Am J Cancer Res 2024;14(4):1649-1661
www.ajcr.us /ISSN:2156-6976/ajcr0153627

Original Article

Clinical characteristics, genetic alterations, and prognosis of adult T-cell leukemia/lymphoma: an 11-year multicenter retrospective study in China

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Received September 25, 2023; Accepted March 10, 2024; Epub April 15, 2024; Published April 30, 2024

Abstract: Adult T-cell leukemia/lymphoma (ATLL) is an aggressive malignancy with a poor prognosis, and there is little data available from the Chinese population. This retrospective study included 115 patients diagnosed with ATLL who were treated across five hospitals in China from June 2011 to December 2022. The median age at diagnosis was 53 years. Several genes involved in T-cell receptor-induced nuclear factor κB (TCR-NF-κB) signaling were commonly mutated, including PLCG1, CIC, PRKCB, CARD11, and IRF4. Eighty-seven patients received chemotherapy. Of these, 13 received a hematopoietic stem cell transplant (HSCT) (allogeneic-HSCT, n=9; autologous-HSCT, n=4) after chemotherapy. Following initial multiagent chemotherapy using EPOCH/CHOEP and other regimens, the overall response rates were 80.6% (complete response [CR], 44.4%) and 42.8% (CR, 14.2%), respectively. The 4-year survival rates (median survival time in days) for EPOCH/CHOEP (n=43), HSCT (n=13), and CHOP-based regimens (n=31) were 12.7% (138), 30.8% (333), and 0% (66), respectively. Lymphadenopathy, EPOCH/CHOEP, and hematopoietic stem cell transplantation were independent prognostic protective factors in patients with aggressive ATLL. Chinese patients exhibit a higher incidence of aggressive-type ATLL, sharing similar genetic alterations with Japanese patients. Etoposide-based chemotherapy (EPOCH or CHOEP) remains the preferred choice for aggressive ATLL, and upfront allogeneic HSCT should be considered in all eligible patients.

Keywords: Characteristics, adult T-cell leukemia/lymphoma, genetics, prognosis, etoposide-based chemotherapy

Introduction

Adult T-cell leukemia/lymphoma (ATLL), a rare malignancy of mature CD4+ T-cells, is caused by infection with the human T-cell lymphotropic virus-1 (HTLV-1) and is associated with an extremely poor prognosis [1]. HTLV-1 is distributed worldwide, with the most pronounced prevalence in Japan, Africa, the Caribbean islands, Melanesia, and South America [2]. It can be transmitted through breastfeeding, sexual intercourse, and blood transfusions. In China, ATLL is highly prevalent in the Fujian Province, with few reports from other provinces [3].

ATLL displays diverse clinical and pathological features, allowing for the classification of patients into four subtypes: acute, lymphoma, chronic, and smoldering type [4]. The "acute" and "lymphoma" subtypes represent predominant aggressive forms of ATLL, whereas the "chronic" and "smoldering" types are categorized as indolent forms. Patients with aggressive ATLL have a median survival of 8-12 months [5]. There is no universally recognized standard therapy for aggressive ATLL, although doxorubicin-based chemotherapy remains the most commonly utilized approach. Understanding the genetic changes in patients with ATLL is crucial to enhance treatment

options. While a substantial amount of clinical data and information on genomic alterations in ATLL have been derived from the Japanese population, there are currently few reports on ATLL in the Chinese population.

This retrospective multicenter study comprehensively analyzed the clinical characteristics, genomic alterations, and prognosis of ATLL in China based on different treatment regimens.

Methods

Subjects

Patients with seropositivity for HTLV-1 or monoclonal HTLV-1 provirus and confirmed peripheral T-cell malignancy through histological or cytological examination who were treated at the Fujian Medical University Union Hospital (Fuzhou, China), the Ningde Hospital Affiliated to Ningde Normal University (Ningde, China), the First Affiliated Hospital of Fujian Medical University (Fuzhou, China), the First Hospital of Putian (Putian, China), and the Second Affiliated Hospital of Fujian Medical University (Quanzhou, China) between June 2011 and December 2022 were enrolled. We collected data on demographic characteristics, patient history, laboratory values, and patient mortality. The inclusion criteria were as follows: (1) initial ATLL diagnosis; (2) age >18 years; and (3) availability of complete clinical and pathological records. The exclusion criteria included suspected ATLL without confirmation of mature T-cell phenotype, HTLV-1 serology, or monoclonal HTLV-1 provirus. Patients were classified according to the Shimoyama criteria [4].

Treatment regimens

The following chemotherapy regimens were primarily used as first-line protocols: (1) dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (DA-EPOCH); (2) cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP); and (3) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Other utilized regimens included brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (Brentuximab vedotin+CHP); cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD) alternating with high-dose methotrexate and cytarabine; gemcitabine, dexamethasone, and cisplatin (GDP); chidamide, vinorelbine, and gemcitabine (GVC); pegaspargase, gemcitabine, and oxaliplatin (P-Gemox); vincristine, daunomycin, cyclophosphamide, asparaginase, and dexamethasone (VDCLP); vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); single-agent chemotherapy; and hematopoietic stem-cell transplantation (HSCT).

Evaluation of treatment efficacy and endpoint definitions

The evaluation of treatment response adhered to the criteria outlined in a 2009 consensus report [6]. To be categorized as complete response (CR), partial response (PR), and stable disease (SD), the duration of each of these responses had to be sustained for at least 4 weeks. Progressive disease (PD) was defined as an increase of 50% or more in the aberrant absolute lymphocyte count, an increase of 50% or more in the total number of detectable disease products from the lowest point of the illness, or the development of additional lesions beyond the skin. The objective response rate (ORR) was calculated as the sum of the CR and PR. Overall survival (OS) was defined as the time from diagnosis to death for any cause or the last follow-up (May 11, 2023).

Whole-exome sequencing (WES)

The IDT × Gen Exome Research Panel v1.0 capture kit was used for exome capture. Library concentrations were measured using a Qubit dsDNA HS Assay Kit and quantified using a QSeq400 fragment analyzer. Paired-end 150 bp sequences were generated using an Illumina NovaSeq 6000 (Illumina, San Diego, CA, USA). Data were then subjected to FASTP filtering, alignment with the National Center for Biotechnology Information human reference genome (hg19/GRCh37) using the Burrows-Wheeler Aligner (BWA), and corrections using dbsnp159. SAMtools was used to assess the sequencing depth, whereas GATK Depth of Coverage computed the coverage in bed regions and at a depth of 20X. Variant calling was performed using GATK 3.8. Mosdepth 0.2.5 was employed to analyze the guanine-cytosine (GC) content. Single-nucleotide polymorphisms and small oligonucleotide fragment insertion/deletions were identified using the Genome Analysis Toolkit (GATK, v4.1.1.0) and

Table 1. Baseline clinical characteristics of the 115 ATLL patients

Characteristic	Value
Age, median (y)	53
Sex, n (%)	
Male	64 (55.7)
Female	51 (44.3)
ATLL subtype, n (%)	
Acute	79 (68.7)
Lymphoma	34 (29.6)
Chronic	2 (1.7)
Smoldering	0 (0.0)
Chief complaint, n (%)	
Lymphadenopathy	39 (33.9)
Skin rash	13 (11.3)
Fever	17 (14.8)
Fatigue	22 (19.1)
Dyspnea	8 (7.0)
Abdominal pain	14 (12.2)
Cough	2 (1.7)
Extranodal Involvement, n (%)	
Bone marrow	79 (68.7)
Skin	24 (20.9)
Bone	11 (9.7)
Lung	6 (5.2)
Liver	29 (25.2)
Gastrointestinal	6 (5.2)
Pleural/peritoneal effusion	11 (9.7)
CNS	1 (0.8)
LDH, n (%)	
Normal	11 (9.6)
<2× normal	42 (36.5)
≥2× normal	62 (53.9)
Hypercalcemia, n (%)	45 (39.1)
Lymphocytosis, n (%)	64 (55.7)
Immunophenotype, n (%)*	
Typical (CD4+/CD8-)	67 (80.7)
Atypical (CD4+/CD8+ or CD4-/CD8- or CD4-/CD8+)	16 (19.3)
Abnormal cytogenetics, n (%)†	24 (36.4)
HTLV-1 detection, n (%)	
Provirus genes‡	100 (100)
Seropositivity§	62 (91.2)

*The expression profiles of CD4 and CD8 were available for 83 patients. †66 patients were tested for cytogenetic abberations at diagnosis. ‡100 patients underwent HTLV-1 proviral DNA examination at diagnosis. §68 patients received HTLV-1 serology examination at diagnosis. LDH, Lactate dehydrogenase; CNS, central nervous system.

annotated using Annovar (v201804). Deleterious mutations were characterized as variants leading to nonfunctional or truncated proteins, including frameshift mutations, splice site mutations, and stop-gain mutations.

Statistics

Baseline characteristics, demographics, and treatments received were summarized using frequency distributions and descriptive statistics. Chi-square and Fisher's exact tests were used to compare categorical variables between the two groups. The Mutation Annotation Format (MAF) file was analyzed and visualized using the R software package "maftools". We used the "GO" package in R for Gene Ontology (GO) analysis and the "KEGG" R package for Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. The abundance point charts were generated utilizing the "DOSE", "enrichplot", and "ggplot2" packages in R. Survival curves were estimated using the Kaplan-Meier method, compared using the log-rank test, and plotted using https://www.bioinformatics.com.cn. Multivariate analysis was conducted using Cox regression and plotted using Sangerbox 3.0 (http://vip.sangerbox.com/). All statistical analyses were performed using SPSS statistical software (IBM, Armonk, NY, USA). A two-sided *P*-value <0.05 indicated statistical significance.

Results

Demographics and clinical features

The baseline characteristics of the 115 patients are summarized in **Table 1**. One-hundred and thirteen (98.3%) patients were from the coastal cities of the Fujian province, which is recognized as an HTLV-1 epidemic area (Supplementary Figure 1). The other two patients were from the Jiangxi and Zhejiang provinces. Of the 115 patients, 55.7% (64/115) were male. The median age at diagnosis was 53 years, and there were no pediatric patients. According to the Shimoyama classifi-

cation, 68.7%, 29.6%, and 1.7% of patients were categorized as having acute, lymphomatous, and chronic disease, respectively. The most commonly affected extranodal sites across all subtypes were the liver (25.2%), skin (20.9%), bone (9.7%), and pleural or peritoneal effusions (9.7%). Elevated levels of lactate dehydrogenase (LDH) were observed in most patients (90.4%, 104/115). Cases were classified into two groups based on the immunophenotype of ATLL cells: typical (CD4+CD8-) and atypical phenotype (CD4+CD8+, CD4-CD8+, or CD4-CD8-). Most ATLL cells exhibited the typical CD4+CD8- immunophenotype (80.7%, 67/83). Hepatitis B virus infection was detected in 29 patients (27.9%, 29/104), and six (5.2%, 6/115) had a history of solid cancer.

HTLV-1 was detected in 96.5% (111/115) of cases and monoclonal integration of HTLV-1 proviral DNA occurred in 87.0% (100/115) of the patients. Among the patients examined, 91.2% (62/68) showed seropositivity for HTLV-1, accounting for 59.1% (68/115) of the total patients assessed. Furthermore, HTLV-1 proviral DNA was detected in the first-degree relatives (spouse, parents, offspring, and/or siblings) of 48 patients, with a positive result observed in 33.8% of individuals (49/145).

Cytogenetic characteristics of ATLL

Of the 65 patients tested for cytogenetic aberrations, 23 exhibited complex karyotypes (Supplementary Table 1). Aneuploidy involving multiple chromosomes, such as -1, +1, -2, +3, +4, +6, -8, +7, +8, -11, +12, -12, +16, -17, -19, -21, -22, +X, and -X, was observed. Deletions affecting chromosomes 1, 3, 4, 6, 14, 16, and 18 were also identified. Recurrent genomic regions affected by deletions or duplications included 4q12. The most common abnormalities were chromosome gains at 14q and 6p, and chromosome losses at 6q and 1.

Genetic alterations in ATLL

WES was conducted in seven patients, revealing numerous somatic mutations within the established ATLL tumors (**Figure 1**). Several genes involved in T-cell receptor nuclear factor κB (TCR-NF-κB) signaling were frequently mutated, including *PLCG1* (57%), *CIC* (57%), *PRKCB* (43%), *CARD11* (43%), *IRF4* (29%), and *RHOA* (14.2%) (**Figure 1A**). Frequent mutations, observed in over 25% of the cases, were identified in the following genes: *ANO3, COL6A2, DMBT1, FAT4, FSIP2, MAP3K14, RYR2, SERPINA7, SH3D19, SH3PXD2B, SLITRK1, TBL1XR1, PDZRN3*, and *CSMD1*. Missense mutations were the most common, with single nucleotide polymorphisms being the predominant variants (**Figure 1B**). Co-occurrence and exclusion analyses showed no significant correlation between gene mutations (**Figure 1C**). Functional enrichment analysis of the mutated genes in the GO and KEGG pathways revealed that these genes were predominantly enriched in the positive regulation of IκB kinase/NF-κB, chemokine signaling, and T-cell receptor signaling pathways (**Figure 1D**, **1E**). Furthermore, we delineated the specific mutation sites in the four most frequently mutated genes (**Figure 1F**).

Comparisons of patient characteristics and clinical data in acute and lymphoma subtypes

Among the 115 ATLL cases, 79 were classified as acute and 34 were categorized as lymphoma. **Table 2** shows a comparison of the clinical features between the two disease subtypes. Lymphadenopathy (χ^2=9.830, P=0.002) was more frequently observed in the lymphoma type. Leukocytosis (P<0.001), lymphocytosis (P<0.001), elevated serum LDH (χ^2= 6.520, P=0.011), bone marrow involvement (χ^2=30.594, P<0.001), hypoalbuminemia (χ^2= 6.840, P=0.009), and liver infiltration (P= 0.034) were associated with acute ATLL. However, there was no significant difference in hypercalcemia between the two subtypes.

Treatment response and survival

Of the 115 patients with ATLL, 28 received only supportive care. Regarding first-line treatment, 47 patients received EPOCH or CHOEP regimens (EPOCH, n=37; CHOEP, n=10), and 40 received alternative regimens, predominantly CHOP regimens (**Table 3**). Among the 87 patients who received chemotherapy, the median number of chemotherapy cycles was two (range: 1-26 cycles). Responses to first-line treatment were assessed in 64 patients, with seven cases lost to follow-up and 16 experiencing premature deaths. The ORR after first-line multiagent chemotherapy using EPOCH/CHOEP and other regimens were 80.6% (CR: 44.4%) and 42.8% (CR: 14.2%), respectively. For the

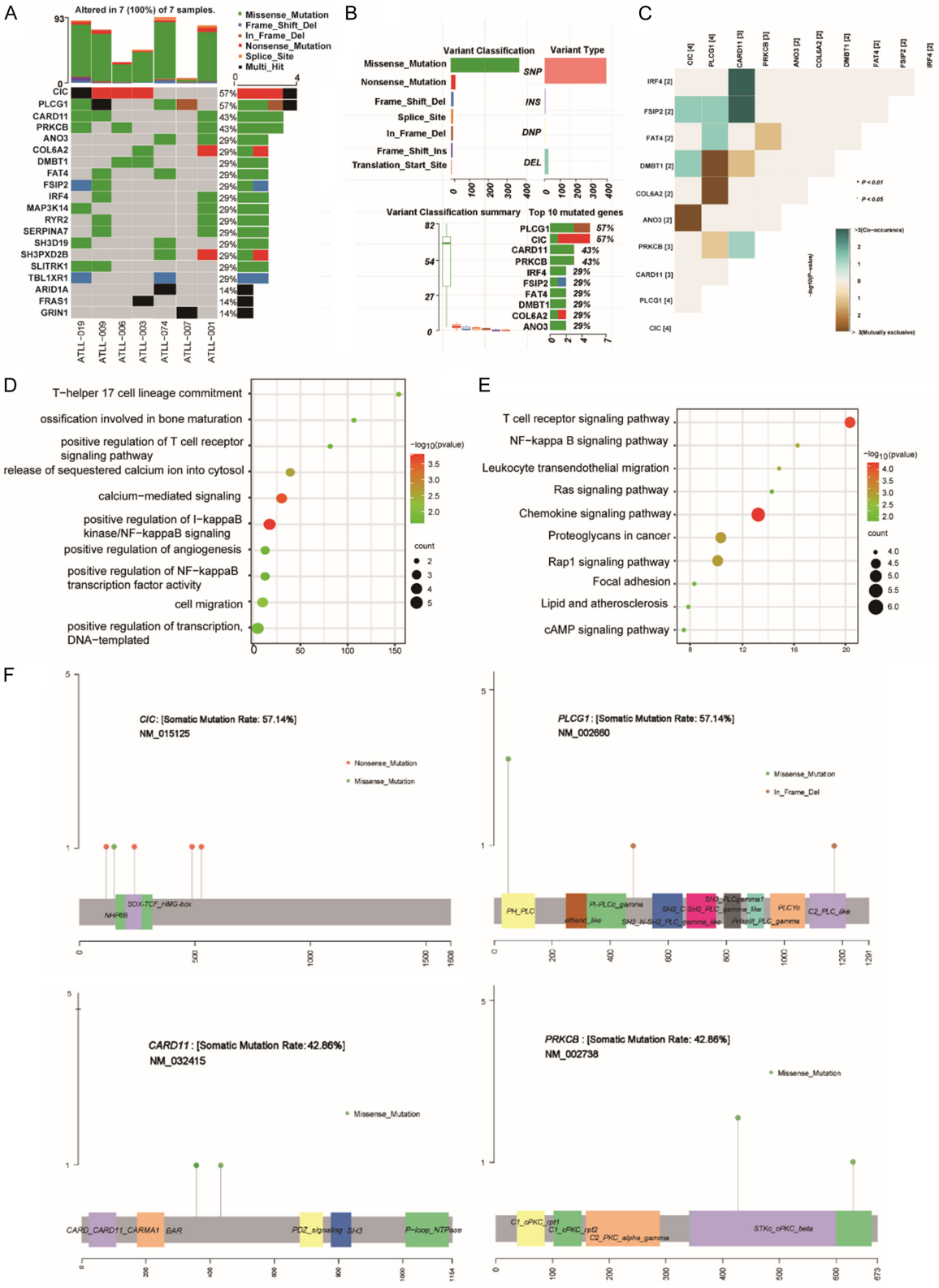

Figure 1. Mutational profile of ATLL. A. Mutation landscape plot of ATLL samples. B. Variation classification, variation type, and SNV category in ATLL samples. C. Exclusivity and co-occurrence of mutated genes. D, E. GO and KEGG pathway analyses of gene mutations in ATLL. F. The distribution of mutations detected at the protein level for *PLCG1* (NM_002660), *CIC* (NM_015125), *CARD11* (NM_032415), and *PRKCB* (NM_002738). SNP, single nucleotide polymorphism; ATLL, adult T-cell leukemia/lymphoma; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes.

Table 2. Comparison of patient characteristics and clinical data between the acute and lymphoma ATLL subtypes

Characteristic	Acute (N=79)	Lymphoma (N=34)	χ^2	*P* value
Age at onset			0.073	0.787
≤60 (years)	49 (62.0)	22 (64.7)		
>60 (years)	30 (38.0)	12 (35.3)		
Gender			0.521	0.471
Male	43 (54.4)	21 (61.8)		
Female	36 (45.6)	13 (38.2)		
Laboratory values				
Leukocytosis	67 (84.8)	4 (11.8)		0.000*
Lymphocytosis	64 (81.0)	0		0.000*
Anemia	23 (29.1)	5 (14.7)	2.647	0.104
Thrombocytopenia	23 (29.1)	5 (14.7)	2.647	0.104
Hypercalcemia	35 (44.3)	10 (29.4)	2.200	0.138
LDH elevated	75 (94.9)	27 (79.4)	6.520	0.011
LDH≥2× normal	47 (59.5)	16 (47.1)	1.490	0.222
Hypoalbuminemia	42 (53.2)	9 (26.5)	6.840	0.009
Organ involvement				
Lymphadenopathy	60 (75.9)	34 (100)	9.830	0.002
Bone marrow	67 (84.8)	11 (32.4)	30.594	0.000
Bone	6 (7.6)	5 (14.7)	1.368	0.242
Hepatomegaly	25 (31.6)	4 (11.8)		0.034
Splenomegaly	41 (51.9)	15 (44.1)	0.576	0.448
Skin	18 (22.8)	5 (14.7)	0.957	0.328
Lung	4 (5.1)	2 (5.9)		1.000*
CNS	1 (1.3)	0		1.000*
Overall survival, months (median)	2.2 (1.779-2.688)	8.7 (7.74-9.726)	13.552	0.000

*Fisher's exact test. LDH, Lactate dehydrogenase; CNS, Central nervous system.

acute (n=56), lymphoma (n=30), and chronic (n=1) types after first-line chemotherapy alone, the ORR rates were 63.9% (CR: 25%), 63.0% (CR: 37%), and 100% (CR: 100%), respectively. Nine patients who achieved complete remission after chemotherapy underwent HSCT (allogeneic-HSCT [allo-HSCT], n=6; autologous-HSCT, n=3), and four patients underwent salvage allo-HSCT during disease progression.

The median follow-up duration was 2.2 months (range: 0.1-104.5 months). At the end of the follow-up period, 59 (74.7%), 21 (61.8%), and 0 (0%) patients were recorded as deceased in the acute, lymphoma, and chronic types, respectively. The 1-year and 4-year OS rates for all 115 patients were 19.3% and 10.9%, respectively, with a median survival of 2.8 months. The 1-year and 4-year survival rates (median survival time, days) for acute (n=79) and lymphoma (n=34)-type ATLL were 12.4% and 3.1% (66), 28.8% and 20.6% (258), respectively (P<0.001) (**Figure 2A**). The median OS for patients in the other regimens (n=31) group, the EPOCH/CHOEP regimen (n=43) group, and the HSCT (n=13) group was 66, 138, and 333 days, respectively (P<0.001). The corresponding 1-year and 4-year survival rates were 26.7% and 12.7% in the EPOCH/CHOEP regimen group and 38.5% and 30.8% in the HSCT group, respectively, whereas the 1-year survival rate was 0% in the other regimen group (**Figure 2B**). Patients with a CR or PR to the initial treatment had significantly better survival rates than non-responsive or unevaluated patients (P<0.001) (Supplementary Figure 2A). A significant difference in prognosis was observed between complete remission and progression at the time of transplantation (Supplementary Figure 2B).

Prognosis analysis

Univariate Cox proportional hazards regression analysis revealed that leukocytosis, lymphocy-

Table 3. Treatment regimens and response rates in ATLL patients

Therapy	Number	Overall Response Rate, % (n)
First-line Therapy (N=87)		
DA-EPOCH	37	81.5 (22/27, CR, 15; PR, 7)
CHOEP	10	77.8 (7/9, CR, 1; PR, 6)
CHOP	24	45.0 (9/20, CR, 2; PR, 7)
CEOP	2	50.0 (1/2, PR, 1)
CHP+BV	1	100 (1/1, CR, 1)
COP	2	N
CP	2	N/SD
CP+Hyper-CVAD	1	N
EDOCP	1	PD
VCAP	1	PD
VDCLP	2	PD
VDCP	1	100 (1/1, CR, 1)
VEPD	1	N
VICLP	1	N
Chidamide+gemcitabine	1	N
Second-line Therapy (N=27)		
DA-EDOCH	12	25.0 (3/12, CR, 3)
CHOEP	1	PD
Chidamide+vinorelbine+gemcitabine	1	PD
P-Gemox	1	N
Interferon	1	SD
Chidamide+COP	1	PD
Chidamide+GDP	2	PD
Chidamide+pred+CAG	1	N
Chidamide+Gemox4	1	PR
Azacitidine+GHA	2	SD/N
VICLP	1	PD
IMRT	1	SD
Chidamide	1	PD
Chidamide+venetoclax+Gemox	1	N

CR, complete response; PR, partial response; SD, Stable disease; N, not assessable; DA-EPOCH, dose-adjusted etoposide, cyclophosphamide, vincristine, doxorubicin, and prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; CEOP, cyclophosphamide, etoposide, vincristine, prednisone; CHOP, cyclophosphamide, vincristine, doxorubicin, and prednisone; CHP+BV, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; GDP, gemcitabine, dexamethasone, and cisplatin; VDCLP, vincristine, daunomycin, cyclophosphamide, asparaginase, and dexamethasone; IMRT, radiotherapy; PD, progression of disease; VCAP, vincristine, cyclophosphamide, doxorubicin and prednisone; P-Gemox, pegaspargase, Gemcitabine, and oxaliplatin.

tosis, thrombocytopenia, hypercalcemia, hyperbilirubinemia, and hypoalbuminemia were associated with a worse OS. Conversely, lymphoma type, EPOCH/CHOEP regimen, and HSCT were protective prognostic factors for OS (**Figure 3A**; Supplementary Table 2). After considering risk factors with a *P*-value <0.10, a further multivariate Cox analysis of OS was conducted. The results revealed that lymphadenopathy (hazards ratio [HR]: 0.36; 95% confidence interval [CI]: 0.16-0.80; P=0.013), the EPOCH/CHOEP regimen (HR: 0.38; 95% CI: 0.20-0.73; P=0.004), and HSCT (HR: 0.18; 95% CI: 0.07-0.46; P<0.001) were independent prognostic protective factors in patients with aggressive ATLL, and hypoalbuminemia (HR:

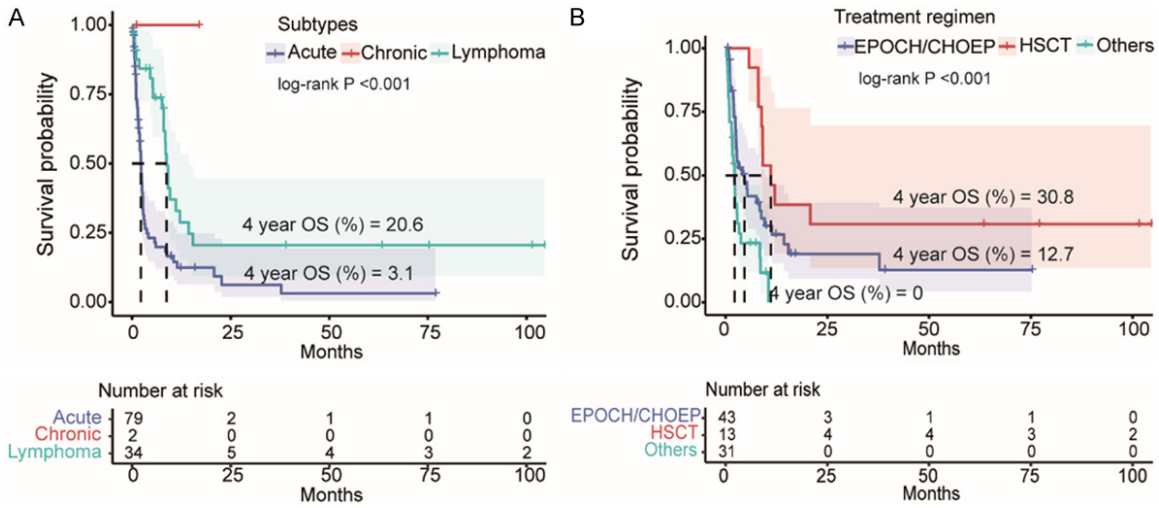

Figure 2. Overall survival of ATLL. Survival analysis based on (A) ATLL subtypes in 115 patients, and (B) treatment regimen in 87 patients. Survival estimates were calculated using the Kaplan-Meier method and compared using the log-rank test. ATLL, adult T-cell leukemia/lymphoma.

2.51; 95% CI: 1.42-4.42; P=0.002) was an adverse factor (**Figure 3B**; Supplementary Table 2).

Next, a nomogram was constructed using the Cox method to assess the prognostic significance of these characteristics in all 115 patients (**Figure 3C**). The overall C-index of the model was 0.76 (95% CI: 0.727-0.801, P=3.24e-44), indicating a high predictive accuracy. A calibration curve was generated to validate the model (**Figure 3D**).

Discussion

In this study, we retrospectively analyzed the data of 115 patients newly diagnosed with ATLL in China. This is the largest study conducted in China to date, providing a comprehensive description of the clinical characteristics, genetic alterations, and treatment outcomes of patients with ATLL, validating the generalizability of this sample to other medical centers in China. We conducted an efficacy comparison between 47 patients who received EPOCH/CHOEP and 40 patients who received other regimens. The initial EPOCH/CHOEP therapy demonstrated a significant enhancement in the ORR and longer OS in patients with aggressive ATLL compared with other therapies. Moreover, HSCT has the potential to improve long-term survival in patients with aggressive ATLL who respond positively to chemotherapy.

In our study, the median age at presentation was similar to that of the Caribbean and South American populations, but was younger than the recently reported median age of 67.5 years in Japan [8]. Further, we found a slight male predominance (male to female ratio, 1.3:1) [7]. Similar to the Japanese population, our patient group exhibited a higher prevalence of acute ATLL (68.7%) compared to lymphomatous ATLL (29.6%). This is in contrast to Afro-Caribbean patients, where only 41% had acute ATLL [5, 9, 10]. There was a notable diversity in the clinical manifestations of ATLL, and elevated levels of LDH along with hypercalcemia were frequently observed. Notably, lymphocytosis, elevated levels of serum LDH, bone marrow involvement, and hypoalbuminemia are more often observed in acute ATLL. In most of the patients in our study, ATLL cells expressed CD2, CD3, CD4, CD5, and CD25, which is consistent with the literature [11]. Additionally, 14.5% (12/83) of cases displayed dual CD4/CD8 expression. Notably, one study revealed that patients with typical phenotypes had a median survival time (MST) of 10.2 months, with a 20% survival rate at 2 years, which was significantly better than that of patients with atypical phenotypes [12]. However, no statistically significant survival disparity was observed between patients with typical and atypical immunophenotypes, possibly due to the small sample size (Supplementary Figure 2C).

Fourteen cases (12.1%) were initially misclassified, and anti-HTLV-1 antibody testing was not

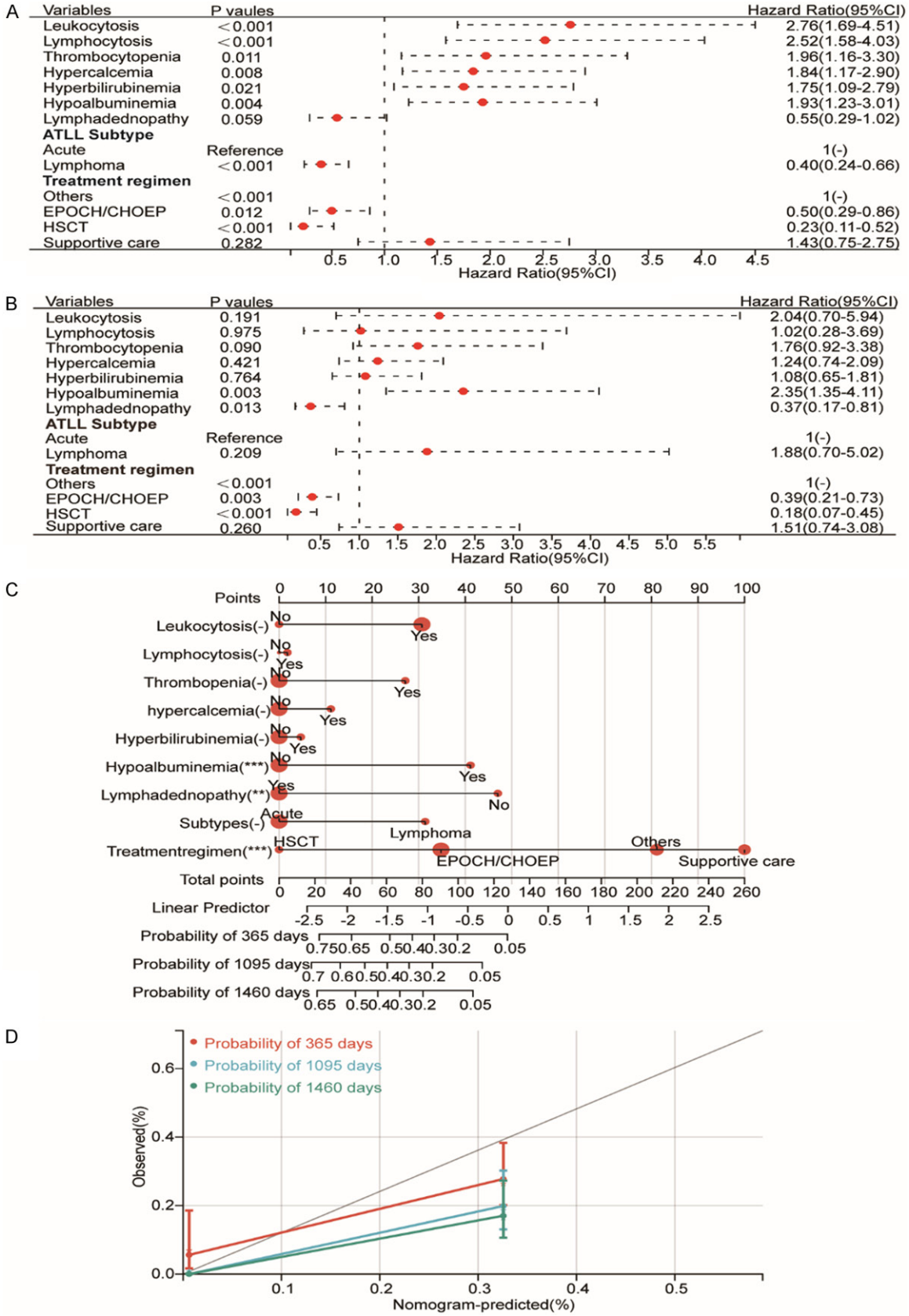

Figure 3. Prognosis analysis of patients with ATLL. A, B. Univariate and multivariate analyses of clinical characteristics associated with prognosis in aggressive ATLL patients. C. A nomogram prediction model based on treatment regimen and associated clinical features. D. Calibration curves for the survival probability at 1-, 3-, and 4-year. **P*<0.05; ***P*<0.01; ****P*<0.001. ATLL, adult T-cell leukemia/lymphoma.

initially performed. These comprised 12 cases of peripheral T-cell lymphoma and two cases of ALK-negative anaplastic large-cell lymphoma. Their reclassification was based on either demographic-driven anti-HTLV-1 serological testing or transformation from a lymphomatous/smoldering neoplasm to a leukemic state, prompting anti-HTLV-1 antibody testing. The rate of misclassification in our study was higher than that reported in the University of Miami study [13]. Accordingly, HTLV-1 analysis should be performed to differentiate ATLL from peripheral T-cell lymphoma not otherwise specified and cutaneous T cell lymphoma, especially where HTLV-1 is endemic [14, 15]. Moreover, among 145 first-degree relatives who underwent HTLV-1 proviral testing, 33.8% were positive; this suggested that lactation and sexual intercourse were two significant patterns of HTLV-1 transmission in China. Given the unfavorable prognosis of ATLL, increasing the awareness of this disease is crucial. Moreover, recognizing the significance of preventing HTLV-1 infection in carriers and interrupting mother-to-infant transmission is essential in eradicating ATLL [16].

The karyotype of ATLL is complex and lacks any characteristic abnormalities, particularly in the acute form. Itoyama et al. reported cytogenetic results of 50 ATLL cases, associating multiple breaks (≥6), chromosomal abnormalities, and partial loss with shorter survival [17]. The mutational profile of our analyzed tumor samples was similar to published data from other patients with ATLL, including those of African ethnicity in America [18] and Japan [19]. Genetic abnormalities in ATLL mainly involve genes associated with T-cell receptor-NF-κB signaling, such as *PLCG1*, *PRKCB*, and *CARD11*, and gain-of function mutations in *CCR4* and *CCR7* [19, 20]; however, *CCR4* gene mutations were not detected in our samples. Kataoka et al. [21] reported the diverse prognostic effects of certain driver mutations in ATLL. Mutations in *IRF4*, *PRKCB, CDKN2A,* and *TP53* were prevalent in aggressive forms, whereas *STAT3* mutations were prominent in the indolent type. The only chronic-type patient who underwent WES in this study also harbored a *STAT3* mutation. Furthermore, patients with *TET2, PRKCB, CD58, EP300, HLA class 1,* and *IRF4* mutations had a worse prognosis [21]. This presents opportunities to utilize these mutations as novel drug targets for improved patient management. Recently, Kameda et al. generated a clinicogenetic risk model, m7-ATL-PI, for risk stratification of aggressive ATLL [22]. Due to the limited number of cases, we were unable to analyze the impact of mutated genes on clinical prognosis.

Despite the availability of numerous combined chemotherapy regimens, there is no clear consensus on the superiority of any regimen [9, 15]. The OS at 4 years was 12.7% in the EPOCH/CHOEP regimen group and 0% in CHOP-based regimens group. EPOCH/CHOEP regimen group had a higher ORR (80.6%, CR: 44.4%) than CHOP-based regimens group (42.8%, CR: 14.2%). The CR rate in EPOCH/CHOEP regimen group was slightly higher than that in the VCAP-AMP-VECP arm reported by the Japan Clinical Oncology Group Study (40%) [23]. Furthermore, multivariate analysis revealed that initial treatment with the EPOCH/CHOEP regimen was an independent risk factor for prognosis. The median OS for all 87 patients who received chemotherapy was 16.4 weeks, which was lower than that observed in the North American cohort [10]. This difference is likely attributable to the predominantly aggressive cases in our study. A Japanese study involving 1594 ATLL patients indicated a median survival of 8.3, 10.6, 31.5, and 55.0 months for acute, lymphoma, chronic, and smoldering subtypes, respectively. The 4-year OS rates were 11%, 16%, 36%, and 52%, respectively [5]. A study from the United States reported that the 4-year survival rates of patients treated with modern therapies were 10%, 4%, 60%, and 83% for the acute, lymphoma, chronic/smoldering, and unfavorable chronic types, respectively [9]. In our study, acute-type patients had a MST of 2.3 months and a 4-year OS rate of 4.4%, which were lower than those of the Japanese and American populations. Conversely, lymphoma-type patients exhibited a higher 4-year OS rate of 21.9%, possibly because nearly half of the acute-type patients received CHOP-based regimens (Supplementary Figure 2D). Further research is warranted to explore and optimize treatment options for patients with acute ATLL.

Allo-HSCT remains the exclusive curative treatment for ATLL. A previous study revealed that approximately 20% of patients with aggressive

ATLL underwent allo-HSCT, resulting in a median survival of 5.9 months and a 4-year OS rate of 26% [5, 24]. In our study, patients who underwent HSCT had a median survival of 11.1 months and a 4-year OS rate of 30.8%, with a significant difference according to disease status at the time of transplantation. For patients with progressive disease, clinical outcomes after allo-HSCT are poor [25]. Therefore, upfront allo-HSCT should be considered while ATLL is under control to maximize the cure rate.

To the best of our knowledge, this is the first study describing the clinical features, cytogenetics, and treatment outcomes of ATLL in a Chinese population. While only 16 cases of ATLL were identified between 1983 and 1993 [3], our study included more than seven times that number, providing enhanced insights into ATLL. Nevertheless, further research is required to improve disease diagnosis and treatment.

Our findings are significant for clinical application; however, our study had some limitations. First, we could not trace HTLV-1 infection risk factors and only included hospitalized cases; thus, we may have missed smoldering types, and the results may only be representative of patients with aggressive ATLL. Second, most patients were from Fujian Province; thus, further clinical research should include patients from other races and regions in China, such as the Guangdong Province. Third, owing to the retrospective design and limited information, certain residual confounders were not considered in the prognostic factor analysis. Therefore, a well-designed prospective randomized trial with a large sample size is required to confirm our findings.

Conclusion

This study confirmed that compared with Japanese patients, ATLL presents at a younger age and has a high incidence of the aggressive type among Chinese patients and exhibits similar genomic alterations. Overall, aggressive ATLL has a poor prognosis, chemotherapy with an etoposide-based regimen (EPOCH/CHOEP) remains the preferred choice, and upfront allo-HSCT should be considered in all suitable patients.

Acknowledgements

We would like to thank Editage (www.editage.cn) for English language editing. This study was supported by National Natural Science Foundation of China (U23A20419, U2005204, 82000142), Joint Funds for the innovation of science and Technology, Fujian province (2021Y9086), and Startup Fund for scientific research, Fujian Medical University (2022QH-2021).

Written informed consent for publication was obtained from the patients.

Disclosure of conflict of interest

None.

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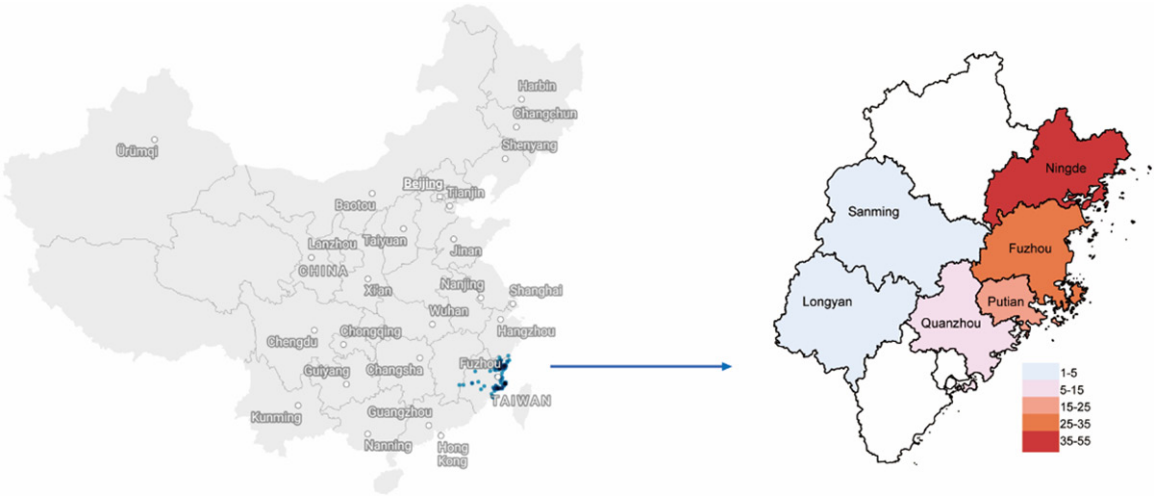
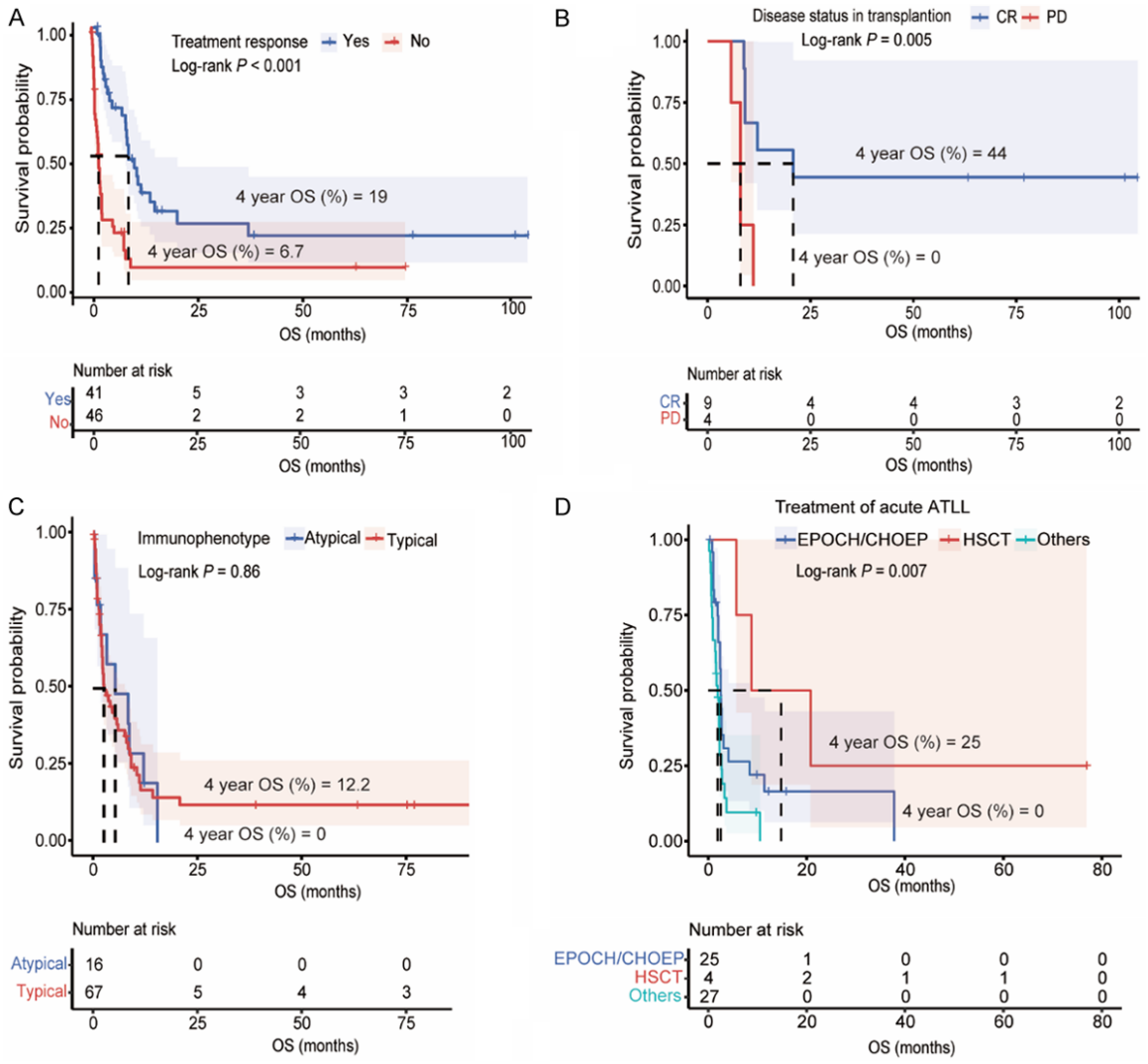


Supplementary Figure 1. Geographical distribution of ATLL patients encountered in China (N=115).

Supplementary Table 1. Abnormal cytogenetic findings in tested patients with ATLL

ID	Subtype	Age	Sex	Karyotype
ATLL-1	Acute	59	M	47-48, XY, +1, del(1)(p11p34),+3,del(3)(q21),t(6;12)(p22;q15)[CP10]/46,XY[8]
ATLL-17	Acute	36	M	46, XY, ins (14,13) (q24, q14q31), dup (20), (q12q13.3) [6]/47, idem, +3[2]
ATLL-24	Lymphoma	49	M	48, XY, +3, +8[7]/46, XY [13]
ATLL-26	Acute	60	M	87-93XXYY, add (8) (q24) *2, add (11) (q25) *2, add (14) (q32) *2, +mar1 *2, +mar*2 (CP6)/46XY, XY (6)
ATLL-32	Acute	62	F	1q+,-2,+4,4q+,4q-,9q-,11p+,12p-,13q+,-17,-21,-21,-22,+mar[7]
ATLL-38	Acute	55	M	48, XY, +add (1) (p13),?dic (3:6) (q21;q13), +6, de1(6)(q21;q23), ?de1(6:6)(q21;q13),dup(7)(q21,2q36),-8,+der(?)t(?,9)(?;q13),add(10)(p11.2)[3]/46,XY[5]
ATLL-43	Acute	42	F	t(1;3), t(10;22),+12,12p+,18p+,+mar[4]
ATLL-55	Acute	62	M	-Y,-1,ins(2;?),5p+,7p+,9p-,-11,-19,20p-[4]
ATLL-60	Acute	64	M	-Y, der (1) del (1) inv (1), +8, -12[10]
ATLL-63	Lymphoma	42	M	46, XY, inv (9) (p12q13), t (13;14) (q22; p12), der (13)t(13;14) inv (13)(q12q22),13ps+ [13]/46, XY, inv (9) (p12q13),13ps+ [7]
ATLL-64	Acute	28	F	46,XX,add(1)(q25),+3,t(4,16)(q25;p12),inc[3]/46,XX,[1]
ATLL-71	Lymphoma	76	M	45,X,-Y[3]/46,XY[17]
ATLL-74	Lymphoma	74	F	49,X,add(X)(q28),del(6)(q15q21),+7,+? der(8),add(14)(q22),del(18)(q22),der(18),+mar[1]/46,XX,[3]
ATLL-75	Acute	55	M	Complex karyotypes
ATLL-76	Acute	62	M	(+3,6q-, +7)
ATLL-83	Lymphoma	30	F	79-88, t(?;1) (?;p11)*2, add(4)(q21)*2, add(6)(p25)*2, del(6) (q13;q23)*2, ?idic(21) (q10)*2, +mar1*2, +mar2*2, inc[CP3]/46, XX[7]
ATLL-85	Acute	34	F	47XX,der(2)(p25),+4,der(6)(q15),der(13)(q34)[5]/46,XX[5]
ATLL-86	Acute	69	F	46,XX,dup(4)(q12q31),dup(7)(q11.2q32)[1]/46,XX[19]
ATLL-88	Acute	72	M	45, X, -Y, inv (3) (p24q29), dup (4) (p12p14), add (6) (p24), der (6)t(5;6) (q13;q14), del (14) (q22q32), del (16) (q11.2), add (17)q25), i(18) (q10), add(22)(p12)[14]/46, XY[6]
ATLL-90	Acute	66	M	48,XY,+x,der(1)t(1;4)(g21;q12)inv(1)(p13q12),del(3)(q21),der(4)del (4)(p15)del (4) (q12q33),t(9;19) (q34:p13), der (19)t(1:19) (q21;p13), add(21)(q22),+mar[15]/46, XY[5];
ATLL-91	Acute	47	M	46,XY,+mar[2]/46,XY[18],47,XY,+mar[1]/46,XY[19]
ATLL-104	Acute	44	F	44,X,-X,add(1)(p36),t(10;20)(p11.2;p13),-21[12]/46,XX[8]
ATLL-112	Acute	56	M	+der (3), der (10), +16



Supplementary Figure 2. Overall survival. (A) By treatment response in 87 patients, (B) By status at transplantation in 13 patients, (C) By immunophenotype in 83 patients, and (D) By treatment regimen in 56 acute ATLL. Survival estimates were calculated by Kaplan-Meier method and compared using the log-rank test.

Supplementary Table 2. Univariate and multivariate cox hazard analysis of OS in 113 aggressive ATLL patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* values	HR (95% CI)	*P* values
Female	1.02 (0.65-1.59)	0.936	-	-
Age ≥60 years	1.24 (0.78-1.96)	0.366	-	-
Leukocytosis	2.76 (1.69-4.51)	<0.001	2.04 (0.70-5.94)	0.191
Lymphocytosis	2.52 (1.58-4.03)	<0.001	1.02 (0.28-3.69)	0.975
Anemia	1.29 (0.76-2.19)	0.341	-	-
Thrombocytopenia	1.96 (1.16-3.30)	0.011	1.76 (0.92-3.38)	0.090
Hypercalcemia	1.84 (1.17-2.90)	0.008	1.24 (0.74-2.09)	0.421
LDH elevated	1.58 (0.76-3.28)	0.225	-	-
LDH≥2× normal	1.18 (0.76-1.84)	0.465	-	-
Hyperbilirubinemia	1.75 (1.09-2.79)	0.021	1.08 (0.65-1.81)	0.764
Hypoalbuminemia	1.93 (1.23-3.01)	0.004	2.35 (1.35-4.11)	0.003
Organ involvement				
Lymphadednopathy	0.55 (0.29-1.02)	0.059	0.37 (0.17-0.81)	0.013
Bone marrow	1.28 (0.79-2.08)	0.309	-	-
Bone	0.88 (0.38-2.03)	0.757	-	-
Hepatomegaly	1.35 (0.83-2.18)	0.223	-	-
Splenomegaly	1.12 (0.72-1.75)	0.607	-	-
Skin	1.12 (0.64-1.97)	0.697	-	-
Lung	1.44 (0.45-4.61)	0.543	-	-
CNS	1.61 (0.22-11.69)	0.638	-	-
ATLL subtype				
Acute	1 (-)	Reference	1 (-)	Reference
Lymphoma	0.40 (0.24-0.66)	<0.001	1.88 (0.70-5.02)	0.209
Treatment regimen				
Others	1	<0.001	1	<0.001
EPOCH/CHOEP	0.50 (0.29-0.86)	0.012	0.39 (0.21-0.73)	0.003
HSCT	0.23 (0.11-0.52)	<0.001	0.18 (0.07-0.45)	<0.001
Supportive care	1.43 (0.75-2.75)	0.282	1.51 (0.74-3.08)	0.260

LDH, lactate dehydrogenase; CNS, central nervous system; CI, Confidence interval; HR, Hazard ratio; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone; HSCT, hematopoietic stem cell transplantation.