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Evaluation of two prognostic indices for adult T-cell leukemia/lymphoma in the subtropical endemic area, Okinawa, Japan

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Aggressive adult T-cell leukemia/lymphoma (ATL) has an extremely poor prognosis and is hyperendemic in Okinawa, Japan. This study evaluated two prognostic indices (PIs) for aggressive ATL, the ATL-PI and Japan Clinical Oncology Group (JCOG)-PI, in a cohort from Okinawa. The PIs were originally developed using two different Japanese cohorts that included few patients from Okinawa. The endpoint was overall survival (OS). Multivariable Cox regression analyses in the cohort of 433 patients revealed that all seven factors for calculating each PI were statistically significant prognostic predictors. Three-year OS rates for ATL-PI were 35.9% (low-risk, n = 66), 10.4% (intermediate-risk, n = 256), and 1.6% (high-risk, n = 111), and those for

Abbreviations: 3yOS, 3-year overall survival; Alb, albumin; allo-SCT, allogeneic stem cell transplantation; ATL, adult T-cell leukemia/lymphoma; BUN, blood urea nitrogen; Ca, calcium; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CI, confidence interval; CS, clinical stage; Hb, hemoglobin; HR, hazard ratio; HTLV-1, human T-cell leukemia virus type-I; JCOG, Japan Clinical Oncology Group; LD, lactic dehydrogenase; MST, median survival time; OS, overall survival; PD-L1, programmed death-ligand 1; PI, prognostic index; Plt, platelet; PS, performance status; sIL-2R, soluble interleukin-2 receptor; WBC, white blood cell.

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JCOG-PI were 22.4% (moderate-risk, n = 176) and 5.3% (high-risk, n = 257). The JCOG-PI moderate-risk group included both the ATL-PI low- and intermediate-risk groups. ATL-PI more clearly identified the low-risk patient subgroup than JCOG-PI. To evaluate the external validity of the two PIs, we also assessed prognostic discriminability among 159 patients who loosely met the eligibility criteria of a previous clinical trial. Three-year OS rates for ATL-PI were 34.5% (low-risk, n = 42), 9.2% (intermediate-risk, n = 109), and 12.5% (high-risk, n = 8). Those for JCOG-PI were 22.4% (moderate-risk, n = 95) and 7.6% (high-risk, n = 64). The low-risk ATL-PI group had a better prognosis than the JCOG-PI moderate-risk group, suggesting that ATL-PI would be more useful than JCOG-PI for establishing and examining novel treatment strategies for ATL patients with a better prognosis. In addition, strongyloidiasis, previously suggested to be associated with ATL-related deaths in Okinawa, was not a prognostic factor in this study.

KEYWORDS
adult T-cell leukemia/lymphoma, ATL-PI, JCOG-PI, Okinawa, strongyloidiasis

1 | INTRODUCTION

Adult T-cell leukemia/lymphoma is a peripheral T-cell lymphoid malignancy caused by HTLV-1.[1-6] A nationwide investigation of ATL patients by the JCOG–Lymphoma Study Group identified five prognostic factors: PS, LD value, age, number of total involved lesions, and hypercalcemia.[7] Patients with ATL are usually classified into four clinical subtypes – acute, lymphoma, chronic, and smoldering[8] – according to the prognostic factors and clinical features, including the number of lymphocytes, percentage of abnormal T-lymphocytes, and presence of flower cells. The classification is widely used to decide the treatment strategy.[9] Compared with indolent ATL (smoldering and favorable chronic types), patients with aggressive ATL (acute, lymphoma, and unfavorable chronic types) present with rapid and aggressive clinical features and extremely poor prognosis.[8,10]

Patients with aggressive ATL often show a diverse clinical course, and two PIs have been developed to evaluate prognosis for more precise risk-adapted treatment strategies: ATL-PI for acute and lymphoma types[11] and JCOG-PI for acute, lymphoma, and unfavorable chronic type ATL.[12] The ATL-PI was developed from a large database of national retrospective survey data in Japan, but included few patients from Okinawa. The dataset was randomly split into training and validation samples, and the index was constructed on a split-sample basis. The JCOG-PI was developed from a training sample of patients who had participated in three JCOG clinical trials, JCOG9109,[13] JCOG9303,[14] and JCOG9801,[15] and the external sample comprised patients from three hospitals that were included in the abovementioned national survey database. Notably, there have been no validation studies to assess the usefulness of both PIs in the same aggressive ATL patient cohort, and uncertainty remains about whether these PIs are useful for patient stratification. Okinawa, located in southwestern Japan, is the country's only subtropical region, and ATL[16] and strongyloidiasis are endemic.[17] Strongyloidiasis is a parasitic disease caused by *Strongyloides stercoralis*,[18] and co-infection of HTLV-1 and *S. stercoralis* is associated with fatal disseminated strongyloidiasis.[19,20] Furthermore, strongyloidiasis is thought to promote the progression of ATL from HTLV-1 carriers.[21,22]

In our previous study, patients with aggressive ATL in Okinawa showed some clinical features different from those in other areas of Japan; for example, our patients had a higher proportion of patients aged ≥90 years, had poorer outcomes, a higher frequency of *S. stercoralis* infection,[23] and showed a different distribution of the HTLV-1 *Tax* genotype compared with mainland Japan.[24] These findings prompted us to question what the precise prognostic factors are of aggressive ATL and to examine the usefulness of ATL-PI and JCOG-PI among patients in Okinawa. To this end, using data from an Okinawa database, we sought to validate and compare the usefulness of the two PIs for aggressive ATL and investigate the impact of strongyloidiasis on the clinical outcomes of aggressive ATL.

2 | MATERIALS AND METHODS

2.1 | Study design and clinical data collection

We retrospectively collected data from patients with aggressive ATL diagnosed between January 2002 and December 2011 from seven institutions in Okinawa: Ryukyu University Hospital (Nishihara), Heartlife Hospital (Nakagusuku), Okinawa Prefectural Chubu Hospital (Uruma), Nakagami Hospital (Okinawa), Naha City Hospital (Naha), Okinawa Prefectural Nambu Medical Center and Children's Medical Center (Haebaru), and Okinawa Red Cross Hospital (Naha). Approval for the study was obtained from the institutional review board of each participating institution. A clinical data collection form was distributed to each institution and returned to Ryukyu University Hospital

between 2012 and 2013, as described in our previous study.[23] The inclusion criteria were diagnosis of acute, lymphoma and unfavorable chronic type ATL, based on the Shimoyama classification system.[8] We collected clinical data on Alb, BUN, LD, corrected Ca, PS, CS, sIL-2R, age, sex, WBC count, Plt count, Hb, and presence of strongyloidiasis. Strongyloidiasis was routinely checked by microscopic stool analysis on admission to each participating institution. The same ATL-PI and JCOG-PI formulae as developed in the original papers were used. ATL-PI was calculated as follows: ATL-PI = 0.65 × (if CS = III or IV) + 0.35 × (if PS > 1) + 0.016 × age (years) − 0.36 × Alb (g/dL) + 0.37 × $\log_{10}$ (sIL-2R [U/mL]). The ATL-PI scores of the high-, intermediate-, and low-risk groups were in the range of ≥2.6, 1.6-2.6, and <1.6, respectively.[11] The JCOG-PI defines the moderate-risk group as both corrected Ca <2.75 mmol/L and PS of 0 or 1, and the high-risk group as corrected Ca ≥2.75 mmol/L and/or PS 2-4.[12]

2.2 | Definition of clinical end-point and statistical analysis

The primary end-point in this study was OS, defined as duration from the time of diagnosis to the date of death from any cause or to the last follow-up date in living patients. We undertook external validation of the two PIs using Cox's proportional hazards model. First, we excluded patients who had missing data for the predictors required to calculate either the ATL-PI or JCOG-PI, and then used the log–rank test to compare the OS of the excluded patients with that of the remaining cohort for analysis, to assess whether these two groups had different patient characteristics. This was carried out because non-negligible differences might complicate the generalizability of results. Second, we used univariable Cox regression analyses that treated each PI as an explanatory variable. Finally, we included in the Cox regression model all factors (Alb, BUN, LD, corrected Ca, PS, CS, sIL-2R, age, sex, WBC, Plt, Hb, and strongyloidiasis) not required for calculating the PIs as well as those that were required, and screened out the prognostic predictors by backward elimination, with statistical significance set at $P < .05$ to identify specific prognostic predictors for ATL patients in Okinawa. The variables Alb, corrected Ca, sIL-2R, and age were first modeled as continuous variables and subsequently modeled as dichotomous variables to assist with interpretation of the results. We carried out the final regression analysis for patients who had no missing data for any of the explanatory variables. Survival curves were estimated using the Kaplan–Meier method and compared using the log–rank test. All reported *P*-values are two-sided, with $P < .05$ considered statistically significant. All statistical analyses were undertaken with SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

Data from a total of 659 patients with aggressive ATL were analyzed. Median follow-up time of censored patients (n = 111) was 23.2 months. Among these 659 patients, 226 were excluded because of missing data that were necessary to calculate their PIs. Of the remaining 433 patients (Figure 1), 10 had missing data for BUN, WBC, Plt, or Hb. The characteristics of these 433 patients are shown in Table 1. The median age was 67 (range, 26-100) years. A total of 300 patients received chemotherapy with multiple chemotherapeutic drugs; the most common chemotherapy regimen was CHOP or a CHOP-like regimen. Among these, 31 underwent allo-SCT and 131 received palliative chemotherapy or supportive care. Two patients had missing data for treatment. Median survival time and 3yOS for the 433 patients with aggressive ATL were 0.5 years (95% CI, 0.5-0.6 years) and 12.3% (95% CI, 9.1%-16.0%), respectively (Figure 2). Median survival times of included and excluded patients were 0.5 years (95% CI, 0.5-0.6 years) and 0.6 years (95% CI, 0.5-0.7 years), respectively, with corresponding 3yOS rates of 12.3% (95% CI, 9.1%-16.0%) and 13.7% (95% CI, 9.4%-18.9%; Figure S1). There were no significant differences in 3yOS between the included and excluded patients ($P = .6909$).

3.2 | Risk stratification of ATL patients according to ATL-PI and JCOG-PI

The ATL-PI and JCOG-PI were computable for all 433 ATL patients. The number of patients in each risk group for the ATL-PI was: low-risk, 62; intermediate-risk, 256; and high-risk, 111. For the JCOG-PI, 176 patients were classed as moderate risk and 257 as high risk (Table 2). Almost all patients in the ATL-PI low-risk and high-risk groups corresponded to the JCOG-PI moderate-risk group (62/66) and high-risk group (103/111), respectively. Of the 256 patients in the ATL-PI intermediate-risk group, 106 and 150 were classified into the JCOG-PI moderate-risk and high-risk groups, respectively (Table 2). According to the ATL-PI, for patients at low risk, intermediate risk, and high risk, the respective MSTs were 2.1 years (95% CI, 1.3-2.7 years), 0.6 years (95% CI, 0.5-0.7 years), and 0.3 years (95% CI, 0.2-0.4 years), and the 3yOS rates were 35.9% (95% CI, 23.5%-48.5%), 10.4% (95% CI, 6.7%-15.1%), and 1.6% (95% CI, 0.2%-7.1%) ($P < .0001$; Figure 3A). According to the JCOG-PI, for patients at moderate risk and high risk, the respective MSTs were 0.8 years (95% CI, 0.6-0.9 years) and 0.4 years (95% CI, 0.4-0.5 years) and the 3yOS rates were 22.4% (95% CI, 16.0%-29.4%) and 5.3% (95% CI, 2.7%-9.2%) ($P < .0001$; Figure 3B). These results indicate that both PIs had good power to stratify ATL patients at risk; however, the ATL-PI, with its three strata, identified low-risk patients more clearly than the dichotomous JCOG-PI.

3.3 | Assessment of prognostic risk factors in ATL patients

We assessed the impact of risk factors for calculating the PIs and strongyloidiasis on survival for the 433 ATL patients. In univariable analyses, all seven variables for calculating each PI showed a significant association with OS (Table 3). The risk of overall mortality for each factor was as follows: Alb (HR, 0.56; 95% CI, 0.48-0.66;

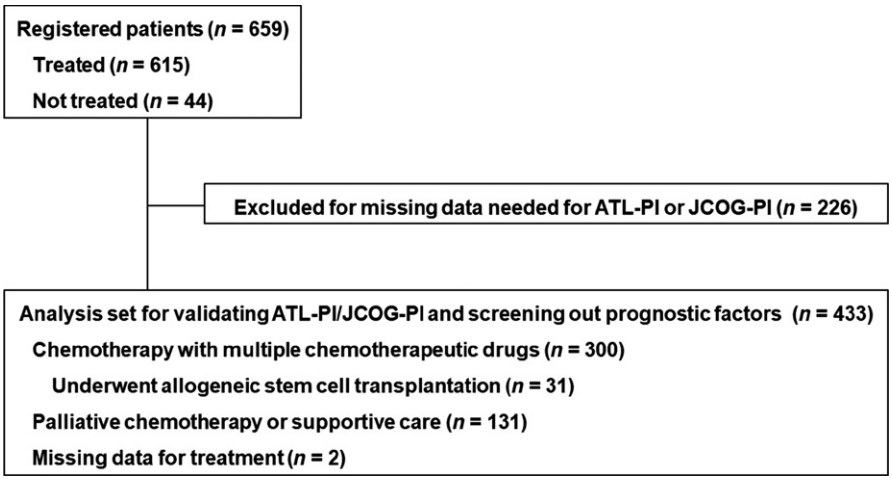

FIGURE 1 Schematic diagram of patients with aggressive adult T-cell leukemia/lymphoma (ATL). A total of 659 patients who received a diagnosis of aggressive ATL in Okinawa prefecture between January 2002 and December 2011. Among them, 615 were treated and 44 were not; 226 patients were excluded because of missing data required to calculate the ATL prognostic index (ATL-PI) or Japan Clinical Oncology Group (JCOG)-PI. Prognostic factors were analyzed and validated with ATL-PI and JCOG-PI among the remaining 433 patients

$P < .0001$), LD (HR, 1.00; 95% CI, 1.00-1.00; $P < .0001$), corrected Ca value (HR, 1.41; 95% CI, 1.23-1.62; $P < .0001$), PS (HR, 1.80; 95% CI, 1.46-2.23; $P < .0001$), CS (HR, 3.21; 95% CI, 1.84-5.59; $P < .0001$), sIL-2R (HR, 1.88; 95% CI, 1.56-2.26; $P < .0001$), and age (HR, 1.02; 95% CI, 1.01-1.03; $P < .0001$). However, strongyloidiasis had little impact on OS (HR, 1.22; 95% CI, 0.90-1.66; $P = .1999$). There was no significant difference in 3yOS between patients with strongyloidiasis (8.2%; 95% CI, 2.6%-17.9%) and without strongyloidiasis (13.0%; 95% CI, 9.5%-17.1%) ($P = .20$; Figure S2). For continuous variables, the trend was consistent (see Table 3) for their dichotomized variables. In multivariable analyses, all the covariables showed significant association with OS (Table 4) as follows; LD (HR, 1.00; 95% CI, 1.00-1.00; $P = .0117$), corrected Ca value (HR, 1.56; 95% CI, 1.22-2.00; $P = .0004$), PS (HR, 1.32; 95% CI, 1.05-1.65; $P = .0171$), CS (HR, 2.94; 95% CI, 1.67-5.20; $P = .0002$), sIL-2R (HR, 1.45; 95% CI, 1.16-1.82; $P = .0013$), and age (HR, 1.74; 95% CI, 1.40-2.18; $P < .0001$).

3.4 | Implications of allo-SCT for prognosis of ATL patients

Among the 433 ATL patients, 31 underwent allo-SCT. We assessed the implications of allo-SCT for the prognosis of ATL patients analyzed in this study, because allo-SCT has been explored as a promising treatment resulting in long-term remission in some patients with aggressive ATL.[25] All patients who underwent allo-SCT were less than 70 years old in the present study, therefore, we investigated the proportion of transplant patients using the age-adjusted ATL-PI for patients aged 70 years or less.[11] The proportion of transplant patients was lowest in the age-adjusted ATL-PI high-risk group (38.7%, 51.6%, and 9.7% in the low-, intermediate-, and high-risk groups, respectively; Table S1), and lower in the JCOG-PI high-risk group than the moderate-risk group (35.5% and 64.5%, respectively; Table S2). These data indicate that some patients, other than those in the high-risk group, had the opportunity to undergo allo-SCT, whereas patients in the high-risk group in our cohort rarely received allo-SCT.

3.5 | Assessment of prognostic factors and risk stratification of ATL patients in a clinical trial setting

To validate and compare the usefulness of the two PIs in patients who were eligible for clinical trials, we analyzed patients in a clinical trial setting. We extracted 231 patients from 659 who met the following criteria used for the JCOG9801 trial: (i) 70 years of age or younger, (ii) ECOG PS of 0-3, (iii) platelet count $\geq$50 000/μL, (iv) serum creatinine level $\leq$2.0 mg/dL, and (v) serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/L. Among the 231 patients, 72 were excluded because the data required to calculate their PIs were missing; thus, the remaining 159 patients were used for validation of the two PIs (Figure S3, Table S3). Median survival time and 3yOS for the 159 patients in the clinical trial setting was 0.8 years (95% CI, 0.6-0.9 years) and 16.3% (95% CI, 10.6%-23.0%), respectively (Figure S4). Median survival time of excluded patients were 0.8 years (95% CI, 0.5-0.9 years) and 3yOS rate were 17.9% (95% CI, 9.6%-28.2%). There were no significant differences in 3yOS between included and excluded patients ($P = .8149$; Figure S5).

The number of patients in each ATL-PI risk group was as follows, low-risk, 42; intermediate-risk, 109; and high-risk, 8. The JCOG-PI groups included 95 moderate-risk and 64 high-risk patients. According to the ATL-PI, for patients at low-, intermediate-, and high-risk, the respective MSTs were 1.8 years (95% CI, 1.2-2.7 years), 0.7 years (95% CI, 0.5-0.8 years), and 0.3 years (95% CI, 0.0-1.0 years) and the 3yOS rates were 34.5% (95% CI, 19.7%-49.7%), 9.2% (95% CI, 4.3%-16.4%), and 12.5% (95% CI, 0.7%-42.3%)

TABLE 1 Characteristics of 433 patients from Okinawa, Japan, with adult T-cell leukemia/lymphoma analyzed in this study

	n = 433
CS	
I/II	25
III/IV	408
PS	
0/1	204
>1	229
Age, years	
≤70	264
>70	169
Median (range)	67 (26-100)
Sex	
Male	223
Female	210
Alb, g/dL	
≥3.5	252
<3.5	181
Median (range)	3.6 (1.2-6.6)
BUN, mg/dL	
Missing data	6
Median (range)	15 (3.5-103)
LD, U/L	
Median (range)	537 (99-11 887)
sIL-2R, U/mL	
≤20 000	181
>20 000	252
Log_{10} (sIL-2R)	
Median (range)	4.42 (2.02-6.28)
Corrected Ca, mmol/L	
<2.75	309
≥2.75	124
Median (range)	2.45 (1.35-5.36)
Strongyloidiasis	
Negative	378
Positive	55

Alb, albumin; BUN, blood urea nitrogen; Ca, calcium; CS, clinical stage; LD, lactic dehydrogenase; PS, performance status; sIL-2R, soluble interleukin-2 receptor.

(P = .0001; Figure S6A). According to the JCOG-PI, the respective MSTs for patients at moderate- and high-risk, were 0.9 years (95% CI, 0.7-1.5 years) and 0.5 years (95% CI, 0.4-0.7 years), and the 3yOS rates were 22.4% (95% CI, 14.0%-32.2%) and 7.6% (95% CI, 2.5%-16.4%) (P = .0005; Figure S6B). The JCOG-PI could stratify ATL patients into moderate- and high-risk groups in this setting. Although the ATL-PI had low power to discriminate between intermediate-risk and high-risk groups, it identified patients at low-risk more clearly than the JCOG-PI.

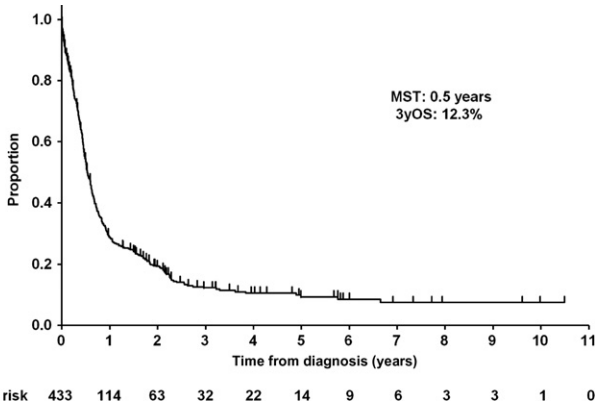

FIGURE 2 Overall survival rate and median survival time in this cohort study of patients with aggressive adult T-cell leukemia/lymphoma (ATL) in Okinawa, Japan. Median survival time (MST) and 3-y overall survival (3yOS) rate of the 433 patients with aggressive ATL were 0.5 y and 12.3%, respectively

TABLE 2 Numbers of adult T-cell leukemia/lymphoma (ATL) patients from Okinawa, Japan, in each risk group according to prognostic indices (PI) ATL-PI and Japan Clinical Oncology Group (JCOG)-PI

	JCOG-PI		
ATL-PI	Moderate risk	High risk	Total
Low risk	62	4	66
Intermediate risk	106	150	256
High risk	8	103	111
	176	257	433

We assessed the impact of risk factors for calculating the PIs and strongyloidiasis in terms of survival for the 159 ATL patients in a clinical trial setting. In univariable analyses, all variables except patient age for each PI showed a significant association with OS (Table S4). In multivariable analyses, Alb and LD were significantly associated with OS (Table S5). Strongyloidiasis showed a significant association with better survival in univariable and multivariable analysis, respectively (Tables S4,S5). However, there were only 10 patients with strongyloidiasis, hence we could not determine the impact of strongyloidiasis on the prognosis of ATL in the clinical trial setting.

4 | DISCUSSION

Our study is the first to evaluate the two previously established PIs in the same aggressive ATL patient cohort and compare their utility in the actual clinical setting. In addition, it has been a subject of debate whether strongyloidiasis has a negative impact on prognosis in patients with aggressive ATL, and we showed for the first time that strongyloidiasis has little impact on their prognosis. Although 226 of the 659 patients were excluded from our dataset because of missing data needed to calculate the PIs, the survival rate of the excluded patients was comparable to that of the included patients,

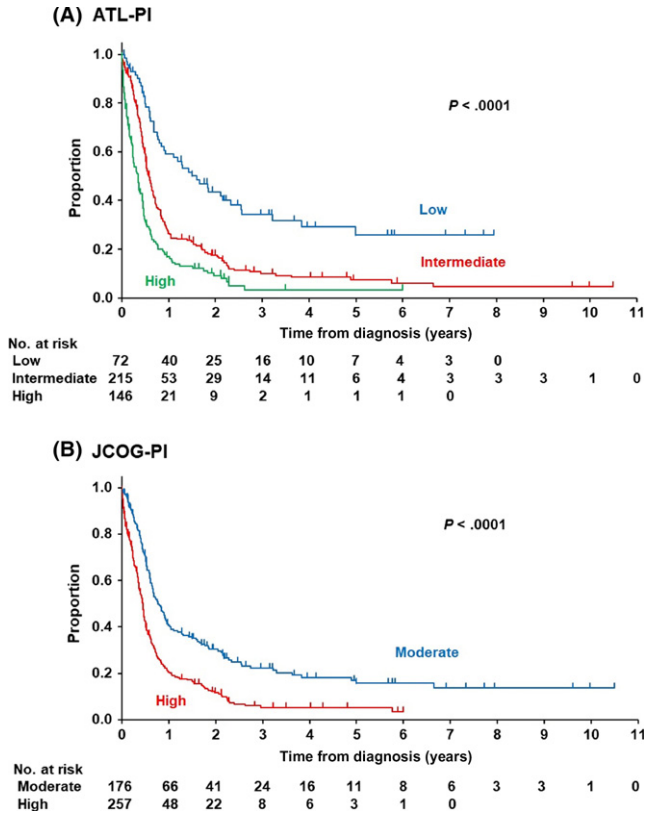

FIGURE 3 Overall survival curves of patients with aggressive adult T-cell leukemia/lymphoma (ATL) in Okinawa according to the ATL prognostic index (ATL-PI) (A) and Japan Clinical Oncology Group (JCOG)-PI (B). According to the ATL-PI, the median survival times (MSTs) were 2.1, 0.6, and 0.3 y, and the 3-y overall survival (3yOS) rates were 35.9%, 10.4%, and 1.6% for patients at low risk, intermediate risk, and high risk, respectively ($P < .0001$). According to the JCOG-PI, MSTs were 0.8 and 0.4 y and 3yOS rates were 22.4% and 5.3% for patients at moderate and high risk, respectively ($P < .0001$)

indicating that the analyzed patients represented those with actual aggressive ATL in Okinawa. Both PIs were reproducible in our cohort; however, the ATL-PI identified low-risk patients more clearly than the JCOG-PI. The ATL-PI stratifies ATL patients into three risk groups using five prognostic factors (CS, PS, age, serum Alb, and sIL-2R), whereas JCOG-PI stratifies them into two groups using only two prognostic factors (PS and corrected Ca). Using the more detailed ATL-PI classification with more prognostic factors might enable risk to be clearly stratified in ATL patients. The ATL-PI also identified low-risk patients more clearly than the JCOG-PI among the patients in a clinical trial setting. There were only eight patients in the ATL-PI high-risk group in this setting, indicating that patients in this category would rarely be eligible for clinical trial participation. In addition, seven of the eight patients in the ATL-PI high-risk group died within a year of diagnosis, hence their prognoses were dismal. If the aim of a clinical trial is to evaluate the treatment efficacy of low-risk patients, the use of ATL-PI would be more advisable. However, further study is needed to validate this finding, which was obtained from a small dataset of only 159 patients.

TABLE 3 Univariable analyses of 433 patients from Okinawa, Japan, with adult T-cell leukemia/lymphoma analyzed in this study

Variable	HR	95% CI	*P*-value
Alb (g/dL)	0.56	0.48-0.66	<.0001
Alb (g/dL)			
≥3.5	Ref.	–	–
<3.5	1.72	1.40-2.13	<.0001
LD (U/L)	1.00	1.00-1.00	<.0001
Corrected Ca (mmol/L)	1.41	1.23-1.62	<.0001
Corrected Ca (mmol/L)			
<2.75	Ref.	–	–
≥2.75	1.83	1.45-2.30	<.0001
PS			
0/1	Ref.	–	–
>1	1.80	1.46-2.23	<.0001
CS			
I/II	Ref.	–	–
III/IV	3.21	1.84-5.59	<.0001
Log_{10} (sIL-2R)	1.88	1.56-2.26	<.0001
sIL-2R			
≤20 000	Ref.	–	–
>20 000	1.72	1.39-2.13	<.0001
Age (years)	1.02	1.01-1.03	<.0001
Age (years)			
≤70	Ref.	–	–
>70	1.50	1.21-1.85	.0002
Sex			
Male	Ref.	–	–
Female	1.01	0.82-1.25	.8953
Strongyloidiasis			
Negative	Ref.	–	–
Positive	1.22	0.90-1.66	.1999
BUN (mg/dL)	1.02	1.02-1.03	<.0001

–, not applicable; Alb, albumin; BUN, blood urea nitrogen; Ca, calcium; CI, confidence interval; CS, clinical stage; HR, hazard ratio; LD, lactic dehydrogenase; PS, performance status; Ref., reference; sIL-2R, soluble interleukin-2 receptor.

Strongyloidiasis is endemic in Okinawa,[17] and our previous study showed its high prevalence in patients with aggressive ATL.[23] It has been speculated that strongyloidiasis is associated with poor prognosis in ATL patients because HTLV-I infection is considered to be a risk factor for disseminated strongyloidiasis.[26,27] However, there have been only a few small-scale retrospective studies on the impact of strongyloidiasis on survival in ATL patients.[28] Our study, with its aim to elucidate the impact of strongyloidiasis on the prognosis of ATL, is the largest undertaken to date and it revealed that strongyloidiasis was not a significant prognostic factor. Adult T-cell leukemia/lymphoma is often complicated by opportunistic infections such as cytomegalovirus, pneumocystis pneumonia, pulmonary aspergillosis, invasive candidiasis, and strongyloidiasis. These infections often

TABLE 4 Multivariable analyses of 433 patients from Okinawa, Japan, with adult T-cell leukemia/lymphoma analyzed in this study

Variable	HR	95% CI	*P*-value
LD (U/L)	1.00	1.00-1.00	.0117
Corrected Ca (mmol/L)			
<2.75	Ref.	–	–
≥2.75	1.56	1.22-2.00	.0004
PS			
0/1	Ref.	–	–
>1	1.32	1.05-1.65	.0171
CS			
I/II	Ref.	–	–
III/IV	2.94	1.67-5.20	.0002
sIL-2R			
≤20 000	Ref.	–	–
>20 000	1.45	1.16-1.82	.0013
Age (years)			
≤70	Ref.	–	–
>70	1.74	1.40-2.18	<.0001

–,not applicable; Ca, calcium; CI, confidence interval; CS, clinical stage; HR, hazard ratio; LD, lactic dehydrogenase; PS, performance status; sIL-2R, soluble interleukin-2 receptor.

cause fatal complications in patients with aggressive ATL.[9,29] Because patients with aggressive ATL routinely undergo fecal tests to detect *S. stercoralis* at the time of hospital admission in Okinawa, they may be able to receive treatment for this disease earlier than patients in other areas of Japan. Our approach to controlling *S. stercoralis* infection might reduce the risk of disseminated strongyloidiasis; thus, the unique background of ATL patients in Okinawa would not affect ATL prognosis.

We should also consider more effective therapeutic strategies against ATL, especially for high-risk patients. Aggressive ATL is currently being treated by mogamulizumab, a humanized anti-CC chemokine receptor 4 mAb,[30] and lenalidomide, an oral immunomodulator.[31] Recently, aberrant PD-L1 expression in ATL cells was reported;[32,33] therefore, anti-PD-1/PD-L1 therapy is a promising therapeutic strategy. To improve the prognosis in patients with aggressive ATL, combination therapy of allo-SCT and various new antitumor agents is needed. Also, immunotherapy such as therapeutic vaccine with Tax peptide-pulsed dendritic cells[34] should be developed for ATL patients who are not eligible for allo-SCT. Efficient clinical trials based on patient risk stratification are necessary to accelerate the development of new drugs for ATL patients.

In conclusion, both ATL-PI and JCOG-PI were reproducible in this external validation study using data from Okinawan patients with aggressive ATL. Because ATL-PI more clearly identified the patient subgroup with low risk than JCOG-PI did, the ATL-PI might have more clinical utility for devising novel treatment strategies for aggressive ATL based on risk stratification. Strongyloidiasis did not affect the prognosis of patients with aggressive ATL.

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CONFLICT OF INTEREST

The authors have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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