

Clinicopathologic Characteristics of Angioimmunoblastic T-Cell Lymphoma: Analysis of the International Peripheral T-Cell Lymphoma Project

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ABSTRACT

Purpose

The International Peripheral T-Cell Lymphoma Project was undertaken to better understand the subtypes of T-cell and natural killer (NK) –cell lymphomas.

Patients and Methods

Angioimmunoblastic T-cell lymphoma (AITL) was diagnosed according to the 2001 WHO criteria by a central review process consisting of panels of expert hematopathologists. Clinical, pathologic, immunophenotyping, treatment, and survival data were correlated.

Results

Of 1,314 patients, 243 (18.5%) were diagnosed with AITL. At presentation, generalized lymphadenopathy was noted in 76% of patients, and 89% had stages III to IV disease. Skin rash was observed in 21% of patients. Hemolytic anemia and hypergammaglobulinemia occurred in 13% and 30% of patients, respectively. Five-year overall and failure-free survivals were 33% and 18%, respectively. At presentation, prognostic models were evaluated, including the standard International Prognostic Index, which comprised the following factors: age \geq 60 years, stages III to IV disease, lactic dehydrogenase (LDH) $>$ normal, extranodal sites (ENSs) $>$ one, and performance status (PS) \geq 2; the Prognostic Index for Peripheral T-Cell Lymphoma, comprising: age \geq 60 years, PS \geq 2, LDH $>$ normal, and bone marrow involvement; and the alternative Prognostic Index for AITL (PIAI), comprising: age $>$ 60 years, PS \geq 2, ENSs $>$ one, B symptoms, and platelet count $<$ $150 \times 10^9/L$. The simplified PIAI had a low-risk group (zero to one factors), with 5-year survival of 44%, and a high-risk group (two to five factors), with 5-year survival of 24% ($P = .0065$).

Conclusion

AITL is a rare clinicopathologic entity characterized by an aggressive course and dismal outcome with current therapies.

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INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a rare subtype of peripheral T-cell lymphoma (PTCL), first described as a distinct clinicopathologic entity in the 1970s.^{1,2} AITL accounts for approximately 1% to 2% of non-Hodgkin's lymphoma and 15% to 20% of PTCL.³ The incidence of AITL is low, with only 0.05 new patient cases per 100,000 people in the United States, without sex predilection.^{3,4}

Typically, the architecture of the lymph node is effaced, with only a few benign follicles retained. A characteristic feature is extension of the infiltrate beyond the lymph node capsule, with a preserved and somewhat dilated subcapsular sinus. Between

the follicles, there is a proliferation of high endothelial venules. The neoplastic T cells are positive for CD2, CD3, CD4, CD10, CXCL-13, PD1, and often BCL-6.⁵⁻⁷ Scattered large immunoblastic cells with more basophilic cytoplasm frequently are CD20 positive, polytypic, and often Epstein Barr Virus (EBV) –encoded RNA (EBER) positive. Stains for follicular dendritic cells such as CD21 and CD23 typically show meshworks of follicular dendritic cells outside of the follicles and often around vessels.⁸ T-cell receptor gene rearrangements are negative in up to 30% of patients with AITL. Conversely, immunoglobulin gene rearrangement can be found in as many as 10% of patients with AITL, most likely representing expanded EBV-positive B-cell clones. The disease is frequently associated with

autoimmune phenomena, such as the presence of circulating immune complexes, cold agglutinins, hemolytic anemia, and rheumatoid factor and antismooth-muscle antibodies. Hypergammaglobulinemia is present in approximately 50% of patients, typically polyclonal.¹

Various treatment modalities have been employed, including steroids, cytotoxic chemotherapy, and immunomodulators.⁹⁻¹¹ The clinical course of AITL is aggressive, with a median survival of fewer than 3 years, regardless of type of treatment.^{12,13} The aim of the present study was to better characterize the diagnostic and clinical aspects of AITL in a large and representative series of patient cases confirmed by central expert pathology review. Herein, we present the findings for 243 patient cases of AITL from the International Peripheral T-Cell Lymphoma Project.¹⁴

PATIENTS AND METHODS

Twenty-two institutions in North America, Europe, and the Far East participated in the study (Appendix Table A1, online only). Approval for the study was obtained from the institutional review board at the coordinating center (University of Nebraska Medical Center, Omaha, NE) and at each participating center as per the institutional standard. Those selected for the study were previously untreated patients age \geq 19 years, with de novo PTCL or natural killer/T-cell lymphoma, excluding mycosis fungoides/Sézary syndrome, who first presented between January 1, 1990, and December 31, 2002. At each institution, the local pathologist reviewed the diagnostic pathology slides and reports for each patient case and recorded the results of local immunophenotypic, cytogenetic, and molecular studies. Clinical characteristics of the patients, including treatment data and follow-up information, were also required.

From each institution, phenotype datasheets, diagnostic slides, and tissue blocks were sent to one of five regional centers for review by an expert hematopathologist. These centers included Omaha, Nebraska (D.D.W.); Leeds, United Kingdom (K.A. MacLennan); Würzburg, Germany (T.R.); Bologna, Italy (S.A.P.); and Nagoya, Japan (S. Nakamura). A standard panel of immunostains was performed on each patient case, including CD20, CD2, CD3, CD4, CD5, CD8, CD30, CD56, TCR- β , TIA-1, Ki67, and in situ hybridization stains for EBERS. Other immunostains, polymerase chain reaction analyses, and fluorescence in situ hybridization cytogenetic studies were performed as needed, and all patients were diagnosed according to 2001 WHO classification criteria.¹⁵ The percentages of transformed tumor cells (blasts) and tumor cells expressing CD30 or Ki67 were estimated in each patient case, as were the percentages of tumor cells and background cells expressing either CD4 or CD8. The number of cells staining for EBERS was evaluated semiquantitatively by counting positive cells in the 10 most positive fields using a 10 \times ocular lens and 20 \times objective and calculating the average number per field (f): $0/f = 0$; $< 1/f = 1+$; 1 to $9/f = 2+$; 10 to $50/f = 3+$; and $> 50/f = 4+$.

At each center, the diagnostic slides for each patient case were classified independently by each expert according to WHO classification criteria. Initial diagnosis was based on examination of the hematoxylin and eosin- and/or Giemsa-stained slides, immunostains, and phenotype datasheets, but with only limited clinical information from the time of initial diagnosis, including biopsy site and site of the largest tumor mass (ie, diagnosis one). After recording this diagnosis, the expert was presented with the complete clinical datasheet, and a second diagnosis was rendered (ie, diagnosis two). The previous diagnosis could not be changed based on the clinical information subsequently revealed.

In addition to the independent diagnosis rendered by each of the four expert hematopathologists, a consensus diagnosis was also reached in each patient case. A consensus was considered to have been reached if at least three of the four experts on the panel agreed on the second diagnosis (diagnosis two). All patient cases without a consensus diagnosis and all unclassifiable cases were jointly reviewed on a multiheaded microscope and discussed by the four experts in a daily consensus conference, and an attempt was made to reach

a consensus diagnosis. If additional sections, immunostains, molecular or cytogenetic studies, or other information were required, a diagnostic algorithm was developed by the panel, and the additional materials were obtained.

The clinical information included coded patient and site identifiers, sex, ethnicity, date of birth, date and site of diagnostic biopsy, other sites of disease, and Ann Arbor stage. Additional data recorded included symptoms at diagnosis, site and diameter of the largest tumor mass, performance status (PS), and history of immunosuppressive therapy or immune system disorder. Laboratory data recorded included hemoglobin, platelet count, WBC count, presence of circulating lymphoma cells, and serologies for HIV and human T-cell leukemia virus 1. The serum lactate dehydrogenase (LDH), β_2 -microglobulin, and C-reactive protein levels, and the presence of hypercalcemia, hypogammaglobulinemia, hypergammaglobulinemia, monoclonal serum immunoglobulin, hemolytic anemia, and hemophagocytic syndrome, were recorded. Initial therapy and response; details of remission, progression, or relapse; and subsequent therapies, along with survival status and cause of death, were recorded.

Treatment outcome was determined by overall survival (OS) and failure-free survival (FFS). OS was defined as the time from diagnosis to death resulting from any cause, with surviving patient follow-up censored at the last contact date. FFS was defined as the time from diagnosis to first occurrence of progression, relapse after response, or death resulting from any cause. Follow-up of patients not experiencing any of these events was censored at the date of last contact. Estimates of OS and FFS distributions were calculated using the Kaplan-Meier method,¹⁶ and time-to-event distributions were compared using the log-rank test.¹⁷ For survival analysis, the International Prognostic Index (IPI)¹⁸ and Prognostic Index for PTCL, Unspecified (PIT),¹⁹ were evaluated. In addition, comparisons of clinical and prognostic factors were performed using the χ^2 or Fisher's exact test. Multivariate analysis was performed with a Cox hazards regression model using stepwise selection. All clinical and pathologic data were centrally analyzed at University of Nebraska Medical Center and presented and discussed at a consensus conference attended by all the investigators.

RESULTS

There were a total of 1,314 patient cases of PTCL, of which 243 (18.5%) were diagnosed as AITL. AITL was more frequent in Europe (28.7% of all PTCL), followed by Asia (17.9%) and North America (16.0%). As shown in Table 1, the median age was 65 years (range, 20 to 86 years), with a male-to-female ratio of 1:3. At presentation, generalized lymphadenopathy was noted in 76% of patients, and splenomegaly and hepatomegaly were present in 35% and 26% of patients, respectively. Overall, 89% of patients had advanced-stage disease by Ann Arbor classification. Extranodal disease was present in 27% of patients. Skin rash was observed in 21% of patients. Hemolytic anemia was seen in 13% of patients, and dysproteinemia represented by hypergammaglobulinemia occurred in 30%; among these, monoclonal serum immunoglobulin was observed in 10% of patients. Overall, 6% of patients were treated with immunosuppressive drugs for treatment of symptoms, mostly steroids, at the time of diagnosis. The IPI and PIT could be calculated in 222 (91%) and 233 (96%) patient cases, respectively.

Diagnostic Accuracy

Two diagnoses were made by each of the four expert hematopathologists in each patient case based mainly on histology, immunophenotype, and molecular genetic data (diagnosis one) and then with the additional complete clinical data (diagnosis two). The agreement of the experts on diagnosis two with consensus diagnosis of AITL was 81%. Change of a diagnosis of AITL (diagnosis one) to the correct

Table 1. Clinical Characteristics of Patients With AITL (N = 243)

Characteristic	No.	%
Age, years		
Median	65	
Range	20-86	
Male sex	137	56
ECOG PS ≥ 2	89 of 239	37
Stages III to IV	214 of 241	89
Extranodal sites \geq two	66	27
BM involvement	67 of 228	28
Systemic symptoms	168	69
Hemolytic anemia	32 of 205	13
Anemia	81 of 205	33
Platelet count $< 150,000/\text{cmm}$	60	25
Elevated LDH	146 of 223	60
Elevated β_2 -microglobulin	53 of 92	22
Elevated CRP	84 of 127	35
Hypercalcemia	3 of 184	1
Hypergammaglobulinemia	74 of 166	30
HTLV-1 positive	6 of 89	2
HIV positive	2 of 151	1
Immunosuppressive drugs	13 of 211	5
Immune system disorder	3 of 210	1
IPI ≥ 2	192 of 222	79
PIT ≥ 2	154 of 233	63

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; BM, bone marrow; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; HTLV-1, human T-cell lymphotropic virus type I; IPI, International Prognostic Index; LDH, lactic dehydrogenase; PIT, Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified.

(consensus) diagnosis after consideration of the clinical data occurred in only nine patient cases, whereas change of a diagnosis of other types of PTCL (diagnosis one) to the correct (consensus) diagnosis of AITL occurred in 17 patient cases.

Treatment and Outcome

Five-year OS for the entire group was 32%, and 5-year FFS was 18% (Fig 1). A majority of the patients (82%) received combination chemotherapy containing an anthracycline, whereas the rest received combination chemotherapy without an anthracycline (7%), single-agent therapy (5%) or no chemotherapy (6%). The decision of no

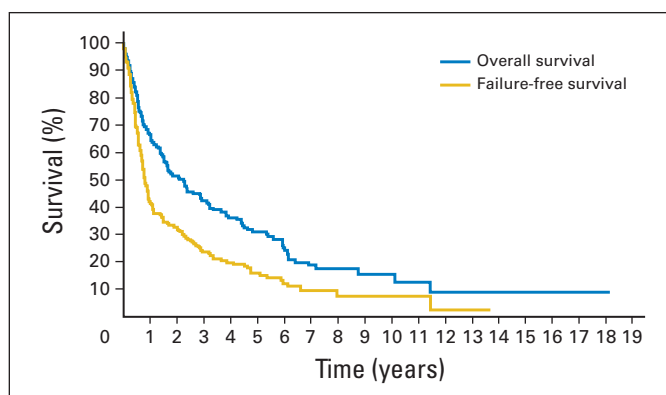


Fig 1. Overall and failure-free survival for 243 patients with angioimmunoblastic T-cell lymphoma.

initial treatment was mostly the result of advanced disease and poor PS. Autologous stem-cell transplantation (ASCT) was administered to 31 patients (17%) and was part of initial treatment in 15 (8%). The complete remission rate for those receiving an anthracycline-containing regimen was 61%. However, there was no survival advantage for patients receiving combination chemotherapy with an anthracycline when compared with those receiving combination chemotherapy without an anthracycline. At the close of the study, 66% of patients had died, and only 9% were in remission at the time of death.

Clinical Prognostic Factors

Of the prognostic factors in the IPI, only age > 60 years ($P = .04$), PS > 2 ($P = .002$), and extranodal sites (ENSs) $> one$ ($P = .012$) were predictive of OS (Fig 2A). For FFS, only PS > 2 ($P < .001$) was predictive (Fig 3A). Neither stage ($P = .60$ and $P = .68$) nor elevated serum LDH ($P = .56$ and $P = .55$) were predictive of OS or FFS, respectively. Therefore, the IPI was not a particularly good prognostic model for AITL. OS and FFS as predicted by PIT score (age ≥ 60 years, PS ≥ 2 , LDH $>$ normal, and bone marrow involvement) are shown in Figures 2B and 3B.

We also evaluated other potential prognostic factors, and the following were adverse predictors of OS and FFS, respectively: B symptoms ($P = .005$ and $P = .01$) and platelet count $< 150 \times 10^9/L$ ($P = .017$ and $P = .28$). Therefore, we constructed a new prognostic model similar to the IPI for AITL using the five significant prognostic factors: age > 60 years, PS > 2 , ENSs $> one$, B symptoms, and platelet count $< 150 \times 10^9/L$ (Figs 2C and 3C). A comparison of the three prognostic models (Table 2) revealed that the new prognostic index for AITL (PIAI) was more predictive of low- and high-risk subsets of patients with AITL.

The PIAI was also tested in an independent set of patients with AITL for validation. The GELA (Groupe d'Etude des Lymphomes de l'Adulte) group analyzed 157 patients from its previously published report on patients with AITL²⁰ using the PIAI prognostic model. In this independent validation cohort, low- versus high-risk PIAI maintained significance for OS and FFS (Figs 2D and 3D).

Pathologic Prognostic Factors

We also evaluated a variety of pathologic features as possible prognostic factors by univariate analysis, and the following were adverse predictors of OS and FFS, respectively: Ki67 proliferation $> 30\%$ ($P = .018$ and $P = .015$) and transformed tumor cells $> 20\%$ ($P = .025$ and $P = .094$). Pathologic features that were not predictive of survival were significant EBV infection (EBERs, three to ≥ 4), CD30 expression, and background CD8-positive T cells $> 10\%$. However, by stepwise multivariate analysis, when controlling for the IPI, neither Ki67 proliferation nor transformed tumor cells was an independent predictor of survival. When controlling for the PIAI, however, Ki67 proliferation $> 30\%$ was an independent predictor of survival, with a hazard ratio of 1.6 for OS ($P = .045$) and 1.6 for FFS ($P = .046$).

DISCUSSION

In our study, AITL mainly affected older individuals, with a median age of 65 years (range, 20 to 86 years), and most patients had advanced stage (89%, stages III to IV), systemic symptoms (69%), extranodal

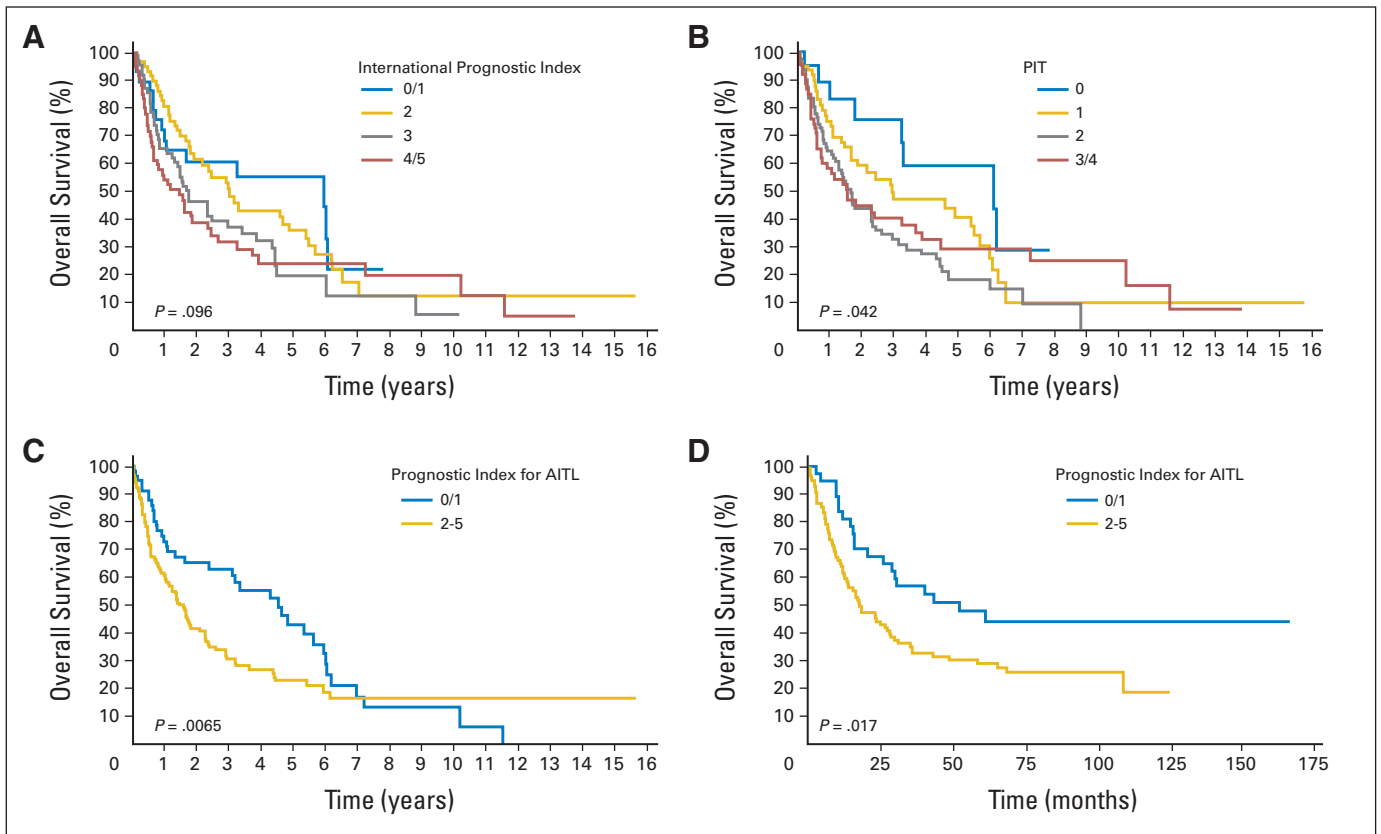


Fig 2. Overall survival (OS) for patients with angioimmunoblastic T-cell lymphoma (AITL) using the (A) International Prognostic Index, (B) Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified (PIT), and (C) Prognostic Index for AITL (PIAI); (D) OS for GELA (Groupe d'Etude des Lymphomes de l'Adulte) validation cohort using the PIAI.

involvement (27%), high IPI scores (79%, ≥ 2), elevated LDH (60%), and hypergammaglobulinemia (30%).

The centralized review of the diagnostic material by panels of expert hematopathologists, coupled with appropriate immunostains, permitted a consistent diagnosis and thereby successful validation of the 2001 WHO classification of this rare but distinct type of T-cell lymphoma. The agreement of the experts with the consensus diagnosis of AITL was 81%. Possible additional diagnostic markers such as CXCL13 or CD279 (PD1) may help to improve the accuracy and reproducibility of this diagnosis. The 28% of patients with large numbers of EBER-positive (three to \geq four) accompanying B cells in our study sample is comparable to the rate (19%) recently reported in patients with AITL treated within GELA trials.²⁰

So far, limited data are available on prognostic factors in AITL, yielding controversial results. Pangalis et al²¹ found that lymphocytopenia was more evident in patients who died as a result of AITL than in those who remained alive ($P = .089$). Aozasa et al²² suggested that the presence of clear and convoluted cells was predictive of poor prognosis. Moreover, achievement of complete remission is an important prognostic factor.^{23,24} The Kiel Lymphoma Study Group analyzed the prognostic impact of clinical observations and laboratory findings at presentation and found that survival was significantly related to age ($P = .032$), stage ($P = .037$), systemic symptoms ($P = .007$), skin rash/pruritus ($P = .038$), edema ($P = .030$), ascites ($P = .013$), high LDH ($P = .007$), and decreased hemoglobin ($P = .020$).⁹ Archimbaud et al²⁴ identified prognostic factors associated with shorter survival,

including rash ($P < .001$), lymph node eosinophilia ($P = .03$), elevated LDH ($P = .03$), and drug exposure in relation to the onset of the disease ($P = .02$); parameters associated with longer survival were localized lymphadenopathy ($P = .01$) and achievement of remission ($P < .001$). In our study, an alternative prognostic model for AITL was constructed using the five clinical prognostic factors: age > 60 years, PS ≥ 2 , ENSs > 1 , B symptoms, and platelet count $< 150 \times 10^9/L$.

We found an OS rate of only 33% at 5 years, which confirms the dismal outcome of AITL, despite the fact that most patients were treated with anthracycline-containing combination chemotherapy. Some patients (17%) also received high-dose chemotherapy (HDT) followed by ASCT. Our results are in agreement with the 5-year OS rate of 33% recently reported by GELA, which treated 157 patients in different clinical trials with intensive chemotherapy regimens, including some patients who also received consolidation with HDT plus ASCT.²⁰ The treatment regimens currently used in most patients with AITL do not result in long-lasting remissions. Thus, novel treatment approaches are warranted. Two recent studies regarding the role of HDT with ASCT are promising. In a study by Schetelig et al²⁵ of 29 patients, 76% experienced an adequate response, and the OS rate at 5 years was 44%. In a more recent large study of 146 patients treated by the European Group for Blood and Marrow Transplantation, an OS of 59% at 4 years was reported, with significantly better survival in those patients who underwent ASCT during first complete remission.²⁶ Additional studies to confirm the results of HDT with ASCT should be considered.²⁷

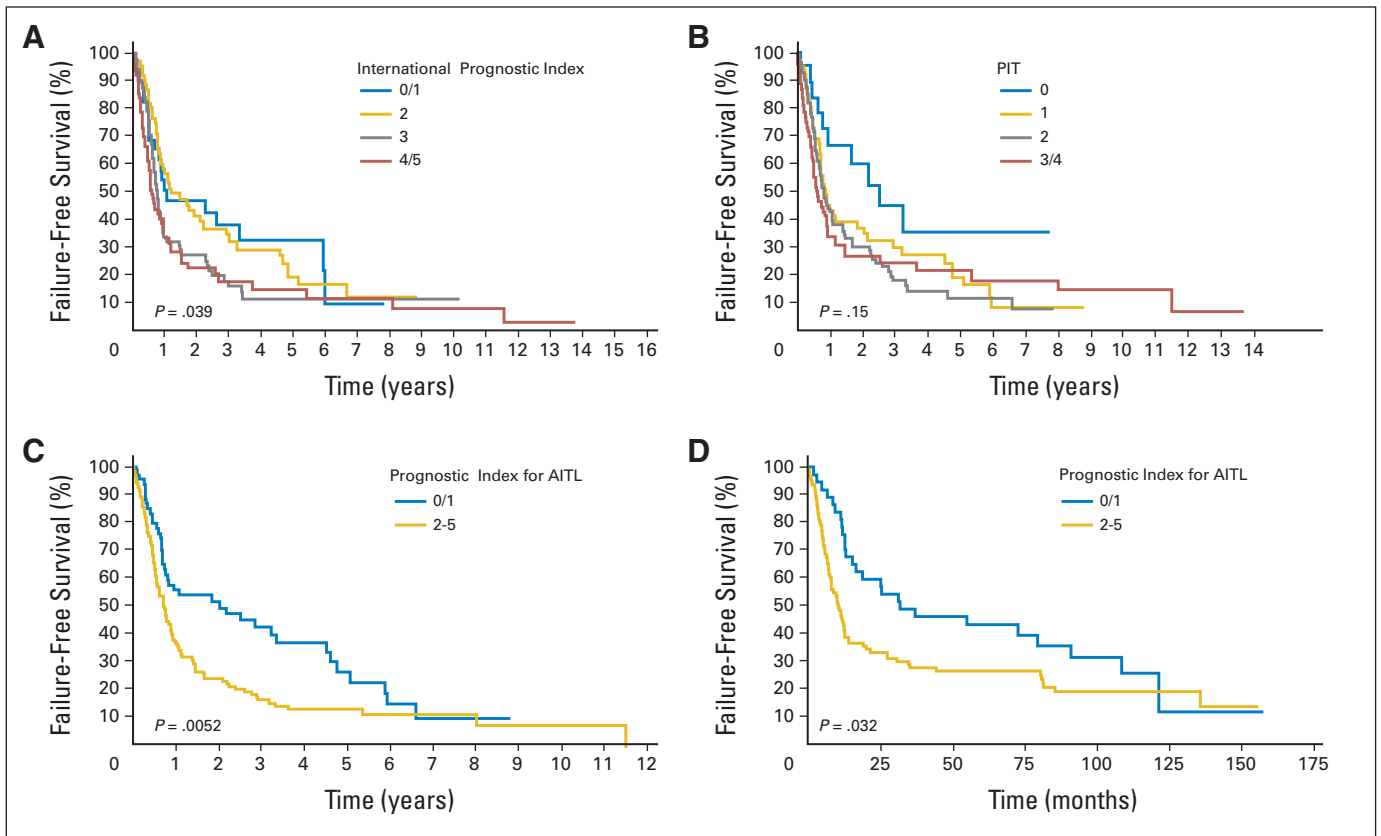


Fig 3. Failure-free survival (FFS) for patients with angioimmunoblastic T-cell lymphoma (AITL) using the (A) International Prognostic Index, (B) Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified (PIT), and (C) Prognostic Index for AITL (PIAI); (D) FFS for GELA (Groupe d'Etude des Lymphomes de l'Adulte) validation cohort using the PIAI.

In addition, new agents with activity against PTCL are currently undergoing further evaluation either alone or in combination. There are a number of histone deacetylase inhibitors with activity in T-cell lymphoma, including vorinostat, romidepsin, panbinostat, and belinostat. Vorinostat and romidepsin are US Food and Drug Administration (FDA) approved for cutaneous T-cell lymphoma, with

response rates in the range of 25% to 30%.^{28,29} A phase II trial of romidepsin for relapsed PTCL demonstrated a 29% overall response rate, which led to FDA approval.³⁰ Belinostat has also been studied in patients with PTCL, with an overall response rate of 32%, including two complete responses.³¹ Histone deacetylase inhibitors may have additive and/or synergistic activity with other agents, including topoisomerase inhibitors, bortezomib, and others.

Pralatrexate, a potent folate antagonist, is also currently FDA approved for relapsed PTCL. This agent is administered intravenously and also has an overall response rate of approximately 30%.³² An immunoconjugate, brentuximab vedotin (SGN-35), has demonstrated an 86% overall response rate and 53% complete response rate for patients with relapsed CD30-positive ALCL.³³ Further evaluation of agents directed at the immunosuppressive microenvironment in AITL is also an area of active research. Cyclosporine has been used in a small number of patients with AITL, with a 60% response rate.³⁴ This is now being tested in a larger clinical trial. Other immune modulation and antiangiogenic agents, including rituximab and lenalidomide, are also being explored as single or combination agents for AITL treatment.^{35,36} However, few patients with AITL have been enrolled onto any of these clinical trials, resulting in limited data.

In conclusion, given the rarity and poor outcome of AITL, more prospective clinical trials are required to understand the pathogenesis of this disease so that specific biologic targeted therapies can be developed. Our more specific prognostic model for patients with AITL may

No. of Risk Factors	Patients (%)	5-Year OS (%)	5-Year FFS (%)
IPI			
0/1	14	56	34
2	28	38	21
3	30	20	12
4/5	28	25	16
PIT			
0/1	36	46	22
2	37	19	12
3/4	27	30	22
PIAI			
0/1	30	44	28
2-5	70	24	15

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; FFS, failure-free survival; IPI, International Prognostic Index; PIAI, Prognostic Index for AITL; PIT, Prognostic Index for Peripheral T-Cell Lymphoma, Unspecified.

also improve our ability to identify patients for alternative therapies. Significant progress in the treatment of AITL can be expected in the future from the use of novel, sophisticated, and powerful technologies of genomics and proteomics.³⁷⁻³⁹

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Manuscript writing: All authors

Final approval of manuscript: All authors

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Appendix

Table A1. Participating Sites and Physicians During the Study

Participants
British Columbia Cancer Agency, Vancouver, British Columbia, Canada Kerry Savage, MD Joseph Connors, MD Randy Gascoyne, MD Mukesh Chhanabhai, MD
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University of Würzburg Hospital, Würzburg, Germany Thomas Rüdiger, MD
Institute of Pathology, University of Würzburg, Würzburg, Germany Konrad Müller-Hermelink, MD Peter Reimer, MD
Krankenhaus Munchen-Schwabing, Munchen, Germany Patrick Adam, MD Martin Wilhelm, MD Norbert Schmitz, MD Christoph Nerl, MD
Saint Bartholomew's Hospital, London, United Kingdom Andrew Lister, MD Andrew Norton, MD
St James Hospital, Leeds, United Kingdom Kenneth A. MacLennan, MD
University of Bologna Hospital, Bologna, Italy Pier Luigi Zinzani, MD Stefano A. Pileri, MD
(continued on following page)

Table A1. Participating Sites and Physicians During the Study (continued)

Participants
Intergruppo Italiano Linfomi, Bologna, Italy Massimo Federico, MD Monica Bellei, PhD Stefano Luminari, MD
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