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Soluble Interleukin-2 Receptor Level at Diagnosis Predicts Prognosis of Patients With Follicular Lymphoma Irrespective of Initial Management Strategy

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Abstract. *Background/Aim: Although various prognostic indices for follicular lymphoma (FL) have been proposed, they are designed specifically for patients requiring immediate therapy. We aimed to develop a new simple prognostic tool applicable for all patients with FL at diagnosis. Materials and Methods: We retrospectively analyzed various clinical, pathological, and laboratory data, including soluble interleukin-2 receptor (sIL2R), from 140 patients with FL from two centers for their impact on prognosis. This study analyzed the impact of soluble interleukin-2 receptor (sIL2R) in order to develop a new simple prognostic tool applicable for all patients with FL at diagnosis. Results: The initial management of these patients was watchful waiting (n=48) or immediate treatment (n=92). Event-free survival at 24 months predicted overall survival. When categorized into three groups according to the sIL2R levels at diagnosis, a very high sIL2R level identified about 20% of patients with a distinctively worse survival compared to the others. Conclusion: sIL2R is a very effective biomarker that can be easily applied in routine practice to predict survival for all patients with FL at diagnosis irrespective of initial management approach.*

Follicular lymphoma (FL) accounts for about 20% of all lymphoma cases and is the most common subtype of indolent B-cell lymphoma (1, 2). Prognosis of FL has improved, with median overall survival reported to be over 18 years (3). However, because the survival curve dose not reach a plateau, FL is still considered incurable. Thus, for patients with asymptomatic disease with a low tumor burden in advanced stage, watchful waiting instead of immediate therapy is often considered appropriate.

Monoclonal antibody combined with chemotherapy is the standard initial therapy for patients with symptomatic FL, for whom various prognostic models have been proposed. The original FL international prognostic index (FLIPI) model and an updated FLIPI2 model were developed in 2004 and 2009, respectively, and have continued to be reliable prognostic models (4). Recently, m7-FLIPI, which includes the mutational status of seven genes as well as the FLIPI factors, was reported to be a better prognostic model (5). However, determination of the precise number of nodal sites involved and mutational analyses are cumbersome and error-prone or difficult to perform, respectively, in routine practice. Moreover, most of the prognostic models have specifically been designed for and applicable to patients with high tumor burden FL requiring immediate therapy.

Therefore, an economical clinical prognostic factor/model applicable to all patients with FL is needed in routine practice. In this regard, beta-2 microglobulin (β2-MG) has been demonstrated as a useful biomarker at least for patients with FL receiving immediate immunochemotherapy (6, 7). Soluble Interleukin-2 receptor (sIL2R) was also reported to be a useful biomarker for FL requiring immediate immunochemotherapy (8, 9). However, the prognostic impact of sIL2R, as compared to β2-MG, has not been well elucidated. Thus, in the present study, we retrospectively analyzed the correlation between sIL2R and survival for consecutive patients with FL at diagnosis irrespective of the initial management approach in order to develop a new prognostic model.

Patients and Methods

Study design and patients. This is a double-institution retrospective analysis of consecutive patients with untreated FL at Tokyo Medical and Dental University Hospital or Yokosuka Kyosai

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Key Words: Soluble interleukin-2 receptor, follicular lymphoma, prognostic factor.

Hospital and was performed with approval of each Institutional Review Board (M2018-231).

All patients were diagnosed by biopsy of the primary lesion. Pathological diagnosis was made according to the World Health Organization classification (1). We included grade 1, 2 and 3A FL and excluded grade 3B FL and histological transformation. From consecutive patients, we selected those who had available data on FL grade, bone marrow involvement, serum lactate dehydrogenase (LDH), and sIL2R. Overall, 140 patients with untreated FL diagnosed between July 2007 and January 2018 were included in the study.

Prognostic factors. Medical records of the enrolled cases were reviewed for patient characteristics, disease characteristics, and laboratory data. Clinical characteristics include age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), and the presence of B symptoms. Disease characteristics include FL grade, Ann Arbor clinical stage, bone marrow involvement, and Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria factors (any site >7 cm, three or more sites greater than 3 cm, compressive symptoms, pleural or peritoneal effusion, spleen below umbilical line, leukemia). Laboratory data included white blood cell count; absolute lymphocyte count; hemoglobin; platelet count; serum LDH, β2-MG and sIL2R [upper limit normal (ULN): 519U/ml].

Statistical analysis. Event-free survival (EFS) was defined as the time from diagnosis until relapse or progression, unplanned retreatment of lymphoma after initial management, or death due to any cause. EFS24 was defined as the EFS status at 24 months from diagnosis. Progression-free survival (PFS) was defined as the time from the start of initial treatment to the date of disease progression or death. Overall survival (OS) was defined as the time from diagnosis until death from any cause, censoring at the date of last follow-up for patients still alive. The Kaplan–Meier method was used to estimate EFS, PFS and OS. Differences in survival between two groups were analyzed by the log-rank test. Cox proportional hazard regression analysis was performed to evaluate high sIL2R as a prognostic factor for survival as well as to assess and adjust for other known prognostic factors. All reported p-values are two-sided, and $p<0.05$ was considered significant. All analyses were carried out using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical computing) (10).

Results

Patient characteristics. Eighty-two and 58 patients were diagnosed at Tokyo Medical and Dental University Hospital and Yokosuka Kyosai Hospital, respectively, with 140 patients in total were analyzed in this study. Patient characteristics are summarized in Table I. The median age of the cohort was 66 (range 34-89) years, and 75% of patients were categorized as having advanced-stage disease. Fifty-three (37.9%) patients presented with bone marrow involvement. While sIL2R was examined in all patients, β2-MG was examined in 56 patients (40%). The median level of sIL2R was 704.5U/ml.

Initial management and treatment. Forty-eight patients were initially managed with watchful waiting. Sixteen of these patients (33.3%) experienced disease progression (median duration from diagnosis to progression: 15.8 months) and received immunochemotherapy at progression (Tables I and II).

Ninety-two patients were managed with immediate therapies (Table I). Almost all patients who received irradiation had limited-stage disease. All the other patients received rituximab with/without chemotherapy [rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP): 43; rituximab, cyclophosphamide, vincristine and prednisolone: 24; rituximab and bendamustine: 6; rituximab monotherapy: 4] (Table II), and only nine patients (8%) received rituximab maintenance therapy after initial treatment (Table II).

Event-free survival. At a median follow-up of 51 months (range=4-142 months), the median EFS and the EFS24 rate in the watchful waiting and immediate treatment group were 28 and 33 months, and 67.6% and 75.6%, respectively. There was no difference between the two groups in EFS (Figure 1A). OS was significantly shorter for patients failing to achieve EFS24 than those achieving it (Figure 1B).

Progression-free survival. Median follow-up after starting initial therapy for patients who received therapy was 47 months (range=0-139 months). PFS was not different between patients receiving initial therapy immediately or after watchful waiting (data not shown).

Prognostic impact of sIL2R. A comparison of characteristics of patients achieving EFS24 or not is summarized in Table III. sIL2R was the only significant factor correlating with EFS24, and the median level of sIL2R at diagnosis in patients achieving EFS24 was significantly lower than those failing to achieve EFS24 (665 and 1208 U/ml, respectively, $p=0.001$). EFS and OS rates were significantly lower in the group with higher sIL2R (sIL2R >median) (2-year EFS: 66.4% *vs*. 87.3%, $p=0.015$; 5-year OS: 96.0% *vs*. 88.9%, $p=0.023$), as shown in Figure 2A and B. When limited to the immediate treatment group, similar results were obtained, although the difference in EFS did not reach the significant level (Figure 2C and D). Next, we investigated the prognostic impact of the degree of increase in sIL2R level. Patients were categorized into three groups according to sIL2R level at diagnosis: low, ≤ULN, n=51; high, ULN to ≤5×ULN, n=62; very high, >5×ULN, n=27). EFS and OS were plotted according to the sIL2R level (Figure 3A, B). Although there was no survival difference between the groups with low and high sIL2R level when limited to patients who received immediate treatment, the group with a very high sIL2R level showed significantly poorer survival (Figure 3C and D).

Table I. *Patient characteristics*.

Characteristic	N=140
Age, years	
Median (range)	66 (34-89)
Gender, n (%)	
Male	65 (46.4%)
Follicular lymphoma grade, n (%)	
1	47 (33.6%)
2	55 (39.3%)
3a	38 (27.1%)
Clinical stage, n (%)	
1	13 (9.3%)
2	22 (15.7%)
3	35 (25.0%)
4	70 (50%)
Bone marrow involvement, n (%)	
Yes	53 (37.9%)
B Symptoms, n (%)	
Yes	5 (3.6%)
Any site >7 cm, n (%)	
Yes	28 (20%)
Three or more sites >3 cm, n (%)	
Yes	18 (12.9%)
Compression symptoms, n (%)	
Yes	21 (15%)
Pleural or peritoneal effusion, n (%)	
Yes	12 (8.6%)
Spleen below umbilical line, n (%)	
Yes	8 (5.7%)
Leukemia, n (%)*	
Yes	1 (0.7%)
White blood count, n/μl	
Median (range)	5,500 (3,000-25,200)
Absolute lymphocyte count, n/μl	
Median (range)	1,302 (400-16,128)
Hemoglobin, g/dl	
Median (range)	13.45 (7.0-17.5)
Platelet count, $n \times 10^4/\mu l$	
Median (range)	21.85 (6.2-63.7)
LDH, U/l	
Median (range)	194.5 (116-1,411)
β-2 Microglobulin, mg/dl	
Median (range)	1.8 (0.82-11.92)
Missing data	84 (60%)
sIL2R, U/ml	
Median (range)	704.5 (159-15,500)
Initial plan, n (%)	
Watchful waiting	48 (34.3%)
Immediate treatment	92 (65.7%)

LDH: Lactate dehydrate; sIL2R: soluble interleukin-2 receptor. *Tumor cells >51,000/μl in peripheral blood.

Table II. *Treatment of study patients*.

	Treatment	N
Immediate (N=92)	Radiation	15
	R monotherapy	4
	R-CHOP	43
	R-CVP	24
	R-Bendamustine	6
	R Maintenance	8
After watchful waiting (N=16)	Radiation	0
	R Monotherapy	1
	R-CHOP	5
	R-CVP	8
	R-Bendamustine	2
	R Maintenance	1

R: Rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP: cyclophosphamide, vincristine and prednisolone.

Univariate and multivariate analyses of survival. Cox proportional hazard regression analysis was performed to evaluate very high sIL2R level as a prognostic factor for EFS and OS, as well as to assess and adjust for other known prognostic factors. Variables analyzed were age, Ann Arbor clinical stage, bone marrow involvement, B symptom, GELF criteria factors, LDH, and sIL2R. The leukemia factor of GELF criteria was excluded because only one patient showed leukemic disease (Table IV). From the univariate analysis, a very high sIL2R level and clinical stage or age were selected for the multivariate analysis for EFS and OS, respectively. As shown in Table IV, a very high sIL2R level was the only independent prognostic factor for both EFS and OS.

Discussion

It is difficult to predict OS of patients with FL at diagnosis because of various initial management approaches available as well as the incurable and prolonged indolent clinical course. Based on data from patients who received immediate immunochemotherapy, recent studies reported that early progression after immunochemotherapy predicts poorer OS (11-13). A more recent study demonstrated that early events as defined by EFS12 predicted OS of all patients newly diagnosed with FL including those observed initially, without treatment, although the impact of EFS12 seemed to be especially important for patients requiring immunochemotherapy immediately (14). The present study has confirmed that early events after diagnosis predict poor outcomes in patients newly diagnosed with FL overall, although EFS24 seemed to have a more powerful impact on survival than EFS12 in our cohort of patients (data not shown).

Of various factors we analyzed in the present study, sIL2R was the only one to show a significant correlation with EFS24, which proved to be a strong prognostic parameter for subsequent OS (Table III). Thus, a higher than median sIL2R level led to lower rates not only for 2-year EFS but also for 5-year OS than did lower sIL2R levels (Figure 2). Previous studies have shown that a high sIL2R level in patients with

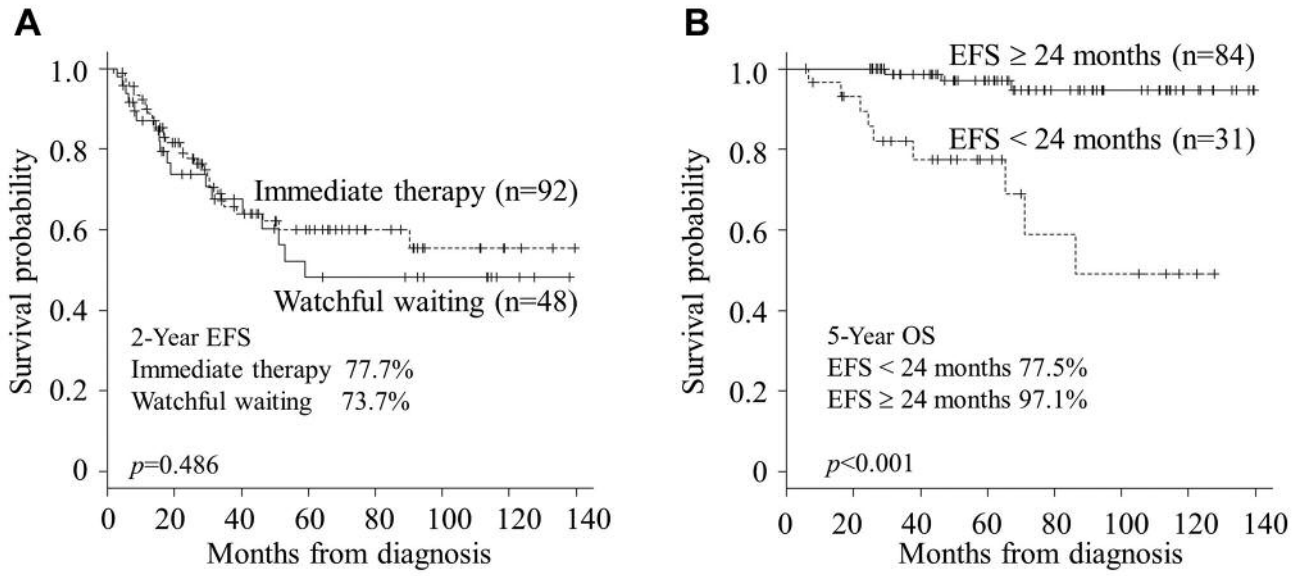

Figure 1. *A: Event-free survival (EFS) according to initial management approaches. B: Overall survival (OS) according to EFS at 24 months (EFS24).*

Table III. *Patient characteristics according to achievement of event-free survival (EFS24).*

Characteristic		EFS		*p*-Value
		≥24 Months (n=84)	<24 Months (n=31)	
Age, years	Median (range)	64 (33-89)	65 (51-80)	0.621
Gender , n (%)	Male	39 (46.4%)	16 (51.6%)	0.677
Clinical stage, n (%)	Advanced*	62 (73.8%)	27 (87.1%)	0.208
Bone marrow involvement, n (%)	Yes	34 (40.5%)	12 (38.7%)	>0.99
B Symptoms, n (%)	Yes	3 (3.6%)	1 (3.2%)	>0.99
Follicular lymphoma grade, n (%)	1	30 (35.7%)	12 (38.7%)	0.895
	2	34 (40.5%)	11 (35.5%)	
	3a	20 (23.8%)	8 (25.8%)	
Any site >7 cm, n (%)	Yes	15 (17.9%)	9 (29.0%)	0.204
Three or more sites >3 cm, n (%)	Yes	10 (12.0%)	4 (12.9%)	>0.99
Compression symptoms, n (%)	Yes	11 (13.1%)	8 (25.8%)	0.154
Pleural or peritoneal effusion, n (%)	Yes	7 (8.3%)	4 (12.9%)	0.484
Initial plan, n (%)	Watchful waiting	25 (29.8%)	12 (38.7%)	0.376
	Immediate treatment	59 (70.2%)	19 (61.3%)	
White blood count, n/μl	Median (range)	5,550 (3,000-25,200)	5,500 (3,600-21,500)	0.412
Absolute lymphocyte count, n/μl	Median (range)	1,324 (400-16,128)	1,302 (430-2,613)	0.962
Hemoglobin, g/dl	Median (range)	13.5 (7.7-17.2)	13.2 (7.0-17.5)	0.451
Platelet count, n×104/μl	Median (range)	20.7 (6.2-40.8)	23.1 (15.7-63.7)	0.105
LDH, U/l	Median (range)	190 (116-407)	198 (116-1411)	0.086
sIL2R, U/ml	Median (range)	644 (159-7,640)	1,208 (208-15,500)	0.001

LDH: Lactate dehydrate; sIL2R: soluble interleukin-2 receptor. *Clinical stage 3 or 4.

FL was also associated significantly with PFS but only marginally with OS, which may be because those studies were limited to patients achieving complete/partial remission after immunochemotherapy or to a small number of only 70 patients (8, 9). Therefore, the present study has not only confirmed but also extended the findings of these previous studies by demonstrating that a high sIL2R level in patients newly diagnosed with FL correlates significantly with poor

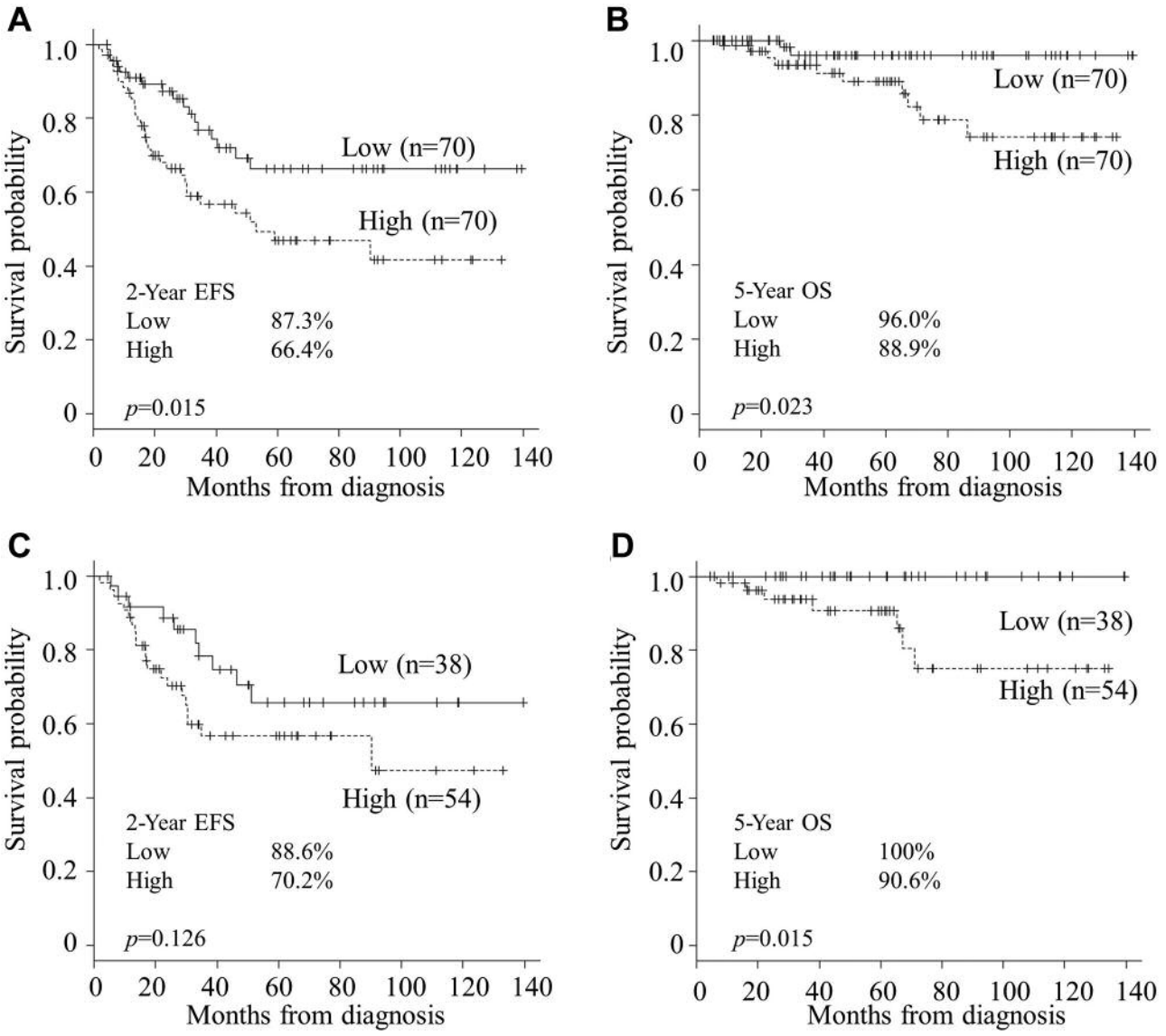

Figure 2. *Event-free survival (EFS) and overall survival (OS) according to the level of soluble interleukin-2 receptor (sIL2R) using the median as a cutoff considering all patients (A and B, respectively) and patients treated immediately (C and D, respectively).*

OS as well as EFS, irrespective of initial management approach. Furthermore, when categorized into three groups, a very high level of sIL2R was identified as the only significant predictor of OS as well as EFS in univariate and multivariate analyses (Table IV). Importantly, the group with a very high sIL2R level, consisting of about 20% of patients with most requiring immediate therapy, had a distinctively poor prognosis with 2-year EFS and 5-year OS of around 50% and 90%, respectively (Figure 3).

Recently, a new simple prognostic index for FL, PRIMA-PI, comprising only two simple parameters (β2-MG and bone marrow involvement) has been proposed to predict PFS and OS (7). However, this tool was built based solely on a cohort of patients treated with initial immunochemotherapy and is not applicable to all patients newly diagnosed with FL. Moreover, with the broader use of positron-emission tomography/computed tomography in the clinical staging assessment of FL, bone marrow biopsy may not be most convenient, especially for patients not requiring immediate immunotherapy in routine practice, as indicated by others (7). β2-MG has also been combined with LDH to provide a simple prognostic index for patients with FL treated immediately with R-CHOP or CHOP followed by radioimmunotherapy (6). Similarly to our model with sIL2-

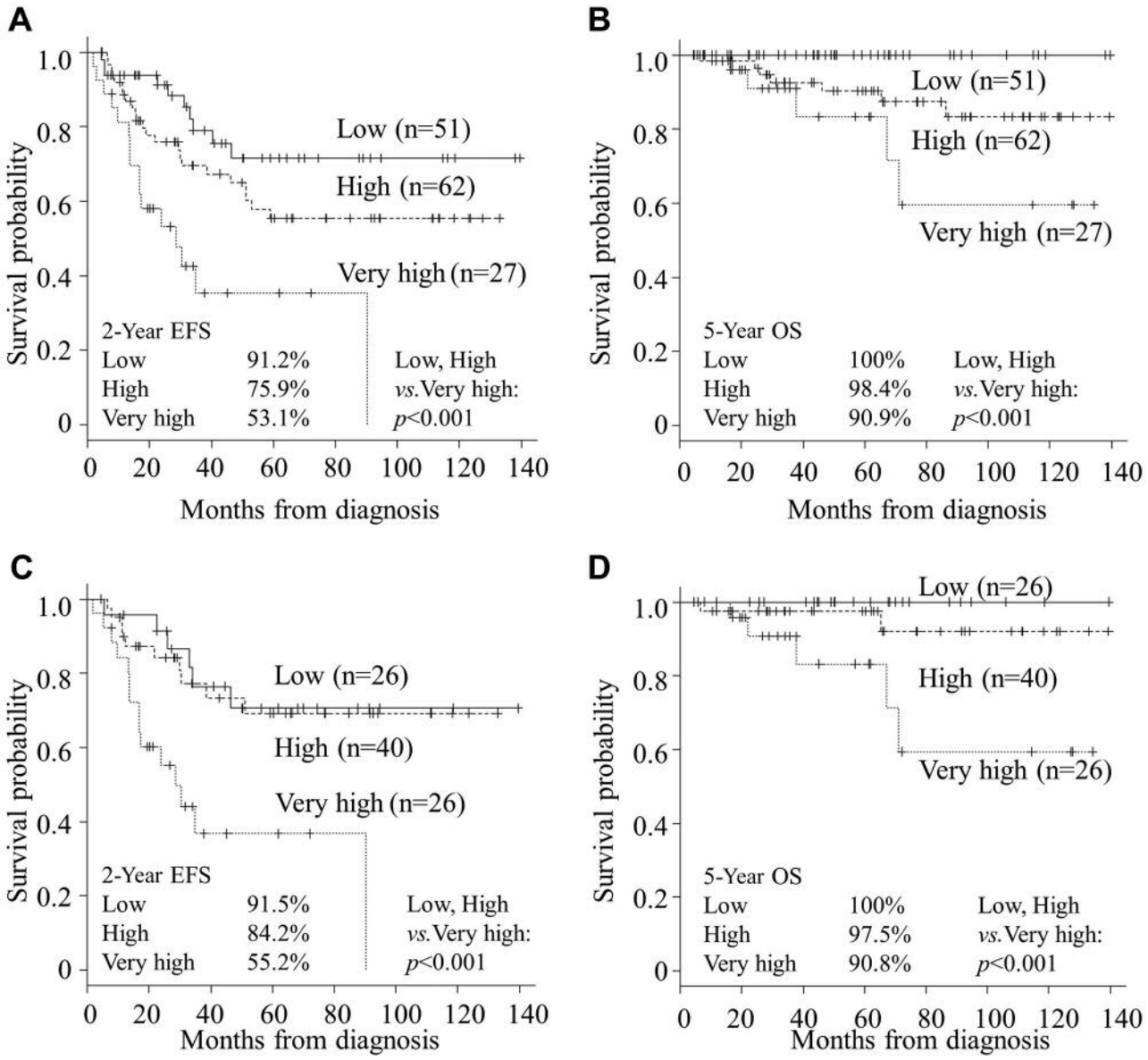

Figure 3. *Event-free survival (EFS) and overall survival (OS) according to soluble interleukin-2 receptor (sIL2R) level considering all patients (A and B, respectively) and patients treated immediately (C and D, respectively). Patients were categorized into three groups according to sIL2R level at diagnosis: Low: Less than the upper limit of normal (ULN), n=51; high: ULN to ≤5×ULN, n=62; very high: >5×ULN, n=27).*

R, an increase of the cutoff for β2-MG enabled identification of about 20% of patients destined for early relapse and poor OS among patients with FL with high-burden disease requiring immediate treatment with immunochemotherapy. As compared with these models using β2-MG, our model is more economical and can be used very easily in routine practice for all patients newly diagnosed with FL to predict OS as well as early progression.

The major limitation of the present study, however, is that it was a retrospective study of a relatively limited number of patients. Therefore, future large prospective studies are warranted to validate the present model and to verify its ability to identify early on the small group of patients with very poor risk, which merits consideration of novel upfront therapeutics, such as obinutuzumab instead of rituximab (15) in order to reduce the early progression rate.

Conflicts of Interest

The Authors declare no conflict of interest in regard to this study

Table IV. *Univariate and multivariate analyses for event-free survival (EFS) and overall survival (OS).*

	EFS						OS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Factor	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value	HR	95% CI	*p*-Value
sIL2R												
>5×ULN	3	1.63-5.51	<0.001	2.68	1.43-5.01	0.002	3.94	1.24-12.48	0.02	3.88	1.22-12.35	0.022
Clinical stage												
Advanced*	2.09	0.94-4.66	0.07	1.66	0.72-3.78	0.232	1.63	0.36-7.46	0.527			
Age												
>70 Years	0.74	0.38-1.45	0.386				3.02	0.97-9.392	0.056	2.97	0.95-9.27	0.061
B Symptoms												
Yes	0.53	0.07-3.87	0.534				4.01	0.5-32.25	0.191			
Bone marrow involvement												
Yes	1.33	0.76-2.35	0.317				1.76	0.56-5.48	0.33			
Pleural or peritoneal effusion												
Yes	0.89	0.32-2.48	0.822				0.98	0.13-7.61	0.987			
Three or more sites >3 cm												
Yes	1.17	0.53-2.61	0.698				-	0-Inf	0.998			
Compression symptoms												
Yes	1.45	0.7-2.99	0.32				2.13	0.57-7.91	0.258			
Any site >7 cm												
Yes	1.24	0.63-2.43	0.53				0.98	0.2-4.31	0.934			
LDH												
>ULN	1.34	0.72-2.49	0.359				1.14	0.31-4.2	0.85			

CI: Confidence intervaI; HR: hazard ratio; LDH: lactate dehydrate; sIL2R: soluble interleukin-2 receptor; ULN: upper limit of normal. *Clinical stage 3 or 4.

Authors' Contributions

Masahide Yamamoto: Study design, data collection, analysis and interpretation of results, statistical analyses, construction of figures, editing and writing of article; Keisuke Tanaka: data collection and patient management; Yoshihiro Umezawa: data collection and patient management; Toshikage Nagao: data collection and patient management; Shigeo Toyota: data collection and patient management; Osamu Miura: supervision of the project, critical revision of the article. All the Authors read and approved the final article.

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