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Serum high-density lipoprotein cholesterol level has a significant prognostic impact on outcomes of follicular lymphoma patients

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Abstract

We investigated the potential of nutritional and inflammatory parameters as prognostic factors for follicular lymphoma (FL), and also examined the predictive value of the early progression of disease within 24 months of first-line chemo-immunotherapy (POD24).

We retrospectively analyzed 46 patients with FL admitted to Teikyo University Hospital and treated with chemo-immunotherapy between May 2009 and July 2019. Physical characteristics, blood parameters, and markers or scores for consumptive/inflammatory and nutritional conditions were used as variables.

Nine parameters correlated with poor overall survival (OS) in univariate analysis: An Eastern Cooperative Oncology Group (ECOG) scale performance status (PS) ≥2, five or more involved nodal sites, positive bone marrow (BM) involvement, a serum albumin level <3.5 g/dL, CRP >0.5 mg/dL, lactate dehydrogenase (LD) higher than the upper normal limit (UNL), high-density lipoprotein cholesterol (HDL-C) <40 mg/dL, modified Glasgow prognostic score of 1–2, and the geriatric nutritional risk index <82. In multivariate analysis, ECOG PS ≥2, positive BM involvement, and a serum HDL-C level <40 mg/dL remained significant for poor progression-free survival. One-year OS rate after receiving salvage chemotherapy was lower in the POD24 group (50%) and POD24 correlated with ECOG PS ≥2, positive BM involvement, a serum lactate dehydrogenase >UNL, and HDL-C <40 mg/dL by Fisher's exact test.

These results indicate that low serum HDL-C levels appear to be important for predicting the risk of POD24 and the worse prognosis of FL.

Abbreviations: Auto = autologous hematopoietic stem/progenitor cell transplantation, BG = bendamustine and obinutuzumab, BM = bone marrow, BR = bendamustine and rituximab, CI = confidence intervals, CONUT = the controlling nutrition status, CR = Complete remission, CRP = C-reactive protein, CT = computed tomography, DLBCL = diffuse large B-cell lymphoma, ECOG = Eastern Cooperative Oncology Group, FL = follicular lymphoma, FLIPI = follicular lymphoma international prognostic index, GELF = Groupe d'Etude des Lymphomes Folliculaires, GNRI = the geriatric nutritional risk index, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratios, HSCT = hematopoietic stem/progenitor cell transplantation, LD = lactate dehydrogenase, LDL-C = low-density lipoprotein cholesterol, mGPS = the modified Glasgow prognostic score, NHL = non-Hodgkin's lymphoma, OS = overall survival, PFS = progression-free survival, PNI = the prognostic nutritional index, POD = progression of disease, POD24 = progression of disease within 24 months of first-line chemo-immunotherapy, PS = performance status, r/r = relapsed/refractory, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, R-CVP = rituximab, cyclophosphamide, vincristine, and prednisolone, R-ESHAP= etoposide, cytarabine, cisplatin, and methylprednisolone, Rit = rituximab, R-THP-COP = rituximab, THP-doxorubicin, cyclophosphamide, vincristine, and prednisolone, U-BMT = unrelated bone marrow transplantation, UCBT = umbilical cord blood transplantation, UNL = the upper normal limit.

Keywords: follicular lymphoma, high-density lipoprotein cholesterol, POD24, prognosis

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The data based on the results of the present study are accessible from the first author and the corresponding author upon reasonable request.

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1. Introduction

Follicular lymphoma (FL) is the second most common non-Hodgkin's lymphoma (NHL) in Western countries and Japan, accounting for 15%–20% of all NHL.[1–3] The median age of patients at diagnosis is 65 years,[2] and the morbidity rate increases in patients older than 60 years.[3] Although FL is an indolent-type lymphoma, most patients already have an advanced disease stage at diagnosis, which is incurable. The prognosis of FL is heterogeneous. It frequently relapses in bone marrow (BM) and often transforms to diffuse large-type NHL, an aggressive lymphoma.[4] The watchful waiting strategy is selected to manage patients with advanced FL until they become symptomatic, which includes an increase in the number of involved nodal and/or extranodal sites, organ damage, B symptoms, or pancytopenia.[5–7] Risk stratification is often performed using the follicular lymphoma international prognostic index (FLIPI) and FLIPI2. FLIPI defines 3 risk groups separated by overall survival (OS) and has been used as a convalescence predictive specialized model for FL.[8,9] FLIPI was built using a retrospective analysis that included data collected before the introduction of rituximab. An updated version, FLIPI2, incorporates rituximab-era data and includes β_2 microglobulin as a new parameter. Instead of OS, progression-free survival (PFS) is introduced as an endpoint because of the incurable nature of FL.[10] The decision to initiate treatment for FL depends on an estimation of the tumor burden volume using the Groupe d'Etude des Lymphomes Folliculaires (GELF)[11] and British National Lymphoma Investigation criteria,[12] but not prognostic scores. Chemo-immunotherapies have been shown to increase OS from one to two decades;[13] however, early relapsed/recurrent and refractory cases to initial chemo-immunotherapies have worse prognoses. The progression of disease (POD) within 24 months of first-line chemo-immunotherapy (POD24) consistently occurs in up to 20% of patients.[6,14] POD24 has been established as a robust predictor of survival in FL and is associated with inferior outcomes, with only 34%–50% of patients remaining alive after 5 years.[5–7] The prognostic indices reported to date have many limitations and do not identify newly diagnosed FL patients at risk of POD24 and short survival.[6,14]

In the present single-institution study, we retrospectively investigated whether the prognosis and POD24 of FL patients treated at our institution (Teikyo University Hospital, Japan) may be stratified from the general condition of patients and routine blood test parameters along with inflammatory and nutritional indices at the initiation of treatment for FL.

2. Materials and Methods

2.1. Study population

The Ethical Committee of Teikyo University Graduate School of Medicine reviewed and approved this clinical retrospective study (No. 20-139). The principles of the Declaration of Helsinki were followed throughout the present study.

Patients with FL admitted to Teikyo University Hospital between May 2009 and July 2019 and treated with at least one course of chemo-immunotherapy were enrolled. The initiation of chemo-immunotherapy was decided according to the GELF criteria. Patients treated with focal radiation therapy only were excluded. Patients with a pathological diagnosis of FL grade 3b were also excluded because the treatment strategy selected for grade 3b FL was similar to that for diffuse large B-cell lymphoma (DLBCL).[15] Pathological diagnoses including molecular analyses were confirmed by pathologists in Teikyo University Hospital as well as a central review (READ system, Kotobiken Medical Laboratories, Japan) according to the World Health Organization classification.[1] Imaging studies using computed tomography (CT), magnetic resonance imaging, and ^{18}F-fluorodeoxyglucose-positron emission tomography/CT were employed to define pretreatment clinical staging and posttherapeutic responses.

Table 1

Patient characteristics.

Number of patients	46
Sex	
Male	27
Female	19
Median age, years (range)	66 (35–83)
<61	12
≥61 (≥76)	34 (6)
ECOG Performance Status	
0–1	44
≥2	2
FL grade	
1–2	34
3a	12
Ann Arbor clinical stage	
I/II	3
III/IV	43
Number of involved nodal sites	
<5	22
≥5	24
Bone marrow involvement	
Absent	22
Present	24
Serum albumin level, g/dL	
≥3.5	40
<3.5	6
Serum CRP level, mg/dL	
≤0.5	35
>0.5	11
Serum LD level	
≤UNL	29
>UNL	17
Blood Hb level, g/dL	
≥12	32
<12	14
Blood absolute lymphocyte count/μL	
≥800	36
<800	10
Serum LDL-C level, mg/dL	
>140	40
≤140	4
Serum HDL-C level, mg/dL	
≥40	30
<40	14
Blood HbA1c level, % ≤6.5	36
>6.5	9
mGPS 0, 1–2	31, 14
CONUT score 0–1, 2–4, 5–8, >8	15, 23, 2, 3
PNI <40, ≥40	8, 37
GNRI Q1(<82), Q2(82–91.9), Q3(92–98), Q4(>98)	3, 4, 4, 34
FLIPI risk group	
Low	6
Intermediate	12
High	28
FLIPI2 risk group	
Low	0
Intermediate	13
High	17
First chemo-immunotherapy	
R-CHOP and R-CHOP-like regimen (With Rit maintenance)	39(16)
BR	4
Rit monotherapy	3

GNRI: 14.89 × serum albumin level (g/dL) + 41.7 × real body weight/ideal body weight.
mGPS: Serum CRP level >0.5 mg/dL and albumin <3.5 g/dL, 2; CRP >0.5 mg/dL and albumin >3.5 g/dL, 1; CRP ≤0.5 mg/dL, 0.
PNI: 10 × serum albumin level (g/dL) + 0.05 × absolute lymphocyte count/μL.
CONUT score: Serum albumin level ≥3.50 g/dL, 0; 3.00–3.49, 2; 2.50–2.99, 4; <2.50, 6. Total cholesterol level ≥180 mg/dL, 0; 140–179, 1; 100–139, 2; <100, 3. Absolute lymphocyte count ≥1600/μL, 0; 1200–1599, 1; 800–1199, 2; <800, 3. The score is the sum of these three parameters.
BR = bendamustine and rituximab, CONUT = controlling nutrition status, ECOG = Eastern Cooperative Oncology Group, FL = follicular lymphoma, FLIPI = follicular lymphoma international prognostic index, GNRI = geriatric nutritional risk index, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, LD = lactate dehydrogenase, LDL-C = low-density lipoprotein cholesterol, mGPS = modified Glasgow prognostic score, PNI = prognostic nutritional index, R-CHOP = rituximab = cyclophosphamide = doxorubicin = vincristine = and prednisolone, Rit = rituximab, UNL = the upper normal limit

Complete remission (CR) was defined as the disappearance of all clinical biological disorders related to FL. Partial remission was defined as >50% decrease in the tumor mass/burden. Progressive disease was defined as >50% increase in the tumor mass/burden. The remaining cases were classified as stable disease.[5]

2.2. Data collection

The clinical cut-off date for the analysis was July 31, 2019. The first day of chemo-immunotherapy was defined as day 1, OS was the time between day 1 and death from any cause, and PFS was the time between day 1 and disease progression or death. The relapsed/refractory (r/r) status was started on day 1 of salvage chemotherapy. If the patients did not receive salvage chemotherapy, the day when r/r FL was confirmed was set as day 1. The POD24 group was defined as a group of FL patients for whom disease progression and/or death from POD occurred within 24 months after the first day of chemo-immunotherapy. The following physical characteristics and blood parameters were analyzed: The performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale,[16] histopathological findings (FL grading),[4] Ann Arbor clinical staging,[6–8] the number of involved nodal and extranodal sites,[6–8] FLIPI score, FLIPI2, blood cell count (including the absolute lymphocyte count), electrolytes, serum albumin levels, C-reactive protein (CRP), immunoglobulin, biochemistry data (liver and kidney functions, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides), blood sugar levels, and hemoglobin A1c. Each standard value complies with Japanese and global standards. The presence or absence of BM involvement was also assessed. To estimate the consumptive/inflammatory condition of patients, the modified Glasgow prognostic score (mGPS), data from a combination of serum CRP and albumin levels, was calculated.[17] The patients' nutritional condition was also employed: the controlling nutrition status (CONUT) score, from serum albumin and total cholesterol levels and the absolute lymphocyte count;[18] the prognostic nutritional index (PNI), from serum albumin levels and the absolute lymphocyte count;[19] and the geriatric nutritional risk index (GNRI), from serum albumin levels and the ratio of real body weight to ideal body weight.[20] Blood data were obtained at disease diagnosis.

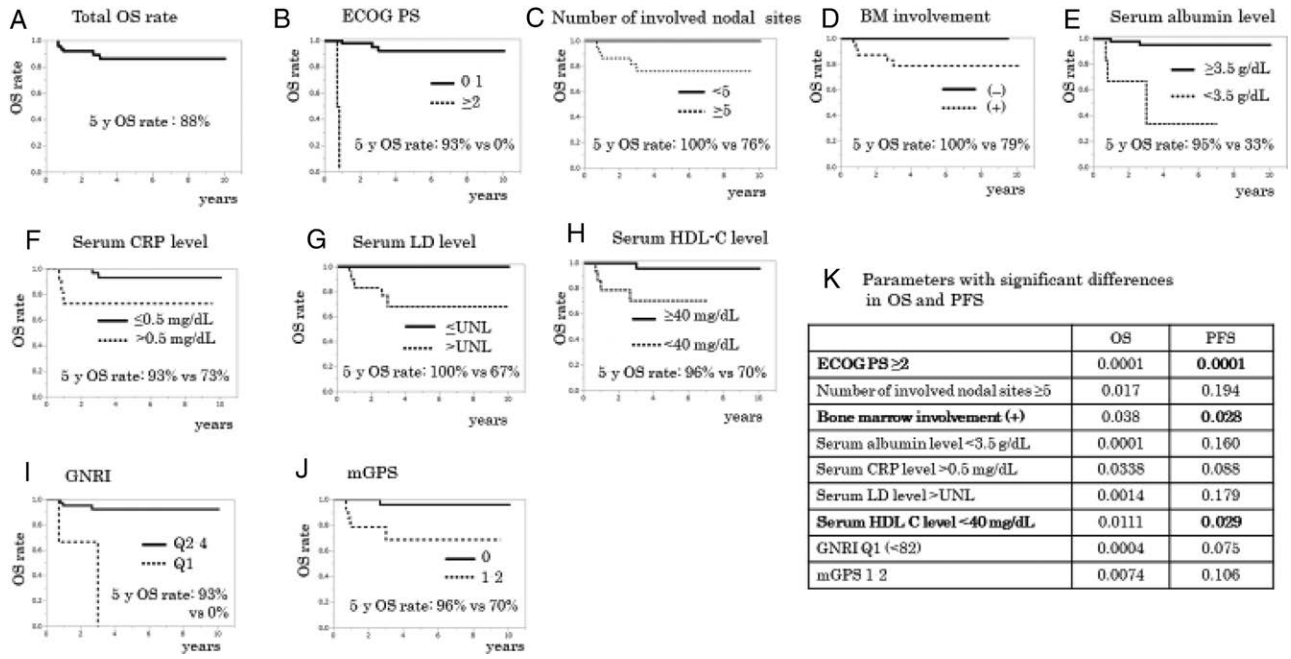
2.3. Statistical methods

Descriptive statistics, including means, standard deviations, medians, and ranges for continuous variables and percentages for categorical variables, were provided. The median follow-up duration, in days and months, was calculated among surviving patients. The Kaplan-Meier method was used to estimate OS and PFS rates, and the log-rank test was employed to assess the significance of differences in OS or PFS between groups. The significance of differences for continuous and categorical variables was calculated by Fisher's exact test. Cox's proportional hazards regression models were performed to calculate hazard ratios (HR) as well as 95% confidence intervals (CI), and to estimate univariate and multivariate analyses of the variables for OS, PFS, and POD24. JMP 14.1.0 statistical software was used for analyses, and significance was set at $P < .05$ and indicated in figures and tables.

3. Results

3.1. Patient characteristics

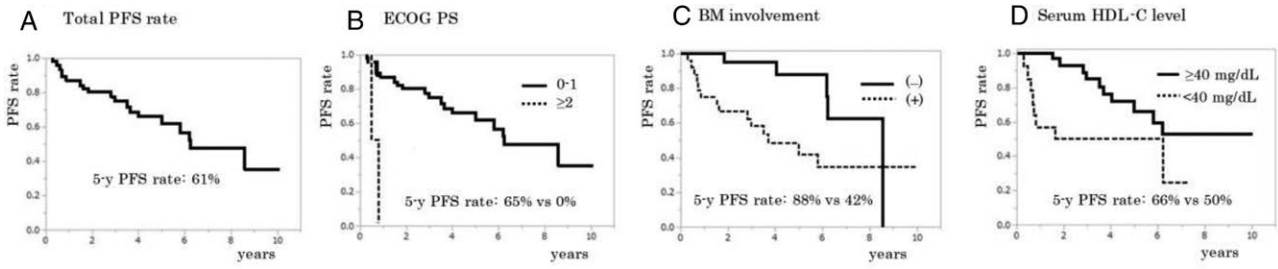
Patient characteristics are summarized in Table 1. Forty-six patients (male 27, female 19) with a median age of 66 years (range: 35–83) were eligible. The median period of posttreatment monitoring was 1650 days (259–3691). ECOG PS was 0/1 in 44 cases and 2–4 in 2. Histopathological FL grading was grade 1 or 2 in 34 cases and grade 3a in 12. The Ann Arbor clinical stage was I/II in 3 cases and III/IV in 43. Five or more involved nodal sites were detected in 24 cases. Twenty-four cases were positive for BM involvement. Serum lactate dehydrogenase (LD) levels were above the upper normal limit (UNL) in 17 cases. Anemia was noted in 14 cases. Serum HDL-C levels were <40 mg/dL in 14 cases. FLIPI risk groups were low in 6 cases, intermediate in 12, and high in 28. Serum β_2 microglobulin levels were



K Parameters with significant differences in OS and PFS

	OS	PFS
ECOG PS ≥2	0.0001	**0.0001**
Number of involved nodal sites ≥5	0.017	0.194
Bone marrow involvement (+)	0.038	**0.028**
Serum albumin level <3.5 g/dL	0.0001	0.160
Serum CRP level >0.5 mg/dL	0.0338	0.088
Serum LD level >UNL	0.0014	0.179
Serum HDL C level <40 mg/dL	0.0111	**0.029**
GNRI Q1 (<82)	0.0004	0.075
mGPS 1 2	0.0074	0.106

Figure 1. Univariate analysis. The log-rank test was used to calculate the statistical differences between subgroups. (A) Total OS rate. (B–J) Significant parameters for OS. (K) *P* values of variables for OS and PFS. Bold type indicates significant variables for PFS ($P < .05$). OS = overall survival, PFS = progression-free survival.



E Parameters correlating with poor PFS

	HR	95% CI	*P* value
ECOG PS ≥2	9.30	1.17-73.80	0.035
Bone marrow involvement(+)	4.04	1.23-13.30	0.022
Serum HDL-C level<40 mg/dL	3.16	1.05-9.45	0.040

Figure 2. Multivariate analysis. (A) Total PFS rate, and (B–D) significant parameters for PFS. The log-rank test was used to calculate the statistical differences between subgroups. (E) Statistical data on three parameters that correlated with poor PFS. Cox's proportional hazards regression models were used to calculate HR and 95% CI. CI = confidence interval, HR = hazard ratio, PFS = progression-free survival.

Table 2

***P* values of variables for OS and PFS (not significant difference).**

	OS	PFS
Age ≥61 y	0.522	0.546
Age >76 y	0.351	0.767
Ann Arbor clinical stage III/IV	0.563	0.494
Follicular Lymphoma grade 3a	0.441	0.335
FLIPI score	0.176	0.375
FLIPI2 score	0.646	0.123
Blood hemoglobin level <12 g/dL	0.103	0.937
Absolute lymphocyte count <800/μL	0.872	0.841
Blood hemoglobin A1c level >6.5%	0.732	0.340
Serum LDL-C level >140 mg/dL	0.339	0.424

The log-rank test was used to calculate the statistical differences between subgroups, and *P* values are presented.
FLIPI = follicular lymphoma international prognostic index, LDL-C = low-density lipoprotein cholesterol, OS = overall survival, PFS = progression-free survival.

not available in 16 cases and FLIPI2 risk groups were low in 0, intermediate in 13, and high in 17. The R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) or R-CHOP-like regimen (R-CVP, rituximab, cyclophosphamide, vincristine, and prednisolone; or R-THP-COP, rituximab, THP-doxorubicin, cyclophosphamide, vincristine, and prednisolone) was administered to 39 cases.

3.2. Clinical outcomes

Five out of 46 patients died, and 5-year OS and PFS rates were 88% and 61%, respectively (Figs. 1A and 2A). Univariate analysis revealed that ECOG PS ≥2, number of involved nodal sites >5, positive BM involvement, a serum albumin level <3.5 g/dL, CRP >0.5 mg/dL, LD >UNL, and HDL-C <40 mg/dL correlated with poor 5-year OS. A GNRI score <82 and mGPS of 1–2 were also significant (Fig. 1B–J). Regarding PFS, ECOG PS ≥2, positive BM involvement, and a serum HDL-C level <40 mg/dL correlated with poor 5-year PFS (Fig. 1K). Multivariate analysis showed that ECOG PS ≥2, positive BM involvement, and a serum HDL-C level <40 mg/dL remained significant for poor PFS (Fig. 2B–E). However, no significant differences in 5-year OS were observed in multivariate analysis because the small number of cases died. FLIPI score, FLIPI2, FL grade 3a, and the absolute lymphocyte count in blood were not significant prognostic factors for OS or PFS in the present study (Table 2).[21]

Table 3

Characteristics of relapsed/refractory cases.

Number of patients/ administered salvage chemo-immunotherapy	19/17
Refractory	5
Relapse <2 y	3
Relapse ≥2 y	9
Sex	
Male	12
Female	5
Median age, years (range) at the start of salvage chemo-immunotherapy	67 (48–86)
≥61 (≥76)	11 (4)
FL grade at disease diagnosis	
1–2	11
3a	6
Re-biopsy (–)	10
Re-biopsy (+) (transformation)	7 (2)
Median observation period, d (range)	324 (28–2273)
Salvage chemo-immunotherapy	
BR	11
R-ESHAP	3
BG	1
R-CHOP	1
Rit monotherapy	1
Alive	12
Dead	5
HSCT cases after salvage chemo-immunotherapy	
Auto	1
U-BMT	2
UCBT	2

Auto = autologous hematopoietic stem/progenitor cell transplantation, BG = bendamustine and obinutuzumab; Rit, rituximab, BR = bendamustine and rituximab, FL = follicular lymphoma, HSCT = hematopoietic stem/progenitor cell transplantation, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone, R-ESHAP = rituximab, etoposide, cytarabine, cisplatin, and methylprednisolone, U-BMT = unrelated bone marrow transplantation, UCBT = umbilical cord blood transplantation.

3.3. POD24 cases

After a median follow-up of 1,650 days, 19 out of 46 patients failed to respond to the first course of chemo-immunotherapy, and 17 (male 12, female 5) were subsequently treated with salvage chemo-immunotherapy: Refractory to first-line treatment, 5 cases; relapsed within 2 years, 3; and relapsed after 2 years, 9. Eight cases were defined as POD24 (17% of all FL cases).

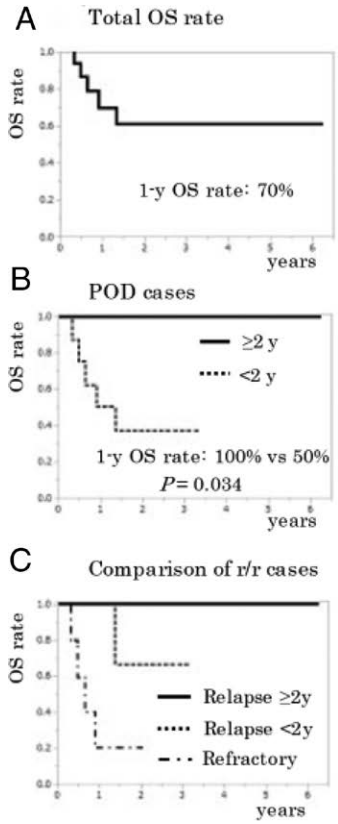
Re-biopsy was performed on 7 patients, with transformation to DLBCL being detected in 2. Salvage chemo-immunotherapy was as follows: Rituximab with bendamustine, 11 cases; R-ESHAP (etoposide, cytarabine, cisplatin, and methylprednisolone), 3; obinutuzumab with bendamustine, 1; R-CHOP, 1; rituximab monotherapy, 1 (Table 3). We analyzed data from POD cases. The median age of 17 POD cases was 67 years (range: 48–86), and the median monitoring period was 324 days (28–2273). One-year OS rates in all r/r cases and the POD24 group were 70% and 50%, respectively (Fig. 3A,B). The OS rate was lower in the POD24 group, with the treatment-refractory group having a dismal prognosis (Fig. 3C). ECOG PS ≥2, positive BM involvement, a serum LD level >UNL, and HDL-C <40 mg/dL were associated with POD24 by Fisher's exact test (Fig. 3D).

Hematopoietic stem/progenitor cell transplantation (HSCT) was performed on 5 cases: Autologous hematopoietic stem/progenitor cell transplantation, 1 case; unrelated bone marrow transplantation (U-BMT), 2; umbilical cord blood transplantation (UCBT), 2 (Table 3). Two transplant cases died of infection. In 8 POD24 cases, 4 received allogeneic HSCT (U-BMT, 2; and UCBT, 2) with 2 maintaining CR.

4. Discussion

Chronic inflammation plays an important role in the transformation of normal cells to malignant cells and several cytokines, including tumor necrosis factor-α and interleukin-1, are produced in such conditions.[22] These cytokines have a negative impact on the patients' nutritional condition, leading to body weight loss, fever, consumption, and emaciation. In the present study, ECOG PS, a serum CRP level, albumin, and mGPS were statistically significant in univariate analysis. These parameters reflect the general condition of patients and the severity of inflammation. GPS was proposed by Forrest et al. in 2003 and has become a prognostic index for non-small-cell lung cancer patients.[23] mGPS using cut-off data of a serum CRP level of 0.5 mg/dL instead of 1.0 mg/dL and albumin 3.5 g/dL effectively predicts survival outcomes of many patients with malignancy.[17] We also used the CONUT score, GNRI, and PNI as nutritional scores. The patients' nutritional condition is used as a prognostic factor for acute phase diseases, the complications of the surgery, and outcomes of malignancies.[24] The CONUT score was proposed as a screening tool to identify undernourished patients in the hospitalized population in 2005.[25] GNRI is also one of the nutritional assessments used for hemodialysis patients, congestive heart failure, and elderly ones.[26] PNI was initially reported by Buzby et al. and calculated using serum albumin levels, triceps skinfold thickness, serum transferrin levels, and a delayed skin hypersensitivity reaction.[27] Onodera et al. proposed a new PNI calculated with serum albumin levels and the absolute lymphocyte count to predict the risk of perioperative complications, and PNI <40 was identified as a contraindication for surgery.[28] PNI has also been used to estimate outcomes of cancer patients.[29] In the present study mGPS of 1–2 and a GNRI score <82 correlated with poor 5-year OS in univariate analysis (Fig. 1).

Chronic inflammation also induces dyslipidemia, particularly a low serum HDL-C level.[30] The relationship between hematological malignancies and low serum HDL-C levels was reported 40 years ago.[31–33] An epidemiological study using information from a base population of more than 21 million individuals as a cohort retrieved for 10 years from six United States Health Plans belonging to the Cancer Research Network showed that 12,103 cases of all-type NHL, including 1,580 FL,



D Parameters to predict POD24 group

	POD24 (%)	Others (%)	*P* value
Sex			
Male	5 (10.9)	22 (47.8)	0.81
Female	3 (6.5)	16 (34.8)	
Age			
≥61	4 (8.7)	8 (17.4)	0.09
<61	4 (8.7)	30 (65.2)	
ECOG PS			
0-1	6 (13.0)	38 (82.6)	**0.0016**
≥2	2 (4.4)	0 (0)	
Bone marrow involvement			
(–)	1 (2.2)	21 (45.7)	**0.0278**
(+)	7 (15.2)	17 (37.0)	
Serum LD level			
≤UNL	2 (4.4)	27 (58.7)	**0.0142**
>UNL	6 (13.0)	11 (23.9)	
Serum HDL-C level mg/dL			
≥40	2 (4.6)	28 (63.6)	**0.0037**
<40	6 (13.6)	8 (18.2)	

Figure 3. Analysis of r/r cases. (A) Total OS rate. (B, and C) OS rate in POD24 cases as well as other r/r cases. The log-rank test was used to calculate the statistical differences between subgroups. (D) Parameters were compared between the POD24 group and other cases. Fisher's exact test was used to calculate the statistical differences between subgroups. Bold type indicates significant difference ($P < .05$). OS = overall survival, POD24 = progression of disease within 24 months of first-line chemo-immunotherapy, r/r = relapsed/refractory.

who were diagnosed with available serum HDL-C data had a low serum HDL-C level several years before the diagnosis of NHL.[34] In another epidemiological study using data from more than 27,000 healthy male smokers, serum HDL-C levels were proposed as a preclinical indicator of NHL, including FL.[35] HDL-C is inversely related to inflammation, and its serum levels are reduced in patients with chronic inflammation from any cause. The scavenger receptor B1, which has high affinity to HDL-C, is more strongly expressed on lymphoma cell surfaces. On the other hand, normal lymphocytes express lower levels of B1. Therefore, serum HDL-C levels decrease during the progression of lymphomas.[36] Besides disease onset, serum HDL-C levels affect the prognosis of lymphomas. In DLBCL cases, low serum HDL-C levels were associated with a poor prognosis.[37] Serum HDL-C and soluble interleukin 2 receptor levels were identified as prognostic factors for NHL and adult T-cell lymphoma/leukemia.[38] In the present study, serum HDL-C level <40 mg/dL correlated with poor 5-year PFS in multivariate analysis (Fig. 2). And we think that it is very important to observe serum HDL-C levels of treated FL patients over time. If HDL-C level comes down and afterwards FL recurs, it may be suggestive of the decision of FL treatment as an early relapse. We will conduct research on lymphoma and serum HDL-C levels from this perspective.

POD24 is an important and highly reproducible marker of poor survival in FL. Casulo et al. reported relationships between POD24 and a poor prognosis and lower OS rates,[14] and POD24 was identified as an important risk factor for a worse prognosis. Since FL is incurable, the stratification of patients at risk of POD24 is critical; however, few studies have examined relevant markers associated with or predictive of POD24. A recent clinical genetic risk model including the mutation status of seven genes along with FLIPI (m7-FLIPI) combined with ECOG PS improved the risk stratification of survival in high-risk FLIPI patients with FL receiving first-line treatment;[39] however, its ability to predict POD24 is limited because the endpoint of m7-FLIPI study was 5-year failure-free survival and OS. Previous studies reported that patients with the early relapsing disease were significantly more likely to have high-risk FLIPI scores than those without early progression;[5,6] however, in our present study FLIPI scores were not significant (Table 2), and ECOG PS two or higher, positive BM involvement, a serum LD level above UNL, and HDL-C <40 mg/dL correlated with POD24. Sortais et al. recently reported that PS of one or higher was predictive of POD24 and proposed POD24 as a relevant endpoint in clinical trials.[40] OS and PFS have been used as endpoints in clinical studies; however, few have employed POD24 (or 2-year PFS) as an endpoint or statistically analyzed parameters associated with POD24. Unfortunately, in the present study significant differences were not observed on POD24 analysis when Cox's regression models were used in multivariate analysis because the number of cases was small (data not shown).

In conclusion, serum HDL-C level <40 mg/dL correlated with poor 5-year PFS of FL. Low serum HDL-C levels appear to be important for predicting the risk of POD24 and worse prognosis. This is the first report on the relationship between POD24 and serum HDL-C levels in our knowledge. Further large-scale clinical studies on FL patients are needed to search for and identify specific parameters or markers that predict POD24. Based on the biological characteristics of POD24, a clinical trial using POD24 as an endpoint is warranted.

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