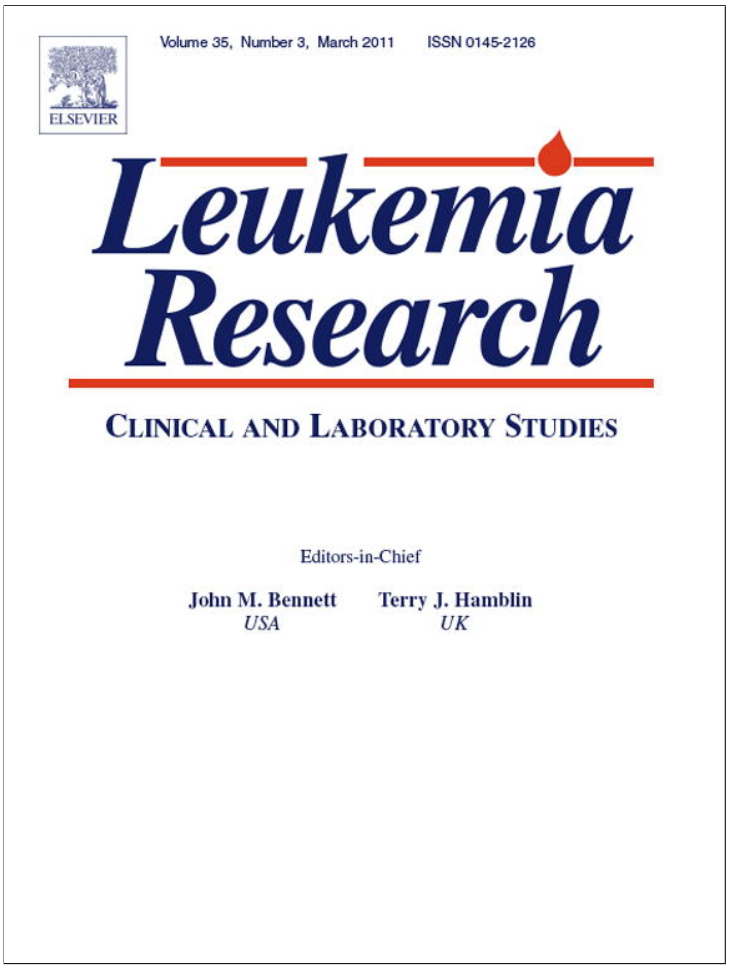

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Different prognostic factors for survival in acute and lymphomatous adult T-cell leukemia/lymphoma

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ABSTRACT

Introduction: Adult T-cell leukemia/lymphoma (ATLL) is a clinically aggressive and heterogeneous entity; hence it is likely that different variants of ATLL have different prognostic factors. *Methods*: 95 patients with ATLL seen at our institution between 1987 and 2008 were included. Clinical data were compared, according to ATLL variant, using the Mann–Whitney and the Chi-square tests for continuous and categorical variables, respectively. Kaplan–Meier estimates compared using the log-rank test and Cox proportional-hazard test were used for the univariate and multivariate analysis, respectively. *Results*: Median age was 61 years with male-to-female ratio of 1.07:1. Patients with acute ATLL were more likely to present with bone marrow, liver and spleen involvement, higher β2-microglobulin and lower albumin levels. Poor performance status, high IPI score, presence of B symptoms, high LDH and low albumin levels were associated with a worse survival in lymphomatous ATLL. High LDH, high β2-microglobulin and high PIT score were associated with worse survival in acute ATLL. In the multivariate analysis, low albumin level and presence of B symptoms were independent factors for worse survival in lymphomatous ATLL, and high β2-microglobulin level was independent factor for worse survival in acute ATLL. *Conclusions*: Aggressive ATLL variants have a distinct, almost mutually exclusive profile of prognostic factors.

1. Introduction

ATLL is a clinically heterogeneous disease with several well-described clinical variants, from which the acute (leukemic) and the lymphomatous subtypes are the most aggressive, characterized by a rapidly progressing disease and short survival [1]. The chronic and smoldering subtypes are more indolent; however, they can progress into more aggressive phases of disease. More recently, cutaneous variants of ATLL have been described, also characterized by a more indolent clinical course [2].

The human T-lymphotropic virus type-1 (HTLV-1) is the pathogenic agent associated with the development of adult T-cell lymphoma/leukemia (ATLL), among other diseases [3]. HTLV-1 is a RNA retrovirus, endemic in Southwestern Japan, the Middle East, North Africa, the Caribbean and South America. Peru is an endemic area for HTLV-1 infection and it is estimated that 1–3% of the healthy adult population are HTLV-1 carriers [4,5]. However, the Peruvian experience in patients with ATLL has not been previously published.

Several clinical factors have been associated with prognosis in patients with ATLL [6–18]. Older studies have identified several clinical factors, such as LDH levels and performance status [12,19], leukocyte count and calcium levels [11,19], among others. More recently, the International Prognostic Index (IPI) score has shown to be of prognostic value in aggressive subtypes of ATLL [13]. However, given the clinical and molecular differences between acute and lymphomatous subtypes of ATLL, it is likely that the clinical factors associated with survival would also be different. Shimamoto and colleagues evaluated this hypothesis in a small cohort of patients with ATLL and found almost exclusive sets of prognostic factors for each subtype [11]. In this study, our main objective was to evaluate the differences in prognostic factors between acute and lymphomatous variants of ATLL.

2. Patients and methods

2.1. Case selection

Clinical data on untreated patients with *de novo* ATLL, who were diagnosed between January 1st 1987 and December 31st 2008 at our Institution, was retrospectively collected. The diagnosis of ATLL was based on histological, immuno-

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Table 1
Clinical characteristics of 95 patients with adult T-cell leukemia/lymphoma according to subtype.

Characteristic	Total *N* (%)	Acute subtype *N* (%)	Lymphomatous subtype *N* (%)	Indolent subtypes *N* (%)	*p*-Value
Sex					
Male	49 (52%)	23 (57%)	18 (44%)	8 (57%)	0.4269
Female	46 (48%)	17 (43%)	23 (56%)	6 (43%)	
Performance					
ECOG 0–1	32 (41%)	12 (32%)	20 (49%)	11 (79%)	0.1637
ECOG ≥2	46 (59%)	25 (68%)	21 (51%)	3 (21%)	
B symptoms					
No	43 (71%)	18 (69%)	25 (71%)	7 (70%)	0.8513
Yes	18 (29%)	8 (31%)	10 (29%)	3 (30%)	
Bone marrow					
Not involved	39 (49%)	6 (19%)	33 (80%)	12 (86%)	<0.0001
Involved	40 (51%)	32 (81%)	8 (20%)	2 (14%)	
Liver					
Not involved	63 (81%	24 (65%)	39 (95%)	14 (100%)	0.0003
Involved	15 (19%)	13 (35%)	2 (5%)	0 (0%)	
Spleen					
Not involved	61 (78%)	22 (60%)	39 (95%)	14 (100%)	0.0001
Involved	17 (22%)	15 (40%)	2 (5%)	0 (0%)	
LDH level					
Normal	10 (13%)	4 (11%)	6 (16%)	5 (50%)	0.5807
Elevated	65 (87%)	33 (89%)	32 (84%)	5 (50%)	
Chemotherapy					
Yes	69 (85%)	31 (77%)	38 (93%)	–	0.1073[a]
No	12 (15%)	9 (23%)	3 (7%)	–	
Response					
Complete	11 (17%)	3 (10%)	8 (22%)	–	0.4746[a]
Partial	7 (11%)	3 (10%)	4 (11%)	–	
Stable disease	1 (2%)	0 (0%)	1 (3%)	–	
Progressive disease	47 (71%)	23 (80%)	24 (65%)	–	

Characteristic	Total, median (range)	Acute subtype median (range)	Lymphomatous subtype median (range)	Indolent subtypes median (range)	*p*-Value
Age (years)	61 (23–92)	58 (34–92)	63 (23–82)	66 (29–82)	0.5237[a]
Hemoglobin (g/dl)	12 (5.2–17.4)	11.3 (6.9–17.4)	11.7 (5.2–15.3)	13.3 (9.2–15.9)	0.7158[a]
Calcium (mg/dl)	5.0 (1.6–23.0)	5.1 (1.6–23.0)	4.6 (2.6–10.7)	4.1 (3.9–8.8)	0.6081[a]
β2-Microglobulin (mg/l)	4.2 (1.1–16.9)	5.5 (2.6–16.9)	3.5 (1.1–10.2)	3.0 (2.4–7.1)	0.0012[a]
Albumin (g/dl)	3.2 (1.8–4.6)	3.1 (1.9–4.4)	3.4 (1.8–4.6)	2.8 (2.2–3.6)	0.0297[a]
LDH (IU/l)[b]	808 (298–13000)	1250 (384–9931)	721 (331–13000)	447 (298–754)	0.0210[c] 0.008[d]

ECOG: Eastern Central Oncology Group; LDH: lactate dehydrogenase.
[a] *p*-Values were obtained comparing acute versus lymphomatous subtype only.
[b] LDH upper limit of normal is 480 IU/l.
[c] Acute versus lymphomatous ATLL.
[d] Lymphomatous versus indolent ATLL.

histochemical and flow cytometric features, and the presence of a positive HTLV-1 serology (ELISA). The distinction between acute, lymphomatous and chronic variants was made according to the Shimoyama classification [20]. All pathological samples were reviewed by two expert hematopathologists (DM and PQ). Other leukemic variants of peripheral T-cell lymphoma (PTCL) such as Sézary syndrome, aggressive NK cell leukemia, prolymphocytic leukemia and large granular lymphocytic leukemia were excluded. More indolent ATLL variants such as chronic, smoldering and primary cutaneous were also excluded.

2.2. Data gathering

We collected clinical data and laboratory findings including ATLL subtype, age, gender, performance status, B symptoms, clinical stage, LDH levels, leukocyte count, absolute lymphocyte count, calcium levels, bone marrow involvement, IPI score, Prognostic Index for PTCL, Unspecified (PIT) score, initial chemotherapy, clinical response, final outcome and overall survival (OS) in months. The IPI was calculated using five clinical variables (age, performance status, LDH level, extranodal involvement and clinical stage) to subdivide patients in two categories: low (0–2 factors) and high (3–5 factors) [21]. The PIT score was calculated using 4 clinical variables (age, performance status, LDH levels and bone marrow involvement) to subdivide patients in two categories: low (0–1 factor) and high (2–4 factors) [22].

2.3. Statistical analysis

Clinicopathological data is presented using descriptive statistics. Continuous variables were dichotomized to facilitate their analysis. The Mann–Whitney test was used to compared medians of the continuous variables and the Chi-square test was used to compare the categorical characteristics between groups according to the ATLL subtype. OS was defined as the lapse of time in months between diagnosis and last follow-up or death. For the univariate survival analyses, the Kaplan–Meier method for incomplete observations was used. Survival curves between groups were compared using the log-rank test. The Cox proportional-hazard regression method was used to perform the multivariate survival analyses. All reported *p*-values were considered significant if were less than 0.05. Calculations and graphics were obtained using the statistical software MedCalc, version 11.2.1.0 (Mariakerke, Belgium).

3. Results

3.1. Clinical characteristics

Ninety five cases with a clinicopathological diagnosis of ATLL were identified from the medical records of our institution. Their main characteristics are shown in Table 1. Forty one patients (43%) were classified as lymphomatous, 40 were classified as acute (42%), and 14 (15%) as chronic ATLL. The clinical characteristics of the 95 patients according to the ATLL subtype are shown in Table 1. Median age was 61 years (range 23–92 years) with a male-to-female ratio of 1.07:1. Patients with acute ATLL were more likely to have bone marrow, liver and spleen involvement ($p < 0.0001$, $p = 0.0003$ and $p = 0.0001$, respectively). Patients with lymphomatous ATLL had higher levels of β2-microglobulin while patients with acute ATLL had higher levels of albumin (*p*-values of 0.006 and 0.04, respectively).

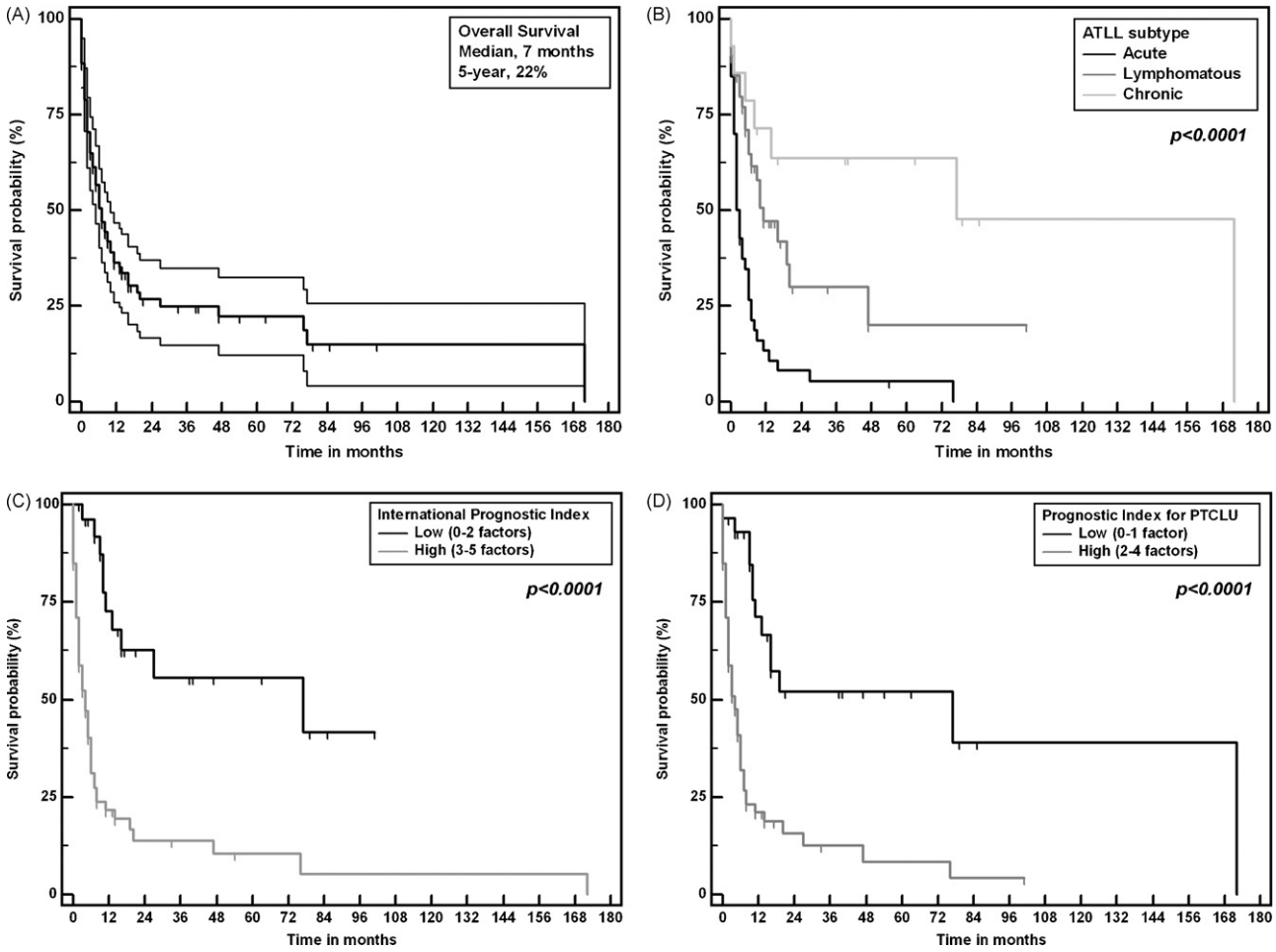

Fig. 1. Kaplan–Meier survival estimates in 95 patients with adult T-cell leukemia/lymphoma for the entire group (A), and according to subtype (B), IPI score (C) and PIT score (D).

3.2. Survival analysis

The median OS for the entire group ($n = 95$) was 7 months with a 5-year OS of 22% (Fig. 1A). The median OS for acute ($n = 40$), lymphomatous ($n = 41$) and chronic ($n = 14$) ATLL were 2, 11 and 77 months, respectively (Fig. 1B). The IPI and the PIT scores were associated with OS (Fig. 1C and D, respectively).

The univariate analysis of prognostic factors for OS according to ATLL subtype is shown in Table 2. Poor performance status (Fig. 2A), high IPI score (Fig. 2B), presence of B symptoms (Fig. 2C), albumin levels <4 g/dl (Fig. 2D) and high LDH levels (data not shown) were associated with worse OS in patients with lymphomatous ATLL. High LDH levels (Fig. 3A), high PIT scores (Fig. 3B) and β2-microglobulin levels ≥4 mg/l (Fig. 3C) were associated with worse OS in patients with acute ATLL. Age ≥40 years, gender, bone marrow involvement, clinical stage or calcium levels ≥10 mg/dl were not associated with OS.

PIT score, β2-microglobulin levels and LDH levels were included in the multivariate analysis of 25 patients with acute ATLL; an elevated β2-microglobulin level was the only independent prognostic

Table 2
Univariate analysis of prognostic factors for overall survival in 81 patients with adult T-cell leukemia/lymphoma according to subtype.

Variable	Acute subtype		Lymphomatous subtype	
	Hazard ratio (95% CI)	*p*-Value	Hazard ratio (95% CI)	*p*-Value
Age ≥40 years	1.8 (0.6–5.9)	0.32	1.4 (0.3–5.4)	0.67
Performance status ECOG ≥2	1.5 (0.7–3.3)	0.26	2.6 (1.1–6.3)	**0.03**
High LDH level	4.4 (1.8–11.1)	**0.0014**	3.3 (1.2–9.1)	**0.02**
Advanced stage	–	–[a]	1.8 (0.7–6.3)	0.26
Bone marrow involvement	1.4 (0.6–3.3)	0.47	1.4 (0.5–4.2)	0.57
Presence of B symptoms	3.2 (0.9–11.1)	0.07	4.8 (1.7–13.7)	**0.003**
High IPI score (≥2)	2.4 (1.0–5.9)	0.06	2.6 (1.1–5.9)	**0.04**
High PIT score (≥2)	2.4 (1.1–5.3)	**0.03**	2.0 (0.8–4.8)	0.13
β2-Microglobulin ≥4 mg/l	6.3 (2.4–16.7)	**0.0002**	1.1 (0.4–3.2)	0.89
Albumin <4 g/dl	1.8 (0.6–5.4)	0.3	2.9 (1.1–7.4)	**0.03**
Calcium ≥10 mg/dl	1.6 (0.3–8.3)	0.56	3.0 (0.8–11.5)	0.11

ECOG: Eastern Central Oncology Group; LDH: lactate dehydrogenase, CI: confidence interval.
[a] All patients had advanced stage.

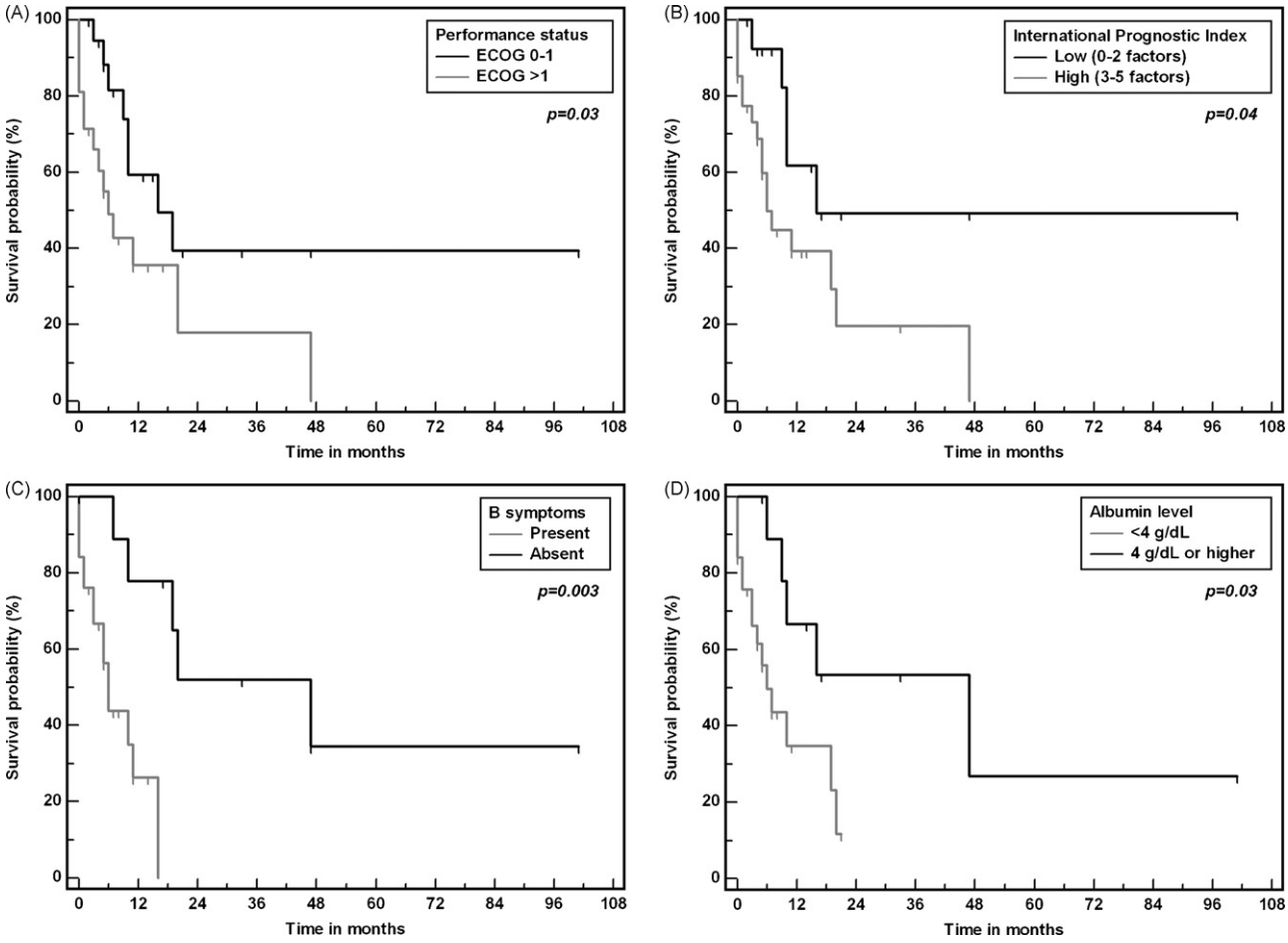

Fig. 2. Kaplan–Meier survival estimates in 40 patients with acute adult T-cell leukemia/lymphoma according to performance status (A), IPI score (B), presence of B symptoms (C) and serum albumin level (D).

factor associated with a worse survival with a hazard ratio (HR) of 9.8 (95% CI 2.2–44.7). For 29 patients with lymphomatous ATLL, IPI score, performance status, LDH levels, albumin levels and B symptoms were used for the multivariate analysis; low albumin levels and presence of B symptoms were independent prognostic factors for OS with HR of 5.6 (95% CI 1.1–29.4) and 4.0 (1.1–14.9), respectively.

4. Discussion

Adult T-cell leukemia/lymphoma (ATLL) is a distinct peripheral T-cell malignancy associated with a retrovirus designated as HTLV-1 [23–25]. The Shimoyama classification establishes four clinical forms: acute, lymphomatous, chronic and smoldering [20]. The acute and the lymphomatous forms are considered aggressive entities with survival times of less than a year, while the remaining variants are considered indolent with survival times between 2 and 5 years. More recently, Bittencourt and colleagues described two cutaneous forms, a smoldering form associated with an indolent course and survival of 58 months and a tumoral form with a survival of 20 months [2].

Our study focused on patients with aggressive variants of ATLL, which approximately account for 80% of all the cases of ATLL [1]. We found that 49% of patients present with acute and 51% present with lymphomatous ATLL; these results are similar to the ones reported in a recent nationwide study from Japan [26]. The acute variant classically presents with a leukemic picture, with the presence of "clover cells" in the peripheral smear, generalized lymphadenopathy, hepatosplenomegaly and hypercalcemia. The lymphomatous variant presents with prominent lymphadenopathy without blood involvement. As a matter of fact, these variants are not only clinically different; they are also associated with distinct molecular and cytogenetic features [27]. Hence, our hypothesis contention is different variants of ATLL should also be associated with a distinct profile of prognostic indicators.

Strengths of our study include the size of the statistical sample ($n = 81$), the pathological evaluation by immunohistochemistry and flow cytometry, making misclassification or misdiagnosis less likely, and the specific focus on the aggressive variants of ATLL. However, our study also carries several weaknesses. First, the clinical data was retrospectively collected, increasing the likelihood of missing information. Second, our patients were not treated uniformly, although the majority received an anthracycline-based regimen. Lastly, the multivariate analysis was performed in smaller subgroups of patients (29 lymphomatous ATLL and 25 acute ATLL). Despite these shortcomings, we were able to show differences in the prognostic factors between ATLL variants.

In our study, patients with acute ATLL presented with higher levels of β2-microglobulin, lower levels of albumin and more frequent bone marrow involvement than patients with lymphomatous ATLL. These findings are consistent with previous reports. In a prior smaller study, high levels of β2-microglobulin were associated with acute ATLL and were an indicator of aggressiveness also related to survival [10]. In another Japanese study, ATLL patients presented with lower levels of albumin than non-Hodgkin lymphoma patients [28]. Lower albumin levels were associated with

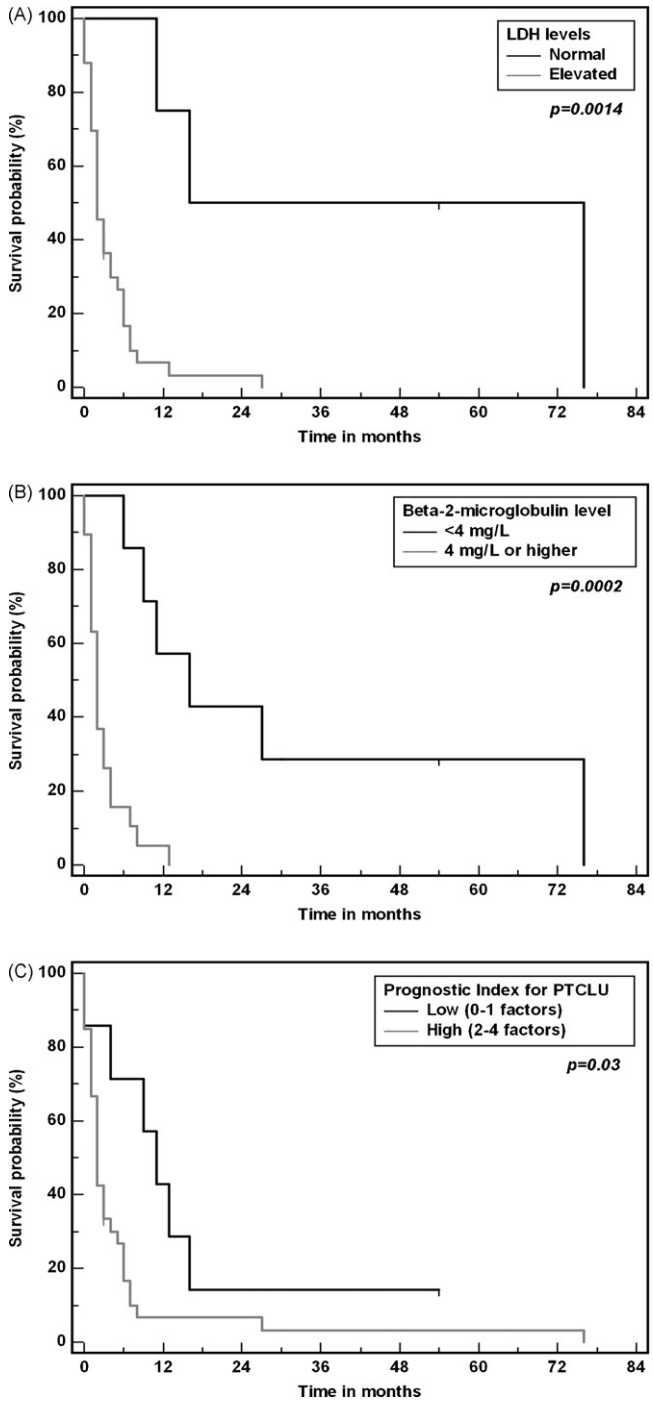

Fig. 3. Kaplan–Meier survival estimates in 41 patients with lymphomatous adult T-cell leukemia/lymphoma according to serum lactate dehydrogenase levels (A), serum β2-microglobulin levels (B) and PIT score (C).

liver dysfunction, since 22 out of 36 ATLL patients undergoing liver biopsies had involvement by ATLL. The latter group had a worse survival; however, in that study there was no differentiation between acute or lymphomatous subtypes. Finally, acute ATLL has previously been associated with more frequent bone marrow involvement (35%) than the lymphomatous variant [1].

Several prognostic factors have been described in ATLL. In one of the largest studies, poor performance status, high LDH levels, age ≥40 years, >3 involved lesions and hypercalcemia were identified as independent prognostic factors in a multivariate analysis [19]. Given the clinical and molecular heterogeneity of ATLL, it is likely that different variants would be associated with distinct prognostic factors. However, few studies have focused on identifying prognostic factors according to the clinical variants of ATLL. A smaller ($n = 44$) Japanese study addressed this specific issue [11]; ATLL cell ratio and leukocyte count were prognostic in acute ATLL while adjusted calcium level was prognostic lymphomatous ATLL. More recently, a report from the International Peripheral T-cell Lymphoma Project showed that the IPI score was the only independent prognostic indicator in patients with lymphomatous but not with acute ATLL [13].

Based on the results of our study, both the IPI and the PIT score appear useful to risk-stratify patients with aggressive ATLL. However, when looking at each ATLL variant separately, we found that high LDH levels, high PIT score and elevated β2-microglobulin were associated with poor survival in patients with acute ATLL, and high LDH levels, high IPI score, low albumin levels, poor performance status and presence of B symptoms were associated with poor survival in patients with lymphomatous ATLL. Furthermore, in the multivariate analysis, β2-microglobulin was an independent prognostic factor for OS in acute ATLL while B symptoms and albumin levels were independent prognostic factors for OS in lymphomatous ATLL. Consistent with a prior report, the profile of prognostic factors of the two aggressive ATLL variants was almost mutually exclusive [11]. All the factors identified by our analysis have been previously reported in other cohorts of patients with ATLL. However, to the best of our knowledge, this is the first study evaluating the PIT score in ATLL. Further studies are needed to validate the PIT score in a larger cohort of patients with lymphomatous ATLL. In addition, our results are consistent with a prior report in which the IPI score was associated with prognosis in patients with lymphomatous, but not acute, ATLL [13].

The clinical outcome in our series of aggressive ATLL was extremely poor, with OS of 2 months for the acute type and 10 months for the lymphomatous type. Anthracycline-based chemotherapy was administered to 81% of our patients with poor results in survival; 3 and 11 months for acute and lymphomatous ATLL, respectively (data not shown). These data are consistent with prior reports in which CHOP and CHOP-like regimens were not effective at improving survival in patients with aggressive variants of ATLL. A recent phase III trial (JCOG 9801) compared the safety and efficacy of a multidrug regimen (VCAP-AMP-VCEP) versus biweekly CHOP in aggressive types of ATLL [29]. The multidrug regimen achieved higher rates of complete response (40% versus 25%, respectively; $p = 0.02$). However, differences in overall response rate, 1-year progression-free survival and 3-year OS did not reach a statistically significance.

Although few studies have shown that myeloablative conditioning regimens followed by allogeneic stem cell transplantation (SCT) could be effective in a limited number of younger patients [30,31], ATLL continues being a hard-to-treat entity and new strategies are necessary to treat this very aggressive lymphoma. According to the International Consensus Meeting proposal published in 2009 [16], novel therapies such as arsenic trioxide, proteasome inhibitors, denileukin diftitox, histone deacetylator inhibitors, antiangiogenic agents, monoclonal antibodies and novel chemotherapeutic agents with or without myeloablative or reduced-intensity SCT should be part of well-designed prospective clinical trials in ATLL.

5. Conclusions

Our study shows that different aggressive ATLL variants are associated with distinct, almost mutually exclusive profiles of prognostic factors for survival. This is a clear reflection of the clinical, molecular and genetic heterogeneity of ATLL. Further research, ideally in prospective settings, is necessary to evaluate these findings.

Conflict of interest statement

The authors have no conflict of interest to disclose.

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Contributions. Conception/Design, Manuscript writing and Data analysis and interpretation: B.B. and J.J.C.; Provision of study material or patients: B.B., D.M. and P.Q.; Collection and/or assembly of data: B.B., D.M., P.Q. and E.C. and Final approval of manuscript: B.B., D.M., P.Q., E.C. and J.J.C.

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