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Clinical characteristics of angioimmunoblastic T-cell lymphoma in China and C-reactive protein as an independent prognostic factor

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is a major subtype of peripheral T-cell lymphoma (PTCL). Due to its low incidence, the characteristics of AITL are still not well understood. The prognostic evaluation of this disease has not been established.

We retrospectively analyzed 52 patients with newly diagnosed AITL in China between January 2008 and September 2016.

Among these patients, the median age at diagnosis was 62 (40–83) and 58% (30/52) of the patients were older than 60 years. Thirty-five patients were male, accounting for 67.3% of the whole. Among these, 90% (47/52) of the diagnoses were estimated at advanced stage. A total of 25 (48%) patients were scored >1 by the ECOG performance status. Systemic B symptoms were described in 34 (65%) patients. When evaluated by International Prognostic Index (IPI), 81% were scored >2, and 77% got >1 score according to the prognostic index for PTCL (PIT) upon diagnosis. The 3-year progression-free survival (PFS) was 44% and the 3-year overall survival (OS) rate was 52%. IPI and PIT scores could not be effectively applied to stratify those AITL patients into subgroups. Our multivariate analysis results found that the elevated serum C-reactive protein (CRP) level was an independent adverse factor to the OS of the AITL patients.

Patients with AITL had a poor outcome. The serum level of CRP may be applied as an independent prognostic factor for AITL.

Abbreviations: β_2-MG = β_2-microglobulin, AITL = angioimmunoblastic T-cell lymphoma, ANA = antinuclear antibody, ASCT = autologous stem cell transplantation, BM = bone marrow, CR = complete remission, CRP = C-reactive protein, CRu = unconfirmed complete remission, EBV = Epstein-Barr virus, ECOG = Eastern Cooperative Oncology Group, IL-6 = interleukin-6, IPI = International Prognostic Index, L-asp = L-asparaginase, LDH = lactate dehydrogenase, NHL = non-Hodgkin lymphoma, OS = overall survival, PFS = progression-free survival, PIT = the prognostic index for PTCL, PR = partial remission, ps = performance status, PTCL = peripheral T-cell lymphoma, TP = total protein, VP$_{16}$ = etoposide, WBC = white blood cells.

Keywords: angioimmunoblastic T-cell lymphoma, clinical characteristics, C-reactive protein, prognostic factor

1. Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a major subtype of peripheral T-cell lymphoma (PTCL), accounting for approximately 15% to 20% of PTCL.[1,2] The disease of AITL is mostly found in the elderly (>60) and shows male predominant.[2] Most of the patients are diagnosed at advanced-stage (III-IV) with the following symptoms: lymphadenopathy, hepatosplenomegaly, extranodal involvement, and B symptoms.[2–5] Several studies have reported 5-year overall survival (OS) rate of AITL patients ranging from 33% to 48% and 5-year progression-free survival (PFS) rate ranging from 18% to 25%.[2,4–7] The International Prognostic Index (IPI) and the prognostic index for PTCL (PIT), have been widely used in patients with various types of non-Hodgkin lymphoma (NHL). However, the application of IPI and PIT scores in AITL are still controversial.[2,6,8] Predictive models for AITL have not been established yet. Many clinical characteristics have been considered as important prognostic factors of AITL in different reports, such as anemia, thrombocytopenia, and more than 1 extra-nodal sites or bone marrow (BM) involvement.[5,6,9]

C-reactive protein (CRP) which is associated with interleukin-6 (IL-6) has been proven to play an important role in lymphoma. Many studies find that the serum CRP level is a prognostic factor in aggressive NHL and Hodgkin lymphoma.[10–12] In this study, we retrospectively analyzed the clinical characteristics of 52 patients with AITL in China and found serum CRP level played an important role in survival.

2. Materials and methods

2.1. Patient selection

This study retrospectively analyzed 52 newly diagnosed AITL patients at the First Affiliated Hospital of Zhejiang University from January 2008 to September 2016 and was permitted by the Ethics Committee of the First Affiliated Hospital of Zhejiang University. The diagnosis of AITL was established by the

histopathological and immunohistochemical report from at least 2 experienced hematopathologists according to 2001 or 2008 WHO criteria.

The study was mainly based on the clinical record of the patients, which included the medical history, physical examination, lab examination, and image examination. The lab examination included the complete blood counts, renal and liver function profiles, serum albumin, serum total protein (TP), lactate dehydrogenase (LDH), β_2-microglobulin (β_2-MG), serum CRP, BM biopsy, antinuclear antibody (ANA), Coombs test and plasma Epstein-Barr virus (EBV) DNA. The image examination mainly referred to the positron emission tomography/computed tomography (PET/CT) scan with the supplement of contrasted computerized tomography or ultrasonography. Ann Arbor classification was applied to stage the patients. And the Eastern Cooperative Oncology Group (ECOG) scale was used to evaluate the performance. IPI and PIT scores were applied to assign the risk stratification.[13,14]

2.2. Treatment and response evaluation

Among the 52 patients, 43 patients received chemotherapies, whereas 9 patients who refused chemotherapy were given supported therapies only. The responses of the treatments were defined according to the revised response criteria for malignant lymphoma, classified as complete remission (CR), unconfirmed complete remission (CRu), partial remission (PR), stable disease (SD) and progressive disease (PD).[15]

2.3. Statistical analysis

The primary endpoints of this study are PFS and OS. PFS was calculated from the date of diagnosis to the date of occurrence of progression, relapse, death as a result of any cause or the last date of follow-up. OS was defined as the time between the date of diagnosis to death or the last date of follow-up. The Kaplan-Meier method was used to estimate survival rates through log-rank test with R software with 95% confidence intervals (CIs). P values for progression or death were computed first in univariate analysis and then in the multivariate analysis using the Cox regression models for factors with P values less than .05. In all analyses, P values were 2-sided and $P < .05$ was considered statistically significant. The cutoff value was estimated by the receiver operating characteristic (ROC) method. All statistical analyses were performed by SPSS version 17.0 software (SPSS Inc) and R version 2.7 software (www.r-project.org).

3. Results

3.1. Clinical characteristics

Clinical characteristics of the patients are summarized in Table 1. The median age at diagnosis was 62 (40–83) and 58% (30/52) patients were older than 60 years. Thirty-five patients were male, accounting for 67.3% of the patients. Among the patients, 90% (47/52) of the diagnoses were estimated at advanced stage. A total of 25 (48%) patients were scored >1 by the ECOG performance status (ps). Systemic B symptoms were described in 34 (65%) patients. Anemia (hemoglobin < 120 g/L), thrombocytopenia (platelet counts $<150 \times 10^9$ L^{-1}), and leukocytosis (WBC $>10 \times 10^9$ L^{-1}) were observed in 73% (n=38), 53% (n=27), and 25% (n=13) patients, respectively. Serum LDH and β_2-MG level were found elevated in more than half of the patients. Hypoalbuminemia (albumin level < 35 mg/L) was found in 48%

Table 1

Clinical characteristics of AITL patients at diagnosis.

	Number (n/N)	Percent	Median of N (range)
Sex (male)	35/52	67%	
Age (>60)	30/52	58%	62 (40–83)
ECOG ps (>1)	25/52	48%	
Stage (III or IV)	47/52	90%	
Present of B symptoms	34/52	65%	
WBC counts (>10.0 × 10⁹ L⁻¹)	13/52	25%	$6.95 (1.7–20.7) \times 10^3$
Hemoglobin (<120 g/L)	38/52	73%	104 (53–154) g/L
Platelet counts (<150 × 10⁹ L⁻¹)	27/51	53%	145 (7–405) 10⁹/L
Serum LDH (>250 U/L)	39/52	75%	369 (148–2067) U/L
Serum β_2-MG (>2.3 mg/L)	28/36	78%	4.1 (1.29–28.17) mg/L
Serum albumin (<35 g/L)	23/48	48%	35.4 (22.7–48.2) g/L
Serum TP (<65 g/L)	18/48	38%	67.3 (40.7–102) g/L
CRP (>20 mg/L)	24/52	46%	16.5 (0.2–90) mg/L
ANA (positive)	7/30	23%	
Coombs test (positive)	3/9	33%	
Plasma EBV DNA (positive)	11/25	44%	
Extranodal involvement			
Hepatomegaly	6/52	12%	
Splenomegaly	25/52	48%	
Skin	15/52	29%	
BM	26/52	50%	
Nose and throat	5/52	10%	
Lung	2/52	4%	
Intestinal	2/52	4%	
Thyroid gland	1/52	2%	
Parotid gland	1/52	2%	
IPI score			
0/1	4/52	8%	
2	6/52	11%	
3	15/52	29%	
4/5	27/52	52%	
PIT score			
0/1	12/52	23%	
2	14/52	27%	
3/4	26/52	50%	

β_2-MG = β_2-microglobulin, AITL = angioimmunoblastic T-cell lymphoma, ANA = antinuclear antibody, BM = bone marrow, CRP = C-reactive protein, EBV = Epstein-Barr virus, ECOG = Eastern Cooperative Oncology Group, IPI = International Prognostic Index, LDH = lactate dehydrogenase, PIT = prognostication score system for PTCL, ps = performance status, TP = total protein, WBC = white blood cells.

patients. The median value of the serum CRP was 16.5 mg/L and the average was 25 mg/L (range: 0.2–90 mg/L). Besides, 46% (24/52) patients had a relatively high serum CRP level (>20 mg/L).

The most common extranodal site involved was BM (50%). Fifteen patients had skin lesions like rash, erythema, and so on. Other extranodal involved sites were uncommon, including nose and throat (n=5), lung (n=2), intestine (n=2), thyroid gland (n=1), and parotid gland (n=1). Eight patients had serous cavity effusion, such as pleural effusion, ascites, and pericardial effusion. Hepatomegaly (n=6, 12%) and splenomegaly (n=25, 48%) were common in AITL patients.

Patients were stratified into 4 risk subgroups by IPI score, in which 0 to 1 point were low risk (n=4), 2 points were low-intermediate risk (n=6), 3 points were high-intermediate risk (n=15), and 4 to 5 points were high risk (n=27). As for PIT score, 23% (n=12) were in low risk, 27% (n=14) were in intermediate risk, and 50% (n=26) were in high risk depending on the numbers of adverse prognostic factors (0–1, 2, 3–4). In total, 81% patients had IPI score >2 and 77% patients had a PIT score >1.
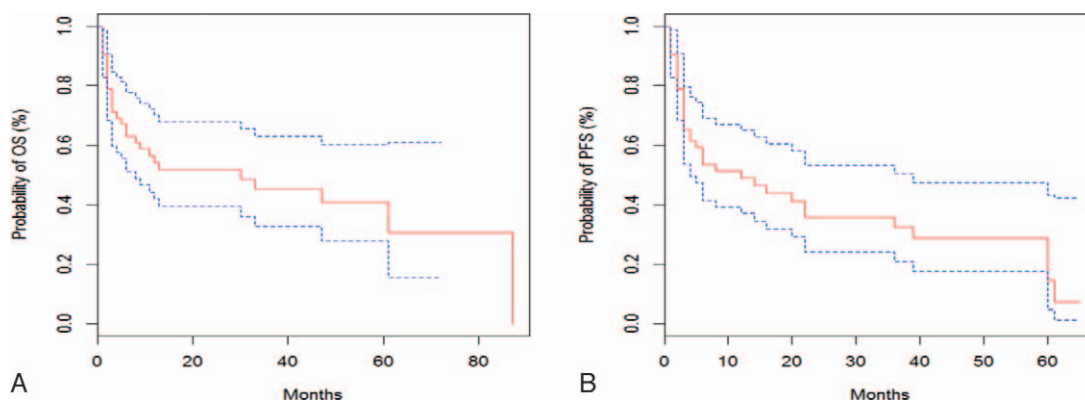
Figure 1. OS of patients with AITL is shown (A). PFS of patients with AITL is shown (B). The red line represents the estimated survival rate, and the blue lines represent the 95% upper and lower limited values of survival rates. OS = overall survival, PFS = progression-free survival.

3.2. Treatment and outcomes

The initial treatment received by AITL patients varied. Among 43 patents who received chemotherapy, CHOP regimen was chosen for most of the patients. Twenty patients received CHOP or mini CHOP regimen, and 17 other patients were treated with CHOP regimen combined with etoposide (VP_{16}) 75 mg/m^2 for 3 days or L-asparaginase (L-asp) 6000 U/m^2 for 3 to 5 days. The remaining 6 patients were given hyper-CVAD regimen. Seventeen (39.5%) patients achieved CR or CRu after the initial therapy, and 6 (12%) patients achieved PR. The second line or salvage chemotherapy regimen applied included MINE, GDP, Gemox, and SMILE. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) was performed in 2 young patients. Both patients achieved CR with hyper-CVAD chemotherapy and underwent ASCT as a consolidation of the first-line treatment.

The median follow-up time in surviving patients was 41.0 months (range 1–89 months). The 3-year OS rates were $52 \pm 7\%$ with a median OS time of 30 (0–63.5) months (Fig. 1A). The 3-year PFS rates were $44 \pm 7\%$ with a median PFS time of 12 (2.2–21.8) months (Fig. 1B).

We calculated OS and PFS curves by diving the patients into 2 groups according to the IPI score (<3 and ≥3) or PIT score (<2 and ≥2). Neither of them showed a significant difference. The OS rates of AITL patients who refused chemotherapy were significantly lower than those who received chemotherapy. Different chemotherapy regimens displayed no significant difference in OS (was not shown).

3.3. Prognostic factors

Analyses of prognostic factors were shown in Table 2. Univariate analysis suggested that ECOG ps (P=.029), WBC counts (P=.023), serum LDH (P=.023), and serum CRP (P=.011) might be prognostic factors (P<.05) for OS. Multivariate analysis identified ECOG ps (P=.04) and serum CRP (P=.045) as independent prognostic factors for OS.

3.4. Serum CRP analysis

The optimal cut-off points of CRP were identified based on ROC curves. The cut-off value was 20.35 mg/L, and the sensitivity and the specificity were 59% and 70%, respective. (See Figure, Supplemental Content, http://links.lww.com/MD/B883 which illustrates the optimal cut-off point of CRP was identified based on ROC curve).

Table 2

Prognostic factors for OS with univariate and multivariate analysis.

Variables	Univariate analysis		Multivariate analysis	
	P value	HR (95% CI)	P value	HR (95% CI)
Age	0.192	1.027 (0.987,1.07)	0.13	1.034 (0.99,1.081)
ECOG ps > 2	**0.029**	2.299 (1.089,4.855)	**0.04**	2.481 (1.042,5.904)
Stage > III	0.273	1.592 (0.693,3.656)		
B symptoms	0.302	1.542 (0.677,3.512)		
WBC counts	**0.023**	1.108 (1.014,1.211)	0.152	1.082 (0.971,1.204)
Hemoglobin	0.132	0.987 (0.971,1.004)		
Platelet counts	0.44	0.998 (0.993,1.003)		
Serum LDH	**0.023**	1.001 (1.000,1.002)	0.377	1 (0.999,1.001)
Serum β$_2$-MG	0.515	1.023 (0.955,1.097)		
Serum albumin	0.052	0.938 (0.878,1.001)	0.084	0.932 (0.861,1.009)
Serum TP	0.445	0.985 (0.949,1.023)		
Serum CRP	**0.011**	2.767 (1.26,6.077)	**0.045**	2.533 (1.022,6.274)
BM involvement	0.182	1.694 (0.781,3.675)	0.445	0.684 (0.257,1.816)

β$_2$-MG = β$_2$ microglobulin, BM = bone marrow, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, LDH = lactate dehydrogenase, OS = overall survival, ps = performance status, TP = total protein, WBC = white blood cells. Bold values signifies P value < 0.05.

As serum CRP was an important factor in our study, patients were divided into 2 groups according to CRP ≥20 mg/L and CRP <20 mg/L. Significant statistical difference in OS is shown in Figure 2 (**P=.009**).

Because of the limited number of patients and to avoid the bias, clinical features were compared between the 2 groups (CRP ≥20 mg/L and CRP <20 mg/L). No statistical difference was found except WBC count, which was admittedly associated with serum CRP (Table 3).

4. Discussion

AITL is a distinct subtype of PTCL with unique clinical manifestation, and the 5-year OS is quite poor (30–35%). Due to its low incidence, clinical characteristics and prognosis evaluation still cannot be well understood. Our study included 52 patients of AITL, which to our knowledge is the biggest serial in single center in China.

Clinical characteristics and outcomes of AITL in our study are similar to previous reports.[2,5,6,9] The results of our study are similar to the famous study in which 157 patients with AITL were treated within GELA trials[2]: the median of age (62–62), the percentage of male (67–60.5), the percentage of stage III or IV
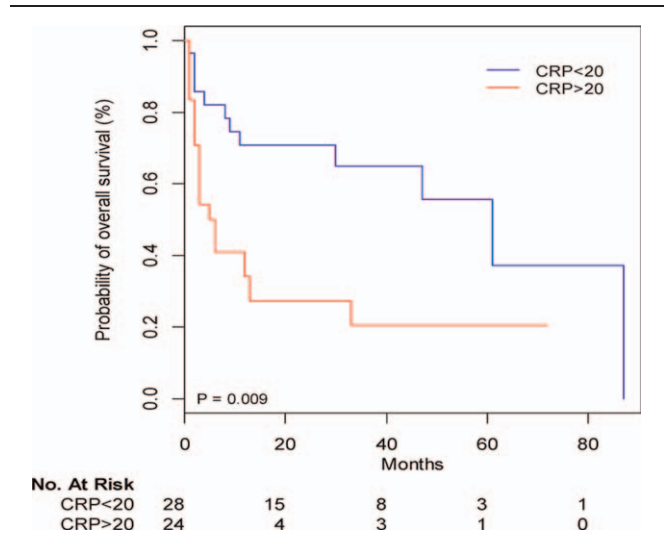

Figure 2. OS of patients with AITL are showed according to the serum CRP at presentation (P=.009). OS = overall survival.

Table 3

Clinical features compared with each other in 2 groups according to serum CRP at presentation (CRP <20 mg/L and CRP ≥20 mg/L).

	CPR <20 mg/L	CPR ≥20 mg/L	P values
n	28	24	
Sex=male n, %	20 (71.4)	15 (62.5)	.698
Age*	61.50 [56.00, 67.00]	64.00 [55.25, 71.25]	.43
ECOG ps n, %			.823
0	5 (17.9)	2 (8.3)	
1	11 (39.3)	9 (37.5)	
2	2 (7.1)	2 (8.3)	
3	9 (32.1)	9 (37.5)	
4	1 (3.6)	2 (8.3)	
Stage n, %			.457
I–II	4 (14.3)	1 (4.2)	
III	8 (28.6)	7 (29.2)	
IV	16 (57.1)	16 (66.7)	
WBC counts ($\times 10^9$ L^{-1}) *	5.80 [4.27, 7.78]	8.60 [6.35, 11.03]	.005
Hemoglobin, g/L*	104.50 [97.00, 124.00]	103.00 [86.53, 119.15]	.393
Platelet counts ($\times 10^9$ L^{-1}) *	145.50 [119.75, 198.25]	141.00 [113.00, 229.50]	.88
B symptoms positive n, %	15 (53.6)	19 (79.2)	.101
LDH, U/L*	349.00 [276.50, 402.50]	347.50 [263.75, 562.00]	.389
β_2-MG, mg/L*	3.40 [2.53, 4.81]	4.39 [3.00, 5.10]	.542
Serum albumin, g/L*	36.90 [32.45, 42.55]	33.70 [29.20, 37.40]	.081
Serum TP, g/L*	68.20 [63.30, 73.65]	66.20 [60.50, 70.60]	.412
CRP, mg/L*	8.00 [4.38, 10.95]	36.75 [29.10, 53.03]	<.001
BM involvement n, %	12 (42.9)	14 (60.9)	.318
IPI score n, %			.852
1	3 (10.7)	1 (4.2)	
2	3 (10.7)	3 (12.5)	
3	9 (32.1)	6 (25.0)	
4	9 (32.1)	10 (41.7)	
5	4 (14.3)	4 (16.7)	
PIT score n, %			.421
0	0 (0.0)	1 (4.2)	
1	8 (28.6)	3 (12.5)	
2	8 (28.6)	6 (25.0)	
3	8 (28.6)	11 (45.8)	
4	4 (14.3)	3 (12.5)	

β_2-MG = β_2 microglobulin, BM = bone marrow, CRP = C-reactive protein, ECOG = Eastern Cooperative Oncology Group, IPI = International Prognostic Index, LDH = lactate dehydrogenase, PIT = prognostication score system for PTCL, ps = performance status, TP = total protein, WBC = white blood cells.
* Median [25%–75% CI].

(90–80.8), the percentage of B symptoms (65–72.3), the percentage of BM involvement (50–47), the percentage of hemoglobin <120 g/L (73–65.2), the percentage of high serum LDH (75–67.1), the percentage of serum albumin level <35 g/L (48–49.7). The rates of IPI score ≥2 and PIT ≥2 score are both similar to the GELA trail (92–88.7% and 77–73.7%). Other important factors, such as serum CRP and ANA which are not described in GELA trails, are similar to another report by Tokunaga et al, a multicenter cooperative study in Japan with 207 patients.[6] Above all, most clinical characteristics of AITL in China show no difference compared with European and other Asian countries. What is different is that the incidence of platelet counts <150 × 10^9 L^−1 in our study (53%) is higher than the GELA trials report (27%) and the report by Tokunaga (34%).[6]

Refer to Tokunaga's study, 3-year OS rate and 3-year PFS rate are 54% and 38%, respectively. In our study, we identified the similar results. The 3-year OS rate is 52%, and the 3-year PFS rate is 44% in China. IPI and PIT scores are still controversial in stratifying the prognosis of AITL. Federico et al[5] in 2012 suggested a new predictive model for AITL (PIAI), using 5 significant prognostic factors: age, ECOG ps, more than 1 extra-nodal sites, B symptoms, and platelet counts. As the predictive models for AITL have not been established, some other reports propose new prognostic factors to design a more suitable prognosis predictive system. Our study finds that the serum CRP level is associated with OS in not only univariate analysis but also multivariate analysis.

Serum CRP is secreted by hepatocytes and promoted by several proinflammatory cytokines, including interleukin-1, tumor necrosis factor-1, and IL-6 which affect the survival, growth, proliferation, and the migration of tumor cells.[16–19] Therefore, elevated serum CRP levels may be a consequence of the change of tumor microenvironment. It has been reported that elevated CRP concentration has prognostic value in gastrointestinal, renal, breast, lung, and hepatocellular carcinoma.[20–25] Besides, IL-6 plays an important role in the pathogenesis of lymphoma and is considered as an independent indicator of long-term outcome in NHL.[26,27] Serum CRP which is associated with IL-6 may play an important role in lymphoma. More and more evidence prove that the serum CRP level is a prognostic factor in aggressive NHL and Hodgkin lymphoma.[10–12] Many reports showed that the Glasgow Prognostic Score, which consist of serum CRP and albumin, was a significant predictor of diffuse large B-cell lymphoma treated with R-CHOP.[28–31] Hanakawa H et al reported that CRP was a simple and independent prognostic factor in extranodal natural killer/T-cell lymphoma, nasal type, which is another subtype of PTCL.[32] Recently, Koyama et al reported that serum CRP was associated with OS in univariate analysis in 78 patients consisting of 39 patients of AITL and 39 patients of PTCL, NOS.[33] According to our study, we propose that serum CRP plays an important role in AITL and conducts as an independent prognostic factor.

Besides, the cutoff levels of CRP in various studies are different.[28–32] In our study, the median of CRP is 16.5 mg/L and the average CRP is 25 mg/L. We finally use ROC analysis to select the most discriminative cut-point as 20.35 mg/L. Therefore, we chose the level of 20 mg/L as cutoff value of CRP. The level of 20 mg/L for CRP was also selected as cutoff value in many previous reports.[6,30] It was shown that CRP >20 mg/L was a poor prognostic factor for 156 patients with diffuse large B-cell lymphoma treated with R-CHOP.[30]

Since serum CRP is an independent prognostic factor, the higher level of CRP means the poorer level of the prognosis.

Clinicians may adjust treatment plan according to the level of CRP. We assume that patients with significantly higher CRP at diagnosis except of obvious bacterial infections may be given intensive treatments to improve long-term survival. Further study which contain a large population and multicenter data are needed to confirm it.

5. Conclusions

In conclusion, AITL patients are always diagnosed with old age, advanced stage and the outcome is quite poor with relatively low rates of OS and PFS. IPI and PIT scores could not be effectively applied to stratify those AITL patients into subgroups. The serum CRP level is an independent prognostic factor for AITL. Because of the limitation of the small number of patients and the retrospective nature of the study, further study should be delivered to confirm.

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