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ORIGINAL ARTICLE

Predictive value of soluble interlukin-2 receptor level at diagnosis on the outcome for patients with classical Hodgkin lymphoma treated with ABVD with or without radiotherapy

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Abstract

We retrospectively analyzed 70 patients with classical Hodgkin lymphoma (cHL) who were treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with or without radiotherapy to assess the influence of the soluble interleukin-2 receptor (sIL-2R) level at diagnosis on the clinical outcome. Receiver operating characteristic analyses determined that the optimal cutoff value of the sIL-2R level for progression-free survival (PFS) was 2490 U/mL. Using this cutoff value, patients were classified into low ($n = 46$) and high ($n = 24$) sIL-2R groups. The patients in the high sIL-2R group exhibited a significantly inferior PFS (44.1% vs. 90.4% at 5 years, $P < 0.001$) and overall survival (OS) (67.6% vs. 94.7% at 5 years, $P = 0.001$) compared with those in the low sIL-2R group. Multivariate analysis showed that a high sIL-2R level was an independent prognostic factor for PFS after adjusting for stage, white blood cell, hemoglobin, and B symptoms, and also OS after adjusting for age and stage (hazard ratio (HR) 6.49, $P < 0.001$ and HR 5.98, $P = 0.009$, respectively). In patients with advanced-stage cHL, a high sIL-2R level predicted 5-year PFS even after adjustment for international prognostic score > 4 (HR 6.00, $P = 0.007$). These results demonstrate that the sIL-2R level can be a useful prognostic factor in patients with cHL treated with ABVD with or without radiotherapy.

Keywords Soluble interleukin-2 receptor · Classical Hodgkin lymphoma · ABVD · Prognostic factor

Introduction

Classical Hodgkin lymphoma (cHL) accounts for approximately 15–25% of all lymphomas and often occurs in children and young adults [1]. The pathology of cHL is characterized by the presence of Hodgkin and Reed-Sternberg (HRS) cells, and it is histologically classified into four subtypes: nodular sclerosis HL, mixed cellularity HL, lymphocyte-rich HL, and lymphocyte-depleted HL [2].

Previous randomized studies have reported that the standard treatment of cHL is a combination of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with or without radiotherapy [3–5]. However, 10–15% of patients with early-stage cHL and approximately 30% of those with advanced-stage cHL experience relapse or are refractory to ABVD with or without radiotherapy [3–5]. Compared with ABVD, BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and procarbazine) showed clinical benefits regarding progression-free survival (PFS), but did not confer any advantage in overall survival (OS) and was associated with serious toxicity [6]. In contrast, a systematic review reported that compared with ABVD and other regimens, the use of BEACOPP improved OS in patients with newly diagnosed advanced-stage cHL [7]. Therefore, to consider treatment strategies for cHL, it is important to be able to identify patients with cHL who cannot be cured with ABVD with or without radiotherapy.

Soluble interleukin-2 receptor (sIL-2R) is a serum cytokine. The sIL-2R level increases under inflammatory conditions [8]. An elevated sIL-2R level at diagnosis was found to be a poor prognostic factor for non-Hodgkin's lymphomas [9–16]. In cHL, a high sIL-2R level was also reported to be

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correlated with a poor prognosis [17]. However, in that study, the treatments for cHL were heterogeneous. It is important to analyze the prognostic impact of sIL-2R in patients with cHL treated with the standard chemotherapy, ABVD with or without radiotherapy. Therefore, the present study is aimed at evaluating the clinical implications of the sIL-2R level in such patients.

Methods

Patients

We retrospectively analyzed 70 patients with newly diagnosed cHL treated with ABVD with or without radiotherapy as the first-line treatment at Jichi Medical University between January 2000 and July 2018. The histological diagnosis of cHL was based on the 2008 World Health Organization classification. Patients who did not have available data regarding the serum sIL-2R level at diagnosis were excluded. The response was assessed according to the 2007 Revised Response Criteria for Malignant Lymphoma [18]. Patients were classified into early-favorable, early-unfavorable, and advanced-stage cHL in accordance with the German Hodgkin Study Group (GHSG) criteria. Patients with early-stage cHL received two to six cycles of ABVD with or without 20–30 Gy involved-field radiotherapy, whereas those with advanced-stage cHL received six to eight cycles of ABVD. Eighteen patients who relapsed or were refractory to ABVD with or without radiotherapy received salvage chemotherapy. Nine of them later underwent autologous stem cell transplantation (SCT) and five underwent allogeneic SCT.

Chemiluminescence enzyme immunoassay (Determiner CL IL-2R, Kyowa Medex Co., Ltd.) was used to measure the sIL-2R level at diagnosis. Patients' clinical data were acquired from medical records. We conducted this retrospective study in accordance with the Declaration of Helsinki, and the study protocol was approved by the Bioethics Committee for Epidemiologic Research, Jichi Medical University.

Statistical methods

We performed receiver operating characteristic (ROC) analyses and assessed the area under the curve (AUC) to determine the optimal cutoff value of the sIL-2R level for PFS (defined as the time from diagnosis until disease progression, death, or last follow-up). In the ROC curve, the point with maximum sensitivity and specificity was selected as the optimal predictive cutoff value. Patients were divided into two groups according to this cutoff value. Correlations between the sIL-2R level and various clinicopathological characteristics were assessed using Fisher's exact and Mann-Whitney *U* tests. We measured PFS from the date of diagnosis until disease progression, death, or last follow-up. OS was measured between the date of diagnosis and the date of death or last follow-up. Disease-free survival (DFS) was calculated from the achievement of complete response (CR) after ABVD with or without radiotherapy to relapse, death, or last follow-up. Survival rates were analyzed using Kaplan-Meier curves and compared using the log-rank test. Variables with at least borderline significance ($P < 0.15$) in univariate analyses were subjected to multivariate analysis using a Cox proportional hazards model with stepwise backward variable selection.

All statistical analyses were performed using EZR 1.30 software (Jichi Medical University Saitama Medical Center), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.2.2). Precisely, it is a modified version of R commander (version 2.2–0) that includes statistical functions frequently used in biostatistics [19]. Two-sided *P* values of less than 0.05 were considered to be statistically significant.

Results

sIL-2R level at diagnosis

The median sIL-2R level at diagnosis in patients with cHL was 1880 U/mL (range 265–20,500 U/mL). Patients with advanced-stage cHL exhibited a significantly higher sIL-2R level (median 2220 U/mL; range 372–20,500 U/mL) than those with early-stage cHL (median 1140 U/mL, range 265–5370 U/mL) ($P = 0.001$). In 39 patients with advanced-stage cHL, international prognostic score (IPS) > 4 was correlated with a higher sIL-2R level (median 10,800 U/mL, range 2164–20,500 U/mL vs. median 2015 U/mL, range 372–11,700 U/mL) ($P = 0.003$). Among patients with early-stage cHL ($n = 31$), 6 had favorable risk, 19 had unfavorable risk, and 6 could not be classified because of insufficient data. The favorable-risk group had a lower sIL-2R level than the unfavorable-risk group (median 504.5 U/mL, range 265–1740 U/mL vs. median 1790 U/mL, range 377–5370 U/mL) ($P = 0.022$). In this cohort, four patients were diagnosed with cHL-associated hemophagocytic lymphohistiocytosis with a median sIL-2R level of 2680 U/mL (range 1890–20,500 U/mL), which was higher than that of the other patients, although the difference was not statistically significant ($P = 0.172$).

Based on the ROC curve analysis for the whole population, we determined that the optimal cutoff value of the sIL-2R level for PFS was 2490 U/mL (sensitivity = 0.72, specificity = 0.79, AUC = 0.78, 95% confidence interval (CI) = 0.66–0.90) (Fig. 1). According to this cutoff value, we classified patients into low ($n = 46$, 65.7%) and high ($n = 24$, 34.3%) sIL-2R groups.

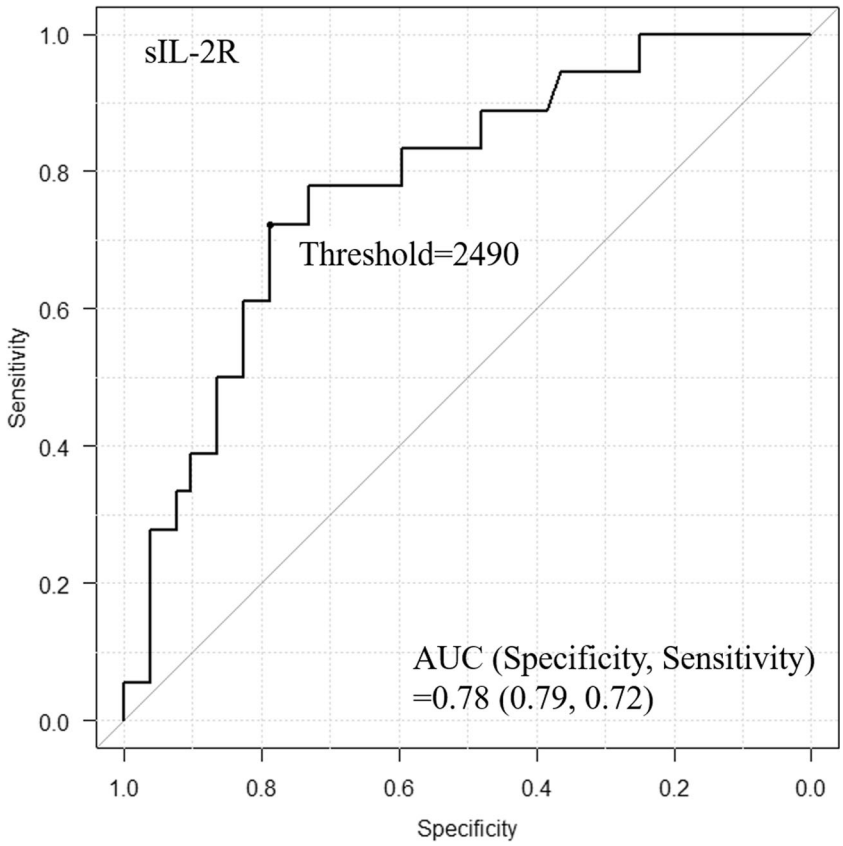

Fig. 1 Receiver operating characteristic (ROC) curve of the serum sIL-2R level at diagnosis for the event of progression-free survival

Patient characteristics

The patient characteristics are shown in Table 1. Our cohort had a median age of 37.9 years (range 14.3–83.2 years), and 41 patients (58.6%) were male. The histology was nodular sclerosis HL in 46, mixed cellularity HL in 16, lymphocyte-rich HL in 4, lymphocyte-depleted HL in 1, and cHL without further specification in 3. The high sIL-2R group correlated with advanced-stage cHL according to GHSG criteria, presence of > 1 extranodal sites, and presence of B symptoms ($P = 0.024$, $P = 0.034$, and $P = 0.042$, respectively).

Table 1 Patient characteristics ($n = 70$)

	sIL-2R ≥ 2490 U/mL ($n = 24$)		sIL-2R < 2490 U/mL ($n = 46$)		
	N	%	*N*	%	*P* value
Sex, male	18	75.0	23	50.0	0.073
Age, years, median (range)	39.7 (15.9–75.8)		37.4 (14.3–83.2)		0.748
≥ 45 years	10	41.7	19	41.3	1.000
Stage by GHSG criteria, advanced	18	75.0	21	45.7	0.024
WBC ≥ 15,000/μL	7	29.2	6	13.0	0.117
ALC < 600/μL	4	16.7	8	17.4	1.000
Hemoglobin < 10.5 g/dL	8	33.3	9	19.6	0.246
Albumin < 4 g/dL	18	75.0	31	67.4	0.590
Extranodal sites > 1	13	54.2	12	26.1	0.034
B symptoms	18	75.0	22	47.8	0.042

sIL-2R soluble interleukin-2 receptor, *GHSG* German Hodgkin Study Group, *WBC* white blood cell, *ALC* absolute lymphocyte count

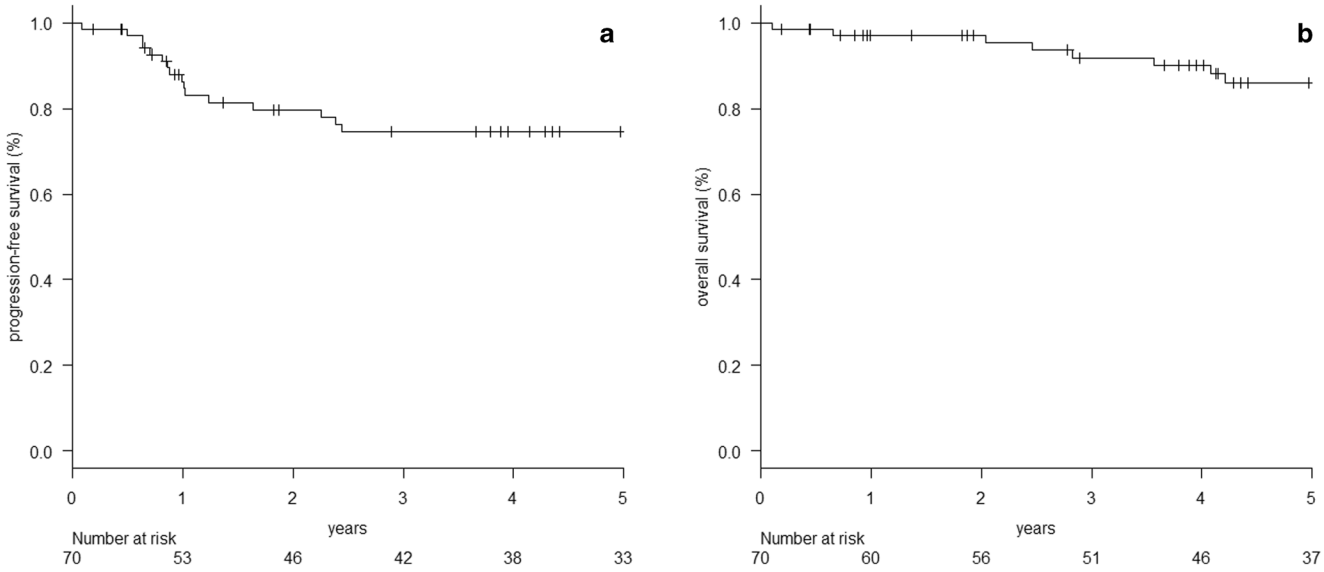

Fig. 2 Kaplan-Meier estimates of progression-free survival (**a**) and overall survival (**b**) for all patients

Response to ABVD with or without radiotherapy

CR, partial response, and disease progression rates were observed in 60 (85.7%), 2 (2.9%), and 8 (11.4%) patients, respectively. CR rates in the high and low sIL-2R groups were 75.0% and 91.3%, respectively ($P = 0.081$). In a multivariate analysis, the sIL-2R level was associated with the CR rate with borderline significance, after being adjusted for other significant covariates (odds ratio (OR) of 3.50 (95% CI = 0.88–13.9, $P = 0.075$)).

Correlations between sIL-2R level and survival rates

The median follow-up duration for survivors was 5.4 years (range 0.2–14.0 years). The probabilities of 5-year PFS and OS were 74.5% (95% CI = 61.7–83.6) and 85.9% (95% CI = 73.7–92.8), respectively (Fig. 2a, b). The PFS and OS curves were divided into two groups according to the sIL-2R level at diagnosis. Patients with a high sIL-2R level had significantly inferior PFS and OS compared with those with a low sIL-2R level (44.1% (95% CI = 22.5–63.7) vs. 90.4% (95% CI = 76.5–96.3), $P < 0.001$ for 5-year PFS and 67.6% (95% CI = 40.5–84.4) vs. 94.7% (95% CI = 80.3–98.6), $P = 0.003$ for 5-year OS) (Fig. 3a, b).

Univariate analyses demonstrated that a high sIL-2R level and advanced-stage cHL according to GHSG criteria significantly affected PFS ($P < 0.001$ and $P = 0.04$, respectively). Multivariate analyses demonstrated that a high sIL-2R level was an independent prognostic factor for PFS (HR 6.49, 95% CI = 2.29–18.4, $P < 0.001$) (Table 2). With regard to OS, univariate analyses revealed that a high sIL-2R level, age ≥ 45 years, and advanced-stage cHL according to GHSG criteria were significant prognostic factors ($P = 0.003$, $P = 0.036$, and $P = 0.012$, respectively). A multivariate analysis revealed that a high sIL-2R level was the only significant prognostic factor for 5-year OS (HR 5.98, 95% CI = 1.57–22.8, $P = 0.009$) (Table 2).

Subgroup analyses were performed by classifying patients according to the GHSG criteria. In patients with advanced-stage cHL ($n = 39$), the high sIL-2R group ($n = 18$) exhibited a significantly inferior 5-year PFS compared with the low sIL-2R group ($n = 21$) (38.7% (95% CI = 15.5–61.6) vs. 84.4% (95% CI = 58.9–94.7), $P = 0.002$) (Fig. 3c). A high sIL-2R level was found to predict 5-year PFS even after adjustment for the group with IPS > 4 (HR 6.00, 95% CI = 1.64–21.9, $P = 0.007$). In patients with early-stage cHL ($n = 31$), the high sIL-2R group ($n = 6$) exhibited inferior 5-year PFS compared with the low sIL-2R group ($n = 25$), but the difference was not statistically significant (60.0% (95% CI = 12.6–88.2) vs. 95.7% (95% CI = 72.9–99.4), $P = 0.131$) (Fig. 3d).

We built a prognostic model that consisted of sIL-2R, white blood cell count, hemoglobin, B symptoms, and stage by GHSG criteria, because these factors were with borderline significance ($P < 0.10$) in terms of PFS. We defined risk groups according to the number of risk factors: 0, low-risk group ($n = 13$); 1–2, intermediate-risk group ($n = 31$); and 3–5, high-risk group ($n = 26$). The 5-year PFS ratios were 100%, 89.5%, and 45.3% (Fig. 3e), and the 1-year OS ratios were 100%, 92.9%, and 67.7%, respectively.

Impact of sIL-2R level in patients successfully treated for cHL

In the 60 patients who achieved CR after ABVD with or without radiotherapy, the 5-year DFS was 86.5% (95% CI =

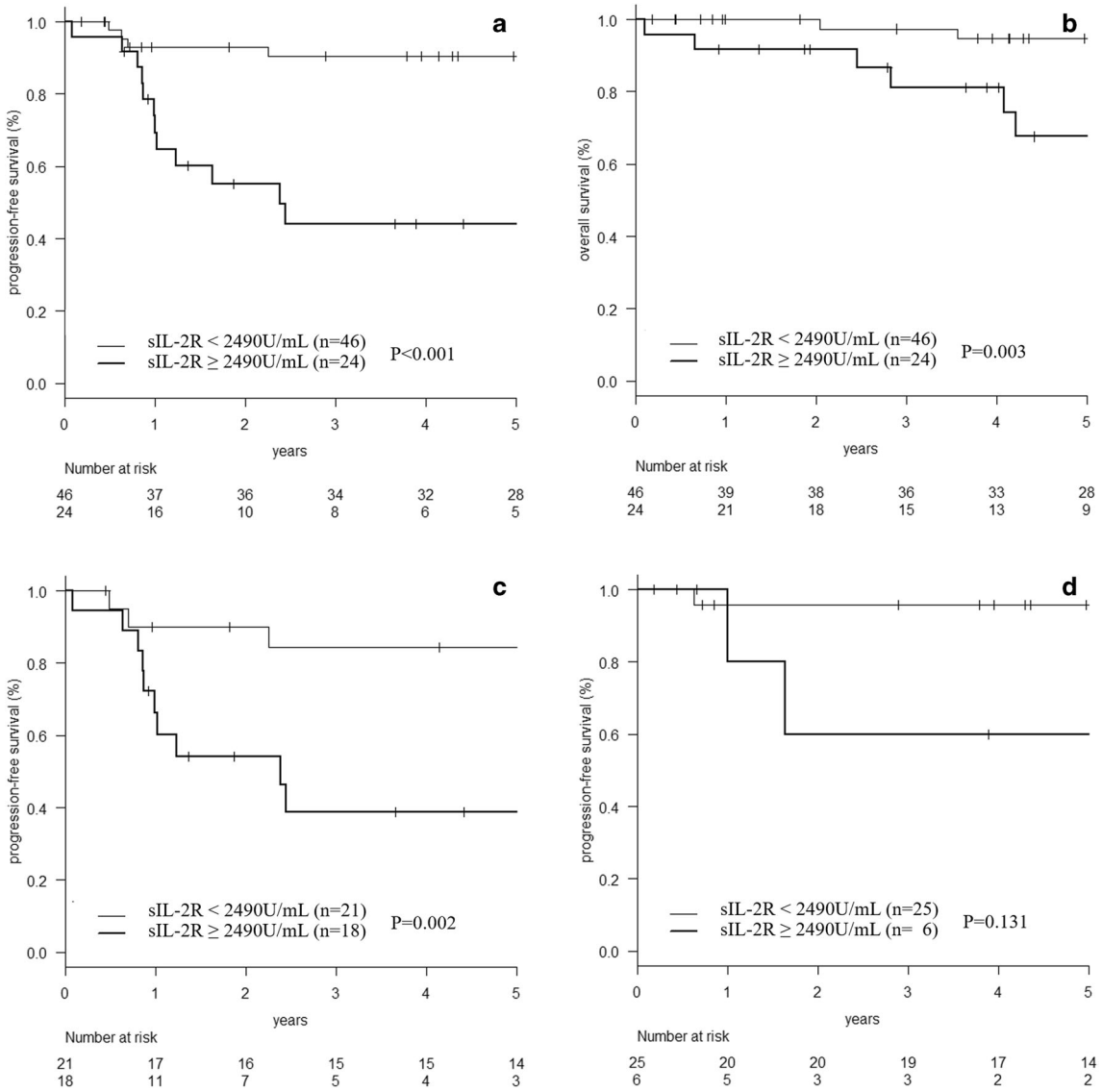

Fig. 3 Progression-free survival (PFS) (**a**) and overall survival (OS) (**b**) according to the sIL-2R level at diagnosis. Subgroup analysis of PFS for advanced-stage (**c**) and early-stage (**d**) patients, grouped according to the sIL-2R level at diagnosis. Kaplan-Meier estimates of PFS for patients grouped according to a risk model that consisted of sIL-2R, white blood cell count, hemoglobin, B symptoms, and stage; low-risk (0 points), intermediate-risk (1–2 points), and high-risk (3–5 points) (**e**). Disease-free survival according to the sIL-2R level at diagnosis (**f**)

73.8–93.3%). Even in patients who achieved CR, a high sIL-2R level was associated with shorter DFS (56.1% (95% CI = 28.9–76.4) vs. 100% (95% CI = 100–100), $P < 0.001$) (Fig. 3f).

Next, we evaluated the predictive value of the sIL-2R level after achieving CR (posttreatment sIL-2R). Posttreatment sIL-2R was evaluated at the discretion of the attending physicians and was measured within 3 months after treatment in all patients. In total, 39 patients had available data regarding posttreatment sIL-2R (median 489 U/mL; range 191–1410 U/mL). We performed ROC analysis and determined that the optimal cutoff value of the posttreatment sIL-2R level for PFS was 606 U/mL (sensitivity = 0.67, specificity = 0.79, AUC = 0.73, 95% CI = 0.48–0.98). According to this cut-off value, patients were divided into two groups. The high posttreatment sIL-2R group ($n = 11$) had inferior 5-year DFS compared with the low posttreatment sIL-2R group ($n = 28$) (70.1% (95% CI = 32.3–89.5) vs. 92.0% (95% CI = 71.6–97.9), $P = 0.014$). To investigate whether the sIL-2R level at diagnosis or posttreatment affected the prognosis, we performed a multivariate analysis including these two factors, which revealed that the sIL-2R level at diagnosis was an independent prognostic factor for DFS

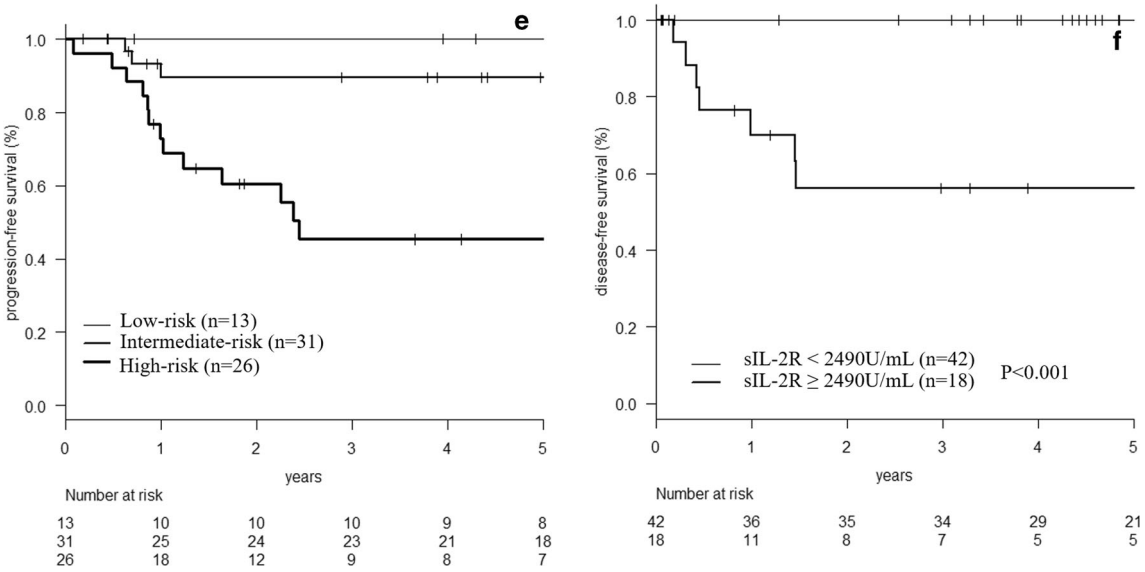

Fig. 3 (continued)

(HR 12.9, 95% CI = 1.49–111.7, $P = 0.020$), whereas the posttreatment sIL-2R level was not (HR 4.50, 95% CI = 0.63–32.1, $P = 0.134$).

Discussion

In the present study, we retrospectively analyzed the relationship between the serum sIL-2R level at diagnosis and the clinical outcome in patients with cHL who were treated with ABVD with or without radiotherapy. We demonstrated that a high sIL-2R level was associated with a poor prognosis, and that, in patients who achieved CR, a high sIL-2R level was also useful for predicting relapse. Furthermore, we developed a prognostic model including the following five factors: sIL-2R, white blood cell count, hemoglobin, B symptoms, and stage. This new prognostic model enabled the risk categorization of patients with cHL into three risk groups.

In our cohort, the sIL-2R level at diagnosis was higher in patients with advanced-stage cHL according to GHSG criteria, presence of > 1 extranodal sites, and presence of B symptoms. Although these have been reported to be adverse prognostic factors for cHL [20–22], a multivariate analysis revealed that a high sIL-2R level was an independent prognostic factor for PFS and OS. In vitro studies showed that sIL-2R is produced by HRS cell lines and plays an important role in host immune suppression by inhibiting normal lymphocyte or T cell proliferation, which facilitates tumor growth [23]. This is a possible explanation of the association between a high sIL-2R level and a poor prognosis.

A subgroup analysis revealed no statistically significant difference between the sIL-2R level and the prognosis in patients with early-stage cHL, possibly because of the good prognosis in patients with early-stage cHL. Recent treatment strategies for patients with early-stage cHL aim at maximal therapeutic effect with minimal toxicity. The pretreatment sIL-2R level may be useful for identifying patients who can be cured with low-intensity treatments, although a prospective study will be required to show its relevance. In contrast, in patients with advanced-stage cHL, a high sIL-2R level had an adverse impact on PFS. Furthermore, a multivariate analysis showed that sIL-2R at diagnosis was a significant predictive factor for PFS even after adjusting for IPS. Therefore, adding the sIL-2R level to the IPS model may enable a more accurate prediction of the outcome. More intensive chemotherapy such as BEACOPP or the addition of brentuximab vedotin to AVD may improve the prognosis of patients who were predicted to have a poor outcome [24, 25].

The prognostic impact of the posttreatment sIL-2R level in lymphoma is controversial. Our previous study reported that the posttreatment sIL-2R level did not affect survival in elderly patients with diffuse large B cell lymphoma (DLBCL) and follicular lymphoma [11, 16] who were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). In contrast, another study reported that a high posttreatment sIL-2R level was correlated with an early relapse in patients with DLBCL treated with R-CHOP [26]. No studies have evaluated posttreatment sIL-2R levels in patients with cHL. In the present study, univariate analyses demonstrated that the posttreatment sIL-2R level influenced DFS. In a multivariate analysis, however, the sIL-2R level at diagnosis, and not posttreatment sIL-2R, had an impact on DFS. This result suggests that evaluation of the sIL-2R

Table 2 Univariate and multivariate analyses of prognostic factors associated with PFS and OS

Factor	Group	*N*	5-year PFS	Univariate	Multivariate		5-year OS	Univariate	Multivariate	
				P value	Hazard ratio	*P* value		*P* Value	Hazard ratio	*P* value
sIL-2R	≥ 2490 U/mL	24	0.44 (0.23–0.64)	< 0.001	6.49 (2.29–18.4)	< 0.001	0.68 (0.41–0.84)	0.003	5.98 (1.57–22.8)	0.009
	< 2490 U/mL	46	0.90 (0.77–0.96)		1		0.95 (0.80–0.99)		1	
Sex	Male	41	0.71 (0.53–0.83)	0.181			0.83 (0.65–0.92)	0.579		
	Female	29	0.80 (0.59–0.91)				0.91 (0.69–0.98)			
Age	≥ 45 years	29	0.74 (0.51–0.88)	0.724			0.74 (0.51–0.88)	0.036	3.85 (0.99–14.9)	0.051
	< 45 years	41	0.74 (0.58–0.85)				0.94 (0.77–0.99)		1	
Stage by GHSG criteria	Advanced	39	0.64 (0.46–0.77)	0.044	2.08 (0.67–6.40)	0.203	0.77 (0.58–0.88)	0.012	3.85 (0.42–34.9)	0.231
	Early	31	0.89 (0.69–0.96)		1		0.97 (0.78–1.00)		1	
WBC	≥ 15,000/μL	13	0.61 (0.29–0.81)	0.067	1.66 (0.60–4.57)	0.330	0.76 (0.42–0.91)	0.287		
	< 15,000/μL	57	0.78 (0.64–0.87)		1		0.89 (0.75–0.95)			
ALC	< 600/μL	12	0.74 (0.39–0.91)	0.936			0.77 (0.35–0.94)	0.809		
	≥ 600 /μL	58	0.75 (0.60–0.85)				0.88 (0.74–0.94)			
Hemoglobin	< 10.5 g/dL	17	0.55 (0.28–0.76)	0.082	1.85 (0.71–4.81)	0.208	0.67 (0.33–0.87)	0.273		
	≥ 10.5 g/dL	53	0.81 (0.66–0.90)		1		0.91 (0.77–0.97)			
Albumin	< 4 g/dL	49	0.71 (0.56–0.82)	0.557			0.85 (0.69–0.93)	0.369		
	≥ 4 g/dL	21	0.83 (0.56–0.94)				0.88 (0.61–0.97)			
B symptoms	Yes	40	0.65 (0.47–0.78)	0.076	1.47 (0.45–4.82)	0.523	0.81 (0.62–0.91)	0.612		
	No	30	0.89 (0.69–0.96)		1		0.92 (0.73–0.98)			

PFS progression-free survival, *OS* overall survival, *sIL-2R* soluble interleukin-2 receptor, *GHSG* German Hodgkin Study Group, *WBC* white blood cell, *ALC* absolute lymphocyte count

level at diagnosis is appropriate for predicting the clinical outcome after ABVD treatment in patients with cHL.

At present, there is no established therapeutic strategy for patients with high sIL-2R levels. However, this study suggests that high sIL-2R levels can help to identify high-risk patients who cannot be cured by ABVD with or without radiotherapy. Therefore, utilizing a more intensive treatment than ABVD may improve the survival chances of patients with cHL with high sIL-2R at diagnosis. In addition, selection of patients with poor prognosis would be useful in the consideration of the candidate for novel agents in clinical studies.

Interim FDG-PET was a strong prognostic factor in patients with cHL who received ABVD treatment [27]. Using a combination of sIL-2R and interim FDG-PET, sIL-2R may help to identify high-risk patients within the group of individuals with a positive interim FDG-PET. This may help to improve the chemotherapeutic strategies to achieve maximal therapeutic effect and minimal toxicity. However, because most patients did not undergo interim FDG-PET, we were unable to evaluate the correlation between sIL-2R and interim FDG-PET.

Independent significant correlations were observed between high sIL-2R and both inferior PFS and OS in the multivariate analysis. It was expected that sIL-2R would increase the accuracy of present prognostic tools, such as the GHSG criteria or interim PET. However, we were unable to construct a new prognostic model, including sIL-2R, GHSG criteria, and interim PET, in the present study owing to the small sample size and the insufficient clinical evaluations.

The present study has several limitations because of its retrospective nature and small sample size. First, we did not perform interim FDG-PET, which has been shown to strongly predict the prognosis, because it was not routinely performed in the period of the present study. However, the sIL-2R level at diagnosis may offer an advantage over interim FDG-PET, because it can be used to select the initial treatment. Second, the sIL-2R level is easily influenced by several inflammatory conditions, such as infection and autoimmune disorders. Third, our cohort included patients with heterogeneous backgrounds, including age, stage, and pathological subgroups.

In conclusion, our data suggest that the sIL-2R level at diagnosis can be a useful prognostic factor for the identification of patients treated with ABVD with or without radiotherapy who have a poor prognosis. Further studies are needed to confirm the current findings before the sIL-2R level can be used as a clinical tool to select treatment strategies.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this retrospective study, formal informed consent is not required. This study was approved by the ethics committee of Jichi Medical University and performed in accordance with the Declaration of Helsinki and its later amendments.

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