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RESEARCH ARTICLE

Poor prognostic factors of Sézary syndrome: A retrospective single-center study from Japan

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Abstract

Objectives: Although the prognosis of Sézary syndrome (SS) is highly unfavorable, the prognostic factors have not been fully understood. In this study, we tried to investigate the prognostic factors in Japanese SS patients for the first time.

Methods: We performed a retrospective cohort study of 19 SS patients who visited our hospital between January 1, 1999, and December 31, 2019. The collected clinical findings were age, gender, performance status (PS), and TNMB staging at diagnosis. TNMB staging was determined according to the International Society for Cutaneous Lymphomas and the cutaneous task force of the European Organization of Research and Treatment of Cancer criteria. The collected hematological findings were serum levels of soluble IL-2 receptor (sIL-2R), lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC), and immunoglobulin E (IgE), Sézary cell count, Sézary cell ratio among white blood cells, and eosinophil count in peripheral blood at diagnosis.

Results: We analyzed the correlations between overall survival and various clinical and hematological findings. In the log-rank test, PS1-3, N2-3 stage, higher serum levels of LDH (≥355 IU/L), sIL-2R (≥1729 U/ml) and TARC (≥19,867 pg/ml), and higher Sézary cell count (≥7480/μl) and Sézary cell ratio among white blood cells (≥52%) at diagnosis were associated with decreased overall survival.

Conclusions: This is the first report evaluating prognostic factors in Asian SS patients. This study may contribute to selecting the treatment strategy and improving survival and quality of life of Asian SS patients.

KEYWORDS
CTCL, prognostic factor, Sézary syndrome, sIL-2R, TNMB staging

1 | INTRODUCTION

Sézary syndrome (SS) is a cutaneous T-cell lymphoma (CTCL) characterized by pruritic erythroderma, lymphadenopathy, and leukemic involvement of peripheral blood.[1] SS accounts for only 3% of CTCL, and SS occurs in about only 0.1 out of million people.[1–3] It affects both male and female and generally begins when patients are in their sixties.[3,4] The prognosis is highly unfavorable, with median survival ranging from 2 to 4 years, and the 5-year survival rate is 24%.[1,5,6] SS and mycosis fungoides (MF), the most common subtype of CTCL, have been recognized as diseases of the same spectrum because of the similarity of histological findings represented by epidermotropism of atypical lymphocytes and immunohistochemical findings. Actually, other than de novo SS, there have been SS cases that develop from MF. The same TNMB staging has been applied to both diseases, and most analyses on prognostic factors include both diseases. A retrospective study including 1398 MF patients, 71% of which had patch/plaque stage disease, and 104 SS patients revealed that T, N, M, and B classification was significantly associated with overall survival (OS) on multivariate analyses.[7] In patients with advanced MF and SS, male, age >60, B1-2, N2-3, and M1 stage were found to be poor prognostic factors.[7] In another international retrospective study of 1275 advanced MF and SS patients, stage IV disease, age > 60, large cell transformation, and elevated lactate dehydrogenase (LDH) level were identified as independent adverse prognostic factors.[8] Similar results are also reported from the analyses on Japanese MF and SS patients.[9,10]

Recently, it has been reported that SS is a malignancy of central memory T cells and that MF originates from skin resident effector memory T cells, suggesting that SS and MF should be considered as separate lymphomas arising from distinct functional T-cell subsets.[11] There is a possibility that different factors are associated with a prognosis between advanced MF and SS. On the contrary, the studies on prognostic factors in SS patients alone are limited. Some retrospective studies have been conducted in Europe and the United States,[6,12,13] whereas there have been no reports on factors associated with prognosis in Asian SS patients. The aim of this study was to analyze the correlations between OS and various clinical and hematological findings by univariate analysis in Japanese patients with SS. Prognostic prediction of SS can help us to choose the better therapeutic options and improve the life prognosis of SS.

2 | MATERIALS AND METHODS

2.1 | Patients

We diagnosed SS based on the presence of the following criteria: 1) skin biopsy suggestive of CTCL on histopathological and immunohistochemical basis, 2) leukemic involvement of peripheral blood (B2 stage), and 3) erythroderma. Although one patient did not have erythroderma, he had symmetric ill-demarcated erythema with itching and met criteria other than erythroderma and we decided to incorporate the patient into this study. Actually, the presence of nonerythrodermic SS has been widely known.[14] The collected clinical findings were age, gender, performance status (PS), and TNMB staging at diagnosis. The collected hematological findings were serum levels of soluble IL-2 receptor (sIL-2R), LDH, thymus and activation-regulated chemokine (TARC), and immunoglobulin E (IgE), Sézary cell count, Sézary cell ratio among white blood cells, and eosinophil count in peripheral blood. TNMB staging of MF and SS was determined according to the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous task force of the European Organization of Research and Treatment of Cancer (EORTC) proposal.[15] The medical ethical committee of the University of Tokyo approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles (approval number: 0695-[17]).

2.2 | Study endpoints

The primary endpoints were OS. OS was calculated from the date of initial diagnosis until the date of death as a result of any cause. Patients who survived beyond the end of the follow-up were censored in December 2019.

2.3 | Patient classification

We divided patients into two groups by setting cutoff values of the following factors: age, serum levels of LDH, sIL-2R, TARC, and IgE, Sézary cell count, Sézary cell ratio among white blood cells, and eosinophil count in peripheral blood and compared OS between two groups. The best discriminating cutoff value of each factor was established using the receiver operating characteristic analysis. The cutoff values of age, serum levels of LDH, sIL-2R, TARC, and IgE, Sézary cell count, Sézary cell ratio among white blood cells, and eosinophil count in peripheral blood were defined as 52 years old, 355 IU/L, 1729 U/ml, 19,867 pg/ml, 567 IU/ml, 7480/μl, 52%, and 300/μl, respectively. Regarding gender, we divided patients into two groups, male and female. Regarding PS, we compared OS between patients with PS0 and patients with PS1-3. Regarding N stage, we compared OS between patients with N0 stage and patients with N2-3 stage.

2.4 | Statistical analysis

OS rates were estimated by the Kaplan-Meier method, and the differences in survival between the two groups were assessed by the log-rank test. A Cox proportional hazards model was used to quantify the prognostic impact of individual covariates, wherein the hazard ratios (HRs) and confidence intervals (CIs) were calculated. An analysis was performed for each of the 11 factors, and $p < .05$ was considered significant. All statistical data were generated using the

Stata 12 software program (Stata Corporation, College Station, TX, USA) and GraphPad Prism software version 8.

3 | RESULTS

3.1 | Patient characteristics

Our study population consisted of 19 SS patients diagnosed in the Department of Dermatology of the University of Tokyo Hospital in Japan between January 1999 and December 2019. Patients' characteristics at diagnosis are summarized in Table 1. Although one patient had a low Sézary cell count of 287/μl, the flow cytometric analysis of peripheral blood revealed $CD4^+CD7^-$ cells of ≥40% (45.5%) and clonal T-cell receptor gene rearrangements in both skin and peripheral blood were detected. The median age at SS diagnosis was 64 years (range: 28-85 years). All patients were Japanese and comprised 14 men and 5 women. One patient underwent surgery for rectal cancer 5 years before the diagnosis as SS and was alive without recurrence. Two patients had cerebral infarctions and took antiplatelet drugs, but the cerebral infarctions were mild and not related to the prognosis. Other patients showed no particular medical or surgical history except for age-related high blood pressure, hyperlipidemia, and hyperuricemia. Pruritus was present in all patients at diagnosis. No patients were diagnosed as having MF prior to SS diagnosis. Eighteen patients (94.7%) had erythroderma (T4), and only 1 patient (5.3%) had patch and plaque lesions in more than 10% of their skin surface (T2b). Peripheral lymphadenopathy was detected in 12 patients (63.2%). Lymph node biopsies were performed in all of them. Lymph node biopsies revealed that 2 patients (16.7%) were histopathologically classified into N2 stage and 10 into N3 (83.3%) stage. No visceral involvement including bone marrow involvement was found in any patient. All patients met B2 stage.

3.2 | Survival

The median OS of all patients was 35 months (range 8-124), and 10 patients died due to causes related to SS during the observation period. Figure 1 shows OS depending on age, gender, PS, N stage, and hematological findings. Among them, age, gender, serum IgE levels, and eosinophil count in peripheral blood did not affect OS in the log-rank test. On the contrary, PS1-3, N2-3 stage, higher serum sIL-2R (≥1729 U/ml), LDH (≥355 IU/L), and TARC levels (≥19,867 pg/ml), and higher Sézary cell count (≥7480/μl) and ratio among white blood cells (≥52%) were significantly associated with shorter OS ($p = .011$, .038, .030, .014, .014, .001, and .008, respectively).

3.3 | Prognostic factors

We next identified poor prognostic factors of SS by univariate analysis. The results are shown in Table 2. The univariate analysis revealed that PS1-3, N2-3 stage, higher serum LDH (≥355 IU/L) and TARC levels (≥19,867 pg/ml), and higher Sézary cell count (≥7480/μl) and ratio among white blood cells (≥52%) significantly increased the risk of death. (HR 11.362; 95% CI 1.408-91.651; $p = .023$; HR 8.340; 95% CI 1.046-67.435; $p = .045$; HR 6.674; 95% CI 1.403-31.744; $p = .017$; HR 4.194; 95% CI 1.043-16.869; $p = .043$; HR 16.905; 95% CI 2.075-137.722; $p = .008$; and HR 7.706; 95% CI 1.587-37.410; $p = .011$, respectively). We did not conduct a multivariate analysis, because the sample number was small.

4 | DISCUSSION

Due to the low prevalence of SS, studies on prognostic factors of SS patients alone are limited and only three retrospective studies from Italy, France, and the United States have been reported.[6,12,13] Prognostic factors in the univariate analyses, reported in more than one previous report, were older age, prior diagnosis of MF, and high serum LDH level. Among them, high serum LDH level was correlated with a poor prognosis in all three studies. Similar to previous reports, high serum LDH level (≥355 IU/L) was also a significant poor prognostic factor in our study, indicating that serum LDH levels can predict the clinical course of SS patients to some extent, regardless of race. As prior diagnosis of MF was not made in any patient in our study, we could not reveal whether the factor can be associated with a poor prognosis in Asian SS patients. Interestingly, older age was not identified as a prognostic factor in our study. In studies that found older age as a poor prognostic factor, the median age of SS patients was 69 years old in one study and the mean age of SS patients in the other study was 66.2 years old.[6,12] The median and mean age of patients in our study were 64 and 60.8 years old, both of which were lower than those in previous studies. The difference in age at diagnosis might be associated with the lack of association between older age and a poor prognosis in our study.

Other than high serum LDH level, we found that PS1-3, N2-3 stage, high serum TARC level (≥19,867 pg/ml), and Sézary cell count (≥7480/μl) and ratio among white blood cells (≥52%) were significant poor prognostic factors for OS in the univariate analysis. PS has been used to quantify the general condition of patients with various diseases.[18] Many studies have reported PS2-4 to be an important prognostic factor of aggressive lymphomas.[16] Although the association of PS with prognosis in CTCL has not been studied so much, Tobisawa et al. reported PS2-4 to be an independent prognostic factor for OS of Japanese patients with MF and SS.[10] We found PS1-3 was a poor prognostic factor instead of PS2-4 in the univariate analysis in SS patients. Considering that all 9 patients with PS1-3 had passed away in the observational period, PS can be an important poor prognostic factor in Japanese SS patients.

Many studies have reported TNMB staging to be an important prognostic factor for MF and SS. Particularly T3, N2-3, M1, and B2 stages have often been reported as poor prognostic factors of the population including both MF and SS patients.[9,17] Concerning T stage in SS patients, there are conflicting reports. Henn et al.

TABLE 1 Patient characteristics at diagnosis

Age	Gender	PS	TNMB staging	LDH (IU/L)	sIL-2R (U/ml)	Sézary cell count (/μl)	Sézary cell ratio (%)	TARC (pg/ml)	Eosinophil count (/μl)	IgE (IU/ml)	Treatment	Observation period (months)	Dead/ alive
28	F	0	T4N0M0B2	183	317	5336	46	204	0	75	TCS, NBUVB, IFN-γ, bexarotene, oral PSL, forodesine	19	Alive
42	M	0	T4N2M0B2	343	1535	1904	24	737	300	NA	TCS, NBUVB, CHOP, allo-HSCT	124	Alive
42	F	2	T4N0M0B2	477	1811	4048	23	49,658	100	15,000	TCS, NBUVB, etretinate, CHOP, allo-HSCT	53	Dead
42	M	0	T4N2M0B2	183	3704	287	7	250	100	268	TCS, NBUVB, etretinate, bexarotene, oral PSL	33	Alive
49	M	0	T4N0M0B2	201	576	5748	48	100	300	10	TCS, NBUVB, etretinate, oral PSL	38	Alive
52	M	1	T4N3M0B2	236	1729	7480	68	17,689	100	3688	TCS, NBUVB, etretinate, CHOP	30	Dead
58	F	2	T4N3M0B2	915	3475	12,712	14	NA	1000	NA	TCS, NBUVB, IFN-γ, MTX, CY	20	Dead
61	F	3	T4N3M0B2	399	2521	13,215	54	32,628	0	4588	TCS, NBUVB, oral PSL, mogamulizumab, etoposide, GEM	24	Dead
63	M	2	T4N3M0B2	355	2943	11,041	61	22,686	100	3100	TCS, PUVA, IFN-γ	47	Dead
64	F	1	T4N3M0B2	380	1881	18,320	80	34,881	100	7686	TCS, NBUVB, oral PSL, vorinostat	66	Dead
66	M	0	T2bN0M0B2	240	1859	4402	36	195	100	118	TCS, NBUVB, oral PSL, IFN-γ, bexarotene, mogamulizumab	15	Alive
66	M	0	T4N0M0B2	191	1368	1800	13	16,596	300	3799	TCS, NBUVB, etretinate	60	Alive
67	M	1	T4N3M0B2	727	6716	13,970	64	26,986	0	37	TCS, NBUVB, oral PSL, IFN-γ, MTX, CY	14	Dead
68	M	0	T4N0M0B2	324	1129	2250	23	995	400	40	TCS, NBUVB, etretinate	110	Alive
74	M	1	T4N3M0B1	540	3642	9302	59	1098	100	42	TCS, NBUVB, etretinate, oral PSL, IFN-γ, mogamulizumab	35	Dead
75	M	0	T4N3M0B2	729	2307	12,309	52	22,591	0	567	TCS, NBUVB, bexarotene, mogamulizumab, etoposide, pralatrexate	8	Dead
76	M	2	T4N3M0B2	266	3134	9802	58	48,850	100	986	TCS, NBUVB, MTX, etoposide	42	Dead
78	M	0	T4N0M0B2	234	2622	4880	40	186	200	NA	TCS, NBUVB, etretinate, oral PSL, mogamulizumab	69	Alive
85	M	0	T4N3M0B2	430	1179	2775	25	18,503	200	857	TCS, NBUVB, etretinate, oral PSL, IFN-γ, bexarotene, forodesine	11	Alive

Abbreviations: allo-HSCT, allogeneic stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CY, cyclophosphamide; GEM, gemcitabine; IFN, interferon; MTX, methotrexate; NA, not available; NBUVB, narrowband ultraviolet B; PSL, prednisolone; PUVA, psoralen-ultraviolet A; TCS, topical corticosteroid.

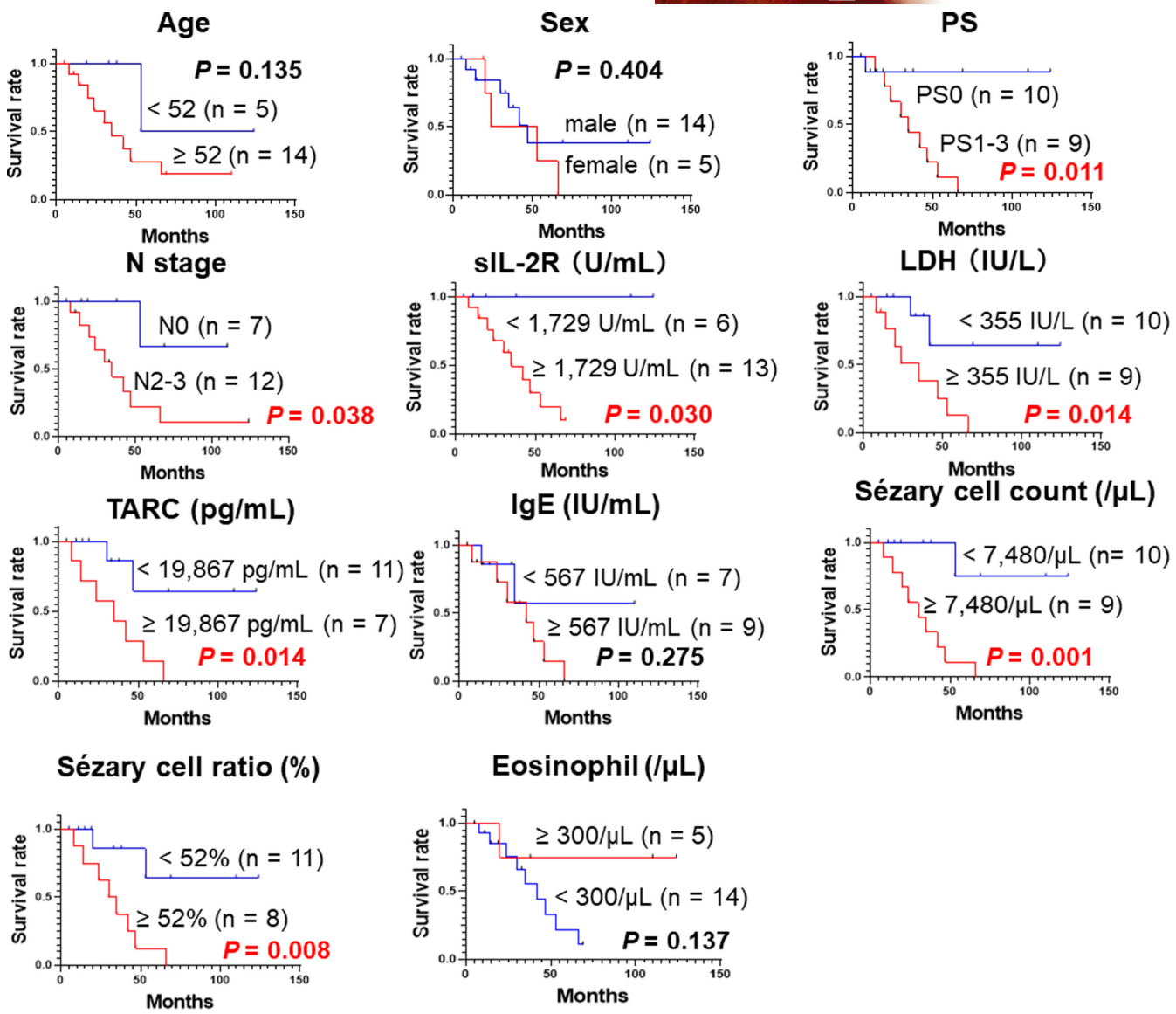

FIGURE 1 Kaplan-Meier survival curves of overall survival (OS) according to age, gender, performance status, N stage, serum soluble IL-2 receptor (sIL-2R), lactate dehydrogenase (LDH), thymus and activation-regulated chemokine (TARC), and immunoglobulin E (IgE) levels, and Sézary cell count, Sézary cell ratio, and eosinophil count in peripheral blood

demonstrated a better prognosis in nonerythrodermic SS than classic SS in 9-year median follow-up.[19] In contrast, Thompson et al. revealed that SS without erythroderma had an equally poor prognosis to classic SS.[20] In our study, as all patients except for one patient had erythroderma, we could not analyze the importance of T stage on prognosis. Similarly, for M stage, all patients were M0 and we could not analyze whether M stage is associated with prognosis. Regarding N stage, 7 patients were classified into N0, 2 into N2, and 10 into N3 stage. There was a statistically significant difference in OS between patients with N0 and N2-3 stage in the univariate analysis in our study, whereas lymph node involvement was not associated with a poor prognosis in two previous studies on SS patients.[6,12] On the contrary, consistent with our result, studies on erythrodermic CTCL including SS found that patients with higher N stage or larger palpable lymph nodes had a worse prognosis compared to those with lower N stage or smaller nodes.[21,22] Although it is not clearly elucidated yet whether N stage is related to a poor prognosis in SS patients, we considered that all SS patients with lymphadenopathy should undergo lymph node biopsy.

In addition to serum LDH level, we found that serum TARC level was also associated with the prognosis of SS patients. TARC, also called CCL17, is a ligand of CCR4, and high expression of TARC is reported in lesional skin of MF and SS.[23] Serum TARC levels are correlated with disease severity in MF and SS patients and regarded as one of the disease severity markers.[24,25] Thus, it is no wonder that serum TARC level can be a prognostic factor in SS patients similar to serum LDH level. Concerning serum sIL-2R level, the other representative disease marker, higher serum sIL-2R levels were associated with a shorter OS based on the log-rank test. Serum sIL-2R levels are significantly higher in advanced CTCL

TABLE 2 Univariate cox proportional hazards model for OS

Factors	HR (95% CI)	*p* value
Age		
<52	1	
≥52	3.695 (0.467-29.217)	.215
Gender		
Male	1	
Female	1.955 (0.547-6.992)	.303
PS		
0	1	
1–3	11.362 (1.408-91.651)	.023
N stage		
N0	1	
N2-3	8.340 (1.046-67.435)	.045
LDH (IU/L)		
<355	1	
≥355	6.674 (1.403-31.744)	.017
sIL-2R (U/ml)		
<1729	1	
≥1729	N.A.[a]	
Sézary cell count (/μl)		
<7480	1	
≥7480	16.905 (2.075-137.722)	.008
Sézary cell ratio (%)		
<52	1	
≥52	7.706 (1.587-37.410	.011
TARC (pg/ml)		
<19,867	1	
≥19,867	4.194 (1.042-16.869)	.043
Eosinophil (/μl)		
<300	1	
≥300	0.179 (0.022-1.426)	.104
IgE (IU/ml)		
<567	1	
≥567	1.993 (0.400-9.923)	.400

Abbreviations: CI, confidence interval; HR, hazard ratio; IgE, immunoglobulin E; LDH, lactate dehydrogenase; PS, performance status; sIL-2R, soluble interleukin-2 receptor; TARC, thymus and activation-regulated chemokine.

[a]Not available. Due to all patients (sIL-2R < 1729) being alive.

patients with nodal involvement compared to those without.[26] The multivariate analysis of various prognostic factors in erythrodermic CTCL patients demonstrated that serum sIL-2R level correlated best with OS.[19] Although we could not analyze the importance of the factor in prognosis in the univariate analysis, because the patients with lower serum sIL-2R levels (sIL-2R < 1729 U/ml) were all alive, serum sIL-2R level can be regarded as an important prognostic factor in this cohort.

Finally, we found that Sézary cell count and ratio among white blood cells were associated with the prognosis of SS patients. Sézary cell count was reported to increase in patients with N3 stage compared to those with N1 stage in SS patients.[27] In addition, Sézary cell count was correlated with serum sIL-2R level, the most sensitive marker in SS.[19,28] Given these reports, Sézary cell count would reflect total tumor burden of SS patients and might be an important prognostic factor in Japanese SS patients similar to other disease severity markers. In this context, it is important to observe the size of each Sézary cell on blood smears carefully. The morphologic detection of Sézary cells in the peripheral blood is not specific to SS, and only large Sézary cells greater than about 12-14 μm are specific to SS.[17,29,30] Smaller cells morphologically identical to Sézary cells are present in the peripheral blood of 20% to 25% of patients with MF, and smaller numbers of the cells are also present in blood and skin specimens of benign inflammatory diseases and some healthy persons.[29–31] Some studies for MF and SS suggest that high ratio of large Sézary cells (≥12 μm) among the total Sézary cells but not Sézary cell count was prognostically important.[13,17,29] Schechter et al. reported that CTCL patients with more than 20% large Sézary cells (>11 μm) of the total lymphocytes had a poorer prognosis than those with a predominately small cell variant.[29] The report on SS prognostic factors from Italy revealed that the presence of larger Sézary cells (≥15 μm) was associated with a poor prognosis. In our department, we count cells larger than about 11-12 μm as Sézary cells. When evaluating Sézary cell count and ratio among white blood cells as a prognostic factor, the size of Sézary cells in peripheral blood should be taken into consideration.

There are some limitations in this study. First, this is a retrospective single-center study that potentially includes several biases. Second, the number of patients is small compared to three previous studies including 62 patients from Italy, 28 patients from France, and 176 patients from the United States.[6,12,13] Third, as there is no established treatment for SS, the treatment strategy was different depending on individual patients.

In conclusion, we found that PS1-3, N2-3 stage, higher serum levels of LDH (≥355 IU/L), sIL-2R (≥1729 U/ml) and TARC (≥19,867 pg/ml), and higher Sézary cell count (≥7480/μl) and Sézary cell ratio among white blood cells (≥52%) at diagnosis were poor prognostic factors in Japanese SS patients. This is the first report evaluating prognostic factors in Asian SS patients. As racial difference may be related to OS in CTCL patients.[17] Accumulating evidences on prognostic factors of SS patients in various races may contribute to selecting the treatment strategy and improving survival and quality of life.

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CONFLICT OF INTEREST

Dr. Shinichi Sato is a member of the Journal of Cutaneous Immunology and Allergy Editorial Board. Management of the peer review process, and all editorial decision-making, for this article was undertaken by Editor in Chief. The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

YM, TM, and HS designed and executed the study and wrote the paper. YM, TM, HS, HK, HB, YK, KO, TH, TO, NS, MS, and SS executed the clinicopathological analysis and revised the paper critically. All authors have approved the final article and provided disclosure information, and all authors support the integrity of the data.

DECLARATION SECTION

Approval of the research protocol: The medical ethical committee of the University of Tokyo approved all described studies, and the study was conducted according to the Declaration of Helsinki Principles (approval number: 0695-[17]).

Informed Consent: All patients were provided written informed consent.

Registry and the Registration No. of the study/trial: N/A.

Animal Studies: N/A.

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