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Predicting In-Hospital Outcome in HIV-Associated *Pneumocystis carinii* Pneumonia

Summary: *Pneumocystis carinii* pneumonia (PCP) in HIV-infected patients remains a life-threatening complication in the course of HIV infection. Despite effective treatment, mortality may still be as high as 10%. The identification of risk factors associated with a lethal outcome might be helpful as a guide to therapy for patients at risk and in the evaluation of new drugs with anti-pneumocystic activity. In a retrospective study 58 first episodes of HIV-associated PCP without prophylaxis were analyzed. Variables associated univariately with higher mortality were identified. A prognostic rule was established in a multivariate approach using canonical discriminant analysis. Cut-off values for parameters included were determined in order to allow a clinically applicable estimate of the individual risk. Variables associated with early mortality were hemoglobin, hematocrit, platelet count, albumin, total protein, γ-globulins, and AaDO₂. LDH values, percentage of neutrophils in the BAL, as well as the cellular immunologic state as indicated by CD4-cell count were not significantly associated with the outcome. The discriminant function yielded the best classification results with the inclusion of hemoglobin, albumin, and γ-globulins (overall accuracy 86%). Two or more of the following parameters were associated with a 14-fold increased risk of in-hospital mortality: hemoglobin less than 10 g/dl, albumin less than 3 g/dl, and γ-globulins less than 1.2 g/dl. This prognostic rule was 80% sensitive and 94% specific with a negative predictive value of 94%, yielding an overall accuracy of 91%. Patients with HIV-associated PCP with a positive prognostic rule have a 14-fold increased risk for in-hospital lethal outcome. This discriminant rule may be helpful in identifying patients at risk.

Introduction

*Pneumocystis carinii* pneumonia continues to contribute to considerable morbidity and mortality in HIV-infected patients [1,2]. This is especially true in patients with a previously unknown HIV-serostatus [3]. The analysis of prognostic variables might therefore be useful in identifying patients at increased risk of lethal outcome. Moreover, prognostic factors may be of value in the evaluation of new therapeutic approaches. A variety of prognostic factors including body mass index [4], AaDO₂ [4–9], lactate dehydrogenase [7,8,10–15], percentage of neutrophils in BAL [6,16], bilateral infiltrates [9], hemoglobin [8,17], albumin [4,10,14], and lymphocyte count [4,17] have been reported in univariate analyses so far. Although the mean values of these variables are sufficiently different in survivors and non-survivors to reach a statistically significant level, they invariably suffer from a considerable overlap and therefore do not predict individual outcome reliably.

In order to establish an easy to handle but powerful predictive tool for in-hospital individual outcome in HIV-associated PCP we performed a prognostic analysis in our population using a multivariate approach.

Patients and Methods

Case definition: The clinical records of 58 HIV-infected patients with the first episode of *P. carinii* pneumonia diagnosed at our institution from 1985 until 1992 were reviewed. A total of 78 cases was retrieved including 58 first episodes without any primary prophylaxis and no medication with known anti-pneumocystic activity. Patients without prophylaxis and episodes diagnosed after 1989 were cases who refused any prophylaxis (n=14), or who had previously unknown HIV-serostatus (n=3). Ten cases with recurrences and ten with breakthrough pneumonia during primary (n=7) and secondary (n=3) aerosolized pentamidine prophylaxis were excluded. All episodes were proven by bronchoalveolar lavage and a set of Giemsa and Grocott stains. HIV infection was proven by ELISA and Western blot technique. All patients belonging to the hemophiliac risk group were part of a group treated at the Bonn Hemophilic Center.

Data Collection: Epidemiological, clinical, laboratory, and microbiological data as well as clinical course and outcome were extracted manually, recorded on study forms and entered into a computerized data base. Eighty independent variables were tested in all. Laboratory variables were obtained within 24 h prior to the diagnosis of PCP. Results of lymphocyte immunophenotyping were recorded within 3 months prior to the diagnosis of PCP.

Statistical analysis: Descriptive statistics for continuous variables

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Figure 1: Kaplan-Meier plot of in-hospital mortality.

Figure 2: Boxplots of variables in the equation for canonical discriminant analysis. Box plots include the median and the 50% confidence intervals. Whiskers extend to the largest and smallest observation that are less than one inter quartile range from the end of the box. Outliers and extremes are not shown, but included in the computation.

Table 1: Age, body mass index (BMI), CD4 + cell counts and duration of symptoms prior to diagnosis in survivors and non-survivors.

<table>
<thead>
<tr>
<th></th>
<th>Survivors (n=48)</th>
<th>Non-survivors (n=10)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36.1±11.6</td>
<td>38.8±14.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.8±2.9</td>
<td>19.9±4.4</td>
<td>n.s.</td>
</tr>
<tr>
<td>CD4+ (cells/mm³)</td>
<td>44.4±49.1</td>
<td>66.3±92.9</td>
<td>n.s.</td>
</tr>
<tr>
<td>Duration of symptoms prior to diagnosis (days)</td>
<td>20.53±17.5</td>
<td>19.78±27.1</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

are expressed as mean ± standard deviation. Differences in mean values between risk groups were compared by Student’s t-test. Time-to-event distributions were calculated by standard Kaplan-Meier methods. Differences in mean values between survivors and non-survivors were assessed by a simple two-factorial analysis of variance (ANOVA) to correct for imbalance in sex distribution. Pearson’s correlation coefficients with one-sided p-values were used to minimize redundancy in variable sets prior to computing multivariate statistics. Fisher’s exact test was used to analyze contingency tables with groupings based on quantitative characteristics [18]. Discrimination between groups was based on canonical discriminant analysis with three variables [19]. A prognostic score was established by defining cut-off values and assigning one point for each parameter under this cut-off value. This hypothesis was tested by grouping cases with a prognostic score of two or more points against cases with less than two. Comparisons with an alpha error of less than 5% were regarded as significant. All statistics were computed on SPSS for Windows™ Software.

Results

Patient Population

Fifty-eight episodes of P. carinii pneumonia occurred in 53 male and five female patients. The population consisted of 34 hemophiliacs, 16 male homosexuals and three intravenous drug abusers (two female, one male). Two patients reported sexual contacts with prostitutes, one female had received a blood transfusion, and two did not belong to any apparent risk group (both female). Hemophiliacs were significantly younger than patients of other risk groups (33.5 ± 10.5 years vs 40.8 ± 13.1 years; p < 0.05). PCP was the first AIDS-defining manifestation in 45 patients; the second in 12, and the third in one of the total of 58. Preceding complications included Candida-esophagitis (three cases), Kaposi’s sarcoma (three), HIV-encephalopathy (two), as well as CMV-esophagitis, anal herpes simplex, cryptosporidiosis, disseminated tuberculosis, non-Hodgkin’s lymphoma, and progressive multifocal leukencephalopathy (one each). Other non-HIV-related diseases with prognostic implications included four cases of liver cirrhosis with underlying chronic aggressive hepatitis B (n=2), B and C, and B and D (one each).

Therapy

All patients were treated according to standard dosage recommendations for co-trimoxazole (n=54) and pentamidine (n=4). The first line therapy with co-trimoxazole was changed to pentamidine in three cases and to eflorentine in one because of treatment failure (n=2) and severe adverse effects of co-trimoxazole (n=2). Of these, one patient taking pentamidine (changed because of adverse effects) and one eflorentine (changed because of treatment failure) died. Corticosteroids were given in 41 cases (71%), including nine with lethal outcome (90%). They have been administered for symptomatic therapy of severe dyspnea since 1986, and regularly since 1990 in cases of mild to severe hypoxemia (pO₂ < 60 mmHg on indoor air). They were also given for therapy of allergic rashes. There were no significant differences in daily dosage for survivors and non-survivors. Three non-survivors received mechanical ventilation; no survivor did.