A New and Validated Clinical Prognostic Model (EPI) for Enteropathy-Associated T-cell Lymphoma

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Abstract

Purpose: Enteropathy-associated T-cell lymphoma (EATL) is a rare intestinal non–Hodgkin lymphoma with a poor, though variable prognosis. The International Prognostic Index (IPI) and the prognostic index for peripheral T-cell lymphoma (PIT) have limited predictive value for outcome of EATL. The purpose of this study was to develop and validate a prognostic model for EATL, which can identify high-risk patients who need more aggressive therapy.

Experimental Design: This retrospective multicenter study was based on 92 patients and included 45 patients diagnosed with EATL between 1999 and 2009 from the Netherlands and 47 patients from England and Scotland, diagnosed with EATL between 1994 and 1998. A new EATL prognostic index (EPI) was constructed using the RPART (recursive partitioning and regression trees) procedure. Validation was performed applying the bootstrap method.

Results: Three risk groups were distinguished (P < 0.0001): a high-risk group, characterized by the presence of B-symptoms [median overall survival (OS) of 2 months]; an intermediate-risk group, comprising patients without B-symptoms and an IPI score ≥ 2 (7 months); and a low-risk group, representing patients without B-symptoms and an IPI score of 0 to 1 (34 months). Internal validation showed stability of statistical significance and prognostic discrimination. In contrast with the IPI and PIT, the EPI better classified patients in risk groups according to their clinical outcome.

Conclusions: Our new, validated, prognostic model EPI accurately predicts survival outcome in EATL and may be used for patient selection for new therapeutic strategies and evaluation of clinical trials. Clin Cancer Res; 21(13); 2015 AACR.

Introduction

Enteropathy-associated T-cell lymphoma (EATL) is a rare extranodal T-cell non–Hodgkin lymphoma (NHL) that arises from intestinal intraepithelial T cells. EATL accounts for approximately 5% of all gastrointestinal lymphomas and has an estimated annual incidence of 0.3 to 1 per million people in Western countries (1, 2). Two types of EATL have been defined by the WHO Classification of tumors of hematopoietic and lymphoid tissues. EATL type I is a large-cell lymphoma, which is associated with celiac disease (CD) and represents 80% to 90% of the EATLs (3, 4). Sporadically, a monomorphic variant of EATL may occur (EATL type II) that has no known relation with CD and seems to represent a distinct disease entity (3–5).

CD is a common disease affecting approximately 0.5% to 1% of the Caucasian population. In individuals with CD, the ingestion of gluten leads to an immune-mediated enteropathy, resulting in chronic inflammation, villous atrophy, and malabsorption (6, 7). The only effective treatment is lifelong gluten withdrawal. Refractory celiac disease (RCD) is a condition in which refractoriness to the gluten-free diet exists and clinical symptoms and histologic abnormalities persist despite strict adherence to the diet. RCD can be subdivided into RCD type I, with phenotypically normal intraepithelial lymphocytes (IEL) and RCD type II, in which more than 20% to 25% of the IEL exhibit an aberrant phenotype (8–11). RCD type II is associated with a strongly increased risk of developing EATL (12).

Based on clinical presentation, CD-associated EATL (EATL type I) can be divided into two subgroups: primary and secondary EATL. Primary EATL develops without a preceding history of CD. The first presentation is often perforation or obstruction, which leads to diagnosis of both EATL and CD. In contrast, secondary EATL is diagnosed in patients with well-established CD or refractory CD. These patients deteriorate and eventually develop EATL (12–14). The current standard treatment strategy for EATL consists of a combination of surgery and high-dose chemotherapy followed by autologous stem cell transplantation (1,15–21). Despite this treatment, overall survival (OS) is poor with 2-year and 5-year survival rates of 20% to 30% and 10% to 20%, respectively.
Entopathy-associated T-cell lymphoma (EATL) is a rare intestinal non–Hodgkin lymphoma with a poor, although variable outcome. As the international prognostic index (IPI) and the prognostic index for peripheral T-cell lymphoma, unspecified (PIT) have limited predictive value for outcome of EATL, a prognostic model specifically for EATL is urgently needed. Therefore, we have developed and validated an EATL prognostic index (EPI), which consists of easily available clinical parameters. The model allows accurate stratification of patients in risk groups according to clinical outcome. Alternative treatments for EATL are evidently needed, and this proposed prognostic model may be used to select patients for new therapeutic strategies and evaluation of clinical trials.

Patients and Methods

This multicenter retrospective study included 94 patients. The study cohort comprised 47 patients diagnosed with EATL between 1999 and 2009 in 22 hospitals throughout the Netherlands and 47 patients from 28 hospitals in England and Scotland, diagnosed with EATL between 1994 and 1998. All data were treated according to the Declaration of Helsinki. Approval for the study was obtained from the Institutional Review Board of the VU University Medical Center.

Criteria for inclusion in this study were age older than 18 years, a histologically confirmed diagnosis of CD, and a histologic diagnosis of EATL according to the WHO classification of tumors of Hematopoietic and Lymphoid tissues confirmed by an expert hematopathologist (3). Patients with any other cause of death than EATL were excluded. Furthermore, patients with the sporadically occurring monomorphic variant EATL type II (n = 2, neither one had CD) or with insufficient data were excluded. Clinical data of 92 patients with CD-associated EATL were collected from the medical files. The phenotypes of the included EATLs were consistent with the phenotype of EATL type I (according to the WHO criteria), see Supplementary Table S1. Only data representing status at time of diagnosis but before onset of treatment were entered.

Staging was scored according to the modified Ann Arbor staging for extranodal lymphomas. Bone marrow involvement was determined using immunohistochemistry and by morphologic evaluation of the bone marrow samples. In addition to the factors of the IPI and the PIT, three clinical parameters were considered for inclusion in the prognostic model, based on their potential prognostic value for EATL: (i) presence of intestinal perforation at presentation, (ii) presence of B-symptoms, and (iii) clinical subgroup of EATL. Presence of intestinal perforation at presentation was included, as this factor was significantly associated with lower survival in a prospective study of 35 intestinal T-cell lymphomas (17). In addition, presence of B-symptoms, which has been associated with increased risk of death in primary intestinal NHLs was evaluated (34). B-symptoms were defined as the presence of fever [≥38°C (100.4°F)] and/or night sweats. Because severe weight loss was present in most of the cases due to the underlying malabsorption syndrome, this parameter was left out of consideration (35). Finally, clinical subgroup of EATL was incorporated, because a clinical history of celiac disease has been associated with reduced survival in patients with EATL (5). Patients were subdivided into the two subgroups of primary or secondary EATL, based on clinical presentation as previously described (12).

Patients received one of the following treatment strategies: (i) surgery alone, (ii) anthracycline-based chemotherapy in combination with surgery, (iii) anthracycline-based chemotherapy alone, and (iv) supportive or palliative care only. The anthracycline-based regimens applied were CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CHOP-c (CHOP combined with alemtuzumab, a monoclonal antibody targeting CD52 found on mature T cells), CNOP (cyclophosphamide, mitoxantrone, vincristine, prednisolone), VAP/BC (vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin), and CHVP/BV (cyclophosphamide, doxorubicin, teniposide, prednisolone, bleomycin, vincristine). Ten patients were treated with allogeneic or autologous stem cell transplantation as consolidation after surgery and/or anthracycline-based chemotherapy (18).

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS 20.0, SPSS Inc.). Differences between the Dutch and the U.K. cohort were evaluated with χ² and Fisher exact tests. OS was defined as time between date of diagnosis and date of death due to EATL or the last follow-up visit. The Kaplan–Meier
New Validated Prognostic Model for EATL

Table 1. Clinical characteristics of the 92 patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dutch cohort (n = 45, %)</th>
<th>U.K. cohort (n = 47, %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>16 (36)</td>
<td>26 (55)</td>
<td>0.057</td>
</tr>
<tr>
<td>&gt;60</td>
<td>29 (64)</td>
<td>21 (45)</td>
<td>0.307</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>24 (53)</td>
<td>30 (64)</td>
<td>0.038</td>
</tr>
<tr>
<td>Women</td>
<td>21 (47)</td>
<td>17 (36)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ann-Arbor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I–II</td>
<td>24 (63)</td>
<td>39 (83)</td>
<td>0.059</td>
</tr>
<tr>
<td>III–IV</td>
<td>14 (37)</td>
<td>8 (17)</td>
<td>0.593</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>16 (41)</td>
<td>4 (9)</td>
<td>0.097</td>
</tr>
<tr>
<td>2–4</td>
<td>23 (59)</td>
<td>41 (91)</td>
<td>0.316</td>
</tr>
<tr>
<td>Serum LDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>29 (67)</td>
<td>14 (61)</td>
<td>0.056</td>
</tr>
<tr>
<td>Higher than normal</td>
<td></td>
<td>14 (33)</td>
<td>0.306</td>
</tr>
<tr>
<td>Intestinal perforation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14 (32)</td>
<td>7 (15)</td>
<td>0.097</td>
</tr>
<tr>
<td>No</td>
<td>30 (68)</td>
<td>40 (85)</td>
<td>0.306</td>
</tr>
<tr>
<td>Subgroup</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary EATL</td>
<td>26 (58)</td>
<td>32 (68)</td>
<td>0.639</td>
</tr>
<tr>
<td>Secondary EATL</td>
<td>19 (42)</td>
<td>15 (32)</td>
<td>0.112</td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low/Intermediate-low</td>
<td></td>
<td>23 (62)</td>
<td>0.041</td>
</tr>
<tr>
<td>Intermediate-high/high</td>
<td></td>
<td>14 (38)</td>
<td>0.041</td>
</tr>
<tr>
<td>PIT</td>
<td>15 (58)</td>
<td>6 (33)</td>
<td>0.041</td>
</tr>
<tr>
<td>1–2</td>
<td>11 (42)</td>
<td>12 (67)</td>
<td>0.041</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline-based chemotherapy + surgery</td>
<td>12 (27)</td>
<td>23 (49)</td>
<td></td>
</tr>
<tr>
<td>Resection alone</td>
<td>12 (27)</td>
<td>14 (30)</td>
<td>0.041</td>
</tr>
<tr>
<td>Anthracycline-based chemotherapy + ASCT</td>
<td>6 (13)</td>
<td>4 (9)</td>
<td></td>
</tr>
<tr>
<td>Anthracycline-based chemotherapy alone</td>
<td>10 (22)</td>
<td>6 (13)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (11)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: N.A., not available.

method and log-rank tests were used to determine the univariate correlation between clinical features and OS.

Construction of the prognostic index was done using the recursive partitioning and regression tree method (RPART, version 3.1-53), which yields OS prognoses for distinct subgroups of patients (36). For combination models including IPI, or PIT with combinations of the additional three clinical parameters, all possible RPART survival trees were generated. For each model, the prediction error was estimated by the 10-fold cross-validation error. The best prediction model was defined as the least complex model whose cross-validation error was not more than one standard error above the minimum cross-validation error.

Internal validation was performed applying the bootstrap method, which allows resampling with replacement from the original population. RPART survival trees were generated using bootstrap re-samples. Patients were (re-)classified in risk groups and predictive accuracy of the EPI model was assessed.

For all analyses, P values ≤ 0.05 were considered statistically significant.

Results

Patient characteristics

The clinical data of the 92 patients included in the study are outlined in Table 1. Patients in the U.K. cohort were younger (median age 57 years) and had higher ECOG scores at time of diagnosis compared with patients from the Netherlands. The median age of the total group of patients at diagnosis was 62 years and the male sex was predominant (59%). Thirty-four cases (37%) presented as secondary EATL, indicating that only a minority of patients had a well-established history of (R)CD. In 10 of the 43 patients with available information of the Dutch cohort (23%), EATL was preceded by RCD type II. None of the patients had RCD type I, before EATL diagnosis. This information was not available for the U.K. cohort.

The primary localization of disease was the small intestine in 87 cases (96%). In 26 patients, the first presentation of the lymphoma was a small intestinal perforation (29%). Other common presenting symptoms were abdominal pain (75%), weight loss (60%), obstruction of the small intestine (21%), nausea/vomiting (27%), and diarrhea (24%). B-symptoms fever and/or night sweats were present in 21 patients (23%). In all patients with B-symptoms, septicemia could be ruled out by negative blood cultures, except for 1 patient. The majority of patients (76%) had a nonambulatory ECOG performance status score ≥ 2. At diagnosis, 74% of the patients were staged I or II according to the Ann-Arbor staging. Involvement of the bone marrow only occurred in four cases (7%).

IPI scoring was available of 55 cases; 33 patients (60%) had low or intermediate–low IPI scores, whereas 22 patients (40%) were categorized as intermediate–high or high risk. According to the PIT, 21 patients (48%) were classified as low or intermediate–low risk and 23 patients (52%) as intermediate–high or high risk.

Survival analysis

The OS rates of the Dutch and the U.K. cohort were almost similar, 5-year OS was 15% and 13%, respectively. Overall 2- and 5-year survival of the 92 EATL patients were 20% and 15%, respectively, the median OS was 7 months (Fig. 1). Most of the patients (66%) received anthracycline-containing treatment. Complete remission was achieved in 38 of the patients (41%), of whom 33 relapsed.

Clinical factors significantly associated with reduced survival in univariate analysis were ECOG performance status ≥2 (P = 0.001), Ann-Arbor stage >III (P = 0.011), bone marrow infiltration (P = 0.014), elevated serum concentration of LDH (P = 0.023), number of extranodal sites (P = 0.049), PIT (P = 0.009), and IPI (P = 0.001). The presence of the B-symptoms fever and/or night sweats was a strong adverse predictor for OS (P < 0.0001). Once these symptoms were present, OS was significantly reduced and no 2-year survival was observed, indicating that the presence of B-symptoms is a potent prognostic factor for identification of patients at high risk. The clinical subgroup of EATL, determined by the presence or absence of a preceding history of (refractory) celiac...
disease, showed borderline prognostic value in univariate analysis ($P = 0.060$). The presence of intestinal perforation was not associated with reduced survival outcome ($P = 0.171$).

**Prognostic index**

A new prognostic index was constructed using the RPART function in R. Several RPART trees were generated using as input all possible combinations of the IPI or PIT with the three clinical parameters. The best prognostic model was selected on the basis of having the lowest complexity (highest CP) among models with a low cross-validation error.

According to this best RPART model, we were able to compose a novel EPI that identified three groups of EATL patients with significantly different outcomes ($P < 0.0001$). The EPI comprised the IPI variables and the clinical parameter B-symptoms. The survival curves according to the new EPI are shown in Fig. 2A. The high-risk group represented patients with B-symptoms fever and/or night sweats. The median OS in this group was only 2 months, and no 2-years or 5-years survival was observed. The intermediate-risk group comprised patients with no B-symptoms and an IPI score of 2 or higher. In this intermediate-risk group, median OS was 7 months and 2- and 5-year OS were 20% and 10%, respectively. The low-risk group represented patients without B-symptoms and an IPI score of 0 or 1. The median OS in the low-risk group was 34 months, and 2- and 5-year OS of this group were 55% and 40%, respectively (Table 2).

The internal validation procedure by the bootstrap method demonstrated stability of statistical significance and prognostic discrimination (Supplementary Table S2, Figure 2B, $P < 0.0001$).

**Comparison with the IPI and the PIT**

The comparison of the EPI with the IPI and the PIT respectively, was performed in the same cohort of patients. According to the IPI, patients were distributed into four IPI risk groups with different survival outcomes (Fig. 3A, $P = 0.001$). However, the IPI did not discriminate well between the intermediate–low, intermediate–high, and high-risk groups ($P = 0.11$). As shown in Fig. 3B, the EPI was able to distinguish patients with these IPI risk groups, accurately ($P = 0.001$). The PIT also separated the patients into four risk groups with different survival outcomes (Fig. 3C, $P = 0.008$). Nevertheless, the PIT did not stratify patients efficiently into prognostic subgroups. The prognostic value of PIT was particularly limited for group 1 and group 2 ($P = 0.76$). The EPI was able to identify high-risk patients in these group 1 and group 2 patients according to the PIT ($P = 0.004$, see Fig. 3D). Thus, in contrast with the IPI and the PIT, the EPI categorized EATL patients in three risk groups with significantly different survival rates.

Based on the EPI, a classification tree for risk stratification of EATL patients was built (Fig. 4).

**Discussion**

OS in patients with EATL is poor, although clinical behavior and outcome varies widely (12,16,17,22). Prognostic markers that enable stratification of patients with EATL in different risk groups for therapy are therefore urgently needed. In the present study we have developed a prognostic model specifically for EATL (EPI) in a large group of 92 EATL patients from 50 institutions. According to the WHO classification, EATL type II occurs sporadically and is considered to be a different disease entity (3–5).
Therefore, EATL type II was excluded from our analyses. As a result, in contrast with other reported series, this study included a relatively homogeneous group of patients.

The 2- and 5-year OS rates in the present study were 20% and 15%, respectively. These survival rates were similar to those described in other studies (5,12, 16, 17, 19, 22).

In our analysis, Ann-Arbor stage, extranodal sites, bone marrow involvement, B-symptoms, and IPI were significant prognostic parameters for survival in univariate analysis. In agreement with the study of Delabie and colleagues, also LDH, ECOG score, and PIT were found to be prognostic, and no clear correlation between subgroup of EATL and OS was observed (5). Nevertheless, disease
stage and IPI were not predictive for OS in the study from the International Peripheral T-Cell Lymphoma Project. We did not find an association with perforation or obstruction, in contrast with the study by Daum and colleagues (17). In this prospective study of 35 intestinal non– Hodgkin T-cell lymphoma patients, no correlation was observed with performance status or clinical symptoms such as fever. However, both these studies were based on a less homogenous group of patients as they also included EATL type II and non-EATL intestinal T-cell lymphomas.

To obtain a simple and accurate index for EATL, we constructed a prognostic model specifically for EATL (EPI), which better classifies patients in risk groups according to their clinical outcome and significantly discriminates the survival outcome of these risk groups. The EPI has superior predictive capacity as compared with IPI and PIT. In agreement with the study by the International T-cell Lymphoma Project, we showed that the majority of patients despite their poor outcome were categorized in the low and intermediate–low risk groups according to IPI (5, 22). Furthermore, the IPI did not discriminate adequately between the intermediate and high-risk groups. The prognostic value of PIT was particularly insufficient for group 1 and group 2, as the PIT also stratified patients with a high risk in these groups. Similar to other studies, we found that bone marrow involvement occurred in only a few patients with EATL, suggesting that this PIT factor may be less important for prognosis (5). The addition of B-symptoms as a parameter in our EPI model resulted in an improved recognition of the patients with an extremely poor prognosis, whereas the patients with a remarkably favorable outcome could be identified by a recalibrated IPI. B-symptoms and the factors of the IPI are routinely used in clinical practice and therefore easily available.

We performed internal validation by the bootstrap method and could confirm a stable prognostic model. However, external validation on an independent data set is recommended to allow general application of the EPI as prognostic index.

The majority of patients with EATL were treated according to the current standards with surgery, high-dose chemotherapy and/or stem cell transplantation. Despite this intensive regimen, overall clinical outcome was still poor due to high complication rates and relapses. Therefore, alternative treatments are evidently needed, especially for the intermediate and high-risk groups of EATL patients. In recent studies by Sieniawski and colleagues, d’Amore and colleagues and Jantunen and colleagues, promising results were obtained with novel regimens of high-dose chemotherapy followed by autologous stem cell transplantation (1, 20, 21). Examples of alternative biologic therapies that are currently being evaluated in EATL include histone deacetylase (HDAC) inhibitors, the anti-CD52 antibody alemtuzumab and new agents such as brentuximab-vedotin and pralatrexate (www.clinicaltrials.gov). The EPI may be useful to identify and select patients for such intensive regimens.

Further research to identify tumor-specific biomarkers and pathogenetic mechanisms enabling more specific targeted therapies for EATL is necessary. Because the three identified risk groups presented with a different clinical course and outcome, different and unique pathogenetic pathways might play a role in each group. In future studies, other features based on molecular profile studies in combination with clinical prognostic factors should be incorporated into a multivariate analysis of survival to improve individual risk profiling of patients with EATL.

In conclusion, we propose a new validated prognostic model specifically for EATL that consists of easily available clinical parameters. Our EATL prognostic index accurately predicts survival outcome in EATL patients and better stratifies patients into prognostic subgroups compared with IPI and PIT. The EPI may be used to select patients for new therapeutic strategies and evaluation of clinical trials. The proposed model should be further validated in a prospective trial in the setting of the modern treatment era.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions


Development of methodology: L.R. de Baaij, S.A.G.M. Gillessen

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): L.R. de Baaij, J.M.W. van de Water, M.K. Sieniawski, M. Radersma, W.H.M. Verbeek, O.J. Visser, C.J.L.M. Meijer, C.J.J. Mulder, A.L. Lennard

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.R. de Baaij, J. Berkhof, J.J. Oudeijans, S.A.G.M. Gillessen


Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.R. de Baaij

Study supervision: S.A.G.M. Gillessen

Other (provision of background knowledge and experience and previous publications in this rare cohort of patients): C.J.J. Mulder, A.L. Lennard

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References


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