

Decreased Apolipoprotein A-I Level Indicates Poor Prognosis in Hodgkin Lymphoma

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Research

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Abstract

Background

Recent studies have reported of an association between Abnormal lipid metabolism and many kind of malignant tumors, and the level of lipid varies with the outcome of the disease. Some data have indicated that the serum level of Apolipoprotein A-I(Apo A-I) in serum was down-regulated in some tumors, but there is few report about it in hodgkin lymphoma. In this study, we aimed to determine the change and clinical significance of serum level Apolipoprotein A-I in hodgkin lymphoma patients.

Methods

A total of 88 newly diagnosed cases of HL were analyzed retrospectively.

Results

Our study showed that the serum level of ApoA-I has significant differences in some clinical features of HL, and it dynamically changed with different stages. Divided patients by whether remission or not, we noticed that the non-remission group had lower ApoA-I than remission group. According the result of multivariate analysis decreased ApoA-I reduction become the independent risk factors of HL. On the basis of Kaplan-Meier survival analysis between high ApoA-I subgroup and low ApoA-I subgroup . we found the lower ApoA-I patients had short OS rate and PFS. The serum ApoA-I level was able to differentiate cases with poor outcomes from cases with good outcomes.

Conclusions

Our results showed that the serum level of ApoA-I was helpful for predicting HL prognosis.

Background

Hodgkin's lymphoma(HL) is one kind of malignant disease of the lymphatic system that accounts for about 10% of lymphoma which mostly in young people[1-2]. In recent years, the cure rate of HL is almost 80%. But there are still nearly 20% patients have progressed or relapsed and eventually to death[3-4]. At present, we often determine the treatment strategy by existing adverse prognosis indicators, such as pathological type , location, score, grade[5]. However, the laboratory indicators can not accurately identify patients with poor clinical outcomes[6]. Abnormal lipid metabolism has been found in many kind of malignant tumors, and the level of lipid varies with the outcome of the disease[7]. Apolipoprotein is important component of blood lipid which not only participates in lipid metabolism, but also shows many innate immune activities. The clinical parameters, treatment effect and influencing factors of hodgkin's lymphoma patients were examined. We explore the relationship between ApoA-I and HL in detail.

Material And Methods

Patients and study design

A retrospective review of the medical records of the patients admitted to our institution, between January 2013 and December 2016, for HL patients who completed 6 courses of regular chemotherapy treatment were performed. Institutional ethical approval was obtained. The criteria for diagnosis, grading, and effective evaluation were based on the guidelines of the World Health Organization. Patients with other hematological disorders, other nonhematological malignant tumor, cardiovascular complaints, hepatic illnesses or incomplete data were excluded. People with normal physical examination (normal blood lipid function) were selected as the control group.

Observation index

In addition to serum Apolipoprotein, clinical parameters including age, sex, Ann Arbor stage, IPS score, b2-MG, LDH, CRP, symptom A / B, bone marrow involvement, date of progression, date of death , and treatment strategy were also reviewed. The serum levels of Apolipoprotein levels were recorded during the evaluation of the treatment efficacy after 6 courses of regular chemotherapy. All the above examinations were conducted by routine laboratory procedures. Blood lipid levels was detected and quantified by immunoturbidimetric endpoint assay (Diasys Diagnostics Systems Gmbh, Shanghai, China). Blood sample for lipid analysis was taken after strict fasting for at least 6 hours. The operational steps were conducted according to the manufacturer's instructions, and an automatic biochemical analyzer was used for the testing. HL patients were followed-up until ended in January 2020 . The primary endpoint was overall survival (OS) and the second end point was progression free survival (PFS) .

Response assessment and statistical analyses

Therapeutic evaluation of the treatment group was conducted by two experienced physicians simultaneously. In the case of dissent, a comprehensive evaluation of the treatment response was conducted by a third physician. According to the treatment response, patients of the treatment group were divided into four subgroups: complete remission (CR), partial response (PR), stable disease(SD), and progressive disease (PD). The CR subgroup included the stringent complete remission (sCR) patients, while the PD subgroup included patients with clinical relapse and those with biochemical PD.

SPSS (version 22.0) was used for data analysis. Normally distributed parameters were described as the mean \pm standard deviation ($\bar{x}\pm s$). The enumeration data was described as the number of cases (n) . Correlation analysis was performed using linear correlation or Spearman rank correlation coefficients. Measurement data were analyzed with the t-test, Mann-Whitney U-test, or oneway analysis of variance (ANOVA). The Chisquare analysis or Fisher's exact test was used to compare categorical variables. Multivariate analysis was performed by logistic regression. The receiver operating characteristic (ROC) curve and Kaplan-Meier method was computed by MedCalcVR Statistical Package (version 15.2.2) . p values $<.05$ were considered statistically significant.

Results

Patient Characteristics

In total, 88 patients (48 male, 40 female; median age, 30 years [range 16–77]) met the inclusion criteria. The clinical characteristics of the 88 patients are listed in [Table 1](#). Some cases presented with localized disease (Ann Arbor stages I/II; n=35, 39.8%). According to the IPS, some patients (41 cases, 46.6%) were classified as low/low-intermediate risk (IPS = 0–1), and 47 patients (52.4%) were categorized as intermediate-high/high risk (IPS = 2–5). Elevated LDH levels were observed for 33 cases (37.5%). Of the 88 patients for whom b2-MG was measured, 36 (40.9%) showed increased. More than half of the patients (78 cases, 88.6%) showed CRP increased. Thirty-one patients (35.2%) presented with B symptoms. Only 9 patients (10.2%) displayed bone marrow involvement. Some cases presented with localized disease (Ann Arbor stages I/II; n=35, 39.8%). More than half of the patients (78 cases, 88.6%) showed CRP increased.

Correlation between apolipoprotein level and HL clinical parameters

The apolipoprotein of patients was grouped according to the clinical characteristics of patients ([Table 1](#)). It can be seen that ApoA-I had significant differences in sex, Ann Arbor stage, IPS score, CRP, LDH and b2-mg ($p < 0.05$), while ApoB had no significant changes. Compared with control group (1.25 ± 0.2 g/l), the serum level of ApoA-I (1.04 ± 0.25 g/l) in patients was significantly lower. But the serum level of ApoB (0.92 ± 0.35 g/l) is no difference with control group (0.89 ± 0.21 g/l) (shown in [Fig. 1A](#)). Therefore, the following text will not be specific analysis of ApoB.

The median value for the baseline ApoA-I levels and 25% and 75% quartiles in all patients was 0.99 g/L (range: 0.55–1.63 g/L) 0.91 and 1.12 g/L. The optimal cutoff value for serum ApoA-I was 0.96 g/L based on the ROC analysis results (area under the curve: 0.726, 95% confidence interval (CI): 66.13–76.92, $P < 0.001$) (shown in [Fig. 2A](#)). The prognostic value of the different cutoff values, including median value (0.99 g/L) and mean value (1.03 g/L), were also evaluated, and 0.96 g/L was found to be the most effective cutoff value. The whole cohort was divided into two groups based on the 0.96 g/L cutoff value. Forty five (51.1%) cases were categorized into the high ApoA-I group, and the remaining 43 (48.9%) patients were categorized into the low ApoA-I group ([Table 1](#)). The baseline features of the cases with ApoA-I ≤ 0.96 g/L were compared with those of cases with ApoA-I > 0.96 g/L ([Table 1](#)). B symptoms, a lower rate of hypercholesterolemia, elevated serum LDH, elevated serum CRP and advanced stage (III/IV) occurred more frequently in the cases from the low ApoA-I group. Additionally, the patients in low ApoA-I group exhibited a higher risk than those in the high ApoA-I group according to the IPS models. No significant intergroup differences in the mean values of continuous or categorical variables were found for any other clinical features examined.

Treatment response

Chemotherapy followed by radiotherapy was administered to 31 (35.2%) patients, chemotherapy alone was administered to 49 (55.7%) patients, immunotherapy alone was administered to five (5.7%) patients,

and clinical trial was administered to three cases (3.4%). No significant differences in treatment modalities were observed between the high and low ApoA-I groups.

According to the treatment response, the patients were divided into 4 groups that CR 47 (53.4%), PR15 (17.1%), SD11 (12.4%) and PD15 (17.1%). We can see the serum level of ApoA-I were significant differences before treatment in each group ($P < 0.05$) (shown in Fig. 1B). The better treatment response patients had higher levels of ApoA-I at the beginning of the disease, on the contrary in other patients. In addition, the comparison of ApoA-I level before and after the regular treatment of six courses, there was statistical difference in the CR, PR and PD/ relapse groups before and after the treatment ($P < 0.05$). There was a slight decrease in the SD group, but the difference was not statistically different ($P > 0.05$) (shown in Fig. 1C). It can be concluded that the patients who get CR/PR, the serum level of ApoA-I increased significantly. However in the SD and PD patients, ApoA-I was not change significantly or continued to decline.

Analysis of the effect of ApoA-I on the prognosis of HL

The cutoff point for follow-up data collection was January 1, 2020. According the cut off value was 0.96 g/l, we dichotomized our cohort into high ApoA-I subgroup and low ApoA-I subgroup. We compared the OS and PFS between two group with Kaplan-Meier survival analysis (shown in Fig. 2B-2C). Due to the follow-up time of 3 years was too short, the median time of OS and PFS are not reach in both groups. But the OS rate and PFS rate of patients of lower ApoA-I subgroup were significantly short than high ApoA-I subgroup ($P < 0.05$).

The CR and PR groups were set as the remission group, and the SD and PD groups as the non-remission group. According to the analysis results, Ann Arbor stage, IPS score, LDH, b2-mg and ApoA-I were all influential factors for the remission of patients (Table 2). Logistic analysis was used to evaluate the risk factors. The result shows that the degree of ApoA-I decrease can affect the prognosis. The decrease of ApoA-I is an independent risk factor in the non-remission group. The III/IV stage and high LDH were also the independent risk factor of non-remission group (Table 3). According to the cutoff value further risk factors were evaluated. The progress risk of patients with $\text{ApoA-I} \leq 0.96 \text{ g/l}$ was 4.372 times higher than that of patients with $>0.96 \text{ g/l}$ (OR: 4.372, 95% CI: 2.723-10.596, $P=0.027$) (Table 4).

Discussion

HL is a lower incidence tumor in the lymphatic system. Most patients have enlarged lymph nodes and progressive growth. In progressive patients, multiple organs can be invaded. It is often manifested as fever, night sweats, emaciation and itchy skin.

In this study, we found the ApoA-I level of patients is lower than control group and had significant differences in many clinical biochemical characteristics, while ApoB had no significant changes. The better treatment response patients had higher levels of ApoA-I at the beginning of the disease. Compared the ApoA-I before and after treatment, if the patients could reach CR/PR, the serum level of ApoA-I

increased significantly. Otherwise, ApoA-I would not change significantly or continue to decline. The ApoA-I level of Ann Arbor stage I/II patients were significantly higher than the person of stage III/IV. The ApoA-I of IPS score 0-2 patients were significantly higher than score of 3-5. The patient who had high LDH, b2-MG and CRP was lower in ApoA-I. Risk factors are logistic analyzed according to whether the group is remission or not, it can be concluded that the decrease of ApoA-I is an independent risk factor for the occurrence of non-remission group. The progress risk of patients with $\text{ApoA-I} \leq 0.96 \text{ g/l}$ was 4.372 times higher than that of patients with $\text{ApoA-I} > 0.96 \text{ g/l}$. On the basis of Kaplan-Meier survival analysis between high ApoA-I subgroup and low ApoA-I subgroup, we found lower ApoA-I patients had short OS rate and PFS. Our data suggest that ApoA-I levels are negatively correlated with HL tumor burden and positively correlated with the prognosis of HL.

The study showed that Apo A1 was abnormal in ovarian cancer, pancreatic cancer, recurrent neuroblastoma in children, bladder cancer and colon cancer [8-10]. The mechanisms underlying the relationship between decreased serum ApoA-I levels and poor prognosis in HL are not clear; however, several potential explanations have been proposed. In animal tumor models established by Zamanian Daryooush [11], injection of human ApoA-I into mice can significantly reduce the tumor load and metastasis, and improve the animal survival rate. However, in the mice without ApoA-I, the tumor growth rate was accelerated. This experiment showed that ApoA-I could increase the expression of CD 8T cells, M1 anti-tumor macrophages, reduce angiogenesis, reduce tumor invasion and metastasis. Other researchers also found that ApoA-I controls the rate of cell proliferation in a tumor and the tumor growth. Pro-inflammatory and pro-angiogenic lysophospholipids such as lysophosphatidic acid (LPA) have been shown to be associated with tumor progression and poor prognosis, and are normally cleared from the serum by Apo A1 [12-13].

Conclusions

We are the first reports about ApoA-I is a new prognosis factor for HL, and decreased ApoA-I indicates poor prognosis. Now there is not a lot of data analysis and basic mechanism research, so further research is needed to clarify the role of ApoA-I in HL. ApoA-I is not only could be used as a marker for tumor burden monitoring, but also could used as a reference for disease severity assessment and prediction. Recently, it has been reported that ApoA-I and ApoA-I mimic peptide can inhibit the growth of ovarian cancer cells, and can be used as an anticancer agent to treat tumors [12]. It can reduce tumor load and metastasis, and improve survival rate. If we can increased the serum level of ApoA-I to increase the prognosis in HL.

Declarations

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Ethics approval and consent to participate

It was received approval from Shengjing Hospital of China Medical University institutional ethics committee. All patients consent to participate this study.

Consent for publication

All authors Consent to publish this manuscript.

Availability of data and material

Data and material is availability.

Competing interests

The authors do not have conflicts of interest to disclose.

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Author Contributions

Jing S designed the study . Jing S and Ronghui Y performed statistical analysis, participated in data collection and drafted the manuscript. Wei Y supervised the scientific work and revising it critically amended the manuscript. She also gave final approval of the version to be published. All authors read and approved the final manuscript.

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Tables

Table1

Baseline characteristics of patients by serum level of apolipoprotein

Variable	ApoA-I	P	ApoB	P
Sex		P=0.02		P=0.31
F (n=40)	1.11±0.18		0.95±0.47	
M (n=48)	0.99±0.28		0.88±0.20	
Age		P=0.23		P=0.6
≤60(n=79)	1.03±0.26		0.89±0.35	
>60(n=9)	1.14±0.13		1.12±0.24	
Ann Arbor stage		P=0.01		P=0.91
II/III(n=35)	1.13±0.24		0.92±0.49	
II/IV(n=53)	0.99±0.23		0.91±0.22	
IPS		P=0.042		0.94
0-1(n=41)	1.09±0.19		0.92±0.44	
≥2(n=47)	0.89±0.29		0.91±0.25	
CRP,mg/L (x±s)		P=0.02		P=0.69
≤3.0(n=10)	1.21±0.2		0.96±0.32	
>3.0(n=78)	1.02±0.25		0.91±0.36	
LDH, U/L (x±s)		P=0.04		P=0.34
≤250(n=57)	1.05±0.23		0.94±0.41	
>250(n=31)	0.93±0.28		0.86±0.21	
b2-MG ,mg/dL (x±s)		P=0.002		P=0.96
≤2.52(n=60)	1.10±0.22		0.92±0.4	
>2.52(n=28)	0.93±0.27		0.91±0.19	
symptom		P=0.38		P=0.41
A (n=57)	1.06±0.27		0.89±0.23	
B (n=31)	1.01±0.2		0.95±0.5	
bone marrow involvement		P=0.95		P=0.72
+(n=9)	1.04±0.22		0.92±0.37	
-(n=79)	1.03±0.43		0.87±0.16	

Table 2
Monofactor analysis of HL patients

Variable	Remission	Non-remission	P
Sex			>0.05
F (n=40)	25	15	
M (n=48)	37	11	
Age			>0.05
≤60(n=79)	57	22	
>60(n=9)	5	4	
Ann Arbor stage			<0.05
I/II(n=35)	29	6	
III/IV(n=53)	33	20	
IPS			<0.05
0-1(n=41)	34	7	
2-5(n=47)	28	19	
CRP,mg/L			0.577
≤3.0(n=10)	7	3	
>3.0(n=78)	55	23	
LDH, U/L			0.021
≤250(n=57)	37	20	
>250(n=31)	25	6	
b2-MG ,mg/dL			0.044
≤2.52(n=60)	44	16	
>2.52(n=28)	18	10	
ApoA-I,g/L			<0.001
≤1.2(n=77)	51	26	
>1.2(n=11)	11	0	
symptom			>0.05

A (n=57)	38	19
B (n=31)	24	7
bone marrow involvement		>0.05
+(n=9)	5	4
-(n=79)	57	22

Table 3
Logistic analysis of risk factors for the progression of HL

Variable	UVA				MVA			
	P	OR	OR 95% CI		P	OR	OR 95% CI	
			Lower limit	Upper limit			Lower limit	Upper limit
ApoA-I	0.039	0.674	0.077	2.341	0.039	0.335	0.043	2.581
Ann Arbor stage(III/IV vs I/II)	0.13	1.235	1.046	1.459	0.046	1.024	0.842	1.245
IPS(2-5 vs 0-1)	0.048	0.998	0.996	1.000	0.013	1.004	0.999	1.009
LDH	0.033	1.005	0.992	1.022	0.033	0.509	0.274	0.948
b2-MG	0.076	0.633	0.382	1.049	0.09	0.998	0.996	1

Table 4
ApoA-I as predictors of SD and PD, using the cutoff value 0.96 mg/L.

Variable	OR 95% CI			P
	OR	Below median	Above median	
ApoA-I ≤ 0.96g/l	4.372	2.723	10.596	0.027
Ann Arbor stage(III/IV vs I/II)	0.034	0.002	0.557	0.018
IPS(2-5 vs 0-1)	0.166	0.042	0.65	0.06
LDH	0.281	0.079	0.652	0.022
b2-MG	0.453	0.287	0.934	0.12

Figures

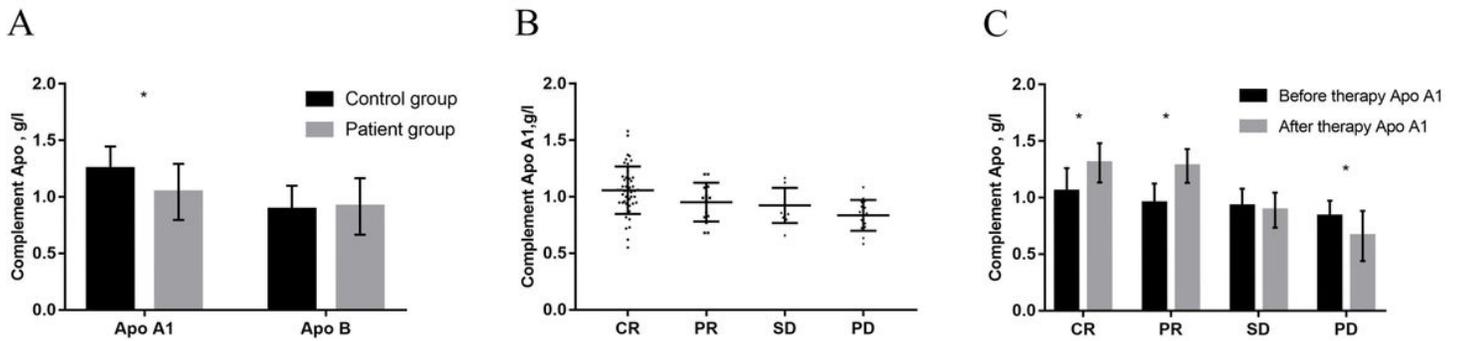


Figure 1

(A) Serum level of ApoA-I and Apo B among HL and healthy control groups ($p < 0.05$); (B) ApoA-I in each treatment response group ($p < 0.05$); (C) ApoA-I before and after the treatment ($p < 0.05$);

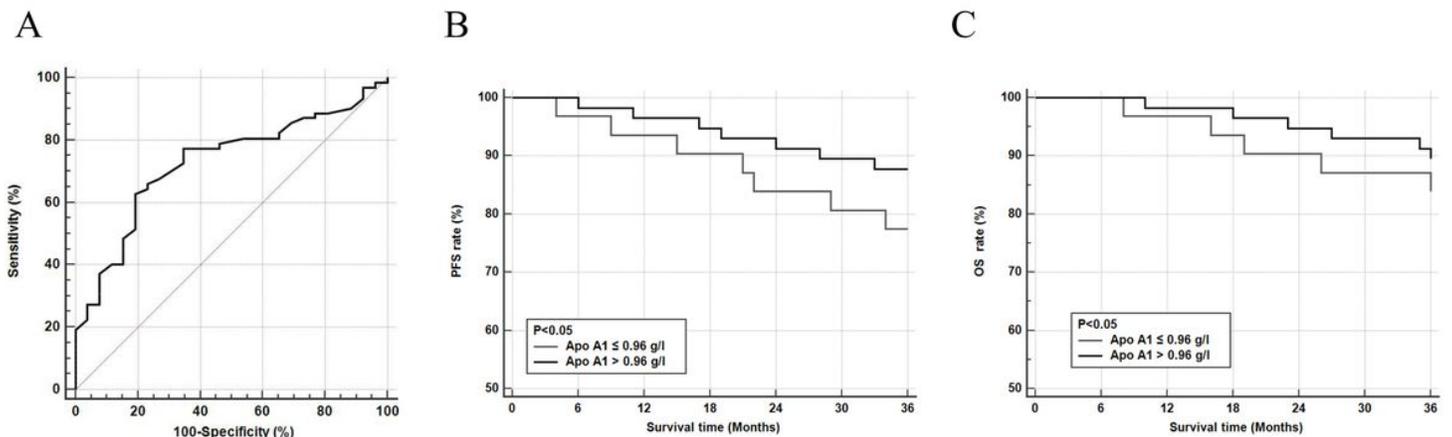


Figure 2

(A) ApoA1 levels for progressive disease prediction. (B) Kaplan Meier survival analysis between group of ApoA1 ≤ 0.96 g/l and ApoA1 > 0.96 g/l in OS; (C) Kaplan Meier survival analysis between group of ApoA1 ≤ 0.96 g/l and ApoA1 > 0.96 g/l in PFS.