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ORIGINAL ARTICLE

# Analysis of clinical characteristics and prognostic factors for angioimmunoblastic T-cell lymphoma

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**Abstract** Angioimmunoblastic T-cell lymphoma (AITL) is a distinct peripheral T-cell lymphoma entity exhibiting peculiar clinical features and poor prognosis. Its clinical characteristics and prognostic factors are not well established. To clarify the clinical characteristics and prognostic features of AITL, we conducted a multicenter, retrospective study. Fifty-six patients were enrolled. The median patient age was 68 years. Immunohistochemical examinations of tumor cells showed positivity for CD10 and T-cell markers, and chromosomal examination detected several types of abnormalities. More than 80 % of patients show advanced disease at diagnosis and poor prognostic scores. A high proportion of patients showed accompanying B symptoms, splenomegaly, and hepatomegaly at diagnosis. The 5-year overall survival (OS) rate was 48 % and progression-free survival was 25 %. Univariate analysis revealed higher age, fever, poor performance status, anemia, and low albumin level to be poor prognostic factors for OS. In addition to these factors, both IPI and PIT were also predictive of OS. Multivariate analysis indicated only a low level of serum albumin to be a significant prognostic factor for OS. Serum albumin may be one of the important prognostic factors for AITL. Further investigation is needed to confirm these results.

**Keywords** AITL · IPI · PIT · Prognostic factor

On behalf of the Tohoku Hematology Forum.

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## Introduction

Angioimmunoblastic T-cell lymphoma (AITL) is a rare subtype of peripheral T-cell lymphoma (PTCL) and accounts for approximately 1–2 % of non-Hodgkin's lymphoma and 15–20 % of PTCL. AITL generally occurs in elderly patients, and the median age of patients is greater than 60 years with male predominance [1, 2]. The neoplastic T cells are positive for CD2, CD3, CD4, CD10, CXCL-13 and PD1, indicating that AITL derives from a follicular helper T-cell subset [3–6]. T-cell receptor (TCR) gene rearrangements are positive in 80–90 % of patients with AITL, and immunoglobulin (Ig) gene rearrangement can be found in as many as 10 % of patients with AITL, most likely representing expanded Epstein–Barr virus (EBV)-positive B-cell clones [7]. AITL is frequently associated with autoimmune phenomena, such as the presence of hemolytic anemia, rheumatoid factor and several types of autoantibodies [8]. Polyclonal hypergammaglobulinemia is present in approximately half of the patients [8]. Various treatment modalities have been developed, including steroids, cytotoxic chemotherapy, and immunomodulators [9–11]. The clinical course of AITL is generally aggressive and shows poor prognosis, with a median survival of fewer than 3 years after conventional chemotherapies [12, 13]. The International Prognostic Index (IPI) and the prognostic model for peripheral T-cell lymphoma (PIT) are useful clinical tools for aggressive lymphoma and PTCL, respectively [14, 15]. However, IPI was not predictive of survival in AITL patients, and a high PIT score was not associated with a good outcome [1]. The identification of prognostic factors is important to establish an optimal treatment strategy for AITL. To characterize the clinical aspects of AITL and to clarify the prognostic factors of AITL, we conducted a multicenter trial in a retrospective series of Japanese patient cases. Herein, we present the findings for fifty-six AITL patients from the Tohoku Hematology Forum study group.

### Patients and methods

A total of 56 patients with confirmed diagnosis of AITL between January 2004 and November 2011 from 11 participating institutions in Japan were retrospectively analyzed. This study was registered with UMIN-CTR [http://www.umin.ac.jp/ctr/] with identification number UMIN000002743. Approval for the study protocol was obtained from the institutional review board in accordance with the Declaration of Helsinki at the coordinating center (Akita University, Akita, Japan), and at another participating ten centers, the approval of the institutional chief was obtained in accordance with the Ethical Guidelines For Epidemiological Research from the Ministry of Health, Labor and Welfare of Japan. The patients were diagnosed based on histopathological and immunohistochemical examinations according to 2001 or 2008 WHO criteria. Of all the patients, 47 cases (84 %) were diagnosed by an expert hematopathologist (R.I), and other typical cases were diagnosed by the local pathologist at each institution. The immunohistochemical results of CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD20, BCL6, presence of EBV-encoded small RNA (EBER) by in situ hybridization (ISH) and the presence of the rearrangement of immunoglobulin (Ig) and T-cell receptor (TCR) genes were collected from case report forms. The following clinical data were also recorded: age, sex, the presence of B symptoms, IPI score, PIT score, Ann Arbor stage at diagnosis, sites of extranodal involvement, laboratory data including positivity of Coombs test, complete blood counts, gamma globulins, lactate dehydrogenase (LDH), total protein, albumin, sIL2 receptor (sIL2R), β2-microglobulin and C-reactive protein (CRP) levels. Patients received treatment according to the respective institutional protocols, and the following treatment data were recorded: type of initial therapy, response and salvage therapy, date of initial therapy, response and salvage therapy, details of progression or relapse, survival status and cause of death. Response to treatment was assessed according to International Working Group criteria or revised response criteria [16, 17], and was recorded in terms of overall survival (OS) and progression-free survival (PFS). OS was defined as the time from diagnosis to death from any cause, with surviving patient follow-up censored at the last contact date. PFS was defined as the time from diagnosis to the first time of disease progression, relapse, death from any cause, with surviving patient follow-up censored at the last contact date. Estimates of OS and PFS distributions were calculated using the Kaplan–Meier method [18] and comparisons of clinical and prognostic factors were performed using the log-rank test [19]. Univariate and multivariate analyses were performed with a Cox hazards regression model using stepwise selection. The results are expressed as a hazard ratio (HR) and 95 % confidence interval (CI). All probability values were 2-sided and had an overall significance level of 0.05. All statistical analyses were performed using the SPSS software (version 11.0; SPSS Inc., Chicago, USA).

## Results

### Clinical characteristics of patients

Fifty-six patients who were treated between January 2004 and November 2011 were included in the study. As shown in Table 1, the median age was 68 years (range 21–86 years) with 75 % of patients being older than

**Table 1** Clinical characteristics of patients

| | *N* | % |
|---|---|---|
| No. of patients | 56 | 100 |
| Age, years | | |
| Median (range) | 68 (21–86) | |
| Older than 60 | 42 | 75 |
| Male sex | 35 | 63 |
| Performance status ≥2 | 27 | 48 |
| Stage III to IV | 54 | 96 |
| Presence of B symptoms | 35 | 63 |
| IPI score at diagnosis | | |
| 0–1 | 1 | 2 |
| 2 | 11 | 20 |
| 3 | 17 | 30 |
| 4–5 | 27 | 48 |
| PIT score at diagnosis | | |
| 0–1 | 11 | 20 |
| 2 | 19 | 34 |
| 3–4 | 26 | 46 |
| Lymphadenopathy | 56 | 100 |
| Extranodal involvement | | |
| Splenomegaly | 31 | 55 |
| Hepatomegaly | 20 | 36 |
| Mediastinum | 19 | 34 |
| Effusion/ascites | 19 | 34 |
| Bone marrow | 19 | 34 |
| Skin | 11 | 20 |
| Lung | 8 | 14 |
| Peripheral blood | 2 | 7 |
| Others[a] | 2 | 7 |
| WBC count >80 × $10^9$/L | 25 | 45 |
| WBC count <35 × $10^9$/L | 8 | 14 |
| Eosinophil count >5 × $10^9$/L | 9 of 54 | 17 |
| Anemia[b] | 36 | 66 |
| Platelet count <150 × $10^9$/L | 15 | 27 |
| Serum LDH level > ULN | 47 | 84 |
| Total protein level <7.0 g/dl | 25 of 54 | 46 |
| Serum albumin level< 3.5 g/dL | 22 of 50 | 44 |
| Serum CRP level >0.3 mg/dL | 48 of 52 | 92 |
| IgG level >1600 mg/dL | 27 of 48 | 56 |
| IgA level >350 mg/dL | 22 of 47 | 47 |
| IgM level >250 mg/dL | 16 of 47 | 34 |
| sIL2R level >530 U/ml | 53 of 53 | 100 |
| Positive Coombs test | 11 of 24 | 46 |
| Positive ANA | 7 of 17 | 41 |
| Immunohistochemical study[c] | | |
| CD3 | 51 of 54 | 98 |
| CD4 | 38 of 45 | 84 |
| CD5 | 40 of 42 | 95 |
| CD7 | 21 of 33 | 64 |
| CD8 | 9 of 37 | 24 |
| CD10 | 19 of 45 | 42 |
| EBER-ISH | 16 of 36 | 56 |
| IgH rearrangement[d] | 2 of 17 | 12 |
| TCR rearrangement[d] | 16 of 23 | 70 |

*IPI* International Prognostic Index, *PIT* prognostic index for peripheral T-cell lymphoma, Unspecified, *WBC* white blood cell, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *CRP* C-reactive protein, *sIL2R* soluble IL-2 receptor, *ANA* antinuclear antibody, *EBER-ISH* Epstein–Barr virus-encoded small RNA by in situ hybridization, *IgH* immunoglobulin heavy chain, *TCR* T-cell receptor

[a] One kidney and one parotid gland

[b] Anemia was defined as a hemoglobin level <130 g/L for men and <110 g/L for women

[c] Positivity for immunohistochemical examination of tumor cells

[d] Positivity for Southern blot analysis of the whole cells of lymph nodes

60 years. The female-to-male ratio was 1:1.7. Almost all patients (54/56; 96 %) presented with advanced-stage disease and B symptoms were observed in 63 %. The IPI score was more than 2 in 78 % of patients, and the PIT score was more than 1 in 80 % of patients. At diagnosis, lymphadenopathy was observed in all patients, and splenomegaly and hepatomegaly were present in 55 and 36 % of patients, respectively. Bone marrow infiltration and skin rash were observed in 34 and 20 % of patients, respectively. Laboratory investigations showed the presence of anemia in 66 %, thrombocytopenia in 27 %, elevated serum LDH level in 84 %, low total protein in 46 %, hypoalbuminemia in 44 %, elevated serum CRP level in 92 %, elevated sIL2R in 100 %, a positive Coombs test in 11 of 24 (46 %), and a positive antinuclear antibody (ANA) in 7 of 17 (41 %) patients. Hypergammaglobulinemia with elevated IgG, IgA, and IgM occurred in 56, 47, and 34 %, respectively.

## Immunophenotypical and biological characteristics

Immunohistochemical examinations of tumor cells showed that CD3 was positive in 98 %, CD4 in 84 %, CD5 in 95 %, CD7 in 64 %, CD8 in 24 %, and CD10 in 42 % of the examined cases. A total of 36 cases were studied for EBV using EBER-ISH, and 16 (56 %) contained varying numbers of EBER positive cells. Presence of the rearrangement of Ig and TCR genes by southern blot analysis was detected in 2 of 17 (12 %) and 16 of 23 (70 %) of the examined cases, respectively. Chromosomal abnormalities of the tumor cells including trisomy, monosomy, reciprocal translocation and deletion or addition of parts of chromosomes were detected (Table 2).

**Table 2** Chromosomal abnormalities observed in this study

| Chromosome number | Abnormalities observed |
|---|---|
| Chromosome 1 | add(1)(p36.1), del(1)(q42), inv(1)(p13q25) |
| Chromosome 2 | +2, t(2;6), inv2(q23;q31) |
| Chromosome 3 | +3, t(3;9), add(3)(p13) |
| Chromosome 4 | add(4)(q21) |
| Chromosome 5 | +5 |
| Chromosome 6 | −6, add(6)(q13) |
| Chromosome 8 | +8, t(8;15) |
| Chromosome 9 | +9, add(9)(p13) |
| Chromosome 10 | −10 |
| Chromosome 11 | add(11)(q23) |
| Chromosome 15 | −15 |
| Chromosome 17 | add(17)(p11.2) |
| Chromosome 18 | +18, dup(18)(q23;21) |
| Chromosome 21 | +21 |
| Chromosome 22 | +22, add(22)(q11.2) |

### Treatment and outcome

As their initial treatment, the majority of patients (95 %) received combination chemotherapy containing anthracycline, while the rest received combination chemotherapy without anthracycline in one patient (2 %) and immunosuppressive therapy with cyclosporine and prednisolone in two patients (3 %). High-dose chemotherapy with autologous stem cell transplantation (ASCT) was administered to four patients (7 %) and was part of the initial treatment in three patients (5 %). One patient (2 %) with refractory disease received allogeneic transplantation with a reduced-intensity conditioning. Twenty-seven of 56 patients (48 %) achieved CR or CR unconfirmed after initial therapy. The median follow-up time in surviving patients was 41.0 months (range 1.6–83.9 months). The 2- and 5-year OS rates were 73 and 48 %, respectively (Fig. 1a), and the 2- and 5-year PFS rates were 39 and 25 %, respectively (Fig. 1b). Both IPI and PIT were predictive of OS (IPI $P = 0.02$; PIT $P = 0.01$; Fig. 2a, b). Overall, there were 25 (45 %) deaths; patients died from lymphoma (38 %), or infection (6 %).

### Prognostic factors (Table 3)

On univariate analysis, five factors including age >60 years ($P = 0.019$), presence of fever ($P = 0.015$), PS >2 ($P = 0.0006$), presence of anemia ($P = 0.027$), and hypoalbuminemia ($P = 0.001$) were identified as poor prognostic factors for OS. On multivariate analysis, only hypoalbuminemia (HR 2.953; 95 % CI 1.090–8.001; $P = 0.033$) was identified as an independent prognostic factor for OS. In contrast, elevated serum LDH ($P = 0.048$) and elevated sIL2R ($P = 0.014$) were identified as poor prognostic factors for PFS according to univariate analysis. In addition to these two factors, PS >2 ($P = 0.09$) and serum albumin level ($P = 0.09$) were included in further analysis. On multivariate analysis, elevated serum LDH (HR 7.161; 95 % CI 1.407–36.451; $P = 0.018$) and elevated sIL2R (HR 2.478; 95 % CI 1.121–5.479; $P = 0.025$) were identified as independent prognostic factors for PFS.

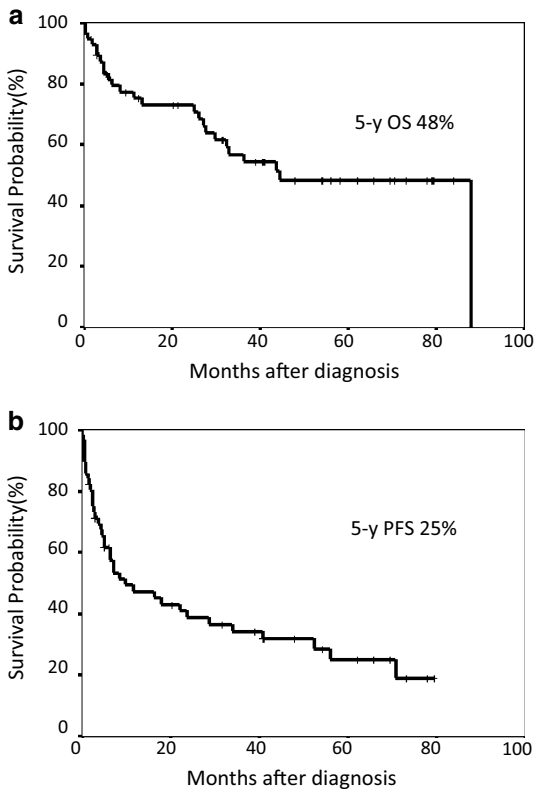


**Fig. 1** Survival of patients with angioimmunoblastic lymphoma. 5-year overall survival (**a**) and 5-year progression-free survival (**b**) are shown. 5y-OS 5-year overall survival, 5y-PFS 5-year progression-free survival

## Discussion

In the present study, we have shown the clinical characteristics and outcomes of patients with AITL. The molecular study of clonality analysis in this study showed the rearrangement of Ig and TCR genes in 2 of 17 (12 %) and 16 of 23 (70 %), respectively. The detection of rearrangement of TCR is positive in 80–90 % in previous studies.

In the previous study, the 5-year OS and PFS of patients with AITL were reported to be 30–40 % and 20–30 %, respectively [1, 20, 21]. Our results showed similar survival outcomes compared with previous studies (5-year OS 48 %, 5-year PFS 25 %). Investigation of the clinical characteristics of this study showed that most patients had

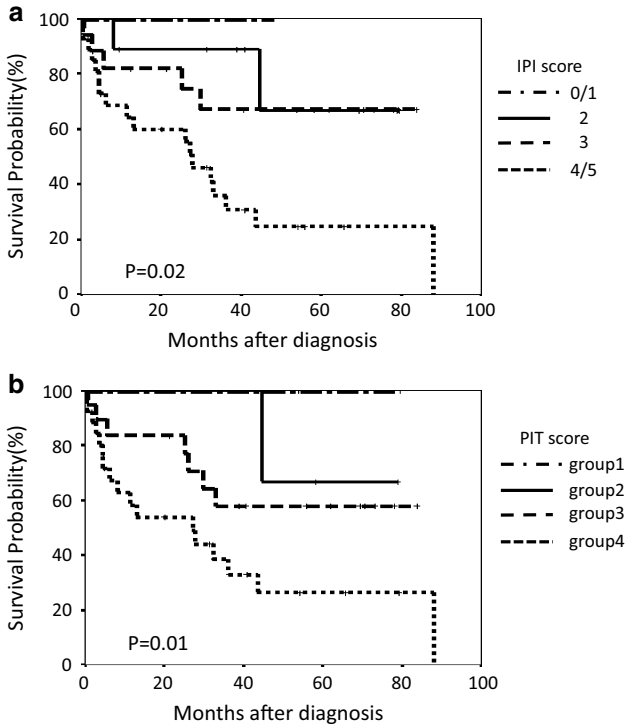


**Fig. 2** Overall survival (OS) of patients with angioimmunoblastic lymphoma according to **a** International Prognostic Index (IPI) and **b** Prognostic index for peripheral T-cell lymphoma, Unspecified (PIT) is shown

features known to be poor prognostic factors for other types of malignant lymphoma. AITL mainly affected elderly patients with a median age of 68 years (range 21–86 years). At presentation, 96 % of patients had advanced stage III to IV, 63 % of patients had B symptoms, 48 % of patients showed PS >2, and 84 % of patients had elevated serum LDH as reported in the previous study [21] except for PS. These clinical characteristics with aggressive behavior were similar to those in previous studies. Therefore, most of the patients had high scores of IPI (78 %, >2) and PIT (80 %, >1). In this study, both IPI and PIT could stratify the prognosis of AITL. However, previous attempts to apply IPI and PIT particularly to patients with AITL showed controversial results; the IPI failed to identify groups with different prognosis in AITL cases [2, 22]. Mourad et al. [1] and Federic et al. [7] also reported that IPI was not predictive of survival in a large Western AITL study. In contrast, a recent study from Japan by Tokunaga et al. [20] reported that IPI and PIT were useful to predict the prognosis, similar to the present study. One possible explanation for this controversy is that these studies used different treatments. In the studies from Japan including this study, almost all patients were treated with CHOP-like chemotherapy [20], on the other hand, in GELA study, the young patients were treated with more intensive chemotherapy (ACVBP or mBACOD) [1]. Another potential reason is that the prognosis of AITL differs depending on the geographic distribution. Other plausible reason is that AITL patients demonstrate different clinical behavior. Therefore, highly progressive patients have been excluded from some studies. However, previous reports have shown that the clinical features at presentation do not seem to be different between patients in Asian and Western countries. The true reason for the difference in the usefulness of IPI between studies is unclear.

To date, several prognostic factors in AITL patients have been reported with controversial results. Pangalis et al. [23] reported that lymphocytopenia seems to have an adverse effect on survival. Siegert et al. [9] found that survival was significantly related to age, stage, systemic symptoms, skin rash, edema, ascites, high LDH and anemia. Archimbaud et al. [24] identified features associated with a shorter survival to be rash, lymph node eosinophilia and elevated LDH. Mourad et al. [1] reported that male sex, mediastinal lymphadenopathy and anemia adversely affected OS. Tokunaga et al. [20] found that age, elevated WBC and IgA, anemia, thrombocytopenia, and extranodal involvement were significant prognostic factors for OS. Federico et al. [7] reported that age, extranodal sites, B symptoms and thrombocytopenia were adverse predictors for OS.

In this study, low serum albumin was identified as a poor prognostic factor for overall survival. The albumin level is important in recognizing the general condition of the patient, and may reflect patient exhaustion resulting from constitutional symptoms. Therefore, the prognostic significance of low serum albumin has been reported among patients with several subtypes of lymphomas including high-grade lymphoma [25], follicular lymphoma [26], intestinal lymphomas [27], adult T-cell leukemia/lymphoma [28], peripheral T-cell lymphoma, [21] and Hodgkin lymphoma [29]. The limitations of our study include the diversity of the initial treatment modalities, the small number of patients, and the retrospective nature of the study. Despite these limitations, our study suggested that a low level of albumin is an important factor for dividing AITL patients into subgroups with good and poor prognosis with respect to survival. To the best of our knowledge, this is the first study to have identified the relationship between the serum level of albumin and overall survival of AITL patients. Further study is needed to confirm the prognostic impact of albumin in AITL.

In this study, five factors (age, fever, PS, anemia and hypoalbuminemia) were identified as the prognostic factors of OS and only two factors (serum LDH and sIL2R) were identified as the prognostic factors of PFS. From these results, we think that the factors related to the tumor burden and tumor activity may influence PFS, and many other factors including age, PS and general condition may influence OS.

**Table 3** Prognostic factors for OS and PFS

| Variables | | OS | | | | | | PFS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Univariate analysis | | | Multivariate analysis | | | Univariate analysis | | | Multivariate analysis | | |
| | | HR | 95 % CI | *P* | HR | 95 % CI | *P* | HR | 95 % CI | *P* | HR | 95 % CI | *P* |
| Sex | Female | 0.501 | 0.198–1.265 | 0.136 | | | | 1.005 | 0519–1.945 | 0.989 | | | |
| Age | >60 | 5.296 | 1.240–22.615 | 0.019 | 2.517 | 0.570–11.112 | 0.223 | 1.655 | 0.780–3.513 | 0.190 | | | |
| Hepatomegaly | + | 0.657 | 0.272–1.586 | 0.346 | | | | 0.720 | 0.361–1.435 | 0.350 | | | |
| Splenomegaly | + | 0.677 | 0.303–1.510 | 0.333 | | | | 0.699 | 0.369–1.327 | 0.273 | | | |
| Effusion/ascites | + | 1.546 | 0.686–3.484 | 0.288 | | | | 1.384 | 0.720–2.662 | 0.330 | | | |
| Bone marrow | + | 1.492 | 0.649–3.426 | 0.347 | | | | 0.931 | 0.459–1.889 | 0.842 | | | |
| Mediastinum | + | 0.888 | 0.380–2.075 | 0.783 | | | | 1.068 | 0.551–2.070 | 0.844 | | | |
| Body weight loss | + | 1.420 | 0.585–3.448 | 0.436 | | | | 1.437 | 0.703–2.939 | 0.321 | | | |
| Fever | + | 2.965 | 1.174–7.484 | 0.016 | 1.343 | 0.449–4.016 | 0.598 | 1.677 | 0.867–3.244 | 0.124 | | | |
| Night sweat | + | 0.809 | 0.276–2.372 | 0.699 | | | | 0.903 | 0.373–2.186 | 0.821 | | | |
| Stage | III to IV | 0.969 | 0.131–7.188 | 0.976 | | | | 1.533 | 0.210–11.211 | 0.674 | | | |
| Performance status | ≥ 2 | 4.228 | 1.737–10.293 | 0.001 | 2.024 | 0.699–5.865 | 0.194 | 1.735 | 0.911–3.307 | 0.094 | 1.433 | 0.625-3.285 | 0.395 |
| Anemia | Presence[a] | 2.906 | 1.078–7.830 | 0.027 | 1.929 | 0.678–5.478 | 0.218 | 1.501 | 0.754–2.988 | 0.247 | | | |
| Platelet count | $<150 \times 10^9$/L | 1.616 | 0.689–3.788 | 0.265 | | | | 1.360 | 0.672–2.750 | 0.392 | | | |
| Eosinophil count | $>5 \times 10^9$/L | 1.607 | 0.633–4.080 | 0.313 | | | | 1.428 | 0.622–3.281 | 0.401 | | | |
| Serum LDH level | >UNL | 2.999 | 0.703–12.793 | 0.099 | 6.587 | 0.576–57.424 | 0.088 | 2.927 | 1.009–8.486 | 0.048 | 7.161 | 1.407-36.451 | 0.018 |
| Total protein level | <7.0 g/dl | 0.860 | 0.376–1.965 | 0.721 | | | | 1.336 | 0.692–2.581 | 0.388 | | | |
| Serum albumin level | <3.5 g/dL | 3.772 | 1.590–8.945 | 0.001 | 2.953 | 1.090–8.001 | 0.033 | 1.787 | 0.915–3.490 | 0.089 | 2.054 | 0.891–4.738 | 0.091 |
| sIL2R level | >530 U/ml | 1.581 | 0.691–3.618 | 0.273 | | | | 2.400 | 1.197–4.813 | 0.014 | 2.478 | 1.121–5.479 | 0.025 |
| EBER-ISH | positive | 0.952 | 0.332–2.727 | 0.927 | | | | 0.652 | 0.285–1.490 | 0.310 | | | |
| IgG level | >1600 mg/dL | 1.315 | 0.497–3.481 | 0.692 | | | | 0.844 | 0.425–1.674 | 0.627 | | | |
| IgA level | >350 mg/dL | 0.862 | 0.350–2.213 | 0.746 | | | | 0.749 | 0.372–1.509 | 0.419 | | | |
| IgM level | >250 mg/dL | 0.997 | 0.392–2.538 | 0.995 | | | | 0.937 | 0.451–1.950 | 0.862 | | | |

*OS* overall survival, *PFS* progression-free survival, *HR* hazard ratio, *CI* confidence interval, *LDH* lactate dehydrogenase, *ULN* upper limit of normal, *sIL2R* soluble IL-2 receptor, *EBER-ISH* Epstein–Barr virus-encoded small RNA by in situ hybridization

[a] Anemia was defined as a hemoglobin level <130 g/L for men and <110 g/L for women

In conclusion, the PIT and IPI may serve as useful tools for categorizing patients with AITL into subgroups. This study shows that serum albumin may be one of the important prognostic factors for AITL. For clinical use, investigation with a larger number of patients is needed to confirm this result and to develop more useful prognostic models for determining the optimal therapeutic strategy for AITL.

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**Conflict of interest** The authors have no conflict of interest to declare.

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