The impact of serum soluble interleukin-2 receptor levels on the diagnosis of malignant lymphoma

Takayuki TSUJIOKA[1)], Mitsuyo KISHIMOTO[2)], Toshinori KONDO[3)], Akihito MATSUOKA[1)], Taizo TASAKA[1)], Takashi SUGIHARA[3)], Hideho WADA[3)], Kaoru TOHYAMA[1)]

1) Department of Laboratory Medicine, 3) Department of Hematology, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
2) Department of Medical Technology, Kawasaki College of Allied Health Professions, 316 Matsushima, Kurashiki, 701-0192, Japan

ABSTRACT Soluble interleukin-2 receptor (sIL-2R) is produced by activated lymphocytes or malignant lymphoma (ML) cells. The aim of this study was to estimate the diagnostic role of serum sIL-2R levels in ML.

The data of serum sIL-2R levels were extracted from the database of 1278 untreated patients admitted to Kawasaki Medical School Hospital from 1997 to 2008 and retrospectively analyzed.

We compared the serum sIL-2R levels of 443 patients newly diagnosed with ML with those of 835 patients with non-hematological diseases to improve the diagnostic accuracy. The serum sIL-2R levels of patients with ML (median:1330 U/ml, range:197-84200) were significantly ($p<0.001$) higher than those with non-hematological diseases (median:827 U/ml, range:106-18100). In the univariate analysis, the non-adjusted odds ratio was 3.123 and the specificity was 0.77 by adjusting the cut-off value of the sIL-2R level at 1500 U/ml. These findings suggested that sIL-2R is useful by itself in the differential diagnosis of ML. In the multivariate analysis, the adjusted odds ratio adding age (≧60 years), WBC counts (<10000/μl) and CRP levels (<0.4 mg/dl) to sIL-2R were 4.047.

Serum sIL-2R levels are useful for the diagnosis of ML, and the diagnostic accuracy of ML is improved by adding the other factors such as age, WBC counts and CRP levels to sIL-2R.

(Accepted on January 19, 2011)

Key words：**Soluble interleukin-2 receptor (sIL-2R), Malignant lymphoma (ML), Non-hematological diseases, Odds ratio, Cut-off value**

INTRODUCTION

Malignant lymphoma (ML) is one of the malignant diseases arising from the lymphoid tissues. As it is heterogenous in terms of classification, the process of definitive diagnosis is obtained by the histological diagnosis of tissue

Corresponding author
Takayuki Tsujioka
Department of Laboratory Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
Phone : 81 86 462 1111
Fax : 81 86 462 1199
E-mail : tsujoka@med.kawasaki-m.ac.jp

specimens. In addition, the stage and prognosis of patients with ML is estimated by the Ann Arbor classification and by the International Prognostic Index (IPI) composed of age, performance status, serum LDH level, number of extranodal lesions and the stage[1, 2]. Although histological diagnosis is absolutely essential for a definitive diagnosis, there is a need for a prudent choice because a biopsy is an invasive procedure and most in patients enlarged lymph nodes or fever of unknown origin (FUO) are composed of non-hematological, infectious diseases or autoimmune diseases.

Interleukin-2 (IL-2) is released from activated T-cells and transmits a growth signal after ligation to the interleukin-2 receptor (IL-2R)[3]. IL-2R has at least three glycopeptide subunits composed of α, β and γ chains. IL-2R α chain notably has a molecular weight of 55kDa and is known as Tac antigen[4, 5]. Rubin, et al. have proven that IL-2R α is released from the cell membrane in a soluble form (soluble IL-2R; sIL-2R)[6, 7]. An enzyme-linked immunosorbent assay (ELISA) with IL-2R α antibody has enabled the detection and quantification of the released soluble form[6]. It is expressed not only on the surface of activated normal T-cells and B-cells[8]but also on malignant lymphoid cells[9, 10]. Its serum level correlates with disease activity, tumor burden, prognosis and relapse in Hodgkin's lymphoma (HL)[11, 12], non-Hodgkin's lymphoma (N-HL)[13-17], chronic lymphocytic leukemia (CLL)[18]and adult T-cell leukemia/lymphoma (ATLL)[19, 20]. In addition, the level of sIL-2R is often elevated by non-hematological diseases including collagen diseases, solid tumors and infectious diseases[21-24]. Therefore, it has long been a difficult problem for clinical physicians to determine the borderline of serum sIL-2R level between ML and non-hematological diseases.

In this study, we compared the serum sIL-2R levels in 443 patients with ML with those in 835 patients with non-hematological diseases and evaluated the role of sIL-2R in newly diagnosed ML.

PATIENTS AND METHODS

Patient population

The study data consisted of 443 patients with a newly diagnosed ML admitted to Kawasaki Medical School Hospital from January 1997 to December 2008 (defined as the ML group). Most of them were diagnosed with ML based on the results of a lymph node biopsy. The histology of ML was defined according to the World Health Organization (WHO) 2008 classifications[25]. The patient characteristics are shown in Table 1. Of these 443 patients, 346 were diagnosed with B-cell lymphoma, 63 with T-cell and NK-cell lymphoma including 17 patients with ATLL, and 26 with Hodgkin's lymphoma. Indolent lymphoma was of the B-cell lineage in 103 patients, including 3 with chronic lymphocytic leukemia, 3 with lymphoplasmocytic lymphoma, 2 with splenic marzinal zone B-cell lymphoma, 1 with plasma cell myeloma, 26 with extranodal marzinal zone lymphoma of mucosa-associated lymphoid tissue, 68 with follicular center lymphoma (grade Ⅰ/Ⅱ). Aggressive lymphoma was of the B-cell lineage in 243 patients and of the T-cell or NK-cell lineage in 65. The aggressive B-cell lymphoma was mantle cell lymphoma in 13 patients, follicular center lymphoma (grade Ⅲ) in 11, diffuse large B-cell lymphoma, not otherwise specified (NOS) in 206 patients, primary mediastinal large B-cell lymphoma in 4 patients, intravascular large B-cell lymphoma in 5 patients and Burkitt lymphoma in 4 patients. Aggressive NK-cell lymphoma was found in 2 patients, extranodal NK/T-cell lymphoma, nasal type in 5, enteropathy-associated T-cell lymphoma in 1, peripheral T-cell lymphoma, not otherwise specified (NOS) in 15, angioimmunoblastic lymphoma (AILD) in 15, anaplastic large cell lymphoma in 8 and T-lymphoblastic leukemia/lymphoma in 2 patients.

Table 1. Patient data with malignant lymphomas

Histology (WHO2008)	No of cases	Age (years) median (range)	M/F	sIL-2R (U/ml) median (range)	WBC (/ml) median (range)	CRP (mg/dl) median (range)	LDH (IU/L) median (range)
Mature B-Cell neoplasms	346						
Chronic lymphocytic leukemia	3	55 (38-65)	2/1	2020 (224-6710)	24100 (9240-33620)	0.20 (0.04-5.11)	216 (188-234)
Splenic B cell marzinal zone lymphoma	2	74 (72-75)	1/1	14050 (13800-14300)	4950 (1640-4950)	9.32 (1.44-17.20)	396 (124-688)
Lymphoplamocytic lymphoma	3	66 (62-71)	1/2	2320 (1100-2450)	5500 (4980-8500)	4.46 (0.18-5.20)	239 (142-304)
Plasma cell myeloma	1	57	0/1	382	8010	0.05	146
Extranodal marzinal zone lymphoma of mucosa-associated lymphoid tissue	26	61 (27-85)	12/14	627 (274-11100)	5460 (2460-9080)	0.16 (0.03-9.20)	188 (89-263)
Follicular lymphoma	79	60 (40-82)	33/46	1090 (299-42900)	5800 (2200-23790)	0.20 (0.03-10.95)	202 (129-571)
Mantle cell lymphoma	13	73 (63-83)	12/1	3350 (774-30100)	7300 (4610-19300)	0.72 (0.03-23.60)	237 (109-607)
Diffuse large B-cell lymphoma, NOS	206	68 (18-90)	120/86	1255 (197-52300)	5635 (10600-20070)	0.51 (0.03-24.00)	232 (34-7325)
Primary mediastinal large B-cell lymphoma	4	63 (30-64)	3/1	878 (791-986)	4825 (4500-11500)	0.59 (0.10-2.30)	231 (140-849)
Intravascular large B-cell lymphoma	5	67 (49-86)	1/4	6960 (3210-11700)	5600 (2500-8600)	6.55 (2.6-27.80)	409 (323-3477)
Burkitt lymphoma	4	65 (18-73)	2/2	1345 (343-6300)	4815 (4300-14000)	1.18 (0.71-3.70)	269 (112-544)
Mature T-cell and NK-cell neoplasms	63						
Aggressive NK cell lymphoma	2	59 (43-75)	2/0	3545 (1580-5580)	6150 (4800-7500)	0.80 (0.4-1.20)	213 (152-274)
Adult T cell leukemia/ T cell lymphoma	17	57 (45-76)	9/8	12400 (607-84200)	8800 (3620-109150)	0.20 (0.03-12.30)	302 (100-466)
Extranodal NK/T cell lymphoma, nasal type	5	66 (20-84)	3/2	580 (282-1680)	5170 (2800-13580)	0.36 (0.04-3.66)	274 (165-539)
Enteropathy-associated T-cell lymphoma	1	50	0/1	2920	9700	6.4	185
Peripheral T-cell lymphoma, NOS	15	69 (45-79)	10/5	1550 (404-59400)	6550 (1600-23500)	1.70 (0.06-23.40)	314 (145-1636)
Angioimmunoblastic T-cell lymphoma	15	76 (58-88)	9/6	6670 (274-28000)	5740 (1620-12270)	0.70 (0.14-11.00)	210 (53-380)
Anaplastic large cell lymphoma	8	29 (8-68)	2/6	6995 (402-27700)	8980 (2300-18440)	1.55 (0.20-21.25)	170 (72-224)
T-lymphoblastic leukemia/ lymphoma	2	19 (6-32)	1/1	708 (287-1130)	15025 (6650-23400)	0.39 (0.18-0.60)	648 (484-813)
Hodgkin's lymphoma	26	63 (14-86)	16/10	1030 (197-24900)	5675 (2620-12350)	0.68 (0.03-9.04)	187 (37-814)
unspecified	6	77 (55-82)	4/2	595 (326-5660)	5350 (3200-5800)	0.15 (0.05-2.68)	221 (156-270)

Clinical staging was assessed according to the Ann Arbor classification. The evaluation included a complete history and physical examination, a chest roentgenography, a bone marrow aspiration and biopsy, a computed tomography of the chest, abdomen and pelvis, a hemogram and routine biochemistry examinations.

The population of the non-hematological diseases group consisted of 835 patients with the newly diagnosed diseases unrelated to hematological disorders (defined as the non-hematological group). These patients' characteristics are shown in Table 2. We divided them into 6 categories composed of autoimmune diseases, non-hematological tumors, infections, fever of unknown origin, lymphadenopathy and others.

Data collection

This study was a retrospective analysis. The data on clinical parameters including age, gender, white blood cell (WBC) counts, serum C-reactive protein (CRP), serum LDH levels, and serum sIL-2R levels were extracted from the database of medical treatment records in Kawasaki Medical School Hospital. The parameters used in this study were obtained at the initial diagnosis. The entire study using patients' data was approved by the ethical committee of Kawasaki Medical School.

ELISA for sIL-2R

The serum sIL-2R levels were measured with a sandwich ELISA (Cell-free Interleukin-2 Receptor Test Kit, T Cell Science, Cambridge, Mass., USA) based on two monoclonal antibodies raised against two different epitopes of the p55 alpha-chain of the IL-2R complex. The normal range of this was defined as from 220~530 U/ml in Japan.

Statistical analyses

All results were shown as median values with ranges. Comparisons between the groups were done using the Mann-Whitney U test. Multivariate analysis to define independent factors was performed using the multivariate logistic regression model. These data were considered statistically significant if p-values were less than 0.05. The analyses were carried out using SPSS for Windows version14.0.

RESULTS

The comparison of the serum soluble IL-2 receptor levels and other parameters between the two groups

Table 2. Patient data with non-hematological diseases

Histology	No of cases	Age (years) median (range)	M/F	sIL-2R (U/ml) median (range)	WBC (/ml) median (range)	CRP (mg/dl) median (range)	LDH (IU/L) median (range)
Non-hematological group							
Autoimmune diseases	126	55 (16-82)	42/84	998 (106-14000)	6420 (2080-29500)	0.84 (0.03-29.70)	192 (99-737)
Non-hematological tumors	188	66 (13-91)	114/74	741 (252-4490)	6515 (20-26560)	0.47 (0.03-32.00)	206 (105-3220)
Infections	204	62 (0-97)	118/86	1025 (131-18100)	6560 (1500-28620)	0.78 (0.02-31.50)	200 (106-2517)
Fever of unknown origin	51	38 (3-84)	24/27	612 (264-8490)	6440 (2330-17850)	0.28 (0.03-22.60)	201 (120-634)
Lymphadenopathy	63	58 (2-87)	40/23	896 (245-5030)	7100 (2760-19570)	1.08 (0.03-27.89)	183 (116-371)
Others	203	63 (15-88)	123/80	657 (156-6260)	6060 (1390-17190)	0.26 (0.02-26.98)	200 (94-1238)

Patients with ML (443 cases) and patients with non-hematological diseases (835 cases) were enrolled in this study. The median age of patients in the ML group was 65 years old (range: 6~90) and 61 years old (range: 0~97) in the non-hematological group, respectively (data not shown). The age distribution in the ML group tended to be higher than that in the non-hematological group.

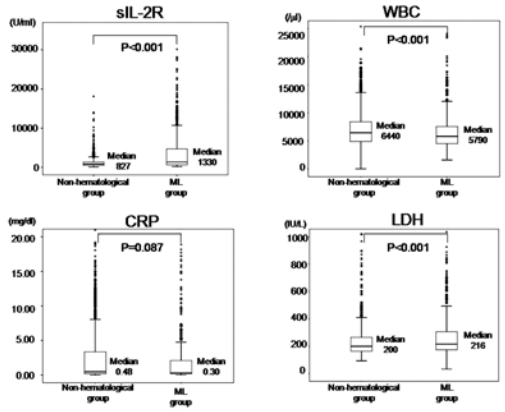

Fig. 1. Differences in the levels of several parameters between the malignant lymphoma group and the non-hematological group by box and whisker plots.

The central box indicates the range from 25 percentiles and 75 percentiles of the measured values with the median value shown by the horizontal line in each box. The vertical whiskers extend to 5 percentiles and 95 percentiles of the measured values. The levels of sIL-2R, WBC, CRP and LDH level are compared between the ML group (n=443) and the non-hematological group (n=835).

The serum sIL-2R levels and other parameters including WBC, CRP and LDH were compared between the ML group and the non-hematological group (Fig. 1). The serum sIL-2R levels in the ML group (median 1330U/ml, range: 197~84200) were significantly ($p<0.001$) higher than that of the non-hematological group (median 827 U/ml, range: 106~18100). The level of LDH in ML group (median 216 IU/L, range: 34~7325) was significantly ($p<0.001$) higher than that of the non-hematological group (median 200 IU/L, range: 94~3220).

The WBC count in the ML group (median 5790/μl, range: 1600~109150) was significantly ($p<0.001$) lower than that of the non-hematological group (median 6440/μl, range: 20~29500). The level of CRP in the ML group (median 0.30 mg/dl, range: 0.03~27.80) appeared to be lower than that of the non-hematological group (median 0.48 mg/dl, range: 0.02~32.00), but the difference was not

Table 3. The impact of serum sIL-2R level on the diagnosis of malignant lymphoma by univariate analysis

sIL-2R	ML	non hematological diseases	sensitivity	specificity	non-adjusted odds ratio (95%confidence interval)	positive predictive value	likelihood ratio
≧500	370	624	0.83	0.25	1.714	0.372	1.118
<500	73	211			(1.275-2.303)		
≧1000	262	344	0.59	0.59	2.066	0.432	1.436
<1000	181	491			(1.635-2.611)		
≧1500	213	191	0.48	0.77	3.123	0.527	2.102
<1500	230	644			(2.440-3.996)		
≧2000	180	136	0.40	0.84	3.517	0.569	2.495
<2000	263	699			(2.702-4.580)		
≧2500	163	95	0.37	0.89	4.535	0.631	3.234
<2500	280	740			(3.400-6.048)		
≧3000	149	68	0.34	0.92	5.716	0.686	4.130
<3000	294	767			(4.164-7.847)		
≧4000	124	36	0.28	0.96	8.627	0.775	6.492
<4000	319	799			(5.823-12.782)		
≧5000	103	22	0.23	0.97	11.195	0.824	8.825
<5000	340	813			(6.945-18.045)		

statistically significant (p=0.087).

The impact of serum sIL-2R level on the diagnosis of malignant lymphoma by the univariate analysis

The patients in the ML group and those in the non-hematological group were divided into sIL-2R-increase-positive and negative populations by adjusting the cut-off value of the sIL-2R level 500~5000 U/ml by every 500 or 1000 U/ml (Table 3). The sensitivity decreased from 0.83 to 0.23 by incrementing the point of the cut-off value. In contrast, the specificity increased from 0.25 to 0.97 by incrementing the point of the cut-off value. The non-adjusted odds ratio was increased by incrementing the point of the cut off value. When the cut-off value was adjusted at 1500 U/ml, the odds ratio was 3.123. Even when the cut-off value was adjusted to 5000 U/ml, the positive predictive value was 0.824 at the highest.

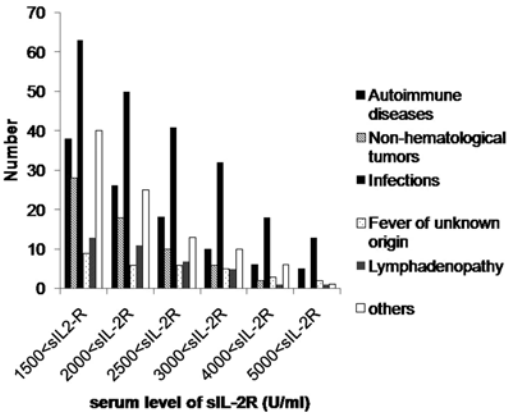

Fig. 2. The distribution of patients with non-hematological diseases who indicated more than 1500 U/ml of serum sIL-2R level

We listed up the distribution of 191 patients with non-hematological diseases with more than 1500 U/ml of serum sIL-2R level by adjusting the cut-off value of 1500~5000 U/ml by every 500 or 1000 U/ml and divided them into 6 categories. Each category was indicated above.

Table 4. Multivariate logistic regression model: risk factors for malignant lymphoma

risk factors	n	adjusted odds ratio (95% confidence interval)	p-value
Age			
<60	538		
≧60	740	1.701 (1.316-2.198)	<0.001
sIL-2R			
<1500	874		
≧1500	404	4.047 (3.057-5.357)	<0.001
WBC			
<10000	1098	1.562 (1.075-2.270)	0.019
≧10000	180		
CRP			
<0.4	626	2.103 (1.601-2.762)	<0.001
≧0.4	652		

The percentages of 191 patients with more than 1500 U/ml of sIL-2R in the non-hematological group was 15.1%, 22.5%, 22.4%, 6.1%, 7.5% and 24.3% in autoimmune diseases, non-hematological tumors, infections, FUO, Lymphadenopathy and others, respectively (Fig. 2). The proportion of non-hematological tumors decreased from 14.7% to 0.0% by incrementing the point of the cut-off value. In contrast, the proportion of infections increased from 33.0 to 59.1% by incrementing the point of the cut-off value.

Risk factors in the diagnosis of malignant lymphoma by multivariate analysis

The multivariate analysis of the serum sIL-2R level and five factors (age, gender, WBC count, LDH and CRP) was performed using the multivariate logistic regression model. Of those, age and LDH were selected to associate with the IPI index. Other parameters were taken from the gender difference of malignancy or factors related inflammation. The adjusted odds ratio of the sIL-2R level was elevated from 3.123 to 4.047 by including participants aged above 60 years, WBC of less than 10000 / μl and CRP of less than 0.4 mg/dl to the sIL-2R cut-off value at 1500 U/ml (Table 4).

DISCUSSION

The serum sIL-2R level has long been investigated in various hematological diseases, such as ATLL, CLL, HL and non-Hodgkin's lymphoma. Notably, a high serum sIL-2R level at the initial diagnosis of ML has been found to associate with a high

incidence of treatment failure, advanced stage and poor prognosis[11-18]. On the other hand, the elevation of the serum sIL-2R level was also observed in autoimmune diseases, infections and non-hematological tumors other than ML[21-24]. Therefore, it was not necessarily a specific marker for lymphoid malignancies. Yasuda N, *et al*. reported the serum sIL-2R levels in patients with various diseases, such as hematological diseases, infectious mononucleosis and HIV infection[22]. Nakase K, *et al*. reported that the sIL-2R level of hematological malignancies was significantly higher than that of solid tumors[23]. Though it is natural that histopathological diagnosis using lymph node specimens is essential for diagnosis of ML, the role of serum sIL-2R level in the definitive diagnosis of ML or the differential diagnosis with non-hematological diseases has been acontroversial object. However, there have been few reports demonstrating the diagnostic accuracy of ML, including other risk factors, and the borderline of sIL-2R level between ML and non-hematological diseases[26].

Goto H, *et al*. reported that the mean serum sIL-2R level of T-cell lymphoma patients was significantly higher than that of B-cell lymphoma patients[15]. The serum sIL-2R level in patients with T-cell lymphoma except ATL (median 4415 U/ml, range: 274~59400 U/ml) in our study was significantly ($p<0.002$) higher than that in patients with B-cell lymphoma (median 1220 U/ml, range: 197~52300 U/ml). The median serum sIL-2R level of the stage I, II, III, IV in ML was 483 U/ml (range: 204~5520), 812 U/ml (range: 197~12600), 1090 U/ml (range: 274~21000) and 3300 U/ml (range: 287~59400), respectively. The median serum sIL-2R level of stage III, IV was significantly ($p<0.01$) higher than that of non-hematological diseases (median 827, range: 106~18100), but it was not the case in stage II ($p=0.626$). Serum sIL-2R is a valuable marker in patients with ML in the advanced phase.

We divided the 835 cases in the non-hematological group into 6 categories. The level of serum sIL-2R has previously been measured in various non-hematological diseases. The majority of these reports have been occupied by 5 main categories that consisted of autoimmune diseases, neoplasia, allograft rejection, infections and others[26]. We had no cases associated with allograft rejection and defined benign tumors and neoplasia, except hematological diseases, as non-hematological tumors. Furthermore, apart from the 5 categories, there were many cases of lymphadenopathy of unknown etiology and FUO which were difficult for a definitive diagnosis in this study.

The positive predictive value was upgraded to 0.824 when the cut-off value of sIL-2R level was elevated to 5000 U/ml. The maximal value of sIL-2R in non-hematological diseases was 18100 U/ml (a case with fulminant hepatitis). Because there were numerous cases indicating a sIL-2R level higher than 5000 U/ml in non-hematological diseases, it was difficult to determine the borderline between ML and non-hematological diseases. In general, tumor markers have been demonstrated not to be valuable for early diagnosis, but to be consistently useful as an adjunct to determine the progress and recurrence of diverse malignant diseases[27-29].

It is very interesting to consider whether the cut-off level of 1500 U/ml on sIL-2R is correlated with event free survival (EFS) or overall survival (OS) in ML. Kono N, *et al*. previously reported a cut-off level of less than 1000U/ml on sIL-2R was associated with better survival in our country. Goto H, *et al*. reported that patients with more than 2000 U/ml sIL-2R revealed a worse prognosis than those with a sIL-2R level of less than 2000. Oki Y, *et al*. reported the impact of sIL-2R for prognostic prediction was most apparent in ML patients with IPI low risk[30]. Further studies will be necessary in order to predict the prognosis of ML patients using the pretreatment sIL-2R level.

The present study suggests that serum sIL-2R level plays a supplementary role in the definitive diagnosis of ML or in the differential diagnosis of FUO and undetermined lymphadenopathy through improving the diagnostic accuracy by adding other parameters to the serum sIL-2R level. We further intend to find the clinical utility of the serum sIL-2R level by analyzing its relation to the lymphoma subtypes.

ACKNOWLEDGMENTS

The authors thank Ms. Aki Kuyama and Ms. Sakura Eda for their editorial assistance.

Conflict-of-interest disclosures

The authors declare no competing financial interests.

REFERENCES

1) Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M: Report of the committee on Hodgkin's disease staging classification. Cancer Res31: 1860-1861, 1971.

2) A predictive model for aggressive non-Hodgkin's lymphomas. The International Non-Hodgkin's Lymphoma Prognostic Factor Project. N Eng J Med329: 987-994, 1993.

3) Gillis S. Interleukin 2: biology and biochemistry. J Clin Immunol3: 1-13, 1983.

4) Uchiyama T, Broder S, Waldmann TA: A monoclonal antibody (anti-Tac) reactive with activated and functionally mature human T cells. Ⅰ. Production of anti-Tac monoclonal antibody and distribution of Tac (+) cells. J Immunol126: 1393-1397, 1981.

5) Waldmann TA: The interleukin-2 receptor. J Biol Chem 266: 2681-2684, 1991.

6) Rubin LA, Kurman CC, Fritz ME, Biddison WE, Boutin B, Yarchoan R, Nelson DL: Soluble interleukin 2 receptors are released from activated human lymphoid cells in vitro. J Immunol135: 3172-3177, 1985.

7) Rubin LA, Jay G, Nelson DL: The released interleukin 2 receptor binds interleukin 2 efficiently. J Immunol 137: 3841-3844, 1986.

8) Waldmann TA, Goldman CK, Robb RJ, Depper JM, Lonard WJ, Sharrow SO, Bongiovanni KF, Korsmeyer SJ, Greene WC: Expression of interleukin 2 receptors on activated human B cells. J Exp Med160: 1450-1466, 1984.

9) Wagner DK, Kiwanuka J, Edward BK, Rubin LA, Nelson DL, Magrath IT: Soluble interleukin-2 receptor levels in patients with undifferentiated and lymphoblastic lymphomas: correlation with survival. J Clin Oncol 5: 1262-1274, 1987.

10) Pizzolo G, Chilosi M, Semenzato G: The soluble interleukin-2 receptor in hematological disorders. Br J hematol 67: 377-380, 1987.

11) Gause A, Roschansky V, Tschiersch A, Smith K, Hasenclever D, Schmits R, Diehl V, Pfreundschuh M: Low serum interleukin-2 receptor levels correlate with a good prognosis in patients with Hodgkin's lymphoma. Ann Oncol Suppl Suppl 2: 43-47, 1991.

12) Ambrosetti A, Nadali G, Vinante F, Carlini S, Veneri D, Todeschini G, Morosato L, de Sabata D, Chilosi M, Maggi E: Serum levels of soluble interleukin-2 receptor in Hodgkin disease. Relationship with clinical stage, tumor burden, and treatment outcome. Cancer 72: 201-206, 1993.

13) Kono N, Kanda Y, Yamamoto R, *et al*. Prognostic significance of serum soluble interleukin-2 receptor level in non-Hodgkin's lymphoma: a single center study in Japan. Leuk lymphoma 37: 151-156, 2000.

14) Niitsu N, Iijima K, Chizuka A: A high serum-soluble interleukin-2 receptor level is associated with a poor outcome of aggressive non-Hodgkin's lymphoma. Eur J Haematol 66: 24-30, 2001.

15) Goto H, Tsurumi H, Takemura M, *et al*.: Serum-soluble interleukin 2 receptor (sIL-2R) level determines clinical outcome in patients with aggressive non- Hodgkin's lymphoma: in combination with the international prognostic index. J Cancer Res Clin Oncol131: 73-79, 2005.

16) Morito T, Fujihara M, Asaoku H, Tari A, Sato Y, Ichimura K, Tanaka T, Takata K, Tamura M, Yoshino T: Serum soluble interleukin-2 receptor level and immunophenotype are prognostic factors for patients with diffuse large B-cell lymphoma. Cancer Sci100: 1255-1260, 2009.

17) Wakao D, Murohashi I, Tominaga K, *et al*.: Serum thymidine kinase and soluble interleukin-2 receptor predict recurrence of malignant lymphoma. Ann

Hematol81: 140-146, 2002.

18) Barak V, Ginzburg M, Kalickman I, Polliack A: Serum soluble interleukin-2 receptor levels are associated with clinical diseases status and histopathological grade in non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Leuk Lymphoma 7: 431-438, 1992.

19) Yasuda N, Lai PK, Ip SH, Kung PC, Hinuma Y, Matsuoka M, Hattori T, Takatsuki T, Putilo DT: Soluble interleukin 2 receptors in sera of Japanese patients with adult T cell leukemia mark activitiy of disease. Blood 71: 1021-1026, 1988.

20) Kamihira S, Atogami S, Sohda H, Momita S, Yamada Y, Tomonaga M: Significance of soluble interleukin-2 receptor levels for evaluation of the progression of adult T-cell leukemia. Cancer 73: 2753-2758, 1994.

21) Pui CH: Serum Interleukin-2 receptor: Clinical and biological implications. Leukemia3: 323-327, 1989.

22) Yasuda N, Takamatsu T, Kanoh T, Uchino H: Serum levels of soluble interleukin 2 receptor in patients with non-haematological disorders. Br J Haematol 69: 573-574, 1988.

23) Nakase K, Tsuji K, Tamaki S, Tanigawa M, Ikeda T, Miyanishi E, Shiku H: Elevated levels of soluble interleukin-2 receptor in serum of patients with hematological or non-hematological malignancies. Cancer Detect Prev 29: 256-259, 2005.

24) Murakami S: Soluble interleukin-2 receptor in cancer. Front Biosci1: 3085-3090, 2004.

25) Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW: editors. WHO Classification of Tumours of Haematopietic and Lymphoid Tissues, 4th ed. Lyon: IARC Press, 2008: 10pp.

26) Bien E, Balcerska A: Serum soluble interleukin 2 receptor α in human cancer of adults and children: a review. Biomarkers13: 1-26, 2008.

27) Persijn JP, Hart AA: Prognostic significance of CEA in colorectal cancer: a statistical study. J Clin Chem Clin Biochem19: 1117-1123, 1981.

28) Kuusela P, Jalanko H, Roberts P, Sipponen P, Mecklin JP, Pitkanen R, Makela O: Comparison of CA19-9 and carcinoembryonic antigen (CEA) levels in the serum of patients with colorectal diseases. Br J cancer 49:135-139, 1984.

29) Jalanko H, Kuusela P, Roberts P, Sipponen P, Haglund CA, Makela O: Comparison of a new tumour marker, CA19-9, with alpha-fetoprotein and carcinoembryonic antigen in patients with upper gastrointestinal diseases. J Clin Pathol37: 218-222, 1984.

30) Oki Y, Kato H, Matsuo K, Kuwatsuka Y, Taji H, Yamamoto K, Kagami Y, Morishima Y: Prognositic value of serum soluble interleukin-2 receptor level in patients with diffuse large B cell lymphoma, treated with CHOP-or RCHOP-based therapy. Leuk Lymphoma 49: 1345-1351, 2008.