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ORIGINAL RESEARCH

Decreased apolipoprotein A-I level indicates poor prognosis in extranodal natural killer/T-cell lymphoma, nasal type

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Background: Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL) is an invasive lymphoid malignancy with unfavorable survival, for which a prognostic model has not yet been validated. We hypothesized that serum apolipoprotein A-I (ApoA-I) may serve as a novel prognostic marker for ENKTL.

Patients and methods: A total of 236 newly diagnosed cases of ENKTL were analyzed retrospectively.

Results: The optimal cutoff value for the serum ApoA-I level was determined to be 0.95 g/L. A total of 154 and 82 cases were assigned to the high and low ApoA-I groups, respectively. Patients in the low ApoA-I group tended to present with poorer clinical features, a lower complete remission rate (P=0.001), and poor median progression-free survival (P<0.001) and overall survival (P<0.001). Multivariate analysis using Cox model showed that the serum ApoA-I level was an independent prognostic marker of overall survival (P<0.001) and progression-free survival (P<0.001) for ENKTL patients. For cases in the low-risk group, as assessed by International Prognostic Index, Prognosis Index for peripheral T-cell lymphoma, unspecified, and Korean Prognostic Index, the serum ApoA-I level was able to differentiate cases with poor outcomes from cases with good outcomes.

Conclusion: Our results showed that the baseline serum ApoA-I level was helpful for predicting ENKTL prognosis.

Keywords: apolipoprotein A-I, extranodal NK/T-cell lymphoma, prognosis

Introduction

Extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL) is a predominantly extranodal lymphoma that is related to Epstein–Barr virus (EBV) infection of tumor cells, and it is much more prevalent in Asian and Hispanic countries.[1–3] ENKTL can emerge with nasal or extranasal involvement, and in 60%–90% of patients, the disease is localized to the upper aerodigestive tract.[4,5] Generally, radiotherapy is administered for the management of early stage disease, and anthracycline- or asparaginase-containing chemotherapy followed by radiotherapy is applied to treat advanced cases. However, treatment failures occur frequently in patients with any stage of the disease.[6,7] Despite radiotherapy and chemotherapy, the survival of ENKTL patients is poor, with less than 50% of patients surviving at 5 years.[4,7,8]

Clinically, the International Prognostic Index (IPI), Korean Prognostic Index (KPI), and Prognosis Index for peripheral T-cell lymphoma, unspecified (PIT) have been applied to predict patient survival and select the optimal therapeutic methods for patients with ENKTL. Past research has shown that ~80% of patients are categorized

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as low risk based on the IPI model, and some of them exhibit unfavorable survival.[9] Although PIT can be effectively used to classify other subtypes of T-cell lymphoma, the role of PIT in ENKTL remains controversial.[10,11] The KPI model has been demonstrated to be more accurate at discriminating different ENKTL subtypes than the IPI and PIT models; however, the prognostic efficacy of KPI was not duplicated in some studies.[3] In conclusion, the optimal therapy and the prognosis of patients with ENKTL have not yet been well established. Therefore, additional prognostic markers should be developed to improve the stratification of patient outcomes. Several potential prognostic biomarkers, such as absolute lymphocyte count, peripheral blood EBV load, serum C-reactive protein (CRP), and fasting blood glucose level, have been shown to predict the clinical outcomes of patients with ENKTL.[12–15]

As a major protein constituent of high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-I (ApoA-I) is synthesized in the liver and the small intestine. ApoA-I plays a key role in reverse cholesterol transport by transferring cholesterol and phospholipids from peripheral organs to the liver for excretion. ApoA-I also functions as a cofactor of lecithin cholesterol acyltransferase and participates in the turnover of cholesterol to cholesteryl ester.[16,17] As recently reported, ApoA-I is related to the generation, progression, and prognosis of cancer. ApoA-I has been identified as a potentially useful biomarker for effectively distinguishing cholangiocarcinoma from benign biliary disease and improving the early diagnosis of ovarian cancer.[18,19] Moreover, decreased serum ApoA-I has been shown to be correlated with worse overall survival (OS) in lung cancer and metastatic nasopharyngeal carcinoma.[20,21] The role of ApoA-I in patients with ENKTL has not yet been reported. In our clinical observation, we found that patients with lower baseline ApoA-I tended to present with a shorter survival time. Therefore, we retrospectively analyzed the prognostic value of baseline serum ApoA-I in patients with ENKTL.

Patients and methods

Patient selection

We included 236 patients pathologically diagnosed with ENKTL from June 2002 to May 2014 at the Sun Yat-Sen University Cancer Center in this study. Cases were included if they met the following criteria: 1) histologically confirmed diagnosis of ENKTL based on the guidelines of the World Health Organization; 2) NK/T-cell type, as proven by immunohistochemistry or flow cytometry findings; 3) no previous tumor-related treatment; and 4) complete medical record and follow-up information. Patients were excluded if they suffered from acute illnesses, including stroke, acute infection, surgery, and trauma. This retrospective study was approved by the Institutional Review Board of Sun Yat-Sen University Cancer Center and by the Ethics Committees of Sun Yat-Sen University Cancer Center.

Clinical data collection and staging

The following data were collected at diagnosis: patient demographics; medical examination results; weight; height; serum lactate dehydrogenase (LDH); serum beta-2 microglobulin (β2M); serum lipids and lipoproteins (total cholesterol, triglyceride, HDL-C, low-density lipoprotein cholesterol [LDL-C], ApoA-I, and apolipoprotein-B [ApoB]); CRP; results of marrow tests, results of endoscopic examination of the nasal and oral cavities; and computed tomography or magnetic resonance scans of the nasopharynx, neck, chest, and abdominopelvic or positron emission tomography/computed tomography of the full body. For all cases, the plasma levels of lipids and lipoproteins in the fasting state were determined by an automatic biochemical analyzer. Prior to use of the patients' sera, written informed consent was obtained from each of the participants.

ENKTL is classified into two categories depending on the site of the lesions: 1) upper aerodigestive tract NK/T-cell lymphoma (UNKTL), defined as a case with the primary tumor located in the nasal cavity, nasopharynx, or upper aerodigestive tract and 2) extra-upper aerodigestive tract NK/T-cell lymphoma (EUNKTL), defined as a case with the primary tumor located at any site other than UNKTL sites. Although these two subclasses share the same pathological characteristics, UNKTL and EUNKTL have obviously different prognoses.[5,22] A standard staging system for NK/T-cell lymphomas is lacking. We staged all cases using the Ann Arbor staging system, which was originally designed for Hodgkin's lymphoma. IPI (performance status [PS], age, extranodal sites, serum LDH, and stage), KPI (B symptoms, regional lymph nodes, serum LDH, and stage), and PIT (PS, age, bone marrow involvement, and serum LDH) were also evaluated to examine patient survival.[3,10,23]

Response assessment and statistical analyses

We utilized the International Working Group Recommendations for Response Criteria for non-Hodgkin's lymphoma (NHL) to evaluate the reactions of the ENKTL patients to the administered therapies.[24] Regular imaging surveillance was performed every 3 months for the first 2 years after treatment, twice a year for the next 3 years, and annually or when clinical signs indicated it thereafter. No pellucid marginal value

for serum lipids or lipoproteins was found to be associated with tumor outcome, so we analyzed the receiver operating characteristic (ROC) curve to provide an optimal critical value for ApoA-I and ApoB. Based on the National Cholesterol and Education Program Adult Treatment Panel III criteria, a total cholesterol serum concentration ≥200 mg/dL, a triglyceride serum concentration ≥150 mg/dL, a HDL-C serum concentration <40 mg/dL, and a LDL-C serum concentration ≥130 mg/dL are defined as hypercholesterolemia, hypertriglyceridemia, categorical low HDL-C, and high LDL-C, respectively.[25]

Statistical analyses were conducted using SPSS standard version 20.0 (IBM Corporation, Armonk, NY, USA) for Windows. OS was defined as the interval between the diagnosis date and the time of death for any reason or last follow-up. Progression-free survival (PFS) was determined from the date of diagnosis to the time of disease progression, relapse after response, last follow-up, or death. Differences in continuous variables were analyzed by nonparametric tests (Mann–Whitney *U*-test or Kruskal–Wallis). Categorical characteristics were compared by the chi-square test. Survival curves were analyzed by the Kaplan–Meier method and the log-rank test was used to compare differences between groups. The multivariate Cox regression model was used to evaluate independent predictive factors associated with survival difference. A two-tailed *P*-value of <0.05 was considered statistically significant.

Results

The clinical baseline features of the 236 cases are listed in Table 1. The median age at diagnosis was 41 years (range: 16–78 years), and 66.5% of the patients were male. The majority of cases originally manifested as the UNKTL subtype (n=198, 83.9%). For the EUNKTL cases, the primary tumor was mainly located in the skin, gastrointestinal tract, testis, and spleen. A total of 221 patients (93.6%) had a favorable PS. More than half of the patients showed B symptoms. A total of 83 cases (35.2%) exhibited increased LDH. Of the 146 patients for whom β2M was measured, 82 (56.9%) showed increased β2M. A total of 130 (55.1%) and 123 (52.1%) patients presented with regional lymph node involvement and two or more extranodal sites, respectively. Only eight patients (3.4%) displayed bone marrow infiltration. Most cases presented with localized disease (Ann Arbor stages I/II; n=185, 78.4%). According to the IPI score, 151 patients (64.0%) with less than two adverse factors were categorized in the low-risk group. The KPI assessment classified 120 patients (50.8%) into the low-risk group. The PIT model classified 215 patients (91.1%) into the low-risk group, and 21 patients (8.1%) exhibited two or more adverse factors.

Correlation between serum ApoA-I and clinical features

The median serum ApoA-I level (range) and 25% and 75% quartiles were 1.06 (0.20–1.80 g/L), 0.89, and 1.26 g/L, respectively. The optimal cutoff value for serum ApoA-I was 0.95 g/L based on the ROC analysis results (area under the curve: 0.719, 95% confidence interval (CI): 0.657–0.775, $P<0.001$) (Figure 1). The prognostic value of the different cutoff values, including median value (1.06 g/L) and mean value (1.07 g/L), were also evaluated, and 0.95 g/L was found to be the most effective cutoff value. The whole cohort was divided into two groups based on the 0.95 g/L cutoff value. One hundred and fifty-four (65.3%) cases were categorized into the high ApoA-I group, and the remaining 82 (34.7%) patients were categorized into the low ApoA-I group (Table 1). The optimal cutoff value for ApoB was 0.88 g/L. The baseline features of the cases with ApoA-I ≤0.95 g/L were compared with those of cases with ApoA-I >0.95 g/L (Table 1). Poor PS, B symptoms, elevated serum LDH, elevated serum β2M, and advanced stage (III/IV) occurred more frequently in the cases from the low ApoA-I group. Patients in the low ApoA-I group tended to show a higher rate of hypercholesterolemia, decreased HDL-C, hypoalbuminemia, and increased CRP. Additionally, the patients in low ApoA-I group exhibited a higher risk than those in the high ApoA-I group according to the IPI, KPI, and PIT models. The continuous variable analyses showed that the ApoA-I level was notably lower in patients with EUNKTL and two or more extranodal sites. No significant intergroup differences in the mean values of continuous or categorical variables were found for any other clinical features examined.

Treatment and response

The therapeutic protocols and responses are summarized in Table 2. Chemotherapy followed by radiotherapy was administered to 148 (62.7%) patients, chemotherapy alone was administered to 66 (28.0%) patients, radiotherapy alone was administered to four (1.7%) patients, surgery followed by chemotherapy was administered to 16 patients (6.8%), and best supportive care alone was administered to two cases (0.8%). No significant differences in treatment modalities were observed between the high and low ApoA-I groups.

The first-line chemotherapy schemes were as follows: cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like (CHOP + L-asparaginase, CHOP + high-dose methotrexate, or CHOP + etoposide); alternating triple therapy (cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin, ifosfamide, methotrexate,

Table 1 Baseline characteristics of patients by serum ApoA-I level

Characteristics	ApoA-I value (mean ± SD) (g/L)	*P*-value	Low ApoA-I group, n (%)	High ApoA-I group, n (%)	*P*-value
Number of cases			82 (34.7)	154 (65.3)	
Age at diagnosis (years)		0.141	41 (16–78)	38 (16–73)	0.297
≤60	1.08±0.27		69 (84.1)	138 (89.6)	
>60	1.01±0.22		13 (15.9)	16 (10.4)	
Sex		0.319			0.668
Male	1.06±0.27		55 (67.1)	102 (66.2)	
Female	1.10±0.27		27 (32.9)	52 (33.8)	
ECOG PS		<0.001			0.003
0, 1	1.09±0.26		71 (91.5)	150 (96.1)	
≥2	0.81±0.27		11 (8.5)	4 (3.9)	
Subtypes		0.006			0.094
UNKTL	1.09±0.26		64 (78.0)	134 (87.0)	
EUNKTL	0.96±0.31		18 (22.0)	20 (13.0)	
B symptoms	1.01±0.28	<0.001	53 (64.6)	67 (43.5)	0.003
Regional lymph node involvement	1.03±0.27	0.057	52 (63.4)	78 (50.6)	0.074
Extranodal sites ≥2	1.03±0.28	0.003	50 (61.0)	73 (47.4)	0.056
Bone marrow involvement	0.94±0.28	0.126	5 (6.1)	3 (1.9)	0.130
Elevated serum LDH	0.99±0.26	0.001	38 (46.3)	45 (29.2)	0.010
Elevated serum β2M*	0.98±0.28	<0.001	41 (50.0)	41 (44.6)	0.001
Ann Arbor stage		<0.001			<0.001
I/II	1.11±0.26		52 (63.4)	133 (86.4)	
III/IV	0.94±0.27		30 (36.6)	21 (13.6)	
IPI score		<0.001			0.010
0–1	1.14±0.26		43 (52.4)	108 (70.1)	
2–5	0.95±0.24		39 (47.6)	46 (29.9)	
KPI score		<0.001			0.004
0–1	1.13±0.26		31 (37.8)	89 (57.8)	
2–4	1.01±0.27		51 (62.2)	65 (42.2)	
PIT score		0.032			0.031
0–1	1.09±0.26		70 (85.4)	145 (94.2)	
2–4	0.95±0.29		12 (14.6)	9 (5.8)	
Cholesterol (≥200 mg/dL)	1.21±0.26	<0.001	11 (13.4)	51 (33.1)	0.001
Triglyceride (≥150 mg/dL)	1.11±0.33	0.334	28 (34.1)	46 (29.9)	0.556
HDL-C (<40 mg/dL)	0.90±0.21	<0.001	68 (82.9)	39 (25.3)	<0.001
LDL-C >2.75 (≥130 mg/dL)	1.21±0.30	0.058	16 (19.5)	43 (27.9)	0.206
ApoB (≥0.88 g/L)	1.13±0.34	0.765	31 (37.8)	35 (22.7)	0.633
Albumin (<35 g/L)	0.93±0.37	<0.001	20 (24.2)	12 (7.8)	0.001
CRP (>10 mg/L)	1.00±0.30	<0.001	60 (73.2)	36 (25.0)	<0.001
BMI (≥25 kg/m^2)	1.01±0.20	0.251	9 (11.0)	18 (11.7)	1.000

Note: *Serum β2M was measured in 146 patients.

Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein-B; β2M, beta-2 microglobulin; BMI, body mass index; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; EUNKTL, extra-upper aerodigestive tract NK/T-cell lymphoma; HDL-C, high-density lipoprotein cholesterol; IPI, International Prognostic Index; KPI, Korean Prognostic Index; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; PIT, Prognosis Index for peripheral T-cell lymphoma, unspecified; SD, standard deviation; UNKTL, upper aerodigestive tract NK/T-cell lymphoma.

etoposide, and dexamethasone, cisplatin, and cytarabine); etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone; oxaliplatin and gemcitabine; oxaliplatin, gemcitabine, and L-asparaginase; and dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide. The patients were administered two to eight courses of initial chemotherapy. At our institute, a total radiotherapy dose of 30–60 Gy with fractional doses of 1.8–2.0 Gy is generally used. Two hundred and twenty-six patients (95.8%) were evaluated to determine their responses to initial chemotherapy, and 104 of these 226 patients (46.0%) exhibited a complete response (CR) or unconfirmed CR, 88 patients (38.9%) achieved a partial response, 17 patients (7.5%) exhibited stable disease, and 17 patients (7.5%) showed progressive disease; therefore, the overall response rate (ORR) was 85.0%. The CR rate and ORR to original treatment were significantly higher in the

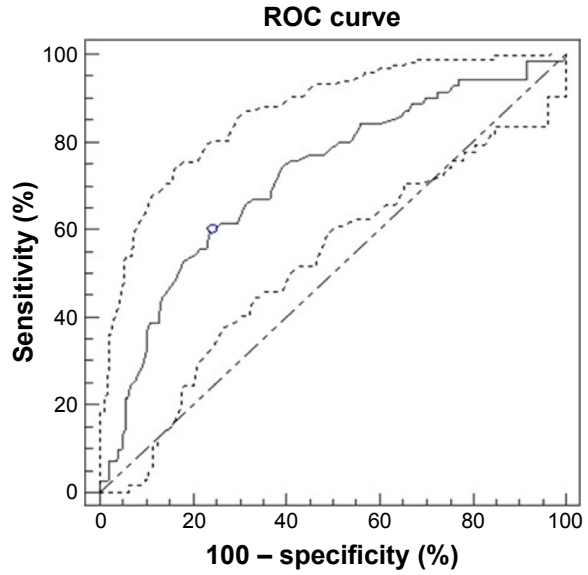

Figure 1 ROC of pretreatment ApoA-I level for outcome prediction.
Notes: Area under the ROC curve: 0.719 (95% CI: 0.657–0.775). The sensitivity and specificity of the point with highest accuracy were 60% and 75.9%, respectively.
Abbreviations: ApoA-I, apolipoprotein A-I; CI, confidence interval; ROC, receiver operating curve.

high ApoA-I group than in the low ApoA-I group (54.1% vs 30.8%, P=0.001; 90.5% vs 74.4%, P=0.005, respectively).

Survival analysis

The cutoff point for follow-up data collection was April 12, 2015, and the median follow-up duration was 27.3 months (range: 2.2–154.2 months). In the current study, the 3-year OS and PFS of the patients were 67.0% and 55.6%, respectively. The patients from the low ApoA-I group exhibited lower PFS (3-year PFS, 66.1% vs 34.4%; P<0.001) and OS (3-year OS, 80% vs 41.0%; P<0.001; Figure 2) than the patients in the high ApoA-I group. The univariate and multivariate analyses of OS and PFS of the 236 patients are presented in Table 3. In the univariate analysis, poor PS, EUNKTL, B symptoms, bone marrow involvement, two or more extranodal sites, regional lymph node involvement, increased serum LDH, increased serum β2M, hypertriglyceridemia, hypoalbuminemia, decreased HDL-C, decreased ApoA-I, advanced stage, and the IPI, PIT, and KPI values were dramatically correlated with poor OS and PFS. Age was significantly correlated with OS (P=0.012), but failed to demonstrate prognostic significance for PFS (P=0.080). The clinical factors that were statistically significant predictors of OS and PFS were included in the multivariate analysis. IPI, KPI, and PIT scores were not included in the multivariate analysis because these scores overlapped with other clinical variables. The multivariate analysis results revealed that the serum ApoA-I level was an independent prognostic indicator of OS (relative risk: 3.709, 95% CI: 1.908–7.210, P<0.001) and PFS (relative risk: 2.669, 95% CI: 1.536–4.640, P=0.001). Additionally, poor PS, EUNKTL, and marrow involvement were considered independent prognostic indicators of OS and PFS.

Discussion

The current study showed that a low level of serum ApoA-I was significantly correlated with inferior OS and PFS in patients with ENKTL. In addition to low ApoA-I, poor PS, EUNKTL, and marrow infiltration were independent prognostic indicators of OS and PFS, which is consistent with the findings of previous studies.[26–29]

The mechanisms underlying the relationship between decreased ApoA-I levels and short survival time have

Table 2 Primary treatment and response in patients with extranodal natural killer (NK)/T-cell lymphoma

Treatment	Low ApoA-I group (number of patients)	High ApoA-I group (number of patients)	*P*-value
Patients treated	81	153	0.649
Treatment modalities			0.401
CT followed by RT	51	97	
CT alone	22	44	
RT alone	0	4	
Surgery followed by CT	8	8	
Best supportive care	1	1	
Chemotherapy regimens			0.826
Adriamycin-used	32	57	
L-asparaginase-used	36	67	
Both	7	11	
Efficacy*			0.001
CR achieved	24	80	

Note: *The response to treatment was evaluated in 226 patients.
Abbreviations: ApoA-I, apolipoprotein A-I; CR, complete remission; CT, chemotherapy; RT, radiotherapy.

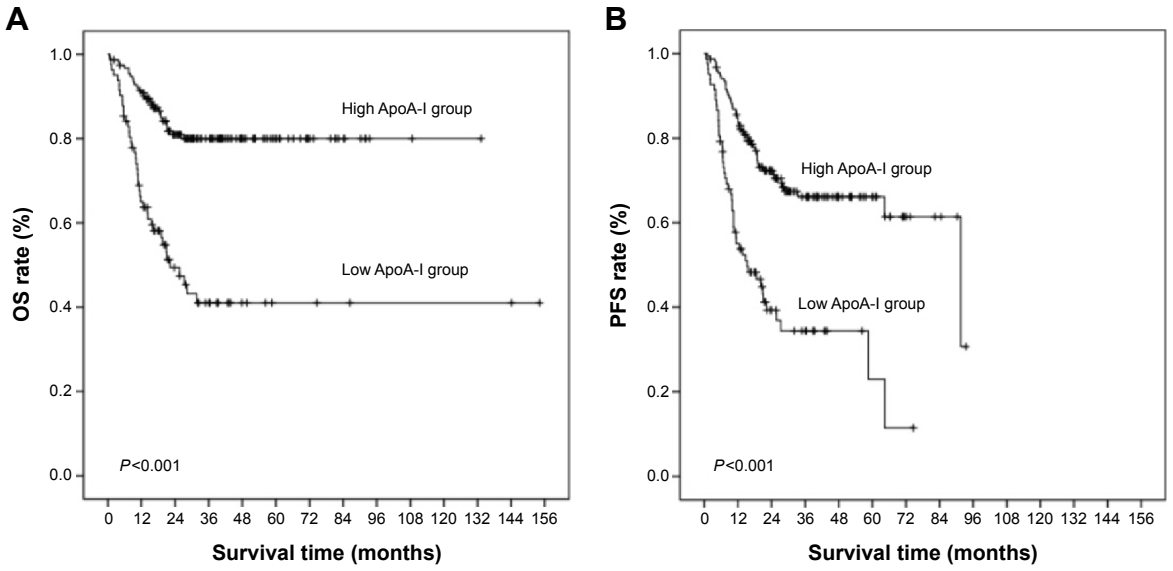

Figure 2 OS and PFS according to ApoA-I level (≤0.95 vs >0.95 g/L). Kaplan–Meier plots of OS (**A**) and PFS (**B**) for all patients.
Abbreviations: ApoA-I, apolipoprotein A-I; OS, overall survival; PFS, progression-free survival.

not been fully elucidated; nevertheless, several potential interpretations have been suggested. First, patients with a low ApoA-I level may have enhanced tumor cell growth and metastatic ability. Chronic inflammation has been shown to be associated with various steps involved in tumorigenesis and development.[30,31] A recent report by Lin et al[27] found that ENKTL patients have a multitude of tumor-associated macrophages, which is one of the most vital actors in the inflammation arena and has been accepted as a crucial marker of inflammation. An increasing number of studies have

Table 3 Results of univariate and multivariate analyses of prognostic factors for PFS and OS in patients with ENKTL

Parameter	PFS			OS		
	Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis	
	P-value	RR (95% CI)	*P*-value	*P*-value	RR (95% CI)	*P*-value
Age >60 years	0.080			0.011		
ECOG PS ≥2	<0.001	2.893 (1.350–6.200)	0.006	<0.001	2.618 (1.202–5.703)	0.015
Subtype, EUNKTL	<0.001	2.690 (1.537–4.706)	0.001	<0.001	2.346 (1.233–4.464)	0.009
B symptoms	0.003			<0.001		
Bone marrow involvement	<0.001	3.699 (1.415–9.668)	0.008	<0.001	3.152 (1.115–8.913)	0.030
Extranodal sites ≥2	<0.001			0.001		
Regional lymph node involvement	0.002			0.001		
LDH (>245 U/L)	<0.001			<0.001		
β2M* (>2.52 mg/L)	<0.001			<0.001		
Stages III–IV	<0.001			<0.001		
Cholesterol (≥200 mg/dL)	0.132			0.212		
Triglyceride (≥150 mg/dL)	0.012			0.032		
HDL-C (<40 mg/dL)	0.009			0.043		
LDL-C (≥130 mg/dL)	0.878			0.429		
ApoA-I (<0.95 g/L)	<0.001	2.669 (1.536–4.640)	0.001	<0.001	3.709 (1.908–7.210)	<0.001
ApoB (≥0.88 g/L)	0.523			0.653		
Albumin (<35.0 g/L)	<0.001			<0.001		
CRP (≥10.0 mg/L)	0.151			0.086		
BMI (≥25 kg/m^2)	0.570			0.507		

Note: *Serum β2M was measured in 146 patients.
Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein-B; β2M, beta-2 microglobulin; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group performance status; ENKTL, extranodal natural killer (NK)/T-cell lymphoma, nasal type; EUNKTL, extra-upper aerodigestive tract NK/T-cell lymphoma; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; OS, overall survival; PFS, progression-free survival; RR, relative risk.

suggested that ApoA-I can potently inhibit tumor development through an expansive repertoire of activities, including anti-inflammatory, antiangiogenic, antithrombotic, and immune-regulatory activities, but not anti-atherosclerotic activities.[17,32–34] A common mechanism of action of the anti-inflammatory effect of ApoA-I is its ability to bind to proinflammatory phospholipids.[32,35] Moreover, ENKTL is associated with EBV infection, and latent membrane protein 1 encoded by EBV has been reported to promote interleukin-6 production.[2,36] Interleukin-6 and tumor necrosis factor-α can decrease the synthesis and secretion rates of ApoA-I by hepatic cells, and a low ApoA-I level indirectly indicates increased cytokine release and a stronger inflammatory response to tumors.[37] Prostacyclin (PGI2) stabilization is considered an important function of ApoA-I. When the ApoA-I level is reduced, the availability of PGI2 at the location of vascular endothelial injury can be reduced, thereby decreasing the protection against thrombocyte aggregation and thrombosis, which is strongly related to tumor cell growth and metastasis.[17,38] Second, patients with low ApoA-I have been proposed to have a poorer response to treatment, and this hypothesis was supported by our results, which demonstrated that the CR rate and ORR in patients with low ApoA-I were significantly inferior to those of patients with high ApoA-I, though no remarkable difference in primary therapeutic strategy was observed between those groups. A possible explanation for this finding is that patients with low ApoA-I may be less tolerant of chemoradiotherapy, which results in the administration of an insufficient dose of chemotherapy or radiotherapy. Third, patients with lower ApoA-I levels had more adverse clinical characteristics, such as poor PS, advanced stage, and B symptoms.

Here, we retrospectively analyzed the relationship between the serum ApoA-I level and clinical characteristics and discovered that low ApoA-I level was more frequent in cases with elevated LDH, elevated β2M, elevated CRP, and decreased albumin. Serum LDH and β2M levels are indicators of tumor burden in patients with ENKTL and suggest that ApoA-I is a potential marker of tumor load to a certain extent.[39,40] A prior study by Li et al observed that high CRP level is associated with unsatisfactory outcomes in ENKTL.[14] Hypoalbuminemia is associated with nutritional deficiency and body weight reduction, which result in a poor PS and increased cancer-related mortality.[41] The results of our univariate survival analyses revealed that elevated LDH, elevated β2M, and low serum albumin were significantly related to PFS and OS in patients with ENKTL. Inconsistent with previous investigations, our results showed that low HDL-C and high CRP were not significantly correlated with poor clinical outcome when other serum lipids and lipoproteins and clinical characteristics were included in the analysis.[14,42] These discrepancies may be associated with selection criteria. For example, Wang et al[42] included patients who received either oxaliplatin, gemcitabine, L-asparaginase or etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone regimens as induction chemotherapy. In addition, the patients with lower ApoA-I levels in our study had other adverse clinical characteristics, including poor PS, advanced stage, and B symptoms, all of which could be responsible for the relationship between decreased serum ApoA-I level and poor prognosis.

We performed univariate analyses of the prognostic values of the IPI, PIT, and KPI models, and the three models were found to have high prognostic value. However, the IPI and PIT prognostic models disproportionately categorized the patients into the low-risk category, with the models categorizing 64.0% and 91.1% of the patients into the low-risk category, respectively (Table 1). Although the KPI model equally distributed patients into the different risk categories, all three models failed to distinguish cases within the low-risk group that had poor clinical outcomes. As shown in Figure 3, serum ApoA-I can be used to divide low-risk cases into two subgroups with different prognoses. In our study, the proportion of low-risk IPI scores was less than that of previous reports due to patient selection criteria.[3,4,12]

As described in the "Introduction", optimal treatment strategies for ENKTL have not been fully defined, and novel drugs for ENKTL should be developed. Recently, some studies suggested that the pharmacological administration of ApoA-I may have a therapeutic benefit as an anticancer agent in melanoma. ApoA-I mimetic peptides engineered to mimic anti-inflammatory and antioxidant functionalities of ApoA-I have recently been reported to suppress ovarian cancer cell growth.[43,44] Although these findings have not yet been successfully confirmed in the clinical context, we expect that ApoA-I and its mimetic peptides will be valuable therapeutic agents to complement antitumor strategies in ENKTL in the near future. We acknowledge that the present study is limited due to its retrospective, single-center design. Some patients with cardiovascular complaints or hepatic illnesses, such as coronary heart disease, hypertension, and chronic hepatitis, were included in this study, and the effects of those disease on lipid metabolism were not considered.

Conclusion

Our study is first to demonstrate that baseline serum ApoA-I can function as a strong and independent indicator of survival outcomes in ENKTL. This biomarker is directly derived from routine blood biochemical tests and can be easily measured in the clinic. Nevertheless, more studies with multicenter or

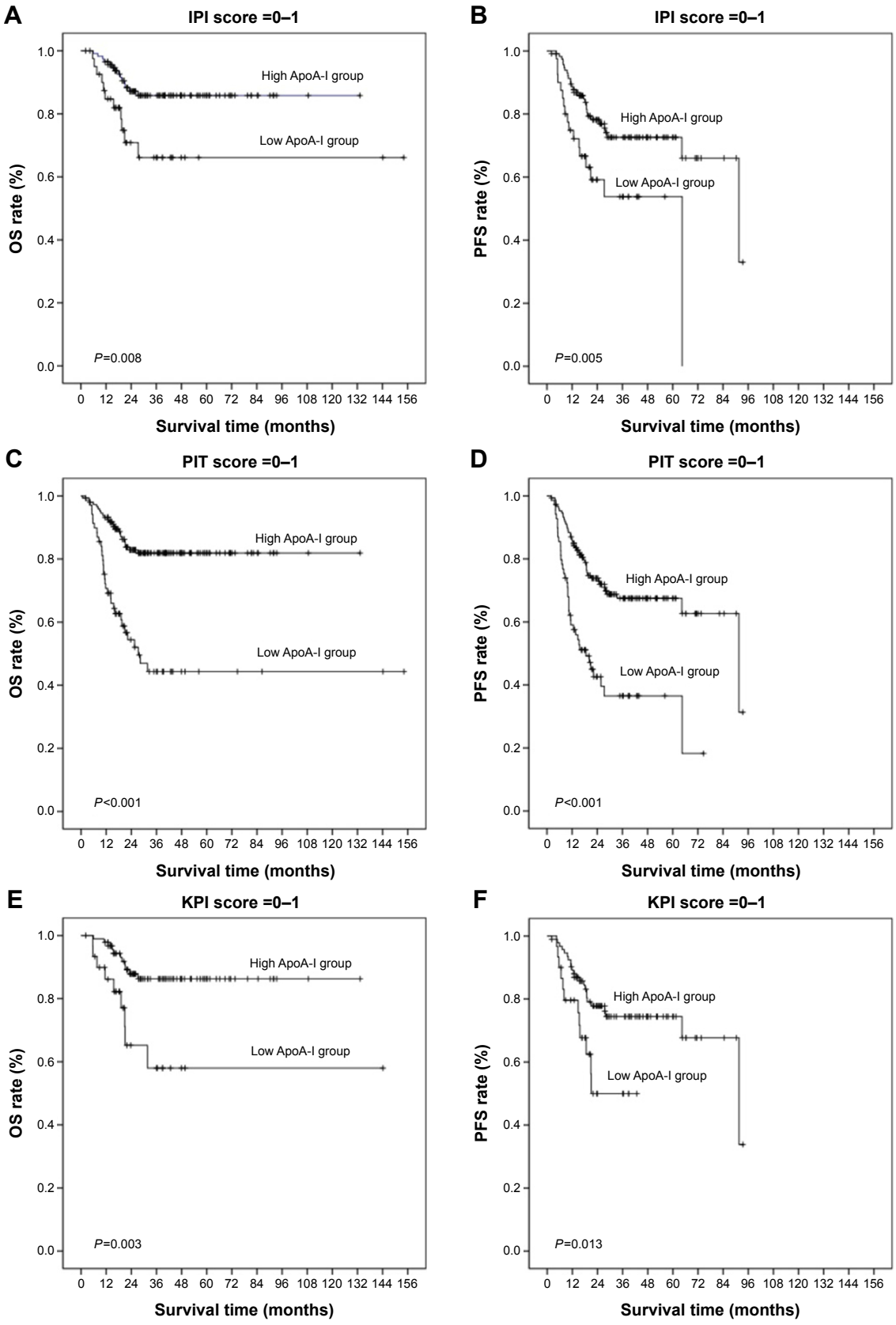

Figure 3 OS and PFS according to ApoA-I level (≤0.95 vs >0.95 g/L) in the subgroups.

Notes: Kaplan–Meier plots of OS (**A**) and PFS (**B**) for subgroups with low IPI scores of 0–1. OS (**C**) and PFS (**D**) for subgroups with low PIT scores of 0–1. OS (**E**) and PFS (**F**) for subgroups with low KPI scores of 0–1.

Abbreviations: ApoA-I, apolipoprotein A-I; IPI, International Prognostic Index; KPI, Korean Prognostic Index; OS, overall survival; PFS, progression-free survival; PIT, Prognosis Index for peripheral T-cell lymphoma, unspecified.

prospective designs are warranted to confirm our findings and to better illustrate the mechanisms underlying the relationship between ApoA-I level and prognosis in ENKTL disease.

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Disclosure

The authors report no conflicts of interest in this work.

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