Survival in Hodgkin’s Disease: The Role of Immunocompetence and Other Major Risk Factors

By Guy B. Faguet and Harry C. Davis

The prognostic value of age, sex, symptoms, histopathology, lymphocyte count, skin tests, immunocompetence (lymphocyte response profile to a spectrum of PHA concentrations), and stage was evaluated in 35 previously untreated patients with Hodgkin’s disease by multiple linear regression and logistic analysis. Immunocompetence exhibited the highest correlation \( R = 0.537 \) with survival status and was required as a common denominator for deriving best sets of two or more variables. In addition, immunocompetence contributed to all other variables combined \( (p = 0.023) \), whereas stage did not \( (p = 0.116) \). Immunocompetence, age, symptoms, and histopathology generated a highly discriminant \( R = 0.784 \) model not improved by stage or by other variables \( (p \geq 0.159) \). The utility and generalizability of this model are shown by a correct classification of 91.2% of cases according to expected versus actual survival status and by a predicted correlation \( R \) of 0.71, respectively, neither improved by sex, lymphocyte count, skin tests, or stage. In comparison, the conventional triad of stage, symptoms, and histopathology correctly classified only 70.6% of cases and showed actual and predicted correlations with survival status of \( R = 0.550 \) and \( R = 0.51 \). We conclude that immunocompetence is a powerful discriminant risk factor in Hodgkin’s disease that exerts a pivotal role on survival and serves as a basis for models of greater discriminant power and generalizability than the conventional stage-based evaluation triad. Immunocompetence-based models are expected to provide a more discriminating basis for clinical evaluation, prediction of prognosis, and treatment selection for patients with Hodgkin’s disease.

With the advent of improved diagnostic assessment of the type and extent of the disease,1,2 the introduction of megavoltage radiotherapy techniques,3 and the development of effective combination chemotherapy regimens,4 the natural course of Hodgkin’s disease has been radically altered and prolonged relapse-free survival is achieved in a high percentage of previously untreated patients.5,6 While discriminant analysis of clinical, pathologic, immunologic, and laboratory profile parameters in large series of patients with Hodgkin’s disease has not yet been done, it appears that at present prognosis is, in various degrees, dependent on extent of disease, presence or absence of constitutional symptoms, histologic type, and age.7 In addition, of the laboratory studies initially proposed to be of prognostic significance, only erythrocyte sedimentation rate6 and status of the patient’s immunocompetence determined by delayed hypersensitivity responses and by quantitative and/or qualitative lymphocyte studies8 have shown even a modest correlation with prognosis.

We have previously shown10,12 that assessment of immunocompetence by studying the entire spectrum of lymphocyte responses to a wide range of phytohemagglutinin (PHA) concentrations revealed a subtle defect in most patients with Hodgkin’s disease. Because of its correlation with stage and with disease status,11 the defect was suggested to be inherent to the disease and of independent prognostic significance. We now demonstrate the prognostic value of this assessment relative to more conventional clinicopathologic and laboratory risk factors by multiple linear regression and logistic analysis in a group of patients with Hodgkin’s disease prospectively evaluated and followed for 72–114 mo.

MATERIALS AND METHODS

Patients

All patients \( (n = 35) \) with previously untreated Hodgkin’s disease seen between 11/71 and 4/74 were entered into the study in order to confirm the existence of a quantifiable defect in in vitro cell-mediated immune function as previously reported12 and to evaluate its possible prognostic significance. Changes in the evaluation protocol dictated termination in patient accrual. Details of the patients’ clinical, pathologic, and immunologic evaluations have previously been reported.12 The treatment included chemotherapy in the form of nitrogen mustard, vincristine, procarbazine, and prednisone (MOPP),4 administered to 13 patients with stages III-B and IV-B; radiotherapy in the form of extended field (2 cases) or total nodal irradiation (8 cases) given to patients with stages I-A, II-A, II-B, and III-A; and dual modality treatment consisting of total nodal irradiation complemented by 6 courses of MOPP chemotherapy delivered to 5 patients with stages II-B, III-A, and III-B. Of the remaining 7 patients, 1 died before therapy could be instituted; 3 died after 1 and 2 courses of chemotherapy and 500 rads radiotherapy, respectively; and 2 refused treatment. Exclusion of minimally treated and untreated patients did not significantly alter the results.

Conventional criteria were used to ascertain the degree of response to treatment. For that purpose, reevaluation was done 1 mo after completion of induction treatment and included repeating tests where results had previously been positive. Patients were followed as necessary during treatment, at 3-mo and 6-mo intervals during the ensuing 2 and 5 yr, respectively, and once a year thereafter.

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Data Analysis

Data from assessment of conventional clinical, pathologic, and laboratory variables of Hodgkin's disease and from evaluation of the patients' cellular immunocompetence were analyzed to determine the prognostic value of each variable independently and in various combinations.

Discriminating variables determined and recorded prior to treatment included in the analysis are as follows: stage, ranked by severity (stages I, II, III, and IV); symptoms, present or absent; histopathology, ranked by severity: 1—lymphocyte predominant, 2—nodular sclerosing, 3—mixed cellularity, 4—lymphocyte depleted; skin test, positive or negative; sex, male or female; age, a continuous variable; lymphocyte count, a continuous variable; and immunocompetence.

The status of cellular immunocompetence was assessed before treatment by the profile of in vitro lymphocyte responses to a wide spectrum of PHA concentrations. Only 1 test of in vitro immunocompetence was performed before treatment on each individual patient. In order to preclude bias, results obtained were not interpreted but rather entered into the program as counts/minute (cpm) of tritiated thymidine incorporation into lymphocyte DNA at each level of PHA stimulation. While not a disease parameter, therapy was also entered in the analysis as 0—inadequate or no therapy, 1—radiotherapy, 2—chemotherapy, 3—combined modality; for the multiple regression analysis and logistic analysis therapy was treated as a categorical variable. The patient population spontaneously segregated into two groups based on the survival status: one group of patients who have shown a relapse-free survival of 72 mo or longer; the other group of patients who have died. Because most patients with such prolonged relapse-free survival are cured of their disease, and by virtue of the fact that all but three deceased patients have died of or with Hodgkin's disease, these two groups of patients are at opposite ends of the survival spectrum in the course of Hodgkin's disease. Such a clear-cut dichotomy maximizes group valuable risk factors. For this reason, one patient with relatively indolent disease alive at 112 mo after recurrences was excluded from the analysis. However, his inclusion did not alter the results significantly. Curves showing the probability of disease-free survival were calculated according to the Kaplan-Meier method and compared by the generalized Kruskal-Wallis test of Breslow. To ascertain the relative and combined influence of the variables on prognosis, discriminant analysis was performed using the minimum Wilks' Lambda stepwise method. The correlation between pairs of variables and between each variable and survival status was calculated by correlation coefficients. Sets of two and more variables with greatest discriminant value were developed by two methods: forward inclusion retaining in the equation selected variables as a basis of subsequent steps; and stepwise method of forward inclusion and backward elimination, which selects models with highest discriminant value without necessarily retaining the same variables from set to set. Subsequently, logistic analysis was used as a check on the results obtained by the multiple linear regression. The utility of the generated models was evaluated by comparing actual versus predicted group membership of each case using the derived function for each model tested. The generalizability of the derived models to future Hodgkin's populations was ascertained by weight correction of their multiple correlation coefficients according to sample size and number of predictors.

RESULTS

Survival Data

As of April 1, 1980, 17 patients (50%) have died with a median survival of 8.3 mo (18.5 mo if untreated and minimally treated patients are excluded). As shown in Table I and Fig. 1B, patients who died were mostly older, symptomatic individuals with more advanced disease of less favorable histopathology, with a higher incidence of anergy, a lower circulating lymphocyte count, and greater impairment of in vitro lymphocyte responsiveness to PHA stimulation than live patients. Seventeen patients (50%) are alive and in continuous complete remission 72–114 mo from diagnosis (median >83 mo). If the seven untreated or minimally treated patients are excluded, 63% of patients adequately treated remain alive and in relapse-free complete remission 6 yr or longer.

Survival probability curves for each variable are calculated according to the Kaplan-Meier method and compared by the generalized Kruskal-Wallis test of Breslow. Patient with clinical stage I who refused laparotomy and treatment. She died of Hodgkin's disease (documented at autopsy) 22 mo later.

Table 1. Characteristics of Our Hodgkin's Patient Population Distributed According to Survival Status

<table>
<thead>
<tr>
<th>Survival Status</th>
<th>Sex</th>
<th>Stage</th>
<th>Symptoms</th>
<th>Histopathology†</th>
<th>Skin Test‡</th>
<th>Therapy§</th>
<th>Survival Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFCR* (n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>M</td>
<td>F</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>11</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Median</td>
<td>27</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.43</td>
</tr>
<tr>
<td>Dead (n=17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td>11</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Median</td>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.12</td>
</tr>
</tbody>
</table>

All data presented as number and percent of patients in each subcategory (vertical columns), except age, LC, and survival time, which are expressed as median values in years, cells (x 10⁹/µl blood), and months, respectively.

*RFCR, relapse-free complete remission (>72 mo).
†LP, lymphocyte predominant; NS, nodular sclerosing; MC, mixed cellularity; LD, lymphocyte depleted.
‡P, positive, N, negative. Skin tests to a battery of recall antigens and dinitrochlorobenzene (see Ref. 12).
§LC, lymphocyte count (x 10⁹/µl blood).
CT, chemotherapy; RT, radiotherapy; CT/RT, combination chemotherapy plus radiotherapy; 0, minimal or no treatment.
*Patient with clinical stage I who refused laparotomy and treatment. She died of Hodgkin's disease (documented at autopsy) 22 mo later.
NORMALS \( (n=35) \)

HODGKIN'S \( (n=34) \)

RFCR \( (n=17) \)

DEAD \( (n=17) \)

Fig. 1. Profile of lymphocyte responses to a wide spectrum of PHA stimulation. The data are expressed as DNA synthesis/10^6 lymphocytes and plotted as mean ± SEM for each PHA concentration. Left panel (A) compares the lymphocyte response profile of all Hodgkin's patients with normal control subjects. Right panel (B) compares the response profiles of normal controls, patients alive, and in relapse-free complete remission for 72 mo or longer, and patients who have died. Significance of difference between patients and normal controls and between patient subgroups as indicated in the text.

presented in Figs. 2 and 3. The pairwise comparison showed no significant effect on survival by sex \( (p = 0.449) \), lymphocyte count \( (p = 0.259) \), and symptoms \( (p = 0.110) \), and only borderline by presence or absence of anergy \( (p = 0.057) \). In contrast, a significant effect on survival was shown by age \( (p = 0.001) \), stage IV (versus stage II, \( p = 0.020 \); versus stage III, \( p = 0.043 \)), and by lymphocyte predominant histologic type (versus mixed cellularity, \( p = 0.014 \); versus lymphocyte depleted, \( p = 0.025 \)). In addition, while not a disease parameter, adequate therapy had a marked effect on survival. Minimally treated or untreated patients fared significantly worse than patients treated adequately with either chemotherapy \( (p = 0.001) \), radiotherapy \( (p = 0.001) \), or with combined modality \( (p = 0.006) \).

Lymphocyte Responsiveness to PHA Stimulation According to Survival Status

As previously reported\(^{12}\) and as shown in Fig. 1A, the shape of the DNA synthesis curve from patients \( (n = 34) \) is at variance with that of normals. While the spontaneous DNA synthesis was not subnormal, Hodgkin's cells were relatively insensitive to low PHA concentrations, thus exhibiting subnormal responses to 1.6, 3.2, and 6.4 µg PHA-protein, but were capable of a normal response when maximally stimulated by 80 µg PHA-protein or more. When the patient population is divided according to survival status (Fig. 1B), differences in the profile of lymphocyte responses to PHA emerged between live and dead patients. While differences in response profile noted between live patients and controls were not statistically significant, dead patients exhibited significantly subnormal DNA
IMMUNOCOMPETENCE IN HODGKIN'S SURVIVAL

Table 2. Correlation With Survival Status of Individual Discriminator Variables

<table>
<thead>
<tr>
<th>Discriminator Variables</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy</td>
<td>0.553</td>
</tr>
<tr>
<td>Immunocompetence</td>
<td>0.537</td>
</tr>
<tr>
<td>Age</td>
<td>0.522</td>
</tr>
<tr>
<td>Histopathology</td>
<td>0.506</td>
</tr>
<tr>
<td>Symptoms</td>
<td>0.314</td>
</tr>
<tr>
<td>Skin test</td>
<td>0.303</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>0.285</td>
</tr>
<tr>
<td>Stage</td>
<td>0.259</td>
</tr>
<tr>
<td>Sex</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Discriminant Analysis

The relationship between pairs of variables and between each variable and survival status were calculated by correlation coefficients. Table 2 presents the correlation coefficient of each individual variable with the dependent variable survival status in a decreasing order of magnitude. While as expected, therapy is the most important factor in the eventual survival of Hodgkin’s patients ($R = 0.553$), immunocompetence exhibits the highest correlation with survival status ($R = 0.537$) of all disease risk factors followed in decreasing order of magnitude by age, histopathology, symptoms, skin test, lymphocyte count, and stage. Sex did not correlate with prognosis. Analysis of within-group correlations showed moderate correlation between stage and symptoms ($r = 0.546$), inverse correlation between stage and skin tests ($r = -0.417$), but no other interdependence of conventional disease risk factors. In contrast, correlations between immunocompetence and the clinicopathologic variables were as follows: histopathology $R = 0.658$, skin test $R = 0.643$, lymphocyte count $R = 0.632$, age $R = 0.514$, stage $R = 0.501$, symptoms $R = 0.401$, and sex $R = 0.343$. These correlations underscore the fact that much of the predictive value of each of these variables is contained within immunocompetence.

Optimal discriminator sets of two and more variables were derived by forward inclusion, taking therapy (the variable with highest correlation) or immunocompetence (the best correlated disease risk factor) as points of departure, retaining in the equation selected variables as a basis for subsequent steps; and by the stepwise method of forward inclusion with backward elimination. Both procedures yielded the same

†The maximum discriminant value of immunocompetence was obtained using the following formula: $[(0.000022512DPM_{PHA}) - (0.005478308DPM_{0PHA}) + (0.01409915DPM_{64PHA}) - (0.00895371DPM_{1PHA}) + (0.00540882DPM_{32PHA}) + (0.0005199015DPM_{64PHA})].$ However, as indicated previously, three weighting coefficients (for 0 PHA, 0.64 PHA, and 1.6 PHA) are largely redundant.
sequence of sets for each analysis with the same point of departure, and therefore the same correlation coefficients (Tables 3 and 4). A best subsets multiple linear regression showed each of the models to be maximal for the number of variables included. For comparison purposes, the discriminant power of the model, including stage, histopathology, and symptoms, was also obtained.

Inclusion or exclusion of therapy does not alter the fact that risk factors with greatest individual or combined correlation with survival status are immunocompetence, age, symptoms, and histopathology with little contribution derived from stage, sex, skin test, and lymphocyte count (Tables 3 and 4). Because of this and the fact that therapy is largely dependent on stage and symptoms (thus inclusion of therapy would underestimate their value), and because the purpose of our study is to evaluate the prognostic value of disease risk factors, therapy is not included in later analyses.

As shown in Table 3, set 9, combination of the three risk factors most relied upon in clinical practice resulted in a discriminant power (multiple \( r = 0.550 \)) only slightly greater than that of immunocompetence alone, but much lower than any set of 2 or more variables based on immunocompetence. One of the models (set 4, Table 3) is of particular interest because it contained most of the information in the least number of variables. This selected model included immunocompetence, the most discriminant disease risk factor; age and symptoms, the variables that most contributed to the model (\( p = 0.010 \) and 0.015, respectively); and histopathology. Histopathology was included because, although it did not significantly improve the model (\( p = 0.104 \), it is by necessity collected for disease diagnosis. Subsequent models are less desirable because stage did not contribute to the model (\( p = 0.159 \)) and is not “cost” free, and the remaining variables were also noncontributory (\( p \geq 0.448 \)). This selected model showed a correlation coefficient with survival status (\( R = 0.784 \)) considerably greater than that of stage, symptoms, and histopathology combined (\( R = 0.550 \)) and only slightly lower than that of all variables combined (\( R = 0.814 \), Table 3, set 8). Because the statistical evidence is not necessarily the most appropriate clinically, the models starting with variables easiest to evaluate (age, sex, symptoms) or necessary for diagnosis (lymph node biopsy), then adding those variables involving more work (blood and skin test), cost, or discomfort to the patient (staging work-up) were evaluated. The correlation coefficient of the model including age, sex, symptoms, histopathology, lymphocyte count, skin test was \( R = 0.687 \). Addition of immunocompetence followed by stage resulted in correlation coefficients of \( R = 0.786 \) (\( p \) of immunocompetence = 0.048), and \( R = 0.814 \) (\( p \) of stage = 0.116), respectively, whereas inverting the sequence generated \( R = 0.703 \) (\( p \) of stage = 0.290), and \( R = 0.814 \) (\( p \) of immunocompetence = 0.023), respectively. This approach shows that IC contributes significant information not contained in the other variables, whereas stage does not. A logistic analysis was done as a check on the results obtained by the discriminant analysis. As can be seen in Table 5, logistic regression included the same variables as the discriminant analysis in each of the optimal models up to and including the four variable models. The two methods differ in the order of variables to be included after histopathology, but for both methods additional variables beyond the three variable models did not make a statistically significant (\( p \leq 0.05 \)) contribution to the model.

The utility of individual variables and of the derived discriminant models was assessed by comparing predicted with actual group membership for each case and the percent of grouped cases correctly classified determined (Table 5). The logistic regression tended to classify more individuals correctly than did the discriminant analysis. Because the two methods gave such similar results, from this point on, results will be given in terms of the more familiar discriminant analysis model. Immunocompetence alone correctly classified 82.4% of the cases, the best score for a single variable, and better than stage, histopathology, and symptoms.
immunocompetence alone showed the highest predicted correlation ($\hat{R} = 0.45$) of any single variable. The selected four variables model was one of the most generalizable ($\hat{R} = 0.71$). Addition of variables to this model appreciably improved its actual correlation coefficient (Table 3), but not its generalizability (Table 5). This is not unexpected. As is always the case, addition of variables to a model results in higher correlations. However, the model with the highest correlation is not necessarily the most generalizable. The combination of stage, symptoms, and histopathology exhibited a lower predicted correlation ($\hat{R} = 0.51$) than any best set of two or more variables and is thus less generalizable than any immunocompetence-based model.

**Discussion**

The existence of a cellular immune defect in Hodgkin's disease manifested as cutaneous anergy, increased susceptibility to certain fungal infections, and impaired homograft rejection was recognized as early as in 1902. In recent years, more advanced techniques and a better understanding of the immune system have led to the identification of abnormalities in the number and function of immunoreactive cells and to the detection of blocking or inhibitory serum factors. While it is generally thought that these abnormalities are involved in the immunoincompetence of Hodgkin's disease, the nature and precise localization of the defect remain elusive and their pathogenetic and prognostic significance unresolved.

Using the profile of lymphocyte responsiveness to a wide range of PHA concentrations as a measure of immunocompetence, we previously demonstrated the presence of an underlying subtle defect in the majority of patients with Hodgkin's disease. We suggested that quantitative evaluation of immunocompetence might prove to be of clinical and prognostic value. The present study demonstrates the major influence of immunocompetence on prognosis and delineates generalizable discriminant functions of highly accurate prognostic value, based on this and other risk factors, not including stage.

Immunocompetence determined by the profile of lymphocyte responsiveness to a wide spectrum of mitogenic stimulation is shown to be a powerful disease risk factor that plays a pivotal role on survival. Other investigators have also addressed the question of the correlation between status of immunocompetence and prognosis. With few exceptions, most such studies in Hodgkin's disease have failed to demonstrate the prognostic value of in vivo or in vitro immune defects. At least three explanations can be found for this lack of correlation: (A) Studies conducted too early in the course of the disease preclude clear definition of survival subgroups. This is true in spite of the development of sophisticated immune evaluation techniques because of the parallel advancement in modern therapeutic approaches that have drastically altered the natural course of the disease and prolonged survival; (B) lack of specificity and sufficient sensitivity of tests generally used to determine the status of immunocompetence; (C) failure to recognize that proper evaluation of the prognostic value of a disease risk factor must exclude the contributing influence of concurrent factors at play. Indeed, most reports dealing with the study of immunocompetence in Hodgkin's disease have studied small groups of patients early in the course of their disease, using relatively insensitive techniques and unsophisticated analytical methodology, thus precluding recognition of its prognostic significance. As pointed out previously, single dose mitogenic stimulation uncovers functional lymphocyte defects in less

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**Table 5. Comparison Between Optimal Linear and Logistic Regression Models, Utility (Percent Correct Classified), and Generalization ($\hat{R}$)**

<table>
<thead>
<tr>
<th>Models</th>
<th>Sets of Variables</th>
<th>Logistic Regression</th>
<th>Linear Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - Immunocompetence</td>
<td></td>
<td>82.4%</td>
<td>82.4%</td>
</tr>
<tr>
<td>2 - Set 1 + age</td>
<td></td>
<td>85.3%</td>
<td>82.4%</td>
</tr>
<tr>
<td>3 - Set 2 + symptoms</td>
<td></td>
<td>91.2%</td>
<td>88.2%</td>
</tr>
<tr>
<td>4 - Set 3 + histopathology</td>
<td></td>
<td>97.1%</td>
<td>91.2%</td>
</tr>
<tr>
<td>5 - Set 4 + lymphocyte count</td>
<td></td>
<td>97.1%</td>
<td>91.2%</td>
</tr>
<tr>
<td>6 - Set 5 + sex</td>
<td></td>
<td>100.0%</td>
<td>91.2%</td>
</tr>
<tr>
<td>7 - Set 6 + stage</td>
<td></td>
<td>100.0%</td>
<td>91.2%</td>
</tr>
<tr>
<td>8 - Set 7 + skin test</td>
<td></td>
<td>100.0%</td>
<td>94.1%</td>
</tr>
<tr>
<td>9 - Stage + symptoms + histopathology</td>
<td></td>
<td>73.5%</td>
<td>70.6%</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The existence of a cellular immune defect in Hodgkin's disease manifested as cutaneous anergy, increased susceptibility to certain fungal infections, and impaired homograft rejection was recognized as early as in 1902. In recent years, more advanced techniques and a better understanding of the immune system have led to the identification of abnormalities in the number and function of immunoreactive cells and to the detection of blocking or inhibitory serum factors. While it is generally thought that these abnormalities are involved in the immunoincompetence of Hodgkin's disease, the nature and precise localization of the defect remain elusive and their pathogenetic and prognostic significance unresolved.

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than 40% of Hodgkin’s patients as compared to 74% by our more sensitive assay system. In addition, the prognostic value of presumed risk factors is often not elicited by common pairwise comparison as shown by the unrevealing results of the survival probability curves of Kaplan-Meier and by the Student’s t-test value of the lymphocyte response profile of live versus dead patients. In contrast, the discriminant prognostic power of the immune status and other risk factors, evaluated by multiple linear regression and logistic analysis at a time when patients expected to differ are segregated at both ends of the survival spectrum, maximizes the possibility of demonstrating the true discriminant power of disease variables, individually or in combination, and of defining real risk factors. While we did not attempt to evaluate the nature of the defect responsible for abnormal lymphocyte responsiveness, intrinsic effector lymphocyte defects, abnormalities in the number and function of immunoregulatory cells, and existence of blocking, cytotoxic, or inhibitory serum factors have all been incriminated in the immune defect of Hodgkin’s disease.

Discriminant functions with greater prognostic value than those derived from the combination stage—symptoms—histopathology can be obtained from immunocompetence-based models excluding stage. For more than a decade, the treatment of Hodgkin’s disease has rested on extensive clinical, surgical, and pathologic patient evaluation. This in turn was based on the recognition that extent of disease was the major determinant of survival, and the understanding that while localized disease could be eradicated with appropriate radiation therapy, advanced cases required combination chemotherapy for disease control. This approach led to such remarkable improvements in the prognosis of Hodgkin’s disease that factors formerly known to influence survival are no longer of prognostic significance. The initially recognized survival differences among stages I, II, and III, for example, are slowly disappearing, though stage IV clearly shows a less favorable prognosis. Likewise, survival differences observed in early series between nodular sclerosing and mixed cellularity histologic types are progressively diminishing. Because of the discomfort, risks, and cost of staging procedures, the increasing success of combination chemotherapy in eradicating advanced disease, and the hazard of secondary neoplasia and other complications of combined modality therapy, further improvements in survival and cure rates in this disease might rest not on more aggressive staging or treatment approaches but rather on delineation and reevaluation of risk factors and on the development of models with greater discriminant power, as shown in this article.

While the clinical advantages of highly discriminant models consisting of inexpensive and easily obtainable variables over the conventional stage-based triad is obvious, the validity of our data and their applicability can be challenged on the grounds of the size of our patient population and the possibility that discriminant functions derived from one group of patients might not be applicable to another. Although admittedly small, our patient population was comparable to larger series in conventional risk factor distribution, response to therapy, and survival. In addition, a recent report involving a large group of patients showed stage not to possess the greatest discriminant power of conventional variables, in agreement with our data. Confirmation of our data in large scale studies is certainly desirable. However, models containing immunocompetence were clearly more generalizable than the conventional stage-based triad. In fact, their predicted correlation with prognosis of future patient samples was only slightly less than their actual correlation with prognosis of the patient population studied. This suggests that the value of the formulation of models containing immunocompetence is not an artifact of this study but reflects the highly discriminant power of immunocompetence and that derived functions should be applicable to other samples of similar types of patients. The major advantage of a larger sample is that the actual prediction formula obtained would be more stable (although not necessarily more generalizable) for future samples, but the determination of which variables to be included should usually be carried out with a relatively small sample in order to avoid an unnecessary waste of resources.

Thus, we do not present the actual prediction formulas obtained from our sample nor do we advocate our in vitro assay system as the test that best reflects the complexities of the immunodeficiency of Hodgkin’s disease. However, our data show that the status of immunocompetence even assessed by a simple in vitro assay may be a pivotal risk factor and can thus be used as a basis for generating powerful discriminant models to predict Hodgkin’s survival. We believe that generalizable models using reliable measurements of immunocompetence and other relatively risk- and cost-free factors as illustrated in this report should provide a more discriminating basis for the evaluation, treatment selection, and for predicting prognosis of patients with Hodgkin’s disease.

Note added in proof: No deaths or relapses have occurred since April 1, 1980. Current median survival is 106 mo (range 95–137 mo).

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Survival in Hodgkin's disease: the role of immunocompetence and other major risk factors

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