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Original Article

The prognostic value of preoperative serum HDL cholesterol in patients with resectable acral melanoma

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Abstract: Background: Acral melanoma is dominant in Asia, which differs from cutaneous melanoma in etiology, mutation loading, and therapy response. Growing evidence indicates that various components of the lipid profile may be associated with cancer clinical outcomes and the disrupted cholesterol homeostasis plays a potential role in melanoma development. Therefore, we examined the prognostic value of the preoperative serum lipid profile in patients with acral melanoma. Methods: This is a retrospective study consisting of 239 patients who underwent radical surgical resection for acral melanoma between 2000 and 2011 at Sun Yat-sen University Cancer Center. Kaplan-Meier survival analysis and Cox proportional model were used to calculate overall survival (OS) and disease-free survival (DFS). Results: Elevated HDL-C levels were significantly associated with longer OS both in univariate (P<0.001) and multivariate (P=0.005) analyses. The median OS of patients with a low HDL-C level was worse than those with a high HDL-C level (38.09 vs. 50.1 months, HR: 2.63). Univariate analyses showed that a shorter DFS was associated with a low HDL-C level (P<0.001) and was still obviously in the multivariate analysis (P=0.043). The median DFS of patients with a low HDL-C level was worse than those with a high HDL-C level (17.26 vs. 30.09 months, HR: 1.739). There was no significant difference in the OS or DFS based on LDL-C, CHO, and TG levels. Conclusion: Preoperative serum HDL-C may serve as a valuable marker to predict the outcomes of acral melanoma patients.

Keywords: Acral melanoma, lipid profile, HDL-cholesterol, prognosis

Introduction

Acral melanoma is defined as a melanoma involving the extremities, especially the non-hair-bearing palm, plantar, and subungual sites. Its clinical and genetic features differ from those of cutaneous melanoma [1]. Although acral melanoma accounts for only 4-6% of all melanoma diagnosed in Caucasians [2], it is the most common subtype in Asia [3].

The prognosis for patients with acral melanoma depends on stage of disease, and it tends to be worse compared to other types of melanoma [4]. The treatment for acral melanoma is similar to that of cutaneous melanomas, which includes a wide local excision to obtain adequate negative margins, appropriate staging including sentinel lymph node mapping, and selective lymphadenectomy when appropriate [5]. However, in most cases, it appears that treatment failure was eventually caused by local recurrence and distant metastasis, failing to improve overall prognosis rates [6]. Therefore, the identification of a simple and cost-effective marker for predicting patient prognosis is of vital importance.

A variety of biomarkers have been postulated to predict clinical outcomes in patients with melanoma. Based on current literature, LDH is the most appropriate prognostic biomarker in patients with stage IV melanoma, S-100B protein has been proven to be a significant prognostic marker independent of tumor stage [7]. Additionally, an elevated pretreatment serum concentration of IL-6 [8] and RUNX3 [9] had been proved to be promising prognostic biomarkers. However, the utility of these markers is limited by the need for complicated detection techniques and high costs.

Measurements of serum lipids are routinely performed by most clinical chemistry autoanalyzers. Prior studies has demonstrated the role of lipid metabolism in different cancers [10], and a higher total serum cholesterol level is linked with higher risk of colon, prostate and testicular cancer and lower risk of stomach, liver and hematopoietic and lymphoid tissues cancer [11]. Additionally, another study suggests that Long-term use of cholesterol-lowering drugs was associated with statistically significantly lower risk of melanoma [12]. Recently, the Cancer Genome Atlas (TCGA) project using next-generation sequencing has profiled the mutational status and expression levels of all the genes in diverse cancers, including those involved in cholesterol metabolism, which demonstrated the potential role of disrupted cholesterol homeostasis in cancer development in melanoma [13]. Thus, we performed this retrospective study to assess the prognosis role of serum lipid profile on patients with acral melanoma.

Materials and methods

Patient eligibility and evaluation

Between 2000 and 2011, 239 patients diagnosed with acral melanoma who had undergone radical surgical resection in Sun Yat-sen University Cancer Center (SYSUCC) were enrolled in this study. The inclusion criteria mandated that all patients were histologically diagnosed and with no history of previous cancer; all patients' data were classified according to the final version of the 2009 American Joint Committee on Cancer (AJCC) melanoma staging and classification system [14]; and blood samples for HDL-C, LDL-C, CHO, and TG had been obtained preoperatively. Patients were excluded if they had dyslipidemia or used a statin treatment. This study was approved by the Institutional Review Board of SYSUCC, and written informed consent was obtained from each patient. Baseline characteristics were obtained from the patients' history, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), body mass index (BMI), lactic dehydrogenase level (LDH), adjuvant therapy, smoking history, hypertension, diabetes, anatomic site of the lesion, ulceration positivity, tumor thickness, and stage of disease. All patients were carefully followed according to the Common Follow-up Recommendations on NCCN guidelines [15], and received dynamic computed tomography (CT) scans at regular intervals (Every 3-month during the first 2 years after resection, at 6-month intervals for 3 to 5 years after resection, and at 12-month intervals thereafter).

Statistical analysis

Overall survivals (OS) were measured from the date of diagnosis to either the end of the follow-up period (June 2016), to the date of death from any cause or to the date of loss to follow-up. Disease-free survival (DFS) was calculated from the date of curative resection to the date of the tumor recurrence or distant metastasis. The associations between HDL-C level and the clinicopathological parameters were assessed via Chi-Square test. Receiver operating characteristic (ROC) analyses were performed to determine the optimal cutoff values, and then the continuous variables were transformed into dichotomous variables. Survival analyses were performed using the Kaplan-Meier method and compared with the log-rank test. The significance of the variables for survival was analyzed using the Cox proportional hazards model (univariate and multivariate analysis). All statistical analyses were performed using SPSS 17.0 software (IBM, Armonk, NY). All tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 239 patients that were pathologically diagnosed with acral melanoma and underwent radical surgical resection between 2000 and 2011 were enrolled in this study. Their general characteristics are presented in **Table 1**. There were 128 men (53.6%) and 111 women (46.4%) with an average age of 55.7 years (range, 18-84 years). Their performance status and disease stage were ascertained at the time of hospital admission. During the follow-up period, 175/239 patients (73.2%) experienced local or regional tumor recurrence and 85/239 patients (35.6%) had died by the end of follow-up.

Identification of lipid profile optimal cut-off points

After performing ROC analysis, the optimal cut-off value were determined to be as follows, HDL-C: 1.075 mmol/L (AUC: 0.657, 95% CI=

Table 1. Basic characteristics of patients and the association of HDL-C level with clinicopathological features

Chracteristic	N (%)	HDL-C<1.075 (mmol/L)	HDL-C≥1.075 (mmol/L)	P
Age at operation (years)				0.030
<60	146 (61.1)	53	93	
≥60	93 (38.9)	47	46	
Gender				0.365
Male	128 (53.6)	57	71	
Female	111 (46.4)	43	68	
PS				0.286
0	185 (77.4)	74	111	
≥1	54 (22.6)	26	28	
BMI				0.028
<25	182 (76.2)	69	113	
≥25	57 (23.8)	31	26	
LDH				0.026
<ULN	221 (92.5)	88	133	
≥ULN	18 (7.5)	12	6	
Adjuvant therapy				0.115
Yes	83 (34.7)	29	54	
No	156 (65.3)	71	85	
Smoking history				0.191
Yes	39 (16.3)	20	19	
No	200 (83.7)	80	120	
Hypertension				0.162
Yes	45 (18.8)	23	22	
No	194 (81.2)	77	117	
Diabetes				0.405
Yes	13 (5.4)	4	9	
No	226 (94.6)	96	130	
Anatomic site				
Foot	211 (88.3)	89	122	0.935
Palm	7 (2.9)	3	4	
Subungual sites	21 (8.8)	8	13	
Ulceration positivity				0.672
Yes	130 (54.4)	56	74	
No	109 (45.6)	44	65	
Tumor thickness				0.132
T1	8 (3.4)	2	6	
T2	39 (16.3)	11	28	
T3	77 (32.2)	32	45	
T4	115 (48.1)	55	60	
AJCC stage				0.005
I	15 (6.3)	3	12	
II	111 (46.4)	38	73	
III	113 (47.3)	59	54	

N, Number; AJCC, American Joint Committee on Cancer; LDH, Lactic dehydrogenase; ULN, Upper limits of the normal range; PS, Performance status; BMI, Body mass index.

0.584-0.730 P<0.001), LDL-C: 2.87 mmol/L (AUC: 0.498, 95% CI=0.420-0.575 P=0.952), CHO: 4.765 mmol/L (AUC: 0.511, 95% CI=0.435-0.587 P=0.776), and TG: 1.315 mmol/L (AUC: 0.483, 95% CI=0.407-0.559 P=0.662). All patients were classified into either a high or low group according to the aforementioned cutoff values.

Association between the HDL-C level and clinicopathological features

Correlations between the HDL-C level and clinicopathological parameters are shown in **Table 1**. The distribution of the HDL-C level differed significantly when the patients were stratified by age (P=0.030), BMI (P=0.028), LDH (P=0.026) and AJCC stage (P=0.005). However, there were no significant differences with regard to PS, gender, adjuvant therapy, smoking history, hypertension, diabetes, anatomic site of lesion, ulceration positivity, tumor thickness between patients in the high and low HDL-C groups.

Prognostic value of the clinicopathological characteristics in acral melanoma

Based on univariate analysis, a low HDL-C level (P<0.001) and other clinicopathological factors, including a high LDH level (>245 U/L) (P=0.004), age (P=0.04), tumor thickness (P=0.025), and advanced AJCC stage (P<0.001) were significantly associated with poor survival. Similarly, univariate analysis showed that a low HDL-C level (P<0.001), high LDH level (>245 U/L) (P=0.042), and an ad-

Table 2. Univariate analysis of prognostic factors regarding OS and DFS

Parameter	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Age at operation (years)				
<60	1 (referent)		1 (referent)	
≥60	1.561 (1.020-2.389)	0.040	1.12 (0.829-1.514)	0.460
Gender				
Male	1 (referent)		1 (referent)	
Female	1.221 (0.797-1.869)	0.359	1.006 (0.748-1.354)	0.967
PS				
0	1 (referent)		1 (referent)	
≥1	1.495 (0.946-2.362)	0.085	1.092 (0.767-1.554)	0.627
BMI				
<25	1 (referent)		1 (referent)	
≥25	1.092 (0.655-1.821)	0.734	1.021 (0.723-1.441)	0.905
LDH				
<ULN	1 (referent)		1 (referent)	
≥ULN	2.58 (1.365-4.875)	0.004	1.707 (1.019-2.857)	0.042
Adjuvant therapy				
Yes	1 (referent)		1 (referent)	
No	1.071 (0.681-1.685)	0.767	1.119 (0.822-1.524)	0.473
Anatomic site				
Foot and palm	1 (referent)		1 (referent)	
Subungual sites	1.168 (0.564-2.419)	0.677	1.152 (0.689-1.927)	0.59
Ulceration positivity				
No	1 (referent)		1 (referent)	
Yes	1.201 (0.780-1.850)	0.406	1.104 (0.82-1.485)	0.515
Tumor thickness				
T1+T2	1 (referent)		1 (referent)	
T3+T4	1.637 (1.065-2.518)	0.025	1.32 (0.981-1.777)	0.067
AJCC stage				
Localised at diagnosis	1 (referent)		1 (referent)	
Metastasised at diagnosis	3.617 (2.287-5.722)	<0.001	2.986 (2.195-4.062)	<0.001
HDL-C (mmol/L)				
<1.075	2.63 (1.703-4.060)		1.739 (1.29-2.345)	
≥1.075	1 (referent)	<0.001	1 (referent)	<0.001
LDL-C (mmol/L)				
<2.87	1 (referent)		1 (referent)	
≥2.87	1.312 (0.856-2.011)	0.861	1.057 (0.781-1.431)	0.72
CHO (mmol/L)				
<4.765	1 (referent)		1 (referent)	
≥4.765	1.180 (0.758-1.835)	0.416	1.175 (0.867-1.593)	0.298
TG (mmol/L)				
<1.315	1 (referent)		1 (referent)	
≥1.315	1.245 (0.814-1.906)	0.312	1.113 (0.827-1.498)	0.479

CI, Confidence interval; HR, Hazard ratio; TG, Triglyceride; CHO, Cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

vanced AJCC stage (P<0.001) were significantly associated with a decreased DFS (**Table 2**).

Cox regression analysis was performed based on Age, LDH, Tumor thickness, AJCC stage and

Table 3. Results from Cox Regression Model (Adjusted for Age, LDH, Tumor thickness, AJCC stage and HDL-C level)

Parameter	OS		DFS	
	HR (95% CI)	P	HR (95% CI)	P
Age at operation (years)				
<60	1 (referent)			
≥60	1.556 (1.010-2.397)	0.045		
LDH				
<ULN	1 (referent)			
≥ULN	2.166 (1.143-4.212)	0.018		
Tumor thickness				
T1+T2				
T3+T4				
AJCC stage				
Localised at diagnosis	1 (referent)		1 (referent)	
Metastasised at diagnosis	3.042 (1.884-4.910)	<0.001	2.766 (2.016-3.796)	<0.001
HDL-C (mmol/L)				
≥1.075	1 (referent)		1 (referent)	
<1.075	1.869 (1.186-2.945)	0.005	1.374 (1.010-1.867)	0.043

CI, Confidence interval; HR, Hazard ratio; TG, Triglyceride; CHO, Cholesterol; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol.

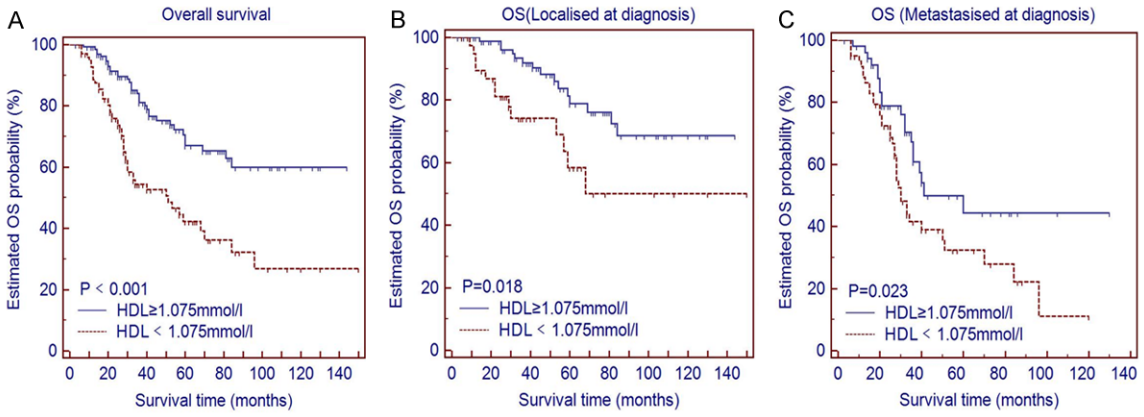

Figure 1. The prognostic value of HDL-C level on Kaplan-Meier curve for OS in acral melanoma patients. A. Kaplan-Meier curve for OS regarding low vs. high HDL-C levels (P<0.001). B. Comparison of OS on patients in limited stage with low vs. high HDL-C levels (P=0.018). C. Comparison of OS on patients in advanced stage with low vs. high HDL-C levels (P=0.023).

HDL-C level. Age (P=0.045), LDH level (P= 0.018), AJCC stage (P<0.001), HDL-C level (P=0.005) were significantly associated with OS. The AJCC stage (P<0.001) and HDL-C level (P=0.043) were significantly associated with DFS (**Table 3**).

Prognostic value of HDL-C in acral melanoma

Among the 239 patients, death occurred in 50 of 100 (50%) patients with a low HDL-C level and in 35 of 139 (25.2%) patients with a high HDL-C level (P<0.001). Additionally, local recurrence or metastatic disease occurred in 85 of 100 (85%) patients with a low HDL-C level and in 90 of 139 (64.7%) patients with a high HDL-C level (P<0.001). The Kaplan-Meier survival analysis showed that patients with a low HDL level had a shorter OS (P<0.001) (**Figure 1A**) and DFS (P<0.001) (**Figure 2A**). The median OS was 38.09 and 50.1 months in the patients with a HDL-C<1.075 mmol/L and HDL-

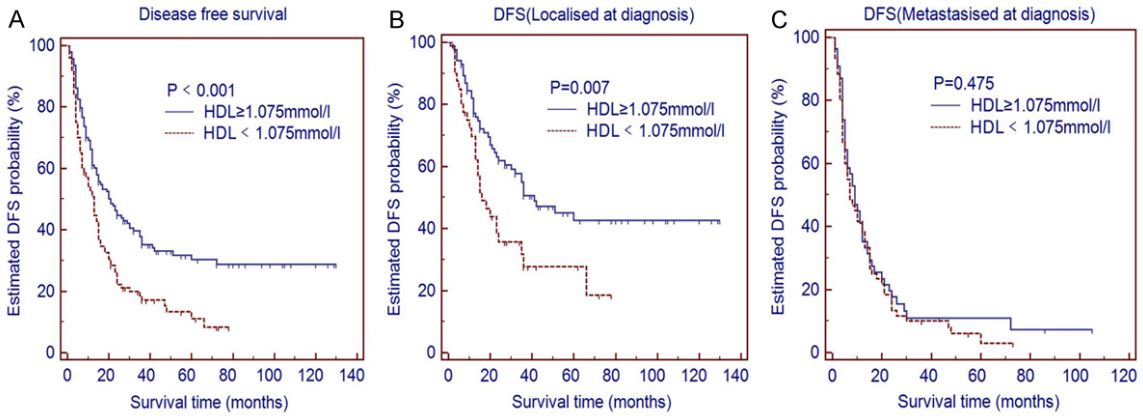

Figure 2. The prognostic value of HDL-C level on Kaplan-Meier curve for DFS in acral melanoma patients. A. Kaplan-Meier curve for DFS regarding low vs. high HDL-C levels (P<0.001). B. Comparison of DFS on patients in limited stage with low vs. high HDL-C levels (P=0.007). C. Comparison of DFS on patients in advanced stage with low vs. high HDL-C levels (P=0.475).

C≥1.075 mmol/L respectively. The median DFS was 17.26 and 30.09 months in the patients with a HDL-C<1.075 mmol/L and HDL-C≥1.075 mmol/L respectively. Similarly, a longer OS was also observed when patients were stratified into limited stages (TNM stage I+II) (P=0.018) and advanced stage (TNM stage III) (P=0.023) (**Figure 1B**, **1C**). However, a longer DFS was observed when patients were stratified into limited stages (P=0.007) but not advanced stage (P=0.475) (**Figure 2B**, **2C**).

Discussion

It is well known that acral melanoma is an aggressive malignancy with an unfavorable prognosis [1]. Therefore, the identification of factors associated with decreased survival would provide the ability to pre-select the patients who would benefit the most from more aggressive treatments. Growing evidence has shown that abnormal lipid profiles was associated with the occurrence and progression of various cancers [16]. In this study, we retrospectively analyzed the prognostic value of the various components of the lipid profile in resectable acral melanoma patients.

The results of our studies are consistent with the findings reported in literature [17], which demonstrated that lower age, limited staging, and normal serum levels of LDH were significantly associated with a longer survival. Although HDL-C was associated with age, BMI, LDH and AJCC stage (**Table 2**), the prognostic impact remained significant after adjustment for other clinicopathological characteristics by multivariate analysis, the HDL-C level independently predicted the OS (P=0.005) and DFS (P=0.043) of patients with acral melanoma (**Table 3**). A subgroup analysis of patients with limited and advanced stage of disease also showed that high HDL-C level group has longer OS. As the blood HDL-C level is influenced by several unhealthy lifestyles, such as obesity and smoking [18], we validated the associations between HDL-C level and Lipid metabolism disorder related diseases. We found no relationship between HDL-C level and smoking, hypertention and diabetes, but BMI was significantly associated with the HDL-C level (**Table 1**). However, we found no association of BMI with DFS and OS in univariate analysis. So it indicated that BMI was not a prognostic factor of acral melanoma.

There are several possible reasons which could account for the association between HDL-C levels and melanoma. First, trauma and chronic inflammation have been implicated in acral melanoma [19]. They both could result in high levels of cytokines and reactive oxygen species, which in turn activate the cellular pathways associated with tumorigenesis as well as pathways that induce genetic instability in melanocytes [20]. HDL inhibits oxidation and inflammation through interaction with the vascular endothelium and circulating inflammatory cells [21, 22]. Decreased HDL-C levels could increase the circulating levels of proinflamma-

tory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-*a* receptors [23]. It has been proven that apolipoprotein A1 (apoA1), the major protein in HDL, could potently suppress tumor growth and metastasis through both innate and adaptive immune processes in the aggressive B16F10L murine malignant melanoma model [24]. Secondly, cholesterol is needed to form cell membranes thus highlighting the involvement of cholesterol metabolism in carcinogenesis [25]. When the balance between cholesterol production, dietary intake and transport in the peripheral circulation is impaired, malignant cells are provided with high cholesterol levels which can facilitate tumor development and migration [26]. Inflammation, oxidation, infection, hyperglycemia and activated platelets may alter HDL components, thus transforming HDL to a dysfunctional molecule [27, 28]. Low HDL-C levels usually reflect the presence of dysfunctional small HDL particles [29]. Of note, several drugs may affect HDL subpopulations; statins, which could improve HDL functionality [30], were associated with lowered risk of melanoma [12]. Furthermore, The TCGA database found that approximately 60% of melanomas had increased expression or chromosomal copy number increases in at least one of the cholesterol synthesis genes. Several of these alterations were associated with known chromosomal amplification sites that harbor well-characterized oncogenes [13]. It has been proved that the deletion of SC5D, one of the key genes in the last steps of cholesterol synthesis pathway, may contribute to cancer progression [31]. This is also supported by TCGA database that melanoma patients having reduced expression of SC5D had decreased survival [13]. However, oncogenes and cholesterol synthesis genes could cooperate to promote disease progression still needs demonstration.

There are several limitations associated with this study. First, the study design is retrospective and a single-center study. Second, the number of patients included in the study is relatively small, which may have limited the statistical power. It is necessary to conduct large-scale multi-center studies to accumulate a greater number of cases and to determine the mechanistic details in-vitro. Despite these limitations, our findings are informative and add to the current body of literature, we showed that a decreased preoperative HDL-C level was associated with decreased DFS and OS rates. To our knowledge, this is the first study to analyze the correlation between HDL-C and the prognosis in patients with acral melanoma.

Conclusions

We are the first to demonstrate that a high HDL-C level predicts favorable survival outcomes and it was an independent prognostic factor of acral melanoma patients. This biomarker can be obtained directly from routine medical laboratories and is easily applied in the clinical setting. It is necessary to conduct large-scale multicentre studies and further research to fully dissect the consequences of these changes and how they modulate cancer development.

Acknowledgements

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Disclosure of conflict of interest

None.

Abbreviations

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CI, confidence interval; HR, hazard ratio; DFS, disease-free survival; OS, overall survival; TG, triglyceride; CHO, cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BMI, body mass index; LDH, lactic dehydrogenase.

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