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The prognostic significance of lymphopenia in peripheral T-cell and natural killer/T-cell lymphomas: A study of 826 cases from the International Peripheral T-cell Lymphoma Project

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Abstract

Lymphopenia is a marker of inferior survival in patients with various malignancies. However, the prognostic significance of lymphopenia in peripheral T-cell lymphoma (PTCL) is unclear. We analyzed the prognostic significance of lymphopenia in 826 patients with different types of PTCL and natural killer/T-cell lymphoma (NKTCL) from the International Peripheral T-cell Lymphoma Project. Lymphopenia was defined as an absolute lymphocyte count of less than 1,000 cells per microliter. The overall frequency of lymphopenia was 35.3%, ranging from 21.1% in ALK^+ anaplastic large cell lymphoma (ALCL) to 47.5% in angioimmunoblastic T-cell lymphoma (AITL). Lymphopenia was independently associated with an inferior overall survival (OS) in patients with the lymphoma type of adult T-cell leukemia/lymphoma (ATLL), with a 2-year OS of 15% versus 40% for those without lymphopenia ($P< 0.001$). Lymphopenia was also an adverse predictor of survival in PTCL, not otherwise specified, but was associated with other unfavorable prognostic factors. A trend toward inferior survival for lymphopenic patients was also observed in AITL, ALK^- ALCL and extranasal NKTCL lymphoma, whereas no difference in survival was found in nasal NKTCL, ALK^+ ALCL, or enteropathy-associated T-cell lymphoma. In this study, lymphopenia was identified as a new adverse prognostic factor in the lymphoma type of ATLL.

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Introduction

Peripheral T-cell lymphoma (PTCL) and natural killer/T-cell lymphoma (NKTCL) are an uncommon and heterogeneous group of disorders comprising approximately 5–20% of all non-Hodgkin lymphoma (NHL) in different parts of the world [1]. According to the current World Health Organization classification [1], PTCL is subclassified into several distinctive subtypes including PTCL, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), adult T-cell leukemia/lymphoma (ATLL), nasal and extranasal NKTCL, enteropathy-associated T-cell lymphoma (EATL), as well as other rare entities. ALCL is further separated into the ALK^+ and ALK^- subtypes and, with the exception of ALK^+ ALCL, patients with PTCL and NKTCL generally have a poor prognosis with standard chemotherapy [2]. However, some patients may benefit from more intensive treatment or the use of novel agents [3]. Although different clinical and pathological prognostic factors have been proposed for PTCL and NKTCL, the International Prognostic Index (IPI) for aggressive lymphoma is still the most widely used prognosticator in PTCL [4,5]. Its prognostic importance has been also confirmed in different entities, including PTCL-NOS [6], ALCL [7], ATLL [8], and NKTCL [9].

Lymphopenia has been recognized since 1970 as an adverse predictor of outcome in patients with advanced cancer [10]. More recently, lymphopenia was incorporated into a prognostic score as a negative predictor of survival in patients with advanced Hodgkin lymphoma [11]. Subsequently, other studies have demonstrated an adverse effect of lymphopenia on the survival of patients with aggressive NHL and diffuse large B-cell lymphoma (DLBCL) [12–17]. In PTCL, however, lymphopenia had no effect on the survival of patients with AITL [18–20] or PTCL-NOS [20]. Nevertheless, lymphopenia was identified as an independent predictor of survival in PTCL-NOS in two recent studies [21,22]. To our knowledge, lymphopenia has not been investigated as a prognostic marker in ATLL. Due to the rarity and heterogeneity of PTCL, most of these studies were underpowered to demonstrate whether lymphopenia represents an independent prognostic marker or is merely associated with more advanced disease or other unfavorable characteristics. Lymphopenia was defined as an absolute lymphocyte count (ALC) of less than 1,000 cells/μl in most of the previous studies [10,12,13,15–17,19–22].

The International Peripheral T-cell Lymphoma Project was undertaken as a large retrospective study of PTCL and NKTCL in North America, Europe, and Asia to provide better characterization of this group of lymphomas [2]. Our aim in this study was to assess the frequency and prognostic significance of lymphopenia in the more common entities in this cohort.

Methods

The International Peripheral T-cell Lymphoma Project included 22 institutions in North America, Europe, and Asia that participated in collection of the cases (Appendix 1). The study included 1,314 previously untreated patients who were diagnosed from January 1, 1990, to December 31, 2002 [2]. All cases were reviewed by four expert hematopathologists and a consensus diagnosis was reached in each case. A total of 826 patients with available

clinical data and an ALC at the time of initial diagnosis were analyzed in this study, including 256 with PTCL-NOS, 200 with AITL, 109 with ALCL (57 ALK^+ and 52 ALK^-), 104 with the lymphoma type of ATLL, 81 with nasal NKTCL, 29 with extranasal NKTCL, and 47 with EATL. The other rare subtypes of PTCL and NKTCL were not included in this analysis. According to most previous studies, lymphopenia in this study was defined as an ALC of less than 1,000 cells/μl, unless otherwise specified.

Of the 126 cases with ATLL in the project, 104 with the lymphoma type of ATLL were included in this analysis. According to the classification of Shimoyama [23], these patients had an ALC of less than 4,000 cells/μl, elevated anti-human T-cell lymphotropic virus type I (HTLV) titer, and histologically proven lymphadenopathy. In six patients, the ALC was unknown, and 16 patients had the acute type of ATLL. Data on all patients with ATLL in the project were previously published [8].

Treatment outcome was determined by overall survival (OS) and failure-free survival (FFS). OS was defined as the time from diagnosis to death from any cause, with surviving patient follow-up being censored at the last contact date. FFS was defined as the time from diagnosis to first progression, relapse after response, or death from any cause. Follow up of patients not experiencing any of these events was censored at the date of last contact. OS and FFS were calculated by the method of Kaplan and Meier [24], and time-to-event distributions were compared using the log-rank test. Comparisons of clinical features and prognostic factors were performed with the chi-square test. Multivariate analysis was performed using the Cox proportional hazards regression model with stepwise selection [25].

Results

The overall frequency of lymphopenia in our cohort of 826 patients was 35.3%, ranging from 21.1% in ALK^+ ALCL to 47.5% in AITL. The frequency of lymphopenia was 35.6% in the lymphoma type of ATLL, 35.3% in PTCLNOS, 25% in ALK^- ALCL, 31.9% in EATL, 27.1% in nasal NKTCL, and 44.8% in extranasal NKTCL.

In ATLL, patients with an ALC of less than 1,000 cells/μl had a significantly inferior survival compared to those with an ALC of 1,000 cells/μl or more (2-year OS of 15% vs. 40%, $P < 0.001$; 2-year FFS of 8% vs. 30%, $P = 0.0061$; Fig. 1). In PTCL-NOS, the differences in survival by ALC were smaller but statistically significant (2-year OS of 43% vs. 53%, $P = 0.034$; 2-year FFS of 23% vs. 36%, $P = 0.0062$; Fig. 2). A trend toward inferior OS and/or FFS for patients with lymphopenia was also observed in AITL ($P = 0.054$ for OS, $P = 0.30$ for FFS), extranasal NKTCL ($P = 0.072$ for OS, $P = 0.088$ for FFS), and ALK^- ALCL ($P = 0.086$ for OS, $P = 0.23$ for FFS), but no survival differences were observed in ALK^+ ALCL, EATL, or nasal NKTCL ($P > 0.10$ for OS and FFS).

The chi-square test was used to assess the possible association of lymphopenia with the IPI score. Patients with lymphopenia were more likely to have high IPI scores (IPI 3–5) in PTCL-NOS ($P = 0.004$), AITL ($P < 0.05$), and extranasal NKTCL ($P < 0.01$). In ATLL, ALCL, EATL, and nasal NKTCL, lymphopenia was not associated with high IPI scores.

The Cox proportional hazards regression model was used to test whether lymphopenia was an independent predictor of survival while controlling for the IPI in ATLL, PTCL-NOS, and AITL (Table I). A high IPI score was a statistically significant predictor of OS and FFS in all three entities. In ATLL, lymphopenia was also predictive of survival with a hazard ratio (HR) of 2.37 for OS ($P = 0.0003$) and 1.93 for FFS ($P = 0.004$). In PTCL-NOS, the HR for lymphopenia was 1.25 for OS ($P = 0.188$) and 1.40 for FFS ($P = 0.028$). In AITL, lymphopenia was not an independent predictor of survival.

We also compared the clinical characteristics of patients with ATLL and PTCL-NOS stratified by the ALC (Table II). In ATLL, patients with lymphopenia were more likely to have a normal serum lactate dehydrogenase (LDH) level ($P = 0.007$), but tended to have less than 150×10^9/l platelets ($P = 0.061$) in comparison with those without lymphopenia. In PTCL-NOS, patients with lymphopenia were more likely to be older than 60 years ($P = 0.036$), have B symptoms ($P = 0.014$), an elevated serum LDH ($P = 0.012$), less than 150×10^9/l platelets ($P = 0.026$), a hemoglobin less than 120 g/l ($P = 0.006$), an elevated beta-2 microglobulin level ($P = 0.001$), and high IPI scores ($P = 0.004$), whereas the association of lymphopenia with stage III/IV disease and performance status was of borderline significance ($P = 0.06$ and 0.056, respectively).

To assess whether more profound lymphopenia results in more inferior OS, we set an ALC of less than 800 cells/μl as a new cut-off value for lymphopenia in ATLL, PTCL-NOS, and AITL. Patients with an ALC of less than 800 cells/μl had inferior OS compared with those with an ALC of 800 cells/μl or more in ATLL ($P < 0.001$), whereas no difference in OS was observed in PTCL-NOS and AITL ($P > 0.10$).

Discussion

Lymphopenia has been used as a prognostic indicator in patients with advanced-stage carcinoma, sarcoma, Hodgkin lymphoma and DLBCL [10–17]. The association of lymphopenia with inferior survival has also been demonstrated in acute myeloid and lymphoid leukemia, multiple myeloma, and in the transplantation setting of Hodgkin lymphoma and DLBCL [26–29]. In PTCL, lymphopenia was reported to have no prognostic significance in AITL [18–20], whereas three studies of PTCL-NOS had inconsistent results [20–22]. Most of these studies are retrospective, single-center studies that included relatively small numbers of patients without an external review of the diagnoses. In contrast, this study included large number of cases that were reviewed by expert hematopathologists and classified according to the World Health Organization classification.

The overall frequency of lymphopenia in PTCL and NKTCL was 35.3% (range, 21.1–47.5%) in our study, which is comparable to that reported in solid tumors and other lymphomas [12,13,15–17,20–22]. Interestingly, the lowest frequency of lymphopenia was found in ALK^+ ALCL, which is prognostically the most favorable subtype of PTCL [2]. In contrast, the highest frequency of lymphopenia was observed in AITL, similar to previous reports [19,20]. AITL is characterized by advanced stage at presentation in about 80% the patients, with a marked paraneoplastic inflammatory response and significant

immunosuppression secondary to the tumor [1,18], all of which may contribute to lymphopenia [12].

Our identification of lymphopenia as a strong and independent prognostic marker of inferior survival in the lymphoma type of ATLL represents a novel finding. ATLL is a peripheral T-cell malignancy caused by a retrovirus, HTLV-1 [1]. ATLL is endemic in several regions of the world, particularly southwestern Japan, the Caribbean basin, Peru, and parts of central Africa. ATLL can be divided into four clinical subtypes, including the smoldering, chronic, acute, and lymphoma types [23]. Adverse prognostic factors in ATLL include a poor performance status, high serum LDH level, age = 40 years, more than three involved sites, and hypercalcemia [30,31]. However, in our previous study, which included these same patients with the lymphoma type of ATLL, the IPI score was the only significant predictor of survival by multivariate analysis, whereas lymphopenia was not assessed [8]. Recently, a new risk model has been developed using some variables of the IPI (age, stage and performance status) and hypercalcemia for patients with predominantly the acute type of ATLL [32]. In this study, lymphopenia in ATLL was not associated with high IPI scores or with other parameters of advanced disease. Therefore, we hypothesize that the mechanism of the lymphopenia in ATLL may be different than in other types of lymphoma or solid tumors. Most likely, the lymphopenia is related to HTLV-1 infection and its lifelong persistence in CD4+ T-cells. HTLV-1 infection causes immunosuppression and increases the likelihood of opportunistic infections, even in patients without lymphoma, most probably due to impaired production of naive T lymphocytes [33]. Similar complications have been observed in patients with lymphoma related to another retrovirus that infects CD4+ T-cells, the human immunodeficiency virus. It has been shown that a low number of CD4+ T-cells is also associated with an inferior OS in human immunodeficiency virus-related B- and T-cell lymphomas [34,35]. As previously reported, the median OS of patients with the lymphoma type of ATLL in our cohort was only 0.8 years, and only 5% of the patients were in complete remission at the time of death [8]. Since most patients die with active disease, it is hard to distinguish lymphoma-related from treatment-related deaths. Nevertheless, further studies are needed to investigate the pathogenesis of lymphopenia in the lymphoma type of ATLL and the possible treatment implications for these patients.

Unlike ATLL, lymphopenia was not an independent predictor of OS in PTCL-NOS and was strongly associated with high IPI scores and other unfavorable prognostic factors, such as elevated serum beta-2 microglobulin and LDH levels, B symptoms, anemia, thrombocytopenia, and older age. In addition, patients with lymphopenia tended to have more advanced stage disease and a poor performance status. Although multivariate analysis showed the prognostic significance of lymphopenia in predicting FFS independent of the IPI (HR 1.40, $P = 0.028$), we conclude that lymphopenia in PTCL-NOS is most likely a reflection of other unfavorable characteristics in these patients. This conclusion is also supported by the finding that patients with an ALC of less than 800 cells/μl did not have inferior OS compared to those an ALC of 800 cells/μl or more, thus demonstrating the lack of association between the degree of lymphopenia and inferior OS in PTCL-NOS.

In conclusion, this study documents the frequency of lymphopenia in the major PTCL and NKTCL entities. Lymphopenia was associated with a significantly inferior survival only in

patients with ATLL and PTCL-NOS. An ALC of less than 1,000 cells/μl appears to be an independent predictor of inferior survival in the lymphoma type of ATLL. In contrast, lymphopenia in PTCL-NOS was a less robust predictor of survival and was most likely related to other unfavorable prognostic factors.

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Appendix

TABLE AI.

Participating Sites and Physicians

Institution	Location	Physicians
British Columbia Cancer Agency	Vancouver, Canada	Kerry Savage, MD; Joseph Connors, MD; Randy Gascoyne, MD; Mukesh Chhanabhai, MD
National Cancer Institute	Bethesda, MD	Wyndham H. Wilson, MD; Elaine S. Jaffe, MD
University of Nebraska Medical Center	Omaha, NE	James Armitage, MD; Julie Vose, MD; Dennis Weisenburger, MD; James Anderson, PhD; Fred Ullrich, MS, Martin Bast, BS
Massachusetts General Hospital	Boston, MA	Ephraim Hochberg, MD; Agata Smogorzewska, MD; Nancy Harris, MD
Norris Cancer Center	Los Angeles, CA	Alexandra Levine, MD; Bharat Nathwani, MD
Arizona Health Sciences Center	Tucson, AZ	Thomas Miller, MD; Lisa Rimsza, MD
University of Barcelona Hospital	Barcelona, Spain	Emili Montserrat, MD; Armando Lopez-Guillermo, MD; Elias Campo, MD
Spanish National Cancer Center	Madrid, Spain	Marta Cuadros, MD; Javier Alvarez Ferreira, MD; Beatriz Martinez Delgado, MD
Norwegian Radium Hospital	Oslo, Norway	Harald Holte, MD; Jan Delabie, MD
University of Würzburg Hospital	Würzburg, Germany	Thomas Rüdiger, MD; Konrad Müller-Hermelink, MD; Peter Reimer, MD; Patrick Adam, MD
	Nürnberg, Germany	Martin Wilhelm, MD
	Hamburg, Germany	Norbert Schmitz, MD
	Munich, Germany	Christoph Nerl, MD
Saint Bartholomew's Hospital	London, UK	Andrew Lister, MD; Andrew Norton, MD
University of Bologna Hospital	Bologna, Italy	Stefano Pileri, MD; Pier Luigi Zinzani, MD
University of Modena Hospital	Modena, Italy	Massimo Federico, MD; Monica Bellei, PhD
Centre Hospitalier Lyon-Sud	Lyon, France	Bertrand Coiffier, MD; Francoise Berger, MD
King Chulalongkorn Hospital	Bangkok, Thailand	Intragumtornchai Tanin, MD; Pongsak Wannakrairot, MD
Queen Mary Hospital	Hong Kong, China	Wing Y. Au, MD; Raymond Liang, MD; Florence Loong, MD
Singapore General Hospital	Singapore	Sandeep Rajan, MD; Ivy Sng, MD
National Cancer Center Hospital of Japan	Tokyo, Japan	Kensei Tobinai, MD; Yoshihiro Matsuno, MD
Aichi Cancer Center	Nagoya, Japan	Yasuo Morishima, MD; Shigeo Nakamura, MD; Masao Seto, MD
Okayama University Hospital	Okayama, Japan	Mitsune Tanimoto, MD; Tadashi Yoshino, MD

Institution	Location	Physicians
Fukuoka University Hospital	Fukuoka, Japan	Junji Suzumiya, MD; Koichi Ohshima, MD
Samsung Medical Center	Seoul, Korea	Won-Seog Kim, MD; Young-Hyeh Ko, MD

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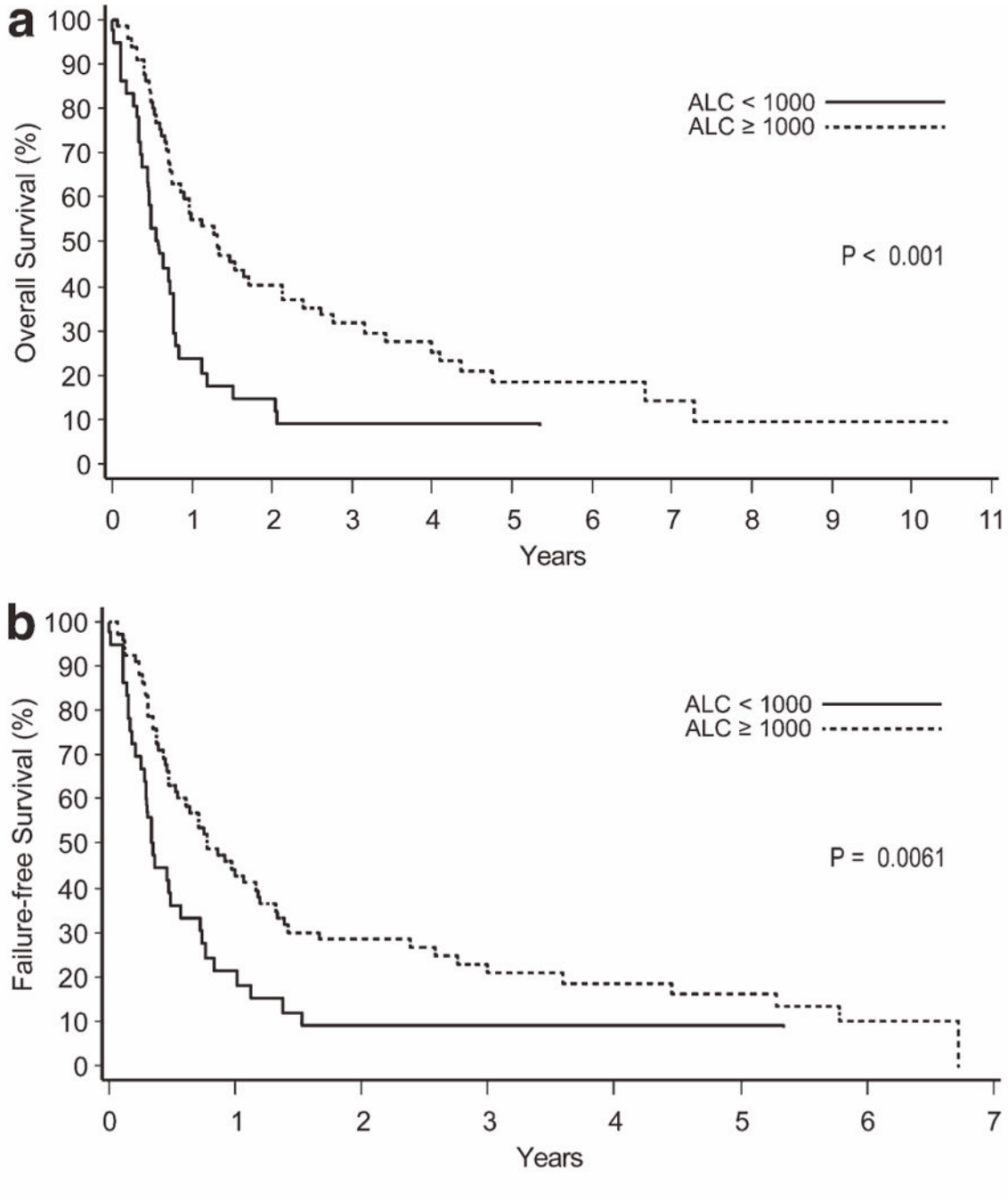

Figure 1.

Overall survival (a) and failure-free survival (b) according to the absolute lymphocyte count (ALC) in the lymphoma type of adult T-cell leukemia/ lymphoma

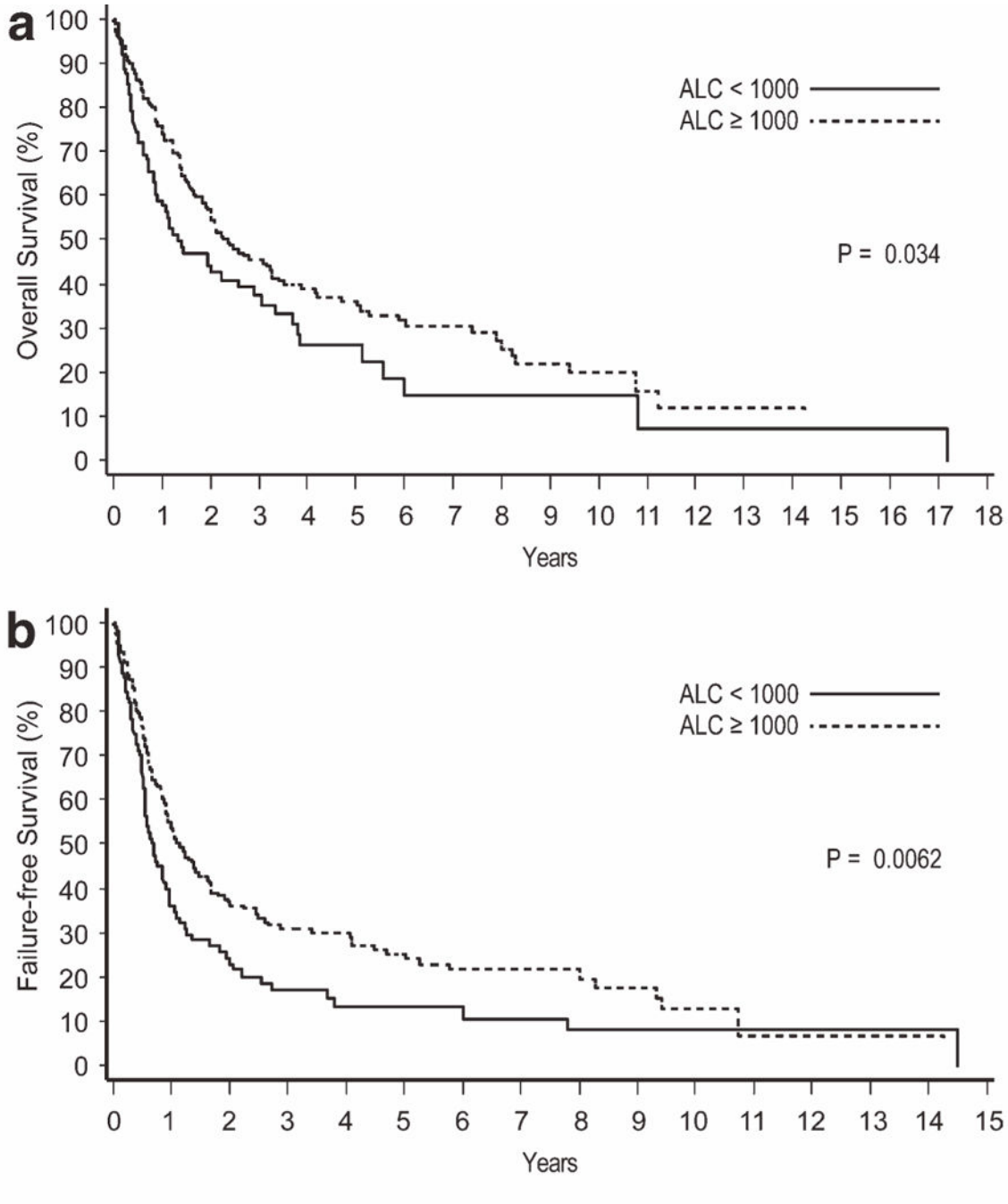

Figure 2.

Overall survival (a) and failure-free survival (b) according to the absolute lymphocyte count (ALC) in peripheral T-cell lymphoma, not otherwise specified.

TABLE I.

Multivariate Analysis of Lymphopenia as a Predictor of Survival when Controlling for the International Prognostic Index (IPI) in Adult T-cell Leukemia/Lymphoma (ATLL), Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL-NOS), and Angioimmunoblastic T-cell Lymphoma (AITL)

PTCL subtype	Hazard ratio	*P* value
ATLL OS		
IPI 3–5	1.85	0.006
Lymphopenia	2.37	0.0003
ATLL FFS		
IPI 3–5	1.56	0.044
Lymphopenia	1.93	0.004
PTCL-NOS OS		
IPI 3–5	2.09	0.0001
Lymphopenia	1.25	0.188
PTCL-NOS FFS		
IPI 3–5	1.63	0.001
Lymphopenia	1.40	0.028
AITL OS		
IPI 3–5	1.57	0.013
Lymphopenia	1.30	0.152
AITL FFS		
IPI 3–5	1.59	0.006
Lymphopenia	1.09	0.605

TABLE II.

Clinical Characteristics of Patients with Adult T-cell Leukemia/Lymphoma (ATLL) and Peripheral T-cell Lymphoma, Not Otherwise Specified (PTCL-NOS), According to the Absolute Lymphocyte Count (ALC)

	ATLL			PTCL-NOS		
	ALC < 1000 *N* (%)	**ALC ≥ 1000 *N* (%)**	***P***	**ALC < 1000 *N* (%)**	**ALC ≥ 1000 *N* (%)**	***P***
Age > 60 years	25 (68)	35 (52)	0.15	53 (59)	74 (45)	0.036
Male	19 (51)	36 (54)	0.84	54 (60)	108 (66)	0.41
B symptoms	10 (27)	17 (25)	1.00	42 (47)	51 (31)	0.014
Stage III/IV	36 (97)	57 (85)	0.09	70 (79)	111 (67)	0.060
Performance status ≥ 2	9 (24)	13 (19)	0.62	21 (24)	23 (14)	0.056
Elevated serum LDH	8 (22)	33 (49)	0.007	53 (60)	69 (42)	0.012
Extranodal sites > 1	9 (24)	23 (34)	0.38	32 (36)	47 (28)	0.26
Bone marrow involved	4 (11)	16 (24)	0.13	21 (23)	35 (21)	0.75
Largest mass ≥ 10 cm	2 (6)	6 (10)	0.71	5 (7)	7 (5)	0.76
Platelets < 150 × 10^9/l	8 (22)	5 (8)	0.061	27 (30)	29 (18)	0.026
Hemoglobin < 120 g/l	13 (35)	19 (28)	0.51	42 (47)	49 (30)	0.006
Elevated CRP	24 (67)	33 (53)	0.21	28 (55)	33 (48)	0.47
Elevated B2M	3 (38)	8 (35)	1.00	24 (53)	16 (23)	0.001
IPI score 3–5	16 (43)	31 (46)	0.84	43 (50)	50 (31)	0.004

LDH, lactate dehydrogenase; CRP, C-reactive protein; B2M, beta-2 microglobulin; IPI, International Prognostic Index.