A PROGNOSTIC SCORE FOR ADVANCED HODGKIN'S DISEASE

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ABSTRACT

Background Two thirds of patients with advanced Hodgkin's disease are cured with current approaches to treatment. Prediction of the outcome is important to avoid overtreating some patients and to identify others in whom standard treatment is likely to fail.

Methods Data were collected from 25 centers and study groups on a total of 5141 patients treated with combination chemotherapy for advanced Hodgkin's disease, with or without radiotherapy. The data included the outcome and 19 demographic and clinical characteristics at diagnosis. The end point was freedom from progression of disease. Complete data were available for 1618 patients; the final Cox model was fitted to these data. Data from an additional 2643 patients were used for partial validation.

Results The prognostic score was defined as the number of adverse prognostic factors present at diagnosis. Seven factors had similar independent prognostic effects: a serum albumin level of less than 4 g per deciliter, a hemoglobin level of less than 10.5 g per deciliter, male sex, an age of 45 years or older, stage IV disease (according to the Ann Arbor classification), leukocytosis (a white-cell count of at least 15,000 per cubic millimeter), and lymphocytopenia (a lymphocyte count of less than 600 per cubic millimeter, a count that was less than 8 percent of the white-cell count, or both). The score predicted the rate of freedom from progression of disease as follows: 0, or no factors (7 percent of the patients), 84 percent; 1 (22 percent of the patients), 77 percent; 2 (29 percent of the patients), 67 percent; 3 (23 percent of the patients), 60 percent; 4 (12 percent of the patients), 51 percent; and 5 or higher (7 percent of the patients), 42 percent.

Conclusions The prognostic score we developed may be useful in designing clinical trials for the treatment of advanced Hodgkin's disease and in making individual therapeutic decisions, but a distinct group of patients at very high risk could not be identified on the basis of routinely documented demographic and clinical characteristics. (N Engl J Med 1998;339: 1506-14.)

SINCE the advent of combination chemotherapy with the MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)[1] and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimens,[2] only minor progress has been made in the treatment of Hodgkin's disease,[3] although ABVD or alternating cycles of MOPP and ABVD may have better results than MOPP alone.[4] Current therapies fail to cure about one third of patients with advanced Hodgkin's disease, and a similar proportion of patients may be overtreated. The latter problem is apparent from long-term remissions in patients who stop treatment after two to six cycles of chemotherapy[5,6] or who receive reduced treatment in an individualized approach.[7]

For these reasons, prediction of the outcome of treatment may allow the identification of patients who are likely to benefit from reduced treatment or who are unlikely to have a sustained response to standard treatment.[8-10] There is an extensive literature on prognostic factors in Hodgkin's disease.[11,12] Several groups have developed prognostic indexes for overall survival on the basis of data from samples of moderate size.[13-19] Some of these indexes have been partially confirmed.[20,21] The International Database on Hodgkin's Disease was used to develop a parametric model for predicting survival. This model was based on data from 5023 patients who were at various stages of the disease and who received various treatments.[3,22]

There is a need for a simple scoring system to predict freedom from progression of disease that is based on data from a large number of similarly treated cases of advanced Hodgkin's disease. An international collaboration was organized to develop such a scoring system for patients treated with combination chemotherapy, with or without radiotherapy.

Freedom from progression of disease was chosen as the main end point because overall survival involves three factors that should be considered separately: the ability of the initial treatment to control the disease, an appreciable second chance of a cure with salvage treatment in the case of recurrent disease,[23-26] and deaths due to late toxicity or disorders unrelated to Hodgkin's disease in patients with continuous complete remissions.

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METHODS

Data Collection

Patients with histologic confirmation of advanced Hodgkin's disease (according to the local definition of advanced disease) were eligible if they had been treated with an established protocol still considered to be state of the art, with at least four planned cycles of combination chemotherapy (preferably containing doxorubicin), with or without radiotherapy. Treatment must have started before January 1, 1992, in order to allow a sufficient period of follow-up. Data for 5141 patients were obtained. Ninety-five percent of the patients started treatment after 1983. Patients were excluded if the outcome was unknown (248 patients), or if they had received outmoded or only palliative therapy (88). Analyses were further restricted to patients between the ages of 15 and 65 years, the age range of a typical study population. Data for the remaining 4695 patients were analyzed. The quality of the data appeared to be adequate on extensive inspection.

Participating centers were asked to specify the treatment strategies used and to provide the relevant protocols or reports.[4,5,7,21,27-47] More than 75 percent of the patients were treated with standard doxorubicin-containing regimens; 20 percent received MOPP or a similar regimen. Sixty percent of the patients received no radiotherapy. Thirty-three percent received full or selected involved-field irradiation; 2 percent underwent more extensive irradiation with a mantle or inverted-Y field, and 5 percent underwent subtotal or total nodal irradiation.

Demographic and Clinical Factors

The following variables documented at diagnosis were analyzed as potential prognostic factors: age; sex; histologic type; Ann Arbor stage of disease; presence or absence of systemic symptoms; mediastinal grade of involvement; presence or absence of inguinal involvement; lung, liver, and bone marrow involvement; hemoglobin level; serum albumin level; erythrocyte sedimentation rate; white-cell and platelet counts; absolute and relative lymphocyte counts; serum alkaline phosphatase level; serum lactate dehydrogenase level; and serum creatinine level.

Since the techniques of measuring mediastinal masses can vary considerably,[48] the participating centers and study groups were asked to grade masses as absent, small, large, or very large, according to their own definitions. Masses graded as large typically occupied more than 33 percent of the thoracic aperture, and those graded as very large occupied more than 45 percent of the thoracic aperture. The centers and study groups were asked to provide their normal ranges for all laboratory values. There was sufficient overlap of the normal ranges to justify a joint analysis, except for the normal ranges of serum alkaline phosphatase and lactate dehydrogenase levels, which were expressed as the ratio of the measured value to the upper limit of the normal range.

End Points

Freedom from progression of disease was defined as the interval from the initiation of primary treatment to the first recurrence of disease (progression or relapse); data on deaths that occurred during remission and that were not preceded by the recurrence of disease were censored. Overall survival was defined as the interval from the initiation of primary treatment to death from any cause.

Statistical Analysis

Time-to-event distributions were estimated with the life-table method with one-month intervals. Univariate curves were compared with generalized Gehan's Wilcoxon k-sample test. Multivariate regression analysis of time to treatment failure was performed with a Cox proportional-hazards model.[49]

Some centers and study groups provided only partial information on mediastinal involvement. Masses were reported as present, with no information on size, in 219 patients, as large or very large in 242, and as small or large in 59. The distribution of the mediastinal mass in the overall study population was estimated on the assumption that the distribution in patients for whom only partial information was available was similar to that in patients for whom full information was available (conditional distribution). For the Cox regression analysis, incomplete data were coded according to the estimated probability that a mass was a given size.

The problem of missing data was resolved by carrying out "complete case" analyses. Since the data appeared to be randomly missing and since the data on potential predictive factors were collected before the data on the outcome of treatment, the complete case analyses should be unbiased. Follow-up times appeared to be unrelated to clinical variables.

The construction of the prognostic model started with a univariate assessment of the prognostic effect of each factor and an analysis of the correlations between the factors in order to identify groups of statistically as well as biologically related items. Laboratory variables were initially coded as continuous variables.

In constructing the model, we had to take into account the degree of completeness of the covariates analyzed. A step-down procedure was used to analyze all variables for which we had nearly complete data (i.e., data from more than 4000 patients). Improvement of the resulting model was investigated by adding variables for which data were missing one by one in a step-up fashion, always with the use of the respective complete data set.

To develop a practical scoring system, all laboratory variables were dichotomized. Cutoff points were chosen to make optimal use of the information, with the conditions that the smaller group contain at least 20 percent of all patients, that the cutoff value demarcate a clearly abnormal state and if possible agree with cutoff values used in the literature, and that the effects of the dichotomized variables be of the same order of magnitude. No dichotomized covariates were entered into the model unless the continuous analogue had a significant independent prognostic effect. This strategy was used to ensure that the selection of prognostic factors for the model would be independent of the choice of the various cutoff points.

All the prognostic effects were small to moderate. Restricting the analysis to the patients for whom complete data were available reduced the sample to 1618 patients. To retain sufficient statistical power, we fitted the model to the set of complete data without setting aside a validation sample. The resulting model was validated with the data from the 2643 patients for whom we had complete information except for albumin values, lymphocyte counts, or both. Missing serum albumin levels were roughly estimated by linear regression from hemoglobin levels and other nearly complete covariates (correlation coefficient, 0.51). Missing lymphocyte counts could not reasonably be estimated from other variables. Since scores with different numbers of factors are difficult to compare, inguinal involvement (the last factor dropped from the model) was used as a surrogate for lymphocytopenia. The estimation of serum albumin levels and the substitution of a variable with a presumably smaller prognostic effect for lymphocytopenia would be expected to reduce the predictive power of the score, and this validation approach should therefore not be biased in favor of the predictive effect of the variables.

RESULTS

Univariate Analyses

At five years, the rate of freedom from progression of disease was 66 percent and the rate of overall survival was 78 percent. The median period of follow-up for the analysis of freedom from progression of disease was 68 months. Table 1 summarizes the results of the univariate analyses. Since the sample was large, most of the factors were significant in the univariate analyses.

The univariate effect of age on freedom from progression of disease was moderate. The effect of

TABLE 1. RESULTS OF THE UNIVARIATE ANALYSIS OF FREEDOM FROM PROGRESSION OF DISEASE AND OVERALL SURVIVAL AT FIVE YEARS.*

VARIABLE	NO. OF PATIENTS (%)	RATE OF FREEDOM FROM PROGRESSION (%)	P VALUE	RATE OF OVERALL SURVIVAL (%)	P VALUE
All patients	4695	66±1		78±1	
Age	4695		<0.001		<0.001
15–24 yr	1334 (28)	65±1		82±1	
25–34 yr	1465 (31)	68±1		82±1	
35–44 yr	905 (19)	69±2		80±2	
45–54 yr	582 (12)	65±2		73±2	
55–65 yr	409 (9)	56±3		57±3	
Sex	4693		0.002		0.003
Male	2882 (61)	64±1		77±1	
Female	1811 (39)	69±1		80±1	
Histologic type	4692		0.12		<0.001
Lymphocyte predominance	162 (3)	66±4		75±4	
Nodular sclerosis	2936 (63)	67±1		80±1	
Mixed cellularity	1202 (26)	65±1		75±1	
Lymphocyte depletion	124 (3)	56±5		62±5	
Unclassified	268 (6)	66±3		73±3	
Ann Arbor stage	4692		<0.001		<0.001
I or II	603 (13)	74±2		84±2	
III	2110 (45)	69±1		81±1	
IV	1979 (42)	60±1		73±1	
Organ involvement in stage IV					
Liver involvement	1908		0.015		<0.001
Absent	1339 (70)	62±1		75±1	
Present	569 (30)	58±2		67±2	
Bone marrow involvement	1965		0.46		0.12
Absent	1351 (69)	61±1		74±2	
Present	614 (31)	60±2		70±2	
Lung involvement	1969		0.34		0.47
Absent	1324 (67)	61±1		72±2	
Present	645 (33)	59±2		73±2	
Number of involved organs in stage IV	1893		0.01		<0.001
0 or 1	1660 (88)	61±1		75±1	
2 or 3	233 (12)	56±3		60±4	
Inguinal involvement	4677		<0.001		<0.001
Absent	3496 (75)	68±1		80±1	
Present	1181 (25)	60±1		73±1	
Mediastinal mass†	3436		0.13		0.01
Absent	1147 (33)	67±1		77±1	
Small	1521 (44)	67±1		80±1	
Large	592 (17)	66±2		78±2	
Very large	176 (5)	56±4		68±4	
Lactate dehydrogenase	1638		0.14		0.075
<1× upper limit of normal	1194 (73)	71±1		82±1	
1–1.74× upper limit of normal	390 (24)	66±3		78±2	
≥1.75× upper limit of normal	54 (3)	68±7		82±6	
Serum creatinine‡	2960		0.25		0.38
<0.7 mg/dl	737 (25)	65±2		80±2	
0.7–0.9 mg/dl	1749 (59)	67±1		80±1	
≥1 mg/dl	474 (16)	67±2		78±2	

age was much greater on overall survival, mainly because of the poor results of salvage chemotherapy among older patients with relapses. Survival rates at five years among patients with a progression or relapse of disease decreased in an orderly fashion with age, from 42 percent in patients who were up to 34 years old at diagnosis to 5 percent in patients who were 55 to 65 years old at diagnosis. Age was the only factor that was predictive of death during continuous complete remission. With cases of disease progression censored at the time of progression, the survival rate among patients with complete continuous remission at seven years was 97 percent for those up to 44 years old, 91 percent for those 45 to 54 years, and 84 percent for those 55 to 65 years.

Histologic type was significantly associated with overall survival but not with freedom from progres-

TABLE 1. CONTINUED.

VARIABLE	NO. OF PATIENTS (%)	RATE OF FREEDOM FROM PROGRESSION (%)	P VALUE	RATE OF OVERALL SURVIVAL (%)	P VALUE
Systemic symptoms	4582		<0.001		<0.001
Absent	1308 (29)	70±1		82±1	
Present	3274 (71)	64±1		76±1	
Erythrocyte sedimentation rate	3019		<0.001		0.006
<30 mm/hr	710 (24)	72±2		83±2	
30–49 mm/hr	539 (18)	70±2		82±2	
50–79 mm/hr	811 (27)	62±2		75±2	
≥80 mm/hr	959 (32)	63±2		77±1	
Hemoglobin	4314		<0.001		<0.001
>14.0 g/dl	640 (15)	73±2		88±2	
12.1–14.0 g/dl	1487 (34)	70±1		81±1	
10.1–12.0 g/dl	1442 (33)	63±1		77±1	
≤10.0 g/dl	745 (17)	55±2		70±2	
Serum albumin	2238		<0.001		<0.001
>4.6 g/dl	195 (9)	76±4		92±3	
4.1–4.6 g/dl	586 (26)	73±2		85±2	
3.5–4.0 g/dl	770 (34)	64±2		78±2	
2.9–3.4 g/dl	457 (20)	58±3		71±3	
≤2.8 g/dl	230 (10)	56±4		63±4	
Serum alkaline phosphatase	3337		<0.001		<0.001
<1× upper limit of normal	2480 (74)	67±1		80±1	
1–1.74× upper limit of normal	594 (18)	60±2		74±2	
≥1.75× upper limit of normal	263 (8)	55±3		67±3	
White-cell count	4330		<0.001		<0.001
$\leq 4.0\times10^3/mm^3$	273 (6)	61±3		67±3	
$4.1–11.0\times10^3/mm^3$	2259 (52)	68±1		79±1	
$11.1–15.0\times10^3/mm^3$	980 (23)	68±2		81±2	
$15.1–20.0\times10^3/mm^3$	514 (12)	59±2		80±2	
$>20.0\times10^3/mm^3$	304 (7)	55±3		71±3	
Platelet count	4308		<0.001		<0.001
$\geq 600\times10^3/mm^3$	638 (15)	61±2		75±2	
$450–599\times10^3/mm^3$	917 (21)	65±2		78±2	
$250–449\times10^3/mm^3$	2093 (49)	69±1		81±1	
$<250\times10^3/mm^3$	660 (15)	62±2		73±2	
Absolute lymphocyte count	2497		<0.001		<0.001
$\geq 2\times10^3/mm^3$	771 (31)	71±2		84±2	
$1.5–1.9\times10^3/mm^3$	502 (20)	68±2		82±2	
$1.0–1.4\times10^3/mm^3$	583 (23)	66±2		80±2	
$0.6–0.9\times10^3/mm^3$	374 (15)	67±3		75±3	
$<0.6\times10^3/mm^3$	267 (11)	57±3		70±3	
Relative lymphocyte count	2478		<0.001		<0.001
≥25.0%	461 (19)	69±2		82±2	
15.0–24.9%	799 (32)	73±2		82±2	
8.0–14.9%	837 (34)	64±2		80±2	
<8.0%	381 (15)	58±3		73±3	

*Plus–minus values are rate estimates ±SE (approximate 95 percent confidence intervals can be calculated as the rate estimates ±2 SE). Percentages may not sum to 100 because of rounding.

†In some cases only partial information was available. A special procedure was used to estimate the frequencies and test the prognostic effect in such cases.

‡To convert the values for creatinine to micromoles per liter, multiply by 88.4.

sion of disease. As reported elsewhere,[3,50] patients with the histologic subtype characterized by lymphocyte depletion had a worse prognosis than those with other subtypes, but this subgroup is very small, and the number of such diagnoses has decreased in recent years.

Seventy-five percent of the study population had classic advanced disease (Ann Arbor stage IIIB, 33 percent; stage IVA, 13 percent; and stage IVB, 29 percent), and 12 percent had stage IIIA disease. Thirteen percent of the patients presented with stage I or II disease (stage I, 1 percent; stage IIA, 4 percent; and stage IIB, 8 percent). These patients were treated for advanced disease because they had additional risk factors indicating an advanced stage: systemic symptoms (fever, sweats, and weight loss) were present in 69 percent, and 43 percent had large mediastinal masses. The presence of these risk factors in pa-

tients with stage I or II disease explains the relatively small prognostic difference we saw between stage I or II and stage III.

In the group of patients with stage IV disease, organ involvement was analyzed to determine whether the combination of stage IV disease and particular sites of involvement had additional prognostic importance.[51] There were only small differences in freedom from progression of disease according to the site of involvement. Liver involvement was associated with poor overall survival because the survival rate among patients with such involvement is low after a relapse regardless of their age. The presence of a mediastinal mass[52] did not appear to have a strong prognostic effect, except in the small subgroup of patients (5 percent) with very large masses (i.e., those occupying more than 45 percent of the thoracic aperture). Serum lactate dehydrogenase also did not appear to be a major prognostic factor in advanced Hodgkin's disease, but this finding must be interpreted cautiously, because missing data considerably reduced the sample size.

Systemic symptoms occurred in 71 percent of the patients. Systemic symptoms together with the erythrocyte sedimentation rate, the hemoglobin level, the serum albumin level, and to a lesser degree, the serum alkaline phosphatase level formed a cluster of moderately correlated clinical factors (correlation coefficient, approximately 0.37 for all pairs of variables), all of which had a prognostic effect in the univariate analyses. In contrast to the erythrocyte sedimentation rate, which undergoes short-term changes, hemoglobin and serum albumin values change over a period of weeks and are thus biometrically more reliable. Both variables were consistently correlated with prognosis over the whole range of values.

Leukocytosis (a white-cell count of at least 15,000 per cubic millimeter) was present in one fifth of the study population.[49] Although 74 percent of the patients presented with normal absolute lymphocyte counts (more than 1000 per cubic millimeter), more than 80 percent had subnormal relative counts (less than 25 percent of the white-cell count). The joint distribution of white-cell and absolute lymphocyte counts reveals a clear shift of the bivariate distribution away from normal values toward leukocytosis and at least relative, if not absolute, lymphocytopenia. This bivariate shift was clearly prognostic. To derive a practical representation, a cutoff point of 15,000 per cubic millimeter was used for the white-cell count, and one unifying item was used for lymphocytopenia (a lymphocyte count of less than 600 per cubic millimeter, a count that was less than 8 percent of the white-cell count, or both). The overlap of the two partial criteria for lymphocytopenia is about 60 percent. On the basis of these criteria, lymphocytopenia was present in 21 percent of the patients.

Multivariate Analyses

The final model (Table 2) incorporates seven prognostic factors: a serum albumin level of less than 4 g per deciliter, a hemoglobin level of less than 10.5 g per deciliter, male sex, an age of 45 years or older, stage IV disease, leukocytosis (a white-cell count of at least 15,000 per cubic millimeter), and lymphocytopenia (a lymphocyte count of less than 600 per cubic millimeter, a count that was less than 8 percent of the white-cell count, or both). All seven factors had a relatively small effect of the same order of magnitude. They can thus be combined into a simple prognostic score without loss of relevant information.

Figure 1A shows that the proposed prognostic score predicts rates of freedom from progression of disease at five years ranging from 42 percent (for a score of 0) to 84 percent (for a score of 5 or higher). The curves for the scores are equally spaced, with each additional factor reducing the plateau by about 8 percent. Table 3 shows the distribution of scores together with rates of freedom from progression of disease and overall survival at five years. Figure 1B shows that the prognostic score is also predictive of overall survival.

The model was validated with the data from 2643 patients for whom albumin or lymphocyte counts were missing, with less-predictive information substituted. As explained in the Methods section, the predictive power of the score should therefore be reduced in this validation sample. Nevertheless, as Figure 2 shows, the separation of the curves was quite good.

To determine the potential effect of differences in treatment, an indicator variable for patients treated with a non–doxorubicin-containing or slightly inferior regimen was added to the final model. This variable provided independent prognostic information — that is, improved the fit of the model to the data

TABLE 2. THE FINAL COX REGRESSION MODEL.*

FACTOR	LOG HAZARD RATIO	P VALUE	RELATIVE RISK
Serum albumin, <4 g/dl	0.40±0.10	<0.001	1.49
Hemoglobin, <10.5 g/dl	0.30±0.11	0.006	1.35
Male sex	0.30±0.09	0.001	1.35
Stage IV disease	0.23±0.09	0.011	1.26
Age, ≥45 yr	0.33±0.10	0.001	1.39
White-cell count, ≥15,000/mm³	0.34±0.11	0.001	1.41
Lymphocyte count, <600/mm³ or <8% of white-cell count	0.31±0.10	0.002	1.38

*Hazard ratios and relative risks are for freedom from progression of disease in patients with the factors as compared with those without the factors. Plus–minus values are rate estimates ±SE (approximate 95 percent confidence intervals can be calculated as the rate estimates ±2 SE).

— but did not interact with the factors forming the prognostic score. The same applies to indicator variables for center or study-group heterogeneity.

DISCUSSION

We developed a seven-factor prognostic scoring system that predicts five-year rates of freedom from progression of disease in the range of 45 to 80 percent. Each additional factor reduced the predicted rate by about 8 percent. The prognostic score is also predictive of overall survival, and the predictive effects were reproducible in a large (partial) validation sample.

The factors incorporated into the prognostic score are well known and make biologic sense. Age and sex frequently influence the outcome of Hodgkin's lymphoma, and the disseminating potential of the disease is noted by stage IV. Inflammatory processes and effects driven by cytokine release are reflected by serum albumin[17,18,53,54] and hemoglobin[14,16-18,20,55,56] levels, as well as by abnormalities of white-cell counts (leukocytosis[49] and lymphocytopenia[14,40,50,57,58]).

The score was derived from a large, broadly representative, and fairly homogeneous set of data provided by 25 study groups and institutions. Most of the patients were treated in the 1980s with ABVD, MOPP and ABVD, a hybrid regimen of MOPP with alternating cycles of doxorubicin, bleomycin, and vinblastine, or a similar regimen. Moderate variations in treatment and moderate center effects appeared to be independent of the prognostic factors and therefore probably did not affect the validity of the prognostic score.

Table 3 shows the prognosis for each subgroup of

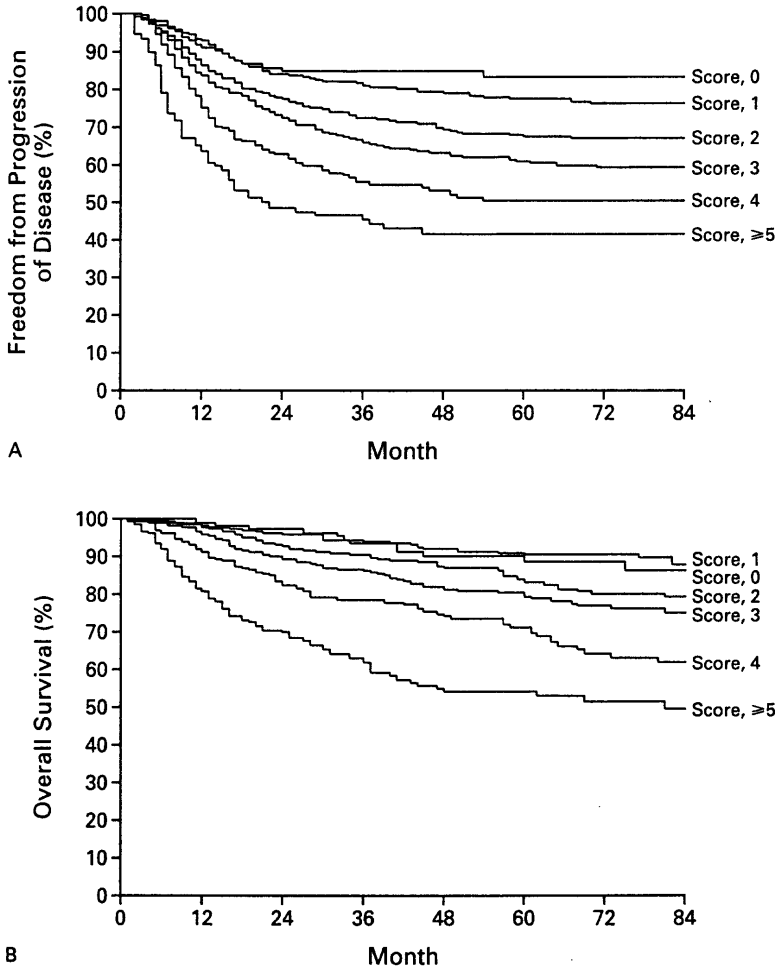

Figure 1. Use of the Prognostic Score to Predict Rates of Freedom from Progression of Disease (Panel A) and Overall Survival (Panel B) in 1618 Patients with Advanced Hodgkin's Disease.

The number and percentage of patients with each score were as follows: a score of 0, 115 patients (7 percent); 1, 360 (22 percent); 2, 464 (29 percent); 3, 378 (23 percent); 4, 190 (12 percent); and 5 or higher, 111 (7 percent).

TABLE 3. RATES OF FREEDOM FROM PROGRESSION OF DISEASE AND OVERALL SURVIVAL AT FIVE YEARS ACCORDING TO INDIVIDUAL AND GROUPED PROGNOSTIC SCORES.*

PROGNOSTIC SCORE	NO. OF PATIENTS (%)	RATE OF FREEDOM FROM PROGRESSION	RATE OF OVERALL SURVIVAL
		percent	
Individual			
0	115 (7)	84±4	89±2
1	360 (22)	77±3	90±2
2	464 (29)	67±2	81±2
3	378 (23)	60±3	78±3
4	190 (12)	51±4	61±4
≥5	111 (7)	42±5	56±5
Grouped			
0 or 1	475 (29)	79±2	90±2
≥2	1143 (71)	60±2	74±2
0–2	939 (58)	74±2	86±2
≥3	679 (42)	55±2	70±2
0–3	1317 (81)	70±2	83±1
≥4	301 (19)	47±2	59±2

*Plus–minus values are rate estimates ±SE (approximate 95 percent confidence intervals can be calculated as the rate estimates ±2 SE).

patients with a given score, as well as for low- and high-risk groups defined on the basis of grouped scores (0 or 1 vs. 2 or higher, 0 to 2 vs. 3 or higher, and 0 to 3 vs. 4 or higher). For each pair of low- and high-risk groups, the difference in freedom from progression of disease at five years was more than 19 percent. This difference should be consistently reproducible in data sets of moderate size.

A score of 3 or more (accounting for 42 percent of the study population) represented a moderately high risk, with an expected 55 percent rate of freedom from progression of disease (Fig. 3) and a 70 percent rate of overall survival at five years. Only 19 percent of the patients had a score of 4 or higher, which was associated with a 47 percent rate of freedom from progression of disease and a 59 percent rate of overall survival at five years. Thus, there was no distinct group of patients with advanced Hodgkin's disease that could be identified as being at very high risk on the basis of routinely documented clinical features.

This finding is relevant to the question of whether early high-dose chemotherapy with autologous stem-cell support should be used as consolidation therapy in patients with responses to induction therapy[8-10,20,59,60] who are nevertheless considered to remain at high risk for a relapse. There may be few such patients.[61,62] Rates of freedom from progression of disease at five years for the patients in our study who had complete remissions were considerably higher than the rates for the entire sample: 73 percent, 70 percent, and 65 percent for patients with scores of at least 2, at least 3, and at least 4, respectively. Thus, toxic effects should be considered carefully in comparing early high-dose chemotherapy and late high-dose chemotherapy (in cases of relapse only).

Finally, the clinical features and laboratory variables incorporated in the prognostic score are biologically rather nonspecific. It is important to obtain sufficient data on more specific features, including

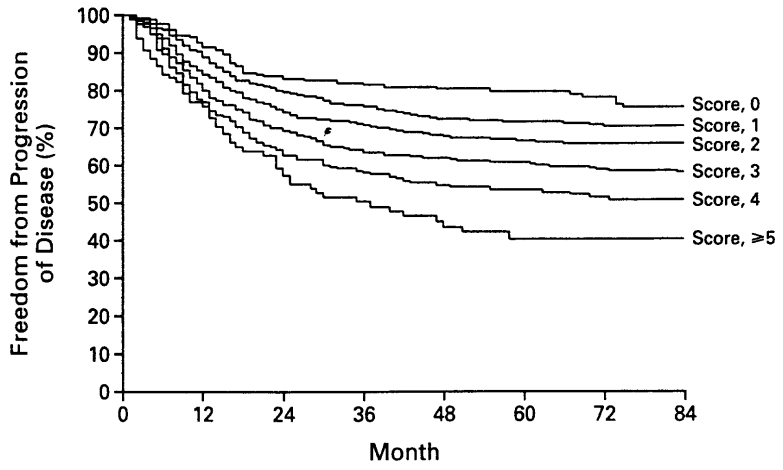

Figure 2. Validation of the Prognostic Score in a Group of 2643 Patients with Incomplete Data on Albumin or Lymphocyte Values.

Surrogate information was substituted for the missing data, as described in the Methods section. The number and percentage of patients with each score were as follows: a score of 0, 196 patients (7 percent); 1, 671 (25 percent); 2, 809 (31 percent); 3, 578 (22 percent); 4, 292 (11 percent); and 5, 97 (4 percent).

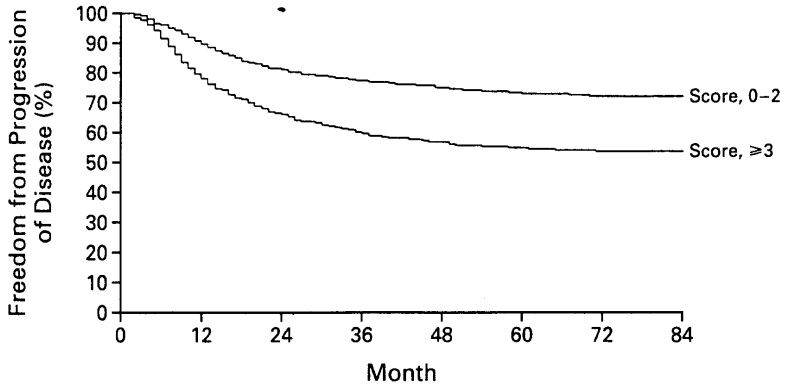

Figure 3. Freedom from Progression of Disease in 1618 Patients According to Whether the Prognostic Score Was 0 to 2 or 3 or Higher.

serum CD30[63,64] and cytokine[65,66] levels. Meanwhile, the proposed prognostic score can be used to establish enrollment criteria and to describe study populations as well as to support decisions about treatment in individual patients.

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APPENDIX

The following persons and institutions or study groups participated in the International Prognostic Factors Project for Advanced Hodgkin's Disease: J. Armitage and M. Bast, Nebraska Lymphoma Study Group, Omaha; D. Assouline and B. Coiffier, Groupe Lyon, Marseille et St. Etienne, Lyons, France; M. Björkholm, U. Axdorph, and G. Grimfors, Karolinska Hospital, Stockholm, Sweden; E. Brusamolino, Istituto di Ematologia, Università di Pavia, Pavia, Italy; G. Canellos, B. Peterson, G. Petroni, and J. Johnson, Cancer and Leukemia Group B, United States; P. Carde, M. Henry-Amar, E. Noordijk, R. Somers, and J. Raemaekers, European Organization for Research and Treatment of Cancer–Lymphoma Cooperative Group, Europe; D. Crowther and D. Ryder, Manchester Lymphoma Group, United Kingdom; D. Cunningham and S. Milan, Royal Marsden Hospital, Sutton, United Kingdom; V. Diehl and D. Hasenclever, German Hodgkin's Lymphoma Study Group, Germany; H. Eghbali and V. Picot, Institut Bergonié, Bordeaux, France; C. Fermé and C. Gisselbrecht, Groupe d'Etude des Lymphomes de l'Adulte, Paris; R. Fisher, Southwest Oncology Group, United States; J. Glick and D. Harrington, Eastern Cooperative Oncology Group, United States; B. Glimelius, G. Enblad, and A. Gustavsson, Swedish Lymphoma Study Group, Sweden; P. Gobbi, V. Silingardi, and M. Federico, Gruppo Italiano per lo Studio dei Linfomi, Italy; H. Holte, Norwegian Radium Hospital, Oslo; S. Horning and J. Allen, Stanford University, Stanford, Calif.; T.A. Lister, St. Bartholomew's Hospital, London; D. Longo and P. Duffey, National Cancer Institute, Frederick, Md.; F. Mandelli, A. Anselmo, and C. Cartoni, Università La Sapienza, Rome; A. Polliack, O. Paltiel, C. Lotan, and B. Uziely, Hadassah University Hospital, Jerusalem, Israel; S. Proctor, P. Taylor, and J. White, Scotland and Newcastle Lymphoma Group, United Kingdom; L. Specht, University of Copenhagen, Copenhagen, Denmark; J. Sweetenham and P. Smartt, University of Southampton, Southampton, United Kingdom; G. Hudson, British National Lymphoma Investigation, United Kingdom.

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CORRESPONDENCE

Prognostic Score for Hodgkin's Disease

To the Editor:

The prognostic scoring system for Hodgkin's disease proposed by Hasenclever and Diehl (Nov. 19 issue) (1) has addressed a difficult challenge for clinicians. We wish to raise two issues of concern regarding this article. First, there was no histologic review, and it is uncertain whether cases of the nodular lymphocyte-predominant subtype were included. This form of Hodgkin's disease is different in both presentation and prognosis from the classic form of the disease. Only 3 percent of cases had lymphocyte-predominant Hodgkin's disease; distortion of the analysis would have been slight, but it would be incorrect to apply the conclusions of the study to this small and unrepresentative subgroup.

Second, we have attempted to place the findings in a population-based setting. There are 1281 patients with classic Hodgkin's disease, all of whom were negative for the human immunodeficiency virus, whose presentation and follow-up data are registered in the Scotland and Newcastle Lymphoma Group data base. This registry represents most cases of Hodgkin's disease diagnosed in our population of 8.5 million since 1986. One hundred eighty-seven (14.6 percent) are at least 66 years old and 41 (3.2 percent) are under 15; these patients were excluded from the scoring system developed by the authors. Of the remaining 1053 patients (82.2 percent), 459 had complete data for the score. The rates of disease-specific survival for these patients are presented in Table 1. We looked at disease-specific survival rather than freedom from progression for three reasons: disease-specific survival is a definitive measure of failure; if disease-specific survival is not related to presentation features, the argument for intensifying initial treatment is diminished; and the assessment of progression is notoriously difficult in patients with Hodgkin's disease in whom residual masses after therapy are common and may be inactive.

In only 17 of 459 patients (3.7 percent) was the prognostic score >4. Fifteen of these 17 had Ann Arbor stage IV disease. We conclude that the system proposed by Hasenclever and Diehl identifies only a small proportion of patients with poor outcome, with nearly all disease-specific deaths occurring in "low-risk" categories. We have long been concerned with the identification of patients for whom conventional four-drug regimens are likely to fail and will continue to use the index of the Scotland and Newcastle Lymphoma Group (2) to select candidates for our eight-drug hybrid regimen. To date, no prognostic system for Hodgkin's disease based on traditional factors has been entirely satisfactory, and we agree with Hasenclever and Diehl that efforts should be intensified in the search for new and more pathologically relevant markers of prognosis.

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To the Editor:

Hasenclever and Diehl describe a prognostic score for advanced Hodgkin's disease based on seven factors, among which four are laboratory measurements (i.e., serum albumin, blood hemoglobin, white-cell count, and lymphocyte count). However, they do not mention the methods used to measure these factors. It would therefore be impossible for an independent team to reproduce their results (a basic principle of good science). It is not possible to compare the prognostic value of any particular laboratory measurements if such measurements are made with different techniques. For example, electrophoretic, colorimetric, turbidimetric, and nephelometric procedures do not yield identical results for serum albumin concentrations, and an international standardization for the measurement of serum protein has been routine practice in most laboratories only since 1995. (1) Such a lack of consistency among methods may exist for most of the other laboratory tests performed in their study.

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Dr. Hasenclever replies:

To the Editor:

Watine is concerned about our using laboratory tests in a prognostic score without fully specifying the methods involved. Our project combined most of the prospectively documented trial data that were collected in the 1980s by leading centers and study groups worldwide. In these data sets, individual normal ranges were not routinely documented or were only documented for laboratory measurements in which the normal range varies considerably (e.g., lactate dehydrogenase and serum alkaline phosphatase). For these tests, only values standardized in units of the upper bound of the normal range were used in the analysis. Concerning the other tests, in

particular those incorporated into the score, the center-specific normal ranges and the center-specific distributions of the values appeared to overlap sufficiently to justify a joint evaluation. In addition, since we used cutoff points chosen to demarcate a clearly abnormal state qualitatively, the error due to differing methods of measurement should be negligible. Nevertheless, we agree with Watine that the quality of data in prospective clinical trials can be improved by systematically collecting information on methods of measurement and normal ranges for all laboratory tests.

Jack et al. correctly point out that the prognostic score applies to classic Hodgkin's disease. There are no specific data on the validity of the score in the recently delineated very small subgroup of patients with the nodular lymphocyte-predominant subtype. Jack et al. applied the score to the Scotland and Newcastle Lymphoma Group data base and concluded that "the system identifies only a small proportion of patients with poor outcome." Their results are fully compatible with the data on the score applied to survival presented in Figure 1B of our paper with regard to both the five-year survival rates and the proportions of patients with a particular number of adverse factors.

Unfortunately, they did not use the main end point, freedom from progression of disease, but instead used disease-specific survival. It should be stressed that the score was constructed and optimized for freedom from progression of disease. As discussed in our article, a score optimized for disease-specific survival would have to give age a much stronger influence, because age is a major prognostic factor for survival after relapse. A validation of the score in the intended context would be preferable.

The score we reported was developed for advanced-stage Hodgkin's disease. Jack et al. appear not to have excluded patients with early stages of the disease (stages I and II, without any risk factors), who were probably treated with therapy that was not as aggressive as the treatment for advanced stages. A recent analysis of the data of the German Hodgkin's Lymphoma Study Group on patients with early stages of disease (1) shows that the prognostic score also works for these patients, although the adverse factor of stage IV disease should be interpreted to encompass any extranodal involvement (E stage). This finding deserves further validation in independent data sets.

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