



Diagnostic Rate of Malignant Lymphoma Using Soluble Interleukin 2 Receptor Levels in Patients with Cervical Lymphadenopathy

Kiyomi Hamaguchi¹ Yota Tobe² Tadashi Ikenaga³ Tetsuhiko Michida¹ Shinji Takebayashi⁴
Keizou Fujiwara¹ Yasushi Naito¹ Shogo Shinohara¹

¹ Department of Otorhinolaryngology—Head and Neck Surgery, Kobe City Medical Center General Hospital, Kobe City, Japan

² Department of Otorhinolaryngology—Head and Neck Surgery, Kyoto University Hospital, Kyoto, Japan

³ Department of Head and Neck Surgery, Nara Prefectural General Medical Center, Nara, Japan

⁴ Department of Otorhinolaryngology, Shiga General Hospital, Shiga, Japan

Address for correspondence Kiyomi Hamaguchi, MD, PhD, Department of Otorhinolaryngology—Head and Neck Surgery, Kobe City Medical Center General Hospital, 2-1-1 Minatojima Minamimachi, Chuo-ku, Kobe City, 650-0047, Japan (e-mail: k_hamaguchi@ent.kuhp.kyoto-u.ac.jp).

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Abstract

Background and Objectives Cervical lymph node enlargement is observed in various diseases, including malignant lymphoma (ML). Open biopsy of the enlarged lymph node is frequently required for diagnosis, especially when ML is suspected. Serum levels of soluble interleukin 2 receptor (sIL-2R) may be useful as a biomarker of ML. This study aimed to determine whether the measurement of serum sIL-2R levels might be useful to diagnose ML.

Materials and Methods We retrospectively reviewed the data of 281 patients who had undergone open cervical lymph node biopsy at our institution between 2015 and 2019, including 157 males and 124 females (age range, 5–90 years). Data on the patients' age, final diagnosis, and serum sIL-2R levels were obtained from their medical records.

Results Overall, 184 cases of MLs and 97 cases of other diseases (non-MLs [NMLs]) were recorded. The mean age was significantly higher and mean serum sIL-2R levels were significantly higher in the ML group than in the NML group. In the ML group, the serum sIL-2R levels were significantly higher in patients with T cell lymphoma than in those with B cell lymphoma. The area under the receiver operating characteristic curve of the serum sIL-2R level for predicting ML was 0.711, and a serum sIL-2R level of 1,246 U/mL was associated with the maximum value of the sensitivity + specificity for the diagnosis of ML. Multivariate analysis revealed that the area under the receiver operating characteristic curve increased to 0.758 for patients aged >61 years and patients with serum sIL-2R levels of >1,246 U/mL.

Conclusions Among patients presenting with cervical lymphadenopathy, the measurement of serum sIL-2R levels could be useful for distinguishing between patients with and without ML, with a cutoff level of 1,246 U/mL for the diagnosis of ML.

Keywords

- ▶ cervical lymph node swelling
- ▶ open biopsy
- ▶ sIL-2R
- ▶ malignant lymphoma

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Introduction

Cervical lymphadenopathy is often seen as the first symptom of malignant lymphoma (ML); however, an extremely broad range of diseases other than ML can present as cervical lymphadenopathies, such as tuberculosis lymphadenopathy, lymph node metastasis of malignant tumors, sarcoidosis, and subacute necrotizing lymphadenitis. Therefore, to diagnose ML, tissue diagnosis is required; in particular, cervical lymph node biopsy is often required.

In contrast, activated T cells secrete interleukin-2 (IL-2) receptors, which comprise only the α -chain as a soluble molecule called soluble IL-2 receptors^{1,2}; therefore, serum soluble IL-2 receptor (sIL-2R) levels are elevated in hematologic malignancies, such as ML, retrovirus infection, and autoimmune disease. A previous study reported that sIL-2R levels may reflect the disease status in leukemia and ML and indicate the related treatment efficacy.³

In this study, we examined the preoperatively measured sIL-2R levels in patients who had undergone cervical lymph node biopsy over the past 5 years and discussed the extent to which sIL-2R measurement can contribute to diagnosing ML.

Materials and Methods

Among the patients who underwent cervical lymph node biopsy at our department from 2015 to 2019, we examined 281 patients in whom sIL-2R levels were measured <1 month preoperatively. Furthermore, the pathological classification of lymphoma was determined in accordance with the 2017 revised World Health Organization (WHO) classification of lymphoid neoplasms.

Of all the patients, 184 were classified into the ML group and 97 into the non-ML (NML) group. The ML group was further classified into 128 patients with B cell lymphoma, 27 with T cell lymphoma, and 19 with Hodgkin's lymphoma. In the ML group, 8 of the 10 patients with drug-associated lymphoproliferative, posttransplant lymphoproliferative, and human immunodeficiency virus (HIV)-related lymphoproliferative disorder were not included in the aforementioned subgroups; therefore, these patients were excluded from the ML group.

In the NML group, 25 patients with metastatic malignant tumors excluding Kaposi's sarcoma were included in the malignant epithelial carcinoma group. The data of this group were compared with that of the ML group.

Mann-Whitney *U*-test was used to compare age and sIL-2R levels between the two groups, and the nonparametric Kruskal-Wallis test was used to compare sIL-2R levels among the three ML subgroups. Statistical analyses were performed using EZR,⁴ and $p < 0.05$ was considered statistically significant.

Results

Of the 281 patients overall, 157 patients were male and 124 were female, aged 5 to 90 years, with a median age of 68 years (►Table 1). The histological classification is presented in ►Table 2; however, the group with "other benign diseases" included 17 patients with lymphadenitis, 2 with lymphoid tissue, and 1 with abscess.

The ML group was significantly older (69 vs. 56 years, $p < 0.001$) and had significantly higher sIL-2R levels (1,181 vs. 516 U/mL, $p < 0.001$) than the NML group (►Fig. 1).

In the three ML subgroups, the median sIL-2R levels were 1,010 (202–31,416) U/mL in the B cell lymphoma group, 1,769 (229–53,868) U/mL in the T cell lymphoma group, and 837 (284–47,695) U/mL in the Hodgkin's lymphoma group, indicating that sIL-2R levels were significantly higher in the T cell lymphoma group than in the B cell lymphoma group ($p = 0.049$; ►Fig. 2).

In the receiver operating characteristic (ROC) curve that examined the feasibility of diagnosing ML based on sIL-2R levels, the cutoff value was 1,246 U/mL, and the area under curve (AUC) was 0.711 (sensitivity, 48.9%; specificity, 85.6%; ►Fig. 3).

On the analysis of sIL-2R alone, the AUC was 0.711; however, when the cutoff value according to age was set to ≥ 61 years, and the AUC increased to 0.758 (►Fig. 3). In the NML group, 14 patients exceeded the cutoff value of 1,246 U/mL, including 2 patients with Castleman's disease, 2 with lymph node metastasis of lung cancer, and 1 each with tuberculosis lymphadenitis, Kimura disease, Epstein-Barr (EB) virus infection, HIV-related Kaposi's sarcoma, and sarcoidosis.

Furthermore, on differentiating malignant epithelial carcinoma from ML, no significant difference in age was found between the malignant epithelial carcinoma group and the ML group (66 vs. 69 years, $p = 0.717$; ►Fig. 4). With regard to sIL-2R levels, the median value in the malignant epithelial carcinoma group was 515 (174–2,987) U/mL; although a significant difference was observed when compared with the

Table 1 Patient background

	All participants	ML group	NML group
Age	5–90 y	5–90 y	13–88 y
Median	68 y	69 y	56 y
Sex			
Male	157 patients (56%)	104 patients (57%)	53 patients (55%)
Female	124 patients (44%)	80 patients (43%)	44 patients (45%)

Abbreviations: ML, malignant lymphoma; NML, non-ML.

Note: The age range and median, as well as the sex and male:female ratio (%), are presented for all participants, ML group, and NML group.

Table 2 Histopathology results

ML group		184	NML group		97
B cell lymphoma		128	Metastatic malignant tumor		26
	Diffuse large B cell lymphoma	62		Squamous epithelial carcinoma	8
	Follicular lymphoma	47		Adenocarcinoma	7
	Nodal marginal zone lymphoma	6		Small-cell carcinoma	2
	Mantle cell lymphoma	3		Undifferentiated carcinoma	2
	Burkitt lymphoma	2		Kaposi's sarcoma	1
	MALT lymphoma	2		Lymphoepithelial carcinoma	1
	Lymphoplasmacytic lymphoma	2		Nonendocrine carcinoma	1
	Small lymphocytic lymphoma	1		Unknown	4
	NOS	3		Nonmalignant tumor	
T cell lymphoma		27	Lymphoid follicular hyperplasia	17	
	Peripheral T cell lymphoma	12	Subacute necrotizing lymphadenitis	12	
	Adult T cell leukemia lymphoma	5	Tuberculous lymphadenitis	6	
	Angioimmunoblastic T cell lymphoma	3	IgG4-related disease	5	
	T cell lymphoblastic lymphoma	2	Sarcoidosis	5	
	NK/T cell lymphoma	2	EB virus infection	2	
	Sezary syndrome	2	Kimura disease	2	
	Anaplastic large-cell lymphoma	1	Castleman's disease	2	
Hodgkin's lymphoma		19	Others	20	
	Hodgkin's lymphoma	18			
	Nodular lymphocyte predominant Hodgkin's lymphoma	1			
Other		10			
	Iatrogenic immunodeficiency-associated lymphoproliferative disorders	8			
	HIV-related malignant lymphoma	1			
	Malignant lymphoma, NOS	1			

Abbreviations: ML, malignant lymphoma; NML, non-ML; NOS, not otherwise specified.

Notes: The ML group was classified into B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, and others. Detailed items in each classification are presented. The NML group was classified into metastatic malignant tumor and nonmalignant tumor. In metastatic malignant tumors, the cancer type is presented, and in nonmalignant tumors, the diagnostic results are provided.

ML group ($p < 0.001$, ► **Fig. 4**), no significant difference was found compared with the NML group (median 516, 182–12,368 U/mL, $p = 1.00$). In the ROC curve comparing ML and malignant epithelial carcinoma, the cutoff value was 848 U/mL, with an AUC of 0.721 (sensitivity, 61.5%; specificity, 80.0%; ► **Fig. 4**).

Discussion

To diagnose ML in patients presenting with cervical lymphadenopathy, a certain number of specimens is needed. In addition, since differential diagnosis includes various conditions such as tuberculosis lymphadenitis, sarcoidosis, and metastasis-related cervical lymphadenopathy, cervical lymph node biopsy is often required. Furthermore, in recent years, immune checkpoint inhibitors became covered by health insurance for lung as well as head and neck cancer,

which require clinical tests such as those involving PD-L1, and in turn require a certain number of specimens, and thus it is extremely highly likely that the need for cytology and cervical lymph node biopsy will increase in the future.

On the other hand, sIL-2R measurement is much less invasive than cervical lymph node biopsy, and it may reflect the disease condition and treatment outcomes of leukemia and ML. However, at present, studies have reported that sIL-2R levels are high in lymphoma (including not only T cell lymphoma but Hodgkin's lymphoma⁵ and B cell lymphoma⁶) nonhematopoietic solid tumors,⁷ tuberculosis,⁸ IgG4-related disease,⁹ chronic liver disease,¹⁰ and sarcoidosis.¹¹ Therefore, in patients with cervical lymphadenopathy, ML cannot be differentiated by sIL-2R levels that are higher than the normal range, and we believe that for differentiation, a higher cutoff value should be set and another indicator must be introduced.

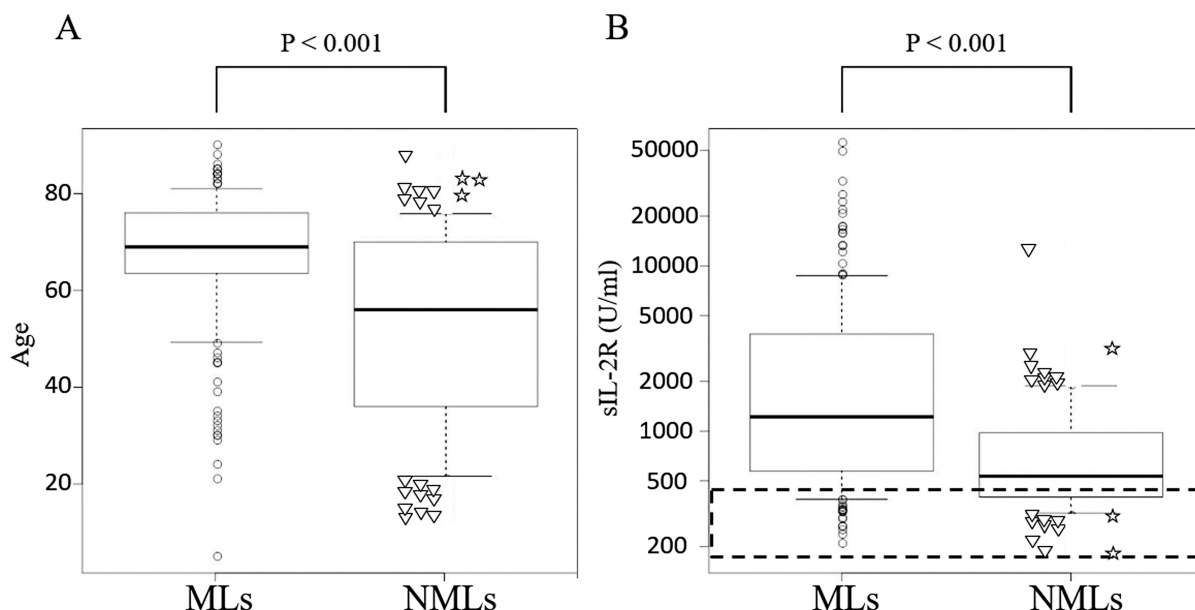


Fig. 1 Comparison of the malignant lymphoma (ML) and non-ML (NML) groups. (A) The patients in the ML group (MLs) were significantly older than those in the NML group (NMLs). (B) The sIL-2R levels were significantly higher for the MLs than for the NMLs. Furthermore, the normal range was 135–483 U/mL as presented by the dotted line. With regard to the NMLs, malignant epithelial tumors are indicated by ☆ and nonmalignant tumors are indicated by ∇. The median age of patients with nonmalignant tumors was 50 years.

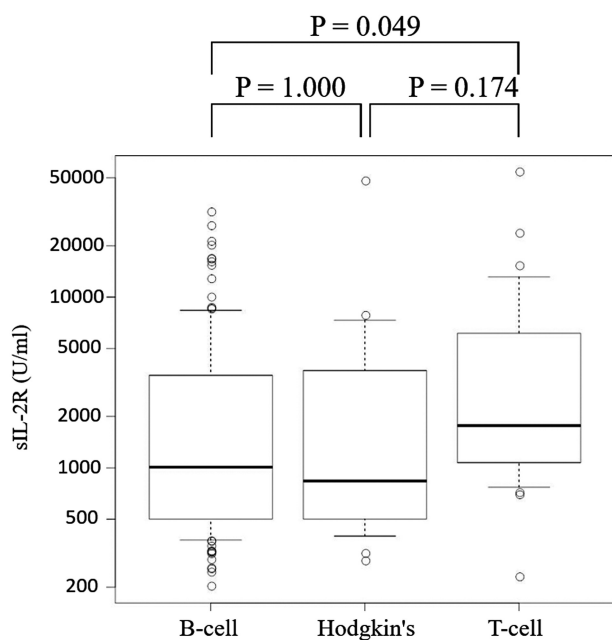


Fig. 2 Comparison between lymphomas. On comparing the B cell, Hodgkin's, and T cell lymphoma groups, the sIL-2R levels in the T cell lymphoma group were found to be significantly higher than that in the B cell lymphoma group.

Furthermore, serum sIL-2R was discovered from the supernatant of adult T cell leukemia cells^{1,2}; however, as mentioned earlier, sIL-2R levels also increase in lymphoma other than T cell lymphoma; therefore, it was thought that the presence or absence of a discrepancy in sIL-2R should be examined.

In the present study, the ML group was significantly older than the NML group. Conceivably, this was attributed to the inclusion of patients with diseases of relatively young onset, such as subacute necrotizing lymphadenitis, in the NML group.¹²

Furthermore, although sIL-2R levels were significantly higher in the T cell lymphoma group than in the B cell lymphoma group, no significant difference was observed between the T cell lymphoma group and the Hodgkin's lymphoma group and between the B cell lymphoma group and the Hodgkin's lymphoma group. This was believed to be caused by the inclusion of low-grade lymphomas (i.e., 26 patients with low-grade follicular lymphoma and 6 patients with marginal zone B cell lymphoma in the B cell lymphoma group), whereas the T cell lymphoma group included many high-grade lymphomas. Regarding the relationship between lymphoma activity and sIL-2R, Murakami et al reported that sIL-2R levels were significantly higher in fast-growing lymphoma than in slow-growing lymphoma,¹³ and a study also reported that sIL-2R level reflects ML activity.¹⁴

As regards the differentiation of ML and other diseases, according to Murakami et al,¹³ the sIL-2R cutoff value was 1,946 U/mL, whereas in the present study the optimal cutoff value was 1,246 U/mL. However, compared with the normal range of 135 to 486 U/mL, both of these cutoff values are extremely high. The cutoff value was lower in the present study than in the report by Murakami et al¹³ because their study included patients with suspected ML, whereas the present study analyzed patients who underwent cervical lymph node biopsy for cervical lymphadenopathy. Therefore, we believe that including various diseases consequently resulted in lower sIL-2R levels in the NML group.

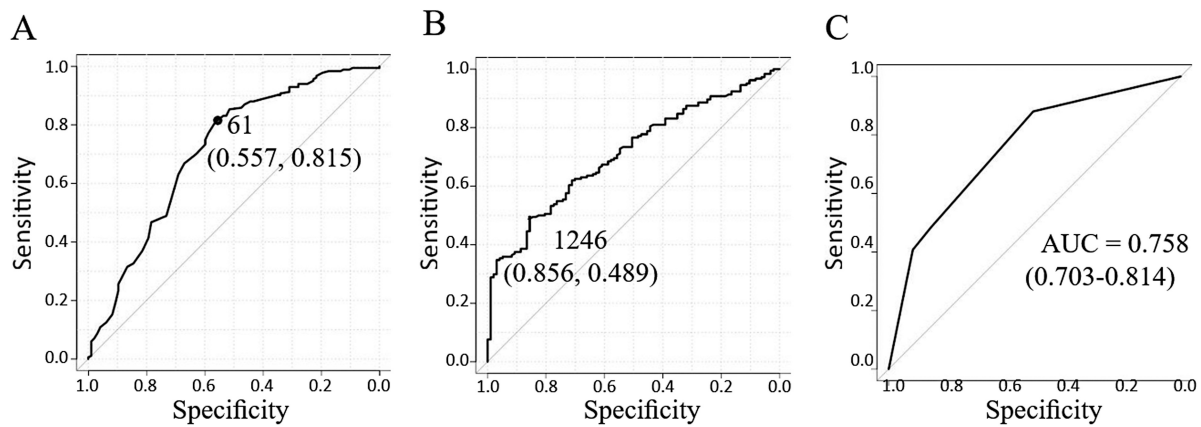


Fig. 3 ROC curve. (A) ROC curve of age. (B) ROC curve of sIL-2R levels (AUC, 0.711). (C) ROC curve according to age ≥ 62 years and sIL-2R levels $> 1,246$ U/mL (AUC, 0.758). AUC, area under the curve; ROC, receiver operating characteristic curve.

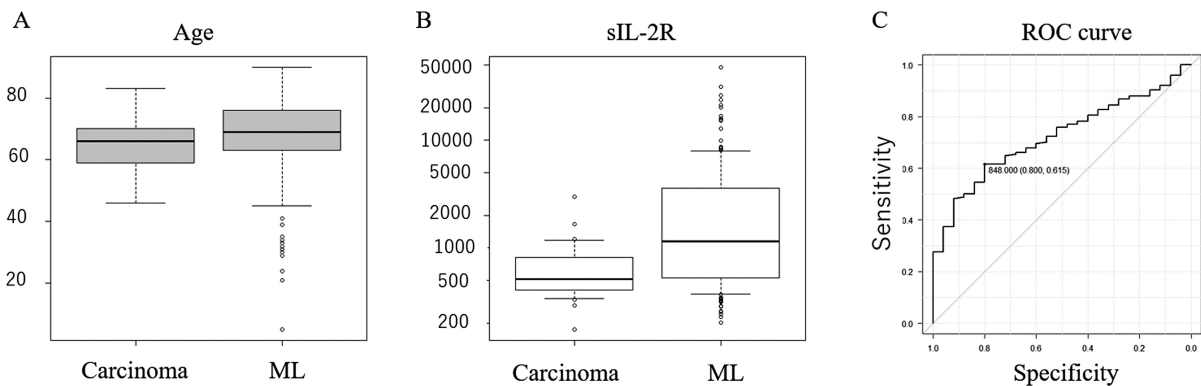


Fig. 4 Comparison of the malignant epithelial carcinoma and ML groups. (A) No significant differences were found in terms of age between the malignant epithelial tumor group (carcinoma) and the ML group (ML). (B) The sIL-2R levels were significantly higher in the ML group than in the malignant epithelial tumor group. (C) ROC curve of sIL-2R (AUC, 0.721). AUC, area under the curve; ROC, receiver operating characteristic curve.

In the ROC analysis using sIL-2R as an indicator, the AUC was 0.711, suggesting that while sIL-2R levels could be a useful biomarker for the diagnosis of ML, the sensitivity is not high at the cutoff value of 48.9%. As mentioned earlier, sIL-2R levels are thought to reflect ML activity, which, in slow-growing lymphoma, results in a lower value. It is possible that such slow-growing lymphoma cannot be diagnosed by the sIL-2R level alone, and we believe that this is a limitation of the present study.

However, compared with the NML group, the ML group had more advanced patient age, and the AUC increased by introducing a cutoff value for age. Although the significant difference according to age vanished when comparing the malignant epithelial tumor group with the ML group, the cutoff value according to the sIL-2R level decreased to 848 U/mL; while the AUC was comparable at 0.721, sensitivity increased to 61.5%. Thus, diagnosis of malignant epithelial tumors by using other indicators and systemic screening could improve the diagnostic accuracy.

Furthermore, in the NML group, the sIL-2R level in 14 patients was higher than the cutoff value. These were false-positive cases with lymphoproliferative disorders, including two patients with Castleman's disease, one with EB virus

infection, one with HIV-related Kaposi's sarcoma, and one with Kimura disease. We included patients with previously reported elevated sIL-2R levels, including metastasis-related cervical lymphadenopathy,⁷ tuberculosis,⁸ and sarcoidosis.¹¹ In Castleman's disease, the level of sIL-2R is known to increase, and in multicentric Castleman's disease, sIL-2R measurement was recommended as a related workup.¹⁵ Furthermore, sIL-2R levels also increase in EB infection,¹⁶ HIV infection,¹⁷ and Kimura disease.¹⁸

In addition to ML, various diseases cause cervical lymphadenopathy, such as metastasis-related cervical lymphadenopathy, tuberculosis, sarcoidosis, Castleman's disease, and EB virus infection; therefore, tests must cover various factors. For a definite diagnosis, cervical lymph node biopsy will still be needed in the future. However, the results of the present study suggested that sIL-2R can serve as a useful biomarker for differentiating ML from other diseases by setting the cutoff value to a higher value than the upper limit of the normal range.

Conclusion

In patients presenting cervical lymphadenopathy, although differentiating ML from other diseases based on sIL-2R levels

alone is difficult, we believe that sIL-2R levels can contribute to ML diagnosis. Furthermore, while the related cutoff value was lower in the present study than in other reports at 1,246 U/mL, it was considerably higher than the normal range.

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None.

Conflict of Interest

None declared.

Acknowledgments

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