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Development of a Novel Clinical Prognostic Model for Patients With Angioimmunoblastic T-Cell Lymphoma

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Abstract

In this study we aimed to identify a set of prognostic factors for angioimmunoblastic T-cell lymphoma (AITL) and establish a novel prognostic model. The clinical data of 64 AITL patients enrolled to the Fourth Hospital of Hebei Medical University (from 2012 Jan to 2017 May) were retrospectively analyzed. The estimated 5-year overall survival and progression-free survival of this cohort of patients were 45.8% and 30.8%, respectively. Univariate analysis showed that age > 60 years, performance status $\geq$2, Ann Arbor stage III/IV, lactate dehydrogenase > 250 U/L, serum albumin (ALB) < 30 g/l, Coombs test positive, and Ki-67 rate $\geq$ 70% were significantly associated with poor prognosis. Multivariate analysis demonstrated that age > 60 years, ALB < 30 g/l, Ki-67 rate $\geq$ 70%, and Coombs test positive were independent prognosis factors for AITL. Here a new prognostic model, named as AITLI, was constructed using the top 5 significant prognostic factors for AITL prognostic prediction. The AITL patients were stratified into 3 risk groups: low, intermediate, and high risk groups. The new prognostic model AITLI showed better performance in predicting prognosis than the International Prognostic Index (IPI) and the prognostic index for PTCL, not otherwise specified (PIT) that were wisely used to predict the outcome for patients with other subtypes of lymphoma.

Keywords

angioimmunoblastic T-cell lymphoma, clinical characteristics, prognosis factor, risk predicting, prognostic model

Abbreviations

AITL, angioimmunoblastic T-cell lymphoma; AITLI, AITL risk index; ALB, serum albumin; HR, hazard ratio; IPI, international prognostic index; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; OS, overall survival; OR, odd ratio; PFS, progression-free survival; PIT, prognostic index for unspecified; PS, performance status; PTCL, peripheral T-cell lymphomas; TFH, T follicular helper; WHO, World Health Organization; β2-MG, β2-microglobulin

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Introduction

Peripheral T-cell lymphoma (PTCL) is a rare but aggressive disease that presents in patients over the age of 60. Angioimmunoblastic T-cell lymphoma (AITL) is a fast-growing subtype of mature PTCL worldwide. AITL only accounts for 1.2% of all patients with non-Hodgkin lymphoma (NHL) and about 18.5% of patients with PTCL.[1] According to the 2017 World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues, the nodal PTCLs (n-PTCLs) include AITL, PTCL, not otherwise specified (PTCL-NOS), and anaplastic large T-cell lymphoma (ALCL). Recently, genetics analyses have demonstrated a T Follicular Helper (TFH) signature in AITL, suggesting AITL represents the prototype of TFH-derived lymphoma.[2] Moreover, some studies showed AITL with poor prognosis is characterized by

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overexpression of certain genes (i.e. IDH2, TET2, FYN, CD28, etc.).[3,4] AITL normally presents in elderly with a median age at diagnosis of 62 (range 59-65) years, and rarely under the age of 30 years.[5,6] Most of the cases were found in advanced phase at the time of diagnosis, with symptoms of fever, rash, bone marrow infiltration, anemia, and low albumin. Accompanying hemolysis and autoimmune diseases is more common than other subtypes of PTCL.[5,7]

Researchers have developed risk prediction and prognostic models to positively impact clinical decision making and subsequent patient outcomes of PTCL. The International Prognostic Index (IPI), that is based on age, performance status, lactate dehydrogenase (LDH), stage, and extranodal involvement, has been the basis for determining prognosis for PTCLs in clinical practice as well as research.[8,9] PTCL is composed of lymphoma subtypes with very high heterogeneity, making the IPI sometimes did not meet expectations for effective identification of distinct subtypes of PTCL. The Prognostic Index for PTCL-unspecified (PIT), which includes age, performance status, LDH, and bone marrow involvement, is a revised version of IPI mainly designed for PTCL-NOS. Up to now, there has been only a few studies specifically focused on the prognostic models for AITL patients.

In this study, we retrospectively investigated the prognostic significance of certain clinical factors of AITL patients who were treated with the intensive chemotherapy regimens known as CHOP and EPOCH (named by the initials of the drugs used in the treatment). Some patients received combination treatments including thalidomide or chidamide. Importantly, this newly developed prognostic model showed improved predicting performance as compared to IPI and PIT for AITL patients.

Materials and Methods

Patients

In total 64 patients with newly diagnosed AITL at the Fourth Hospital of Hebei Medical University from 2012 January to 2017 May were enrolled in the present study. The research protocol was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University, and performed in accordance with the principles of the Declaration of Helsinki. Written informed consents were obtained from all patients. The inclusion criteria were as follows: 1) all pathological specimens were subjected for lymph node biopsy to confirm the diagnosis of AITL according to the 2008 WHO lymphoma classification criteria; 2) only untreated patients were recruited; 3) no history of malignancy; 4) patients with a complete record of clinical data. All patients endured chemotherapy. The chemotherapy regimens given were as follows: 1) CHOP (cyclophosphamide, doxorubicin or epirubicin, vincristine, and prednisone); 2) EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). Among the total of 64 patients, 24 patients received combination treatment together with thalidomide (a synthetic glutamic acid derivative used as a sedative and antiemetic) while 5 patients received additional oral administration of chidamide (a selective oral inhibitor for histone deacetylase).

Clinical Laboratory Data

Clinical laboratory data during the course of clinical care was collected from our electronic medical records system using a database query tool. The prognostic factors evaluated in the present study included the sex, age, B symptoms, performance status (PS), Ki-67 index, extranodal involvement, serum albumin (ALB), lactate dehydrogenase (LDH), β2-microglobulin (β2-MG), Coombs, Ann Arbor stage (I/II versus III/IV), IPI, and PIT.

Statistical Analysis

The Overall Survival (OS) was defined as the time interval from diagnosis of AITL to death (regardless of cause). The Progression-free Survival (PFS) was defined as the time interval from diagnosis of AITL to disease progression or death from any cause. The 5-year survival rate was defined as the percentage of people in the group who are alive 5 years after they were diagnosed of AITL. Statistical analysis was performed using IBM SPSS Statistic v22.0 (SPSS Inc., Chicago, IL, USA). The OS and PFS were generated using Kaplan-Meier plots, while the survival between groups were compared using the log rank test. Cox proportional hazards regression was applied for univariate and multivariate analyses to evaluate the prognostic value of clinical factors associated with survival. A score N was provided for every prognostic factor based on its HR value from multivariate analysis, in order to calculate the Prognostic Index for AITL. The N of each factor was calculated as half value of the rounded down value of HR. For example, if HR = 3.2, then N = ½ × 3.0 = 1.5. To generate the AITL risk index (AITLI), the total AITLI score is the sum of each N of individual factors. The patients in the whole cohort were divided into 3 or 4 groups according to the cut-off values of IPI with Low (score: 0 or 1), Low-intermediate (score: 2), High-intermediate, (score: 3), High(score: 4 or 5), PIT with Group1 (score: 0), Group2 (score: 1), Group3 (score: 2), Group4 (score: 3 or 4), as well as Prognostic Index for AITL (2.5 and 4.5). The categorical variables were compared using the chi-square test. *P* value less than 0.05 was considered statistically significant and all *P* values presented were 2-tailed.

Result

Clinical Characteristics

The clinical features of 64 patients were summarized as showed in Table 1. The median age was 59.5 (range 32-78) years, and the male to female ratio was 1.1:1. About 52 (81%) patients were found with B symptoms, 37 (58%) patients with high LDH, 17 (27%) patients with PS > 1, 18 (28%) patients with extranodal involvement > 1, 20 (31%) patients with positive Coombs. Around 44 (69%) and 26 (41%) patients accompanied with high levels of β2-MG (>2.7ug/ml) and low levels

Table 1. Univariate and Multivariate Cox-Regression Analysis of Clinical Characteristics Correlated to Overall Survival.

			Univariate analysis		Multivariate analysis		
Characteristics		Total ($n = 64$)	χ^2	P value	HR (95% CI)	P value	Score
Sex	Male	34	1.827	0.177	-	-	0
	Female	30					
Age (y), Median 59.5 (range, 32-78)	≤ 60	34	8.616	0.003*	4.252 (1.576,11.47)	0.003*	2
	> 60	30					
B symptoms	Presence	52	0.475	0.491	-	-	0
	Absence	12					
Extranodal involvement	> 1 site	18	3.304	0.069	-	-	0
	≤ 1 site	46					
Ann Arbor stage	I/II	21	4.450	0.035*	2.112 (0.821,5.433)	0.121	1
	III/IV	43					
PS	< 2	47	5.552	0.018*	0.533 (0.208,1.369)	0.191	0
	≥ 2	17					
Ki-67 (%)	≥ 70	23	28.438	< 0.001*	2.548 (1.035,6.269)	0.042*	1
	< 70	41					
LDH	> 250U/L	27	4.639	0.031*	1.341 (0.58,3.098)	0.439	0
	≤ 250U/L	37					
ALB	≥ 30 g/l	38	17.840	< 0.001*	3.109 (1.381,7.002)	0.006*	1.5
	< 30 g/l	26					
Coombs test	Positive	20	14.637	< 0.001*	4.471 (1.936,10.328)	< 0.001*	2
	Negative	44					
Chemotherapy	CHOP	35	3.198	0.074	-	-	0
	EPOCH	29					
β2-MG	> 2.7 ug/ml	44	1.057	0.304	-	-	0
	≤ 2.7 ug/ml	20					

PS, performance status; LDH, lactate dehydrogenase; ALB, serum albumin;β2-MG, β2-microglobulin; χ^2, chi-square value; HR, hazard ratio; CI, confidence interval. *$P < 0.05$.

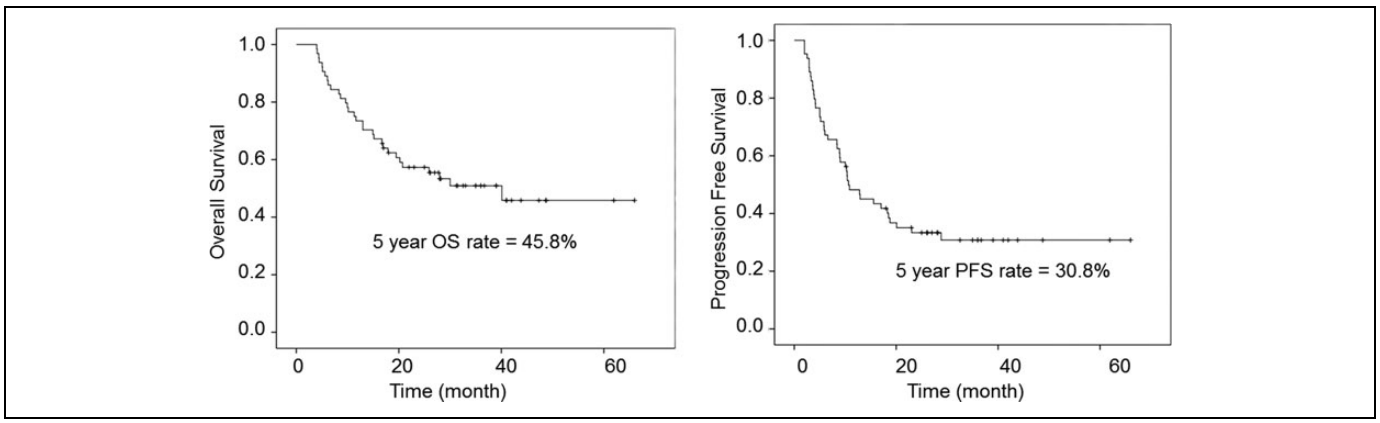

Figure 1. Kaplan-Meier curves with estimates of 5-year OS and PFS rates in AITL patients.

of ALB (<30 g/l), respectively. Additionally, high Ki67 index a (>70%) was found in 23 (36%) patients while Ann Arbor stage III-IV was seen in 43 (67%) patients. The patients were stratified into 4 risk-predicting groups by IPI value: 40.6% ($n = 26$) of patients in low group, 17.2% ($n = 11$) in low-intermediate group, 19% ($n = 12$) in high-intermediate group, and 23% ($n = 15$) in high group. According to the PIT value, the patients were divided into 4 groups: group 1 ($n = 14$), group 2 ($n = 20$), group 3 ($n = 19$), and group 4 ($n = 11$).

The Association of Clinical Characteristics With Survival Outcome

The median follow-up time was 35.0 months (range, 4 to 66 months). The average survival was 38.7 months (odds ratio [OR]: 3.529, 95%CI: 31.789-45.622). The 3-year OS and PFS rates in the whole cohort were 50.9% and 45% respectively. The Kaplan-Meier curve estimated 5-year OS and PFS rates as 45.8% and 30.8%, respectively (Figure 1). Univariate analysis

Table 2. Paired Comparison of Survival Outcomes Between 4 IPI Groups.

		Low		Low-intermediate		High-intermediate	
IPI groups	Total ($n = 64$)	χ^2	P value	χ^2	P value	χ^2	P value
Low	26	-	-	-	-	-	-
Low-intermediate	11	1.823	0.177	-	-	-	-
High-intermediate	12	8.493	0.004	1.388	0.239	-	-
High	15	13.545	< 0.001	3.134	0.077	0.368	0.544

IPI, International Prognostic Index; χ^2, chi-square value.

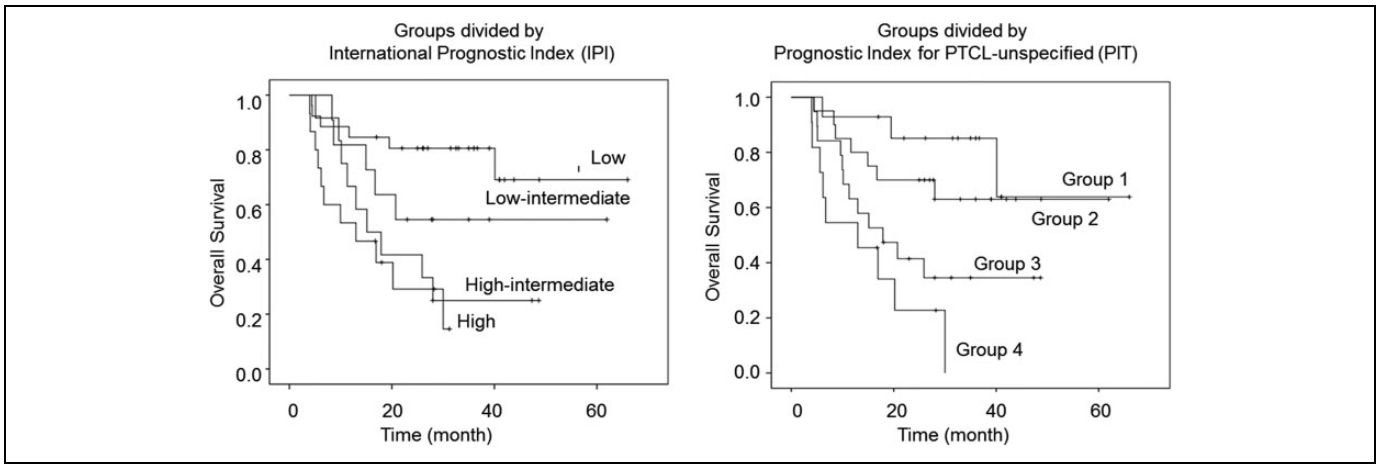

Figure 2. Kaplan-Meier curves with estimates of 5-year OS in AITL patients stratified by IPI or PIT.

Table 3. Paired Comparison of Survival Outcomes Between 4 PIT Groups.

		Group 1		Group 2		Group 3	
PIT groups	Total ($n = 64$)	χ^2	P value	χ^2	P value	χ^2	P value
Group 1	14	-	-	-	-	-	-
Group 2	20	0.846	0.358	-	-	-	-
Group 3	19	6.155	0.013	3.106	0.078	-	-
Group 4	11	13.981	0000	8.159	0.004	1.677	0.195

PIT, prognostic index for PTCL, unspecified; χ^2, chi-square value.

indicated the following variables were associated with poor survival: age > 60 years ($P = 0.003$), PS $\geq$ 2 ($P = 0.018$), Ann Arbor stage III/IV ($P = 0.035$), LDH > 250 U/L ($P = 0.031$), ALB < 30 g/l ($P < 0.001$), Coombs test positive ($P < 0.001$), and Ki-67 $\geq$ 70% ($P < 0.001$). Multivariate analysis showed that age > 60 years ($P = 0.003$), ALB < 30 g/l ($P = 0.006$), Ki-67 $\geq$ 70% ($P = 0.042$), and Coombs test positive ($P < 0.001$) were independent significant prognostic factor indicating poor survival of patients with AITL (Table 1).

Kaplan-Meier survival analysis as performed in the log rank test was constructed to determine if the survival outcomes were correlated with the prognostic indexing systems for AITL patients. Among the patient groups divided by IPI, only the OS of low-risk group was significantly different from the other 3 groups ($P < 0.05$), and there was no significant difference among the other groups ($P > 0.05$) (Table 2; Figure 2 left). Among the patient groups divided by PIT, the OS of group 1 was significantly different from the group 3 and 4 ($P < 0.05$), group 2 was significantly different from the group 4 ($P = 0.004$), while no significant difference was observed among the other groups ($P > 0.05$) (Table 3, Figure 2 right). These analyses suggested neither IPI nor PIT showed good prognostic performance for AITL patients.

According to the calculation method of AITLI score, the N scores for each factors were generated individually. For instance, 2 points were given to factors age (HR: 4.252) and Coombs (HR: 4.471); 1 point was given to Ki67 (HR: 2.548) and Ann Arbor stage III/IV (HR: 2.112); 1.5 point was given to ALB (HR: 3.109) (Table 1). Thus, the total AITLI score was calculated and ranged from 0 to 7.5 for this cohort of patients.

Table 4. Paired Comparison of Survival Outcomes Between AITL Groups.

PI-AITLI groups	Total ($n = 64$)	Low-risk (0-2.5)		Intermediate-risk (3-4)	
		χ^2	P value	χ^2	P value
low-risk (0-2.5)	26	-	-	-	-
Intermediate-risk (3-4)	11	12.346	< 0.001	-	-
High-risk (4.5-7.5)	15	38.553	< 0.001	6.688	0.010

AITLI, AITL risk index; χ^2, chi-square value.

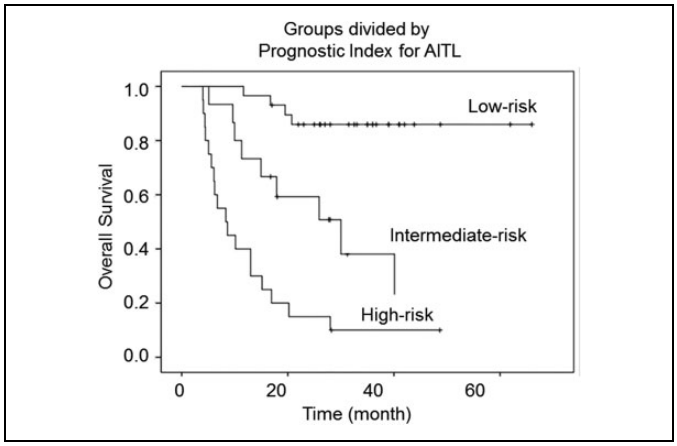

Figure 3. Kaplan-Meier curves with estimates of 5-year OS in AITL patients stratified by AITLI.

Then the patients were stratified into 3 risk groups based on their AITLI scores: low (score between 0 and 2.5), intermediate (score between 3 and 4), and high (score between 4.5 and 7.5). The 3-year OS of low-risk group, intermediate-risk group and high-risk group were 85.9%, 38.1%, and 10%, respectively. Statistically significant differences were found in pairwise survival comparison between these groups (all $P < 0.001$) (Table 4, Figure 3).

Discussion

In the 2016 revised WHO classification, AITL is a newly proposed entity grouped with nodal PTCL with a TFH phenotype.[10] Prognostic model that enable stratification of patients with AITL, but not other well-studied subtypes of PTCL, for decision making and treatment selection is urgently needed. In the present study a novel prognostic model is developed specifically for AITL in a large group of 64 patients. As a result, in contrast with other reported prognostic models such as IPI and PIT, this new index IATLI showed improved prognostic value and could be to stratify patients for risk-adapted therapies.

AITL is a rare subtype of malignant lymphoma which has unique clinicopathological features and biological behavior. The etiology and pathogenesis of this disease are not completely clear. Recent study indicated the median OS of AITL is less than 3 years, and the 5-year OS is only about 30%.[11] There is currently no standard treatment and prognostic factors. AITL is more common in elderly patients attributed to the age-related premalignant mutations.[12] To date, the largest study recruited 1207 AITL patients confirmed that age > 60 years, progressive stage, and male were adverse factors of prognosis.[13] Somatic mutations were detected in 95% of individuals aged between 50 and 60 years old.[14] A study named International Peripheral T-Cell Lymphoma Project investigated 243 AITL patients and found 76% of them were generalized lymphadenopathy and 89% of them had stages III to IV disease.[11]

The clinical characteristics of AITL in our current cohort were similar to those reported in previous studies. In our study, the median age was 59.5 years and the incidence of males and females is similar. Age was identified as a significant prognostic factor in our cohort but not the gender. In agree with the previous studies, we identified 67% patients with Ann Arbor stage III/IV had worse prognosis than the rest patients. AITL can progress rapidly and are extensively involved with extranodal organs. High level of ki-67 expression is commonly found in AITL patients with poor prognosis, but currently no standard cut-off value is provided.[8,9] A study conducted in Spanish National Cancer Research Centre showed only a high level of Ki-67 expression (more than 80% positive) indicated poor prognosis ($P = 0.022$).[15] In support with that, our univariate and multivariate analysis for survival both demonstrated that high Ki-67 rate significantly predicted bad prognosis. The cut-off value of Ki-67 rate used in our study was 70%.

At present, CHOP and CHOP-like regimens are still the most preferred treatments in regular clinical practice for AITL. After the initial treatment, both the remission rate and the recurrence rate are high.[16] Other additional treatment options include hematopoietic stem cell transplantation, targeted agents, and many new drugs. Maintenance therapy containing new drugs may effectively improve the prognosis.[17,18] In our study, all 64 patients were treated with CHOP or EPOCH regimens, or combination treatments involving Thalidomide or Chidamide. The 5-year OS rate in my study was slightly higher than the one reported by International Peripheral T-cell Lymphoma Project (45.8% *vs* 33%), which might benefit from the lower median age (59.5 *vs* 65 year), fewer extranodal disease (27% *vs* 18%), and better maintenance treatment with new drug.[11]

Various predicting modeling tools have been developed to identify clinical variables that are influential in predicting patient outcome. IPI is widely used in the evaluation of prognosis in patients with non-Hodgkin's lymphoma, while PIT is mainly used for the PTCL, unspecified. However, the use of these 2 prognostic models for AITL still remain controversial. Some studies suggested that both IPI and PIT were poor predictive factors of survival for AITL patients.[11,16,19-21] On the other hands, researchers such as Tokunaga et al. showed that IPI score showed certain predictive value on AITL patients.[22] Our study showed that neither IPI nor PIT could significantly predict the survival outcome difference between all risk groups, especially not between the high-intermediate and high

risk groups. Some literatures reported that male, mediastinal lymphadenopathy, anemia, age > 60 years, positive circulating epstein-barr virus (EBV) DNA, and extranodal involvement >1 were poor prognostic factors for AITL.[9,23,24] In our study, the univariate analysis showed that age > 60 years, PS $\geq$ 2, Ann Arbor stage III/IV, LDH > 250 U/L, ALB < 30 g/l, Coombs test positive, and Ki67 $\geq$ 70% indicated poor OS for AITL patients ($P < 0.05$). The multivariate analysis confirmed that factors such as age > 60 years, ALB < 30 g/l, Ki-67 $\geq$ 70%, and Coombs test positive were independent prognosis factors of AITL. We further developed a novel prognostic model, AITLI, including age, ALB, Ki67, Coombs, and Ann Arbor stage, which successfully stratified the prognosis of patients with AITL. The simplified prognostic index will need validation in other cohorts. Due to the relative small sample size, the impact of different treatment options on the prognosis of AILT patients were not fully investigated in the present study. Although it is a retrospective study and this novel prognostic model AILTI should be validated in future multi-center investigations, our novel findings could provide valuable information to optimize treatment strategies for AITL.

The molecular cytogenetic factors were also reported as prognostic factors in patients with lymphomas and the implication of molecular biology in the diagnosis of lymphomas is getting attention globally. Recent progress in next-generation sequencing has provided emerging evidence of characteristic genetic abnormalities in AITL. To date, the information provided by cytogenetics can only assist diagnosis finitely.[12] Given the genetic similarity of TFH to AITL cells, molecular signature of TFH cells may be associated with the biologic aspects of AITL and thus could be adopted in the newly developed AITL prognostic model in future.

No significant survival improvement was noticed for AITL patients over the past 2 decades despite all the new treatment options.[13] Here our study developed a new prognostic model which clearly defined risk groups in AITL patients and identified patients with relatively better prognosis, as compared to the existing prognostic models. Hence this novel prognostic model specially designed for AITL may facilitate risk-based stratification and therapy. The novel technologies of genomics and proteomics will be expected to become more accurate prognostic indicators and therapeutic targets. Therefore, we conclude that this novel prognostic model provided enough of a basis to warrant future analysis and will aid clinical decision making in clinical practice for AITL patients.

Authors' Note

Our study was approved by The Fourth Hospital of Hebei Medical University Ethics Committee (approval no. 2016MEC069). All patients provided written informed consent prior to enrollment in the study.

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Declaration of Conflicting Interests

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