chronic lung diseases, and for both sexes, different combinations of parameters are relevant. The method is recommended to select patients who should undergo an invasive examination of pulmonary haemodynamics.

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The development of pulmonary hypertension (PH) in patients with chronic obstructive pulmonary disease (COPD) [1-3] or silicosis [3] is linked with a poorer prognosis. Therefore, it is desirable to detect PH early. Single non-invasive variables, with the exception perhaps of variables obtained from Doppler echocardiography, do not permit precise prediction of the pulmonary arterial pressure (PAP) [4]. Better results are obtained by a combination of several simple tests [5, 6]. However, multiple regression equations explain less than half of the variance of PAP. Combinations of threshold values can improve the sensitivity, but diminish the specificity. In 1985, our working group published results of a discriminant analysis (DA) to calculate the probability of PH in males with COPD, using simple non-invasive variables [7]. Applying this discriminant function, with spirometric, X-ray, and blood gas values, to a new group of patients, we obtained a correct identification of patients with manifest PH in more than 80%. Thus, the results of the former study could be confirmed. Patients with latent PH were in more than 60% classified as PH.

In 1986, we started another prospective multicentric study, applying the discriminant function with four variables to patients from 10 chest hospitals. The new DA was carried out in males and females with COPD and in males with silicosis, including results obtained during exercise and data of body plethysmography and blood viscosity. Our intention was to use only parameters which are directly available to a pneumologist. Therefore, we did not include recent, highly sophisticated methods such as Doppler echocardiography in the analysis. The aim of the study was to develop a screening for PH in patients with chronic lung diseases.

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Patients

Males and females with COPD, and males with silicosis, recognized as an industrial disease, were admitted to the prospective investigation. The patients were aged 20-65 yrs, were in a clinically stable condition, and showed a manifest ventilatory obstruction ($FEV_1/FVC < 60\%$) (forced expiratory volume/forced

vital capacity). Patients with one of the following conditions were excluded: typical bronchial asthma; systemic hypertension (under resting conditions: >155 mmHg systolic, >95 mmHg diastolic); congenital or acquired heart defect; chronic ischaemic heart disease; recurrent lung embolism; bronchiectasis, cystic fibrosis; state after major thoracic surgery; liver failure; kidney failure; anaemia (haemoglobin <7 mmol·l⁻¹).

In total, 710 patients were admitted (315 males and 109 females with COPD, and 286 males with silicosis). After detailed information, all patients consented to the trial.

Methods

The catheterization of the right heart was performed with floating catheters Pulmoflex 3 F (Vygon). The measurement of PAP under resting conditions was performed in a supine position, and during light exercise in a sitting position. The method of investigation and reference values were previously described in detail [8]. A manifest PH was defined as a mean pulmonary arterial pressure (PAP) >20 mmHg (2.7 kPa). A latent PH was considered as a PAP at rest ≤20 mmHg but a PAP >28 mmHg (3.7 kPa) during light exercise in the sitting position (mean oxygen uptake ($\dot{V}O_2$), 1.05 l·min⁻¹, steady-state). Patients with PAP below these threshold values were considered to be without PH.

The spirometric, body plethysmographic and blood gas measurements were performed according to standard recommendations [9]. In addition, heart rate (HR) and systemic blood pressure (BP) were determined.

The diameter of the right descending branch (RDB) of the pulmonary artery was measured on standard X-rays of the thorax with a focus-film-distance of 1.5 m, according to the method of TEICHMANN *et al.* [10] at the proximal part of the truncus intermedius about 1 cm below the level of the right upper lobe bronchus.

Since X-ray criteria and results of ergometry were not available from all patients, we used different sets of data for the multivariate statistical evaluation.

The linear DA were performed using the BMDP 7M Statistical Software (University of California, Los Angeles, USA). We confronted the subgroups with manifest PH and without PH. The program selects stepwise that variable which will minimize Wilks' Lambda. The entry criterion for the variable at each step is the F value calculated during variance analysis. The stepwise procedure is continued until the remaining F level is insufficient for further computation. Thereby, one obtains a function which consists of the relevant variables, multiplied by coefficients, and one constant:

$$y = d_1x_1 + d_2x_2 + d_3x_3 \dots + c$$

When y falls below a threshold value the patient is categorized as having PH. This may be the most practicable form of application.

The program calculates two further different functions of the same structure: S_1 , and S_2 . If S_1

becomes higher than S_2 , the patient is classified as having PH. From S_1 and S_2 , the probability of the existence of PH (P1) can be calculated by the following equation:

$$P1 = \frac{e^{S_1}}{e^{S_1} + e^{S_2}}$$

Results

COPD patients

Of 315 males with COPD, 105 had a manifest, 75 a latent, and 135 no PH. In 11 patients from all three subgroups together (3.5%), RDB could not be measured on the X-ray film. To the remaining 304 male COPD patients, we applied the discriminant function previously developed by the method of AHRENS and LÄUTER [11]. We had calculated this function in 1985 from a sample of 227 men with PH and 145 men without PH [7]. The function consists in its reduced version of four variables:

$$v = 0.385 \text{ RDB (mm)} - 0.050 \text{ FVC (\% pred)} - 0.091 \text{ FEV}_1/\text{FVC (\%)} - 0.353 \text{ Pao}_2 \text{ at rest (kPa)}$$

Pao_2 is the arterial oxygen tension. If v becomes higher than -1.42, the patient is classified as having PH.

Of 102 males with manifest PH, 85 were correctly classified by this method (sensitivity 83.3%). Of 69 patients with latent PH, 44 (63.7%) had results allocating them to PH. Thus, the sensitivity for both subgroups combined was 75.4%. The specificity was 86.5%, *i.e.* the prediction was correct in 115 out of 133 persons without PH.

For the new DA, the subgroups with manifest PH and without PH are confronted. The mean values and standard deviations (SD) of the subgroups, and the stepwise discrimination using only the measurements under resting conditions are evident from table 1. Only the variables mentioned in the lower part of the table are contributing to the separation of the subgroups. The discriminant function is:

$$y = -0.274 \text{ RDB (mm)} + 1.305 \text{ FEV}_1 \text{ (l)} + 0.375 \text{ Pao}_2 \text{ at rest (kPa)} + 0.039 \text{ age (yrs)} - 2.852$$

If y becomes lower than -0.129, the patient is considered as having PH.

The result of the reclassification using these functions is somewhat better compared to the previously developed formula. The sensitivity for manifest PH is 84.3% (86 out of 102 patients correctly classified). Of 69 males with latent PH, 46 (66.7%) were declared as having PH. Thus, the overall sensitivity is 77.2%. The specificity amounts to 88.7% (118 out of 133 patients without PH were correctly allocated).

If results of ergometry are included, Pao_2 during light exercise replaces Pao_2 at rest in the discriminant function. Otherwise, no essential modification results (table 2).

Table 1. — Men with COPD: mean±sd and stepwise discrimination between the subgroups without and with manifest PH (data set only with resting values)

Parameter	Subgroup without PH n=133	Subgroup with manifest PH n=102	Entry criterion F
FVC l	3.14±0.78	2.43±0.74	50.3
FVC % pred	74±15.3	58±15.3	62.9
FEV ₁ l	1.66±0.58	1.04±0.41	83.9
FEV ₁ /FVC %	53±11.9	43±9.7	43.4
Pao ₂ -rest kPa	9.7±1.1	8.7±1.1	53.3
RDB mm	15.3±2.1	18.3±2.6	93.7
Hb g·dl ⁻¹	15.8±1.6	16.3±1.4	5.4
PCV %	48.8±5.0	50.8±4.8	7.8
Age yrs	54±7.4	55±7.5	1.2

Step no.	Variable	F value to enter	Wilks' lambda
1	RDB	93.7	0.71
2	FEV ₁	58.0	0.57
3	Pao ₂ -rest	16.5	0.53
4	Age	8.4	0.51

Approximate F-statistic 54.4. FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; Pao₂: arterial oxygen tension; RDB: diameter right descending branch of pulmonary artery; Hb: haemoglobin; PCV: packed cell volume; PH: pulmonary hypertension; COPD: chronic obstructive pulmonary disease.

Table 2. — Men with COPD examined during exercise: mean±sd and stepwise discrimination between the subgroups without and with manifest PH

Parameter	Subgroup without PH n=129	Subgroup with manifest PH n=70	Entry criterion F
FVC l	3.16±0.77	2.47±0.76	36.8
FVC % pred	74±15.2	59±15.6	45.7
FEV ₁ l	1.65±0.58	1.08±0.42	52.8
FEV ₁ /FVC %	52±11.8	44±9.5	22.5
Pao ₂ -rest kPa	9.8±1.0	9±1.0	27.4
-exercise kPa	9.9±1.2	8.5±1.4	58.4
HR-rest b·min ⁻¹	86±14.6	86±17.5	0.1
-exercise b·min ⁻¹	113±15.5	119±19.3	6.3
Syst. BP-rest mmHg	138±13.1	136±12.3	1.2
-exercise mmHg	172±20.0	177±27.0	2.2
RDB mm	15.4±2.1	18.1±2.6	63.3
Hb g·dl ⁻¹	15.8±1.6	16.3±1.4	4.7
PCV %	48.8±5.0	50.8±4.8	7.2
Age yrs	53±7.4	54±7.8	0.7

Step no.	Variable	F value to enter	Wilks' lambda
1	RDB	63.3	0.76
2	FEV ₁	31.6	0.67
3	Pao ₂ -exercise	21.6	0.57
4	Age	8.5	0.54

Approximate F-statistic 41.1. HR: heart rate; Syst. BP: systolic blood pressure. For further abbreviations see legend to table 1.

Table 3. — Men with COPD: mean±sd and stepwise discrimination between the subgroups without and with manifest PH (resting data set without RDB)

Parameter	Subgroup without PH n=135	Subgroup with manifest PH n=105	Entry criterion F
FVC l	3.15±0.79	2.44±0.74	51.0
FVC % pred	74±15.6	58±15.1	64.7
FEV ₁ l	1.65±0.57	1.04±0.41	86.6
FEV ₁ /FVC %	53±12.0	43±9.6	43.9
Pao ₂ -rest kPa	9.7±1.1	8.7±1.1	54.4
Age yrs	53±7.4	55±7.5	1.2
Step no.	Variable	F value to enter	Wilks' lambda
1	FEV ₁	86.6	0.73
2	Pao ₂ -rest	33.1	0.64
3	Age	5.1	0.63

Approximate F-statistic 46.2. For abbreviations see legend to table 1.

Table 4. — Women with COPD: mean±sd and stepwise discrimination between the subgroups without and with manifest PH (data set only with resting values)

Parameter	Subgroup without PH n=58	Subgroup with manifest PH n=28	Entry criterion F
FVC l	2.45±0.69	2.05±0.58	7.0
FVC % pred	79±20.0	64±15.4	12.2
FEV ₁ l	1.33±0.55	0.89±0.29	15.8
FEV ₁ /FVC %	53±12.6	44±9.9	12.4
Pao ₂ -rest kPa	10.2±1.2	9±1.2	16.9
RDB mm	14±2.0	16.5±2.6	24.9
Hb g·dl ⁻¹	15.1±1.4	15.8±1.9	3.1
PVC %	47.6±4.4	49.9±5.5	4.5
Age yrs	49±8.1	48±9.9	0.2
Step no.	Variable	F value to enter	Wilks' lambda
1	RDB	24.9	0.77
2	FEV ₁ /FVC	10.2	0.69
3	Pao ₂ -rest	7.4	0.63

Approximate F-statistic 16.1. For abbreviations see legend to table 1.

Omitting the X-ray parameter, all 315 males can be included in the analysis. The sequence of the remaining variables remains unchanged (table 3). The discriminant function is now:

$$y = 1.619 \text{ FEV}_1 (l) + 0.578 \text{ Pao}_2 \text{ at rest (kPa)} + 0.034 \text{ age (yrs)} - 9.433$$

If y becomes lower than -0.096, PH must be presumed.

In this reclassification a decrease of the sensitivity by 2.4% and of the specificity by 9.4% occurs, compared to the function including RDB.

In the group of 109 females with COPD, 29 had a manifest, 20 a latent, and 60 no PH. Table 4 shows

the results in the two polar subgroups, and the stepwise discrimination. Only the X-ray criterion RDB, the FEV₁/FVC ratio, and Pao₂ were shown to be relevant for the separation of the subgroups. The result of the reclassification is distinctly worse than in males. The sensitivity for manifest PH is 75.0% (21 out of 28 correctly allocated). The specificity is 79.3% (46 out of 58). Without RDB, an additional loss of sensitivity by 2.6%, and of specificity by 6.0% occurred. The discriminant function, including RDB, is as follows:

$$y = -0.301 \text{ RDB (mm)} + 0.042 \text{ FEV}_1/\text{FVC (\%)} + 0.188 \text{ Pao}_2 \text{ at rest (kPa)} - 1.496$$

If y becomes lower than -0.282, PH must be presumed.

Table 5. - Men with silicosis: mean±sd and stepwise discrimination between the subgroups without and with manifest PH (complete data set)

Parameter	Subgroup without PH n=27	Subgroup with manifest PH n=93	Entry criterion F
FVC l	3.58±0.47	3.13±0.63	11.5
FVC % pred	87±13.7	77±15.4	9.7
FEV ₁ l	2.38±0.45	1.81±0.51	26.9
FEV ₁ /FVC %	67±10.5	58±11.7	13.1
Raw kPa·s·l ⁻¹	0.32±0.15	0.62±0.34	18.8
RV l	1.96±0.81	1.87±0.76	0.3
RV/TLC %	34±10.2	36±11.5	0.6
Pao ₂ -rest kPa	10.8±0.8	10.2±0.7	15.2
-exercise kPa	10.4±0.8	9.6±0.8	18.2
HR-rest b·min ⁻¹	83±12.0	79±11.8	2.0
-exercise b·min ⁻¹	109±11.7	109±14.9	0.0
Syst. BP-rest mmHg	134±12.8	138±13.1	1.6
-exercise mmHg	167±24.8	181±27.2	5.6
RDB mm	17.3±2.6	19.1±2.5	9.7
Hb g·d ⁻¹	16.1±1.6	15.9±1.1	0.1
PVC %	49.6±4.2	49.6±3.4	0.0
Age yrs	59±3.7	59±5.8	0.1

Step no.	Variable	F value to enter	Wilks' lambda
1	FEV ₁	26.9	0.81
2	Pao ₂ -exercise	9.8	0.75
3	RDB	5.6	0.72

Approximate F-statistic 15.3. For abbreviations see legends to tables 1 and 2.

Silicosis

In the 286 males with silicosis we found in 172 cases a manifest, in 73 cases a latent, and in 41 cases no PH. The values of the lung function (tables 5 and 6) show that with silicosis PH already occurs in the presence of relatively better results of these tests. The criterion of RDB could not be evaluated in 55 patients (19.2%). Moreover, the precise measurement of this parameter is frequently difficult or distorted by silicotic alterations in the hilar region. The mean of the RDB in the subgroup of silicotic patients without PH is distinctly greater than in healthy persons or COPD patients with equal PAP values (table 1). In the DA, including all parameters measured at rest and during exercise, only 27 patients without PH and 93 with manifest PH can be evaluated (table 5), because measurement of all variables is a precondition for the application of DA. The following rank order occurs: FEV₁, Pao₂ during light exercise, RDB (table 5). All remaining variables are not suitable for an improvement of the separation of the subgroups. The discriminant function with a border value of +0.41 is as follows:

$$y = 1.368 \text{ FEV}_1 (l) + 0.585 \text{ Pao}_2 \text{ during exercise (kPa)} - 0.160 \text{ RDB (mm)} - 5.409$$

The reclassification using this formula results in a sensitivity for manifest PH of 78.5% (73 of 93 patients

correctly classified) and a specificity of 81.5% (22 out of 27). Latent PH is in 54.0% (34 out of 63) allocated to PH.

Without the X-ray parameter RDB, a greater number of patients can be included in the analysis (table 6). The first and second place in the rank order are again occupied by FEV₁ and Pao₂ during light exercise. In addition, residual volume (RV) and airways resistance (Raw) improve the separation of the subgroups. The discriminant function is:

$$y = 0.745 \text{ FEV}_1 (l) + 0.660 \text{ Pao}_2 \text{ during exercise (kPa)} - 0.030 \text{ systolic BP at rest (mmHg)} + 0.563 \text{ RV (l)} - 1.551 \text{ Raw (kPa}\cdot\text{s}\cdot\text{l}^{-1}) - 3.928$$

The border value is +0.49.

Reclassification using this function shows a sensitivity for manifest PH of 77.6% (97 out of 125) and a specificity of 87.1% (27 out of 31). The application to the subgroup with latent PH resulted in 63.2% (43 out of 68) in a classification as PH. The sensitivity for manifest and latent PH combined is 72.5% (140 out of 193).

Restriction of the DA to the resting values allows the evaluation of the total number of silicosis patients, but the results of reclassification are distinctly worse than those found by the function including Pao₂ during exercise. Then, the sensitivity for manifest PH is only 70.3% (121 out of 172) and the specificity 70.7% (29 out of 41).

Table 6. — Men with silicosis: mean±SD and stepwise discrimination between the subgroups without and with manifest PH (data set without RDB)

Parameter	Subgroup without PH n=31	Subgroup with manifest PH n=125	Entry criterion F
FVC l	3.56±0.51	3.07±0.63	15.9
FVC % pred	86±13.9	75±15.9	12.5
FEV ₁ l	2.34±0.43	1.79±0.52	29.8
FEV ₁ /FVC %	67±11.0	58±11.9	12.5
Raw kPa·s·l ⁻¹	0.34±0.16	0.62±0.33	20.7
RV l	1.99±0.79	1.85±0.72	0.9
RV/TLC %	35±10.4	36±11.1	0.6
Pao ₂ -rest kPa	10.8±0.7	10.1±0.7	18.4
-exercise kPa	10.4±0.8	9.5±0.9	23.4
HR-rest b·min ⁻¹	83±11.8	87±12.3	1.1
-exercise b·min ⁻¹	109±11.4	110±14.2	0.1
Syst. BP-rest mmHg	133±12.8	138±12.8	3.6
-exercise mmHg	166±23.5	182±27.2	8.8
Hb g·dl ⁻¹	15.9±1.6	16.1±1.3	0.03
PCV %	49.4±4.2	49.8±3.6	0.3
Age yrs	59±3.6	59±5.3	0.4

Step no.	Variable	F value to enter	Wilks' lambda
1	FEV ₁	29.8	0.84
2	Pao ₂ -exercise	11.3	0.78
3	Syst. BP-rest	5.3	0.75
4	RV	5.6	0.73
5	Raw	5.2	0.70

Approximate F-statistic 14.9. For abbreviations see legends to tables 1 and 2.

Discussion

Until now, all efforts to assess the PAP using simple non-invasive data were finally disappointing and did not result in sufficient reliability. It is more promising to perform a separation of groups using a multivariate statistical method, with the aim of selecting by such screening procedure the patients with a high probability of PH for invasive measurement of PAP [12–15]. To make such a screening feasible for all out-patients with chronic pulmonary diseases, a restriction to easily measured data is essential. Dispensing with an assessment of PAP, the discriminant analysis appears to be more favourable than the multiple regression analysis, since the former aims from the very beginning at a separation into groups, selects step-by-step the relevant variables, and weighs them [11]. Our first results with a defined group of patients (males with COPD) confirmed this assumption [7].

In the meantime the World Health Organization (WHO) working group, led by J. Bishop, has also published its experience with different multivariate statistical methods [15]. Their published figures concerning sensitivity and specificity of discriminant functions in COPD patients are of a similar order of magnitude to ours, but in total somewhat lower. The

authors used various thresholds (PAP 20, 25 or 30 mmHg), at which sensitivity and specificity were, as expected, reciprocal. Males and females were, obviously, not separately evaluated. In our experience (unpublished results), this reduces the precision.

In addition to the DA, for the application of which a multidimensional normal distribution is a prerequisite [11], non-parametric statistical procedures were also used. Of these, Fisher's exact test was better than the Kolmogoroff-Smirnoff statistics [15]. With Fisher's exact test and a border value of 20 mmHg, the sensitivity was 88.7%, but the specificity only 55.4%. This value is too low even for a screening procedure. A good specificity (91.3%) was only obtained by raising the discriminating point to 30 mmHg. Herewith, the sensitivity with 83.3% was still good. But this latter border is not useful in practice. Only patients with mild PH (PAP 21–30 mmHg) are to be considered as a good indicator of the efficiency of a method [14]. In the majority of COPD patients, the PAP does not exceed 30 mmHg [2]. But even below this value life expectancy is obviously reduced [2, 16]. Disregard of latent PH is also a deficiency in many previously published papers. By discrimination only at the base of 20 mmHg at rest, cases with latent PH are allocated to the group with normal PAP.

In males with COPD using DA, a balanced relationship between sensitivity and specificity could be obtained also including mild PH. Our material is possibly more homogeneous than the multinational group of patients of BISHOP and CSUKAS [15]. In East Germany, lung function diagnostics and measurement of PAP were performed for years according to uniform standards [8, 9]. Conversely, the linear DA is considered to be relatively robust towards deviations from the normal distribution of data [11]. In females with COPD, the same methods of examination as in males turned out to be relevant: chest X-ray, spirometry, Pao_2 . Differences exist with regard to the respective weight of the variables. Concerning RDB this is understandable, since in healthy males the average is somewhat greater than in females [17].

Furthermore, the precision of the prediction of PH is different according to the sex. Whether this is due only to the smaller number and possibly the more inhomogeneous nature of the female group, or whether the females have *a priori* worse preconditions for prediction of PH, cannot precisely be decided. In the actual material, the correlation coefficients between non-invasive data and \overline{PAP} calculated by linear regression analysis are actually somewhat lower in females than in males. In a group investigated earlier [18] this was true only for RDB, but not for data of spirometry and blood gases. According to earlier reports, linear regression analyses in patients with silicosis showed significant correlations between Pao_2 , arterial oxygen saturation (So_2), FEV_1 , vital capacity (VC), Raw, RV, and \overline{PAP} , in the same order of magnitude as with COPD [6, 19]. Using a multiple regression analysis, amongst others, a regression equation from Pao_2 , FEV_1 , and right Sokolow-Lyon index has been established [20]. However, even in silicosis, because of great residual variation, such a regression equation was not appropriate to assess \overline{PAP} . Discriminant analytical investigations on silicotic patients apparently do not exist in the literature. Our results show that a prediction of a manifest PH with a sensitivity and a specificity of about 80% is possible. The X-ray sign of RDB is of less importance than in COPD patients. In many of the silicotic patients the measurement of this sign is disturbed or impossible. To obtain a sufficient predictive value, a higher functional diagnostic implementation is necessary in silicosis than in COPD. Data from body plethysmography and ergometry considerably increase sensitivity.

The efficiency of the established discriminant functions is better in males with COPD than in females or in males with silicosis. Moreover, the results in COPD are corroborated, since the present multicentre study confirmed the results of the previous trial. Generally, the discriminant functions are only valid for those groups of diagnosis for which they were set up. In all three investigated groups of patients the application of the method improves the indication of right heart catheterization. The follow-up of this prospective investigation will show whether after long-term observation of patients with these chronic lung diseases

a better determination of the prognosis can also be obtained.

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