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Original Article

Predictive role of high-density lipoprotein and body mass index in differentiated thyroid carcinoma

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Abstract: Objective: High-density lipoprotein (HDL) and body mass index (BMI) have been implicated in carcinogenesis. However, the significance of HDL and BMI in differentiated thyroid carcinoma (DTC) has not been elucidated. The aim of this study was to assess the roles of HDL and BMI in carcinogenesis and in the prognosis of DTC. Methods: HDL concentrations and BMI values were measured in 155 male patients with DTC and in 65 male patients with benign thyroid nodules. Multivariate logistic regression and Cox regression analyses were performed to evaluate the correlation between variables. Receiver operating characteristic (ROC) curves were constructed to assess the performance of HDL and BMI in the diagnosis of DTC and the prediction of four-year recurrence. Results: HDL (OR, 0.581; 95% CI, 0.371-0.909; $p = 0.018$) and BMI (OR, 1.174; 95% CI, 1.051-1.130, $p = 0.004$) were both independent risk factors of DTC. HDL was negatively correlated with distant metastasis (OR, 0.006; 95% CI, 0.000-0.517; $p = 0.025$), while BMI was significantly correlated with capsule invasion (OR, 1.193; 95% CI, 1.057-1.347; $p = 0.004$) and multifocality (OR, 1.208; 95% CI, 1.079-1.353; $p = 0.001$). ROC analysis indicated that HDL could be a good marker for the diagnosis of DTC (AUC, 0.857; 95% CI, 0.805-0.910; $p = 0.006$) at a cutoff value of 1.37 mmol/L and the prediction of four-year recurrence (AUC, 0.730; 95% CI, 0.585-0.875; $p = 0.006$) at a cutoff value of 1.14 mmol/L. Multivariate Cox regression analysis showed that a low HDL level (≤ 1.14 mmol/L) was able to predict four-year recurrence (HR, 0.199; 95% CI, 0.059-0.667; $p = 0.009$) and a worse outcome. Conclusion: A low HDL level incurs an increased risk of DTC and four-year recurrence, while a high BMI is associated with capsule invasion and multifocality. However, more advanced research is needed in the future to confirm these results.

Keywords: Differentiated thyroid carcinoma, high-density lipoprotein, body mass index, prognosis

Introduction

Thyroid cancer is the most common malignancy in the endocrine system [1], and its prevalence has increased dramatically worldwide [2]. Most thyroid cancers are found to be differentiated thyroid carcinoma (DTC), including papillary and follicular thyroid carcinomas [3, 4].

Lipids are considered to be involved in atherosclerosis [5], anti-inflammation [6], carcinogenesis [7, 8], and carcinoma prognosis [9]. Cancer cells require an adequate amount of cholesterol to maintain a high level of proliferation, and high-density lipoprotein (HDL) is one of the main suppliers of cholesterol [7]. Despite this property, a low HDL level increases the risk for colorectal cancer [10], breast cancer [11], and primary liver cancer [12]. HDL has been reported to exert antitumor activity and protects against melanoma growth and metastasis [13]. Also, a high HDL level reduces the risk of mortality by 46% in non-small cell lung cancer patients [14]. In addition, it has been shown that a decreased HDL level is an independent risk factor that predicts worse outcomes in breast cancer patients [11]. However, some researchers believe that there is no special link between HDL and cancer development. It has been shown that HDL is not an independent risk factor for colorectal cancer [8], while another study has demonstrated that HDL has no correlation with recurrence-free survival in prostate cancer patients who underwent a radical prostatectomy [15].

Currently, obesity has reached epidemic proportions in some areas of the world, posing a

threat to the health of the population [16]. There is convincing evidence that obesity is a risk factor for various types of cancer [16, 17]. On the other hand, avoiding weight gain decreases the risk of cancer [18]. As an indicator of obesity, the body mass index (BMI) has been reported to be implicated in carcinogenesis [19]. However, its role in the pathogenesis of thyroid cancer is still ambiguous. For example, BMI has been positively associated with the risk of thyroid cancer in one study [17]. In another study performed by Brindel et al., French women with a BMI of ≥ 25 kg/m^2 exhibited an increased risk of thyroid cancer [20]. In Norway, the risk of thyroid cancer increased moderately with an increased BMI in both genders [21]. Also, a positive association between thyroid cancer incidence and a high BMI has been found in populations aged less than 50 years old [22]. However, some researchers have denied BMI as a risk factor for thyroid cancer [23, 24]. Several previous studies have evaluated the relationship between BMI and clinicopathological features, but the results have been controversial. Some studies have demonstrated that BMI is correlated with a larger tumor size [25], lymph node metastasis (LNM) [26], extrathyroidal invasion [25, 27, 28], and an advanced tumor-node-metastasis (TNM) stage [25, 28]. Other studies have revealed that no correlation exists between BMI and TNM stage, vascular invasion, or LNM [26, 28]. Thus, further investigation is needed to explore the exact role of BMI in DTC.

In this study, we investigated HDL levels and BMI values in 155 male patients with DTC versus 65 male patients with a benign thyroid nodule (BTN). Furthermore, we explored the predictive roles of these factors in the diagnosis and prognosis of DTC by analyzing their relationships with the clinicopathological features and disease recurrence during four-year follow ups in these patients.

Materials and methods

Subjects

A total of 220 consecutive male patients with DTC (n = 155) or BTN (n = 65) who underwent a thyroidectomy or lobectomy at The First Hospital of Jilin University from June 2012 to June 2013 were enrolled. A bilateral central-compartment neck dissection was routinely performed during the total thyroidectomy. Lateral or modified neck dissection was conducted in patients with clinically definite or imaging-detected metastatic cervical lymph nodes.

All of the eligible patients were included in this study, and the male patients with DTC had newly diagnosed primary DTC. The exclusion criteria were as follows: (a) carcinomas other than DTC; (b) metastases from another carcinoma to the thyroid; (c) a history of thyroid surgery, medication, or radiation therapy within any time before admission; (d) severe complications, such as renal failure, heart failure, liver cirrhosis, and malignant hematologic disease; (e) incomplete data.

Clinicopathological features, including malignancy, LNM, capsule invasion, multifocality, tumor size, extrathyroidal invasion, vascular invasion, and TNM stage, were recorded. The patients were classified according to the American Joint Committee on Cancer (AJCC) TNM staging system [27]. Patients were stratified by age, < 45 years old versus ≥ 45 years old, according to the AJCC/TNM classification strategy for DTC. Recurrence was defined as persistent structural disease identified following a period of no evidence of disease. The recurrence-free time was defined as the interval between the date of operation and recurrence or last follow up. Four-year recurrence was recorded as the prognosis index. Ultrasound, fine-needle aspiration biopsy, computed tomography, and magnetic resonance imaging were used for the diagnosis of DTC and four-year recurrence, which were finally confirmed by histopathology.

Patients were registered in a prospectively collected database and were followed up every three months until June 2017. Approval was obtained from the Ethics Committee of The First Hospital of Jilin University, and all of the subjects provided informed consent to participate.

BMI and HDL measurements

BMI was calculated using the measurements of weight and height reported on the anesthesia summary, as weight in kilograms divided by the square of height in meters (kg/m^2) in the morning when patients had fasted for more than 6

Table 1. Relationship of BMI and HDL with clinicopathological variables

Variable	N (%)	BMI, kg/m^2	*p* value	HDL, mmol/L	*p* value
Age at DTC diagnosis, years			0.230		0.505
< 45	98 (63.2)	26.62 ± 3.71		1.33 ± 1.00	
≥ 45	57 (36.8)	25.92 ± 3.18		1.24 ± 0.21	
Malignancy			< 0.001		0.020
BTN	65 (29.5)	24.54 ± 3.02		1.54 ± 0.20	
DTC	155 (70.5)	26.36 ± 3.53		1.30 ± 0.81	
LNM			0.219		0.833
No	56 (36.1)	25.90 ± 3.35		1.28 ± 0.18	
Yes	99 (63.9)	26.63 ± 3.63		1.31 ± 1.00	
Capsule invasion			0.001		0.032
No	46 (29.7)	24.87 ± 3.36		1.51 ± 1.44	
Yes	109 (70.3)	27.00 ± 3.42		1.2 ± 0.20	
Multifocality			< 0.001		0.477
No	79 (51.0)	25.36 ± 3.44		1.25 ± 0.18	
Yes	76 (41.0)	27.41 ± 3.33		1.35 ± 1.14	
Tumor size, cm			0.861		0.326
≤ 1	105 (67.7)	26.40 ± 3.52		1.34 ± 0.97	
> 1	50 (32.3)	26.29 ± 3.59		1.21 ± 0.19	
Extrathyroidal invasion			0.400		0.429
No	124 (80.0)	26.24 ± 3.52		1.33 ± 0.89	
Yes	31 (20.0)	26.84 ± 3.57		1.20 ± 0.23	
Vascular invasion			0.055		0.440
No	144 (92.9)	26.21 ± 3.53		1.31 ± 0.83	
Yes	11 (7.1)	28.33 ± 2.96		1.12 ± 0.31	
Distant metastasis			0.73		0.477
No	148 (95.5)	26.34 ± 3.55		1.31 ± 0.82	
Yes	7 (4.5)	26.82 ± 3.17		1.09 ± 0.28	
TNM stage			0.597		0.403
I+II	122 (78.7)	26.28 ± 3.64		1.33 ± 0.90	
III+IV	33 (21.3)	26.65 ± 3.11		1.20 ± 0.22	

BMI, body mass index; HDL, high-density lipoprotein; DTC, differentiated thyroid carcinoma; BTN, benign thyroid nodule; LNM, lymph node metastasis; TNM, tumor, node, and metastasis.

hours. The pretreatment blood samples were taken. The HDL level was determined by an enzymatic colorimetric method. All of the patients received the same laboratory test reference standards, and all of the test thresholds were prespecified.

Statistical analysis

Statistical analysis was performed using the SPSS software package (version 18.0; SPSS Inc., Chicago, IL, USA). For continuous data, the Kolmogorov-Smirnov test was used to test for normality. Normally distributed continuous data were expressed as the mean ± standard deviation. Categorical data were expressed as an absolute value and percentage. Comparisons of continuous variables between the groups were performed using the independent t-test for normally distributed data, and the nonparametric test for data that were not normally distributed. The proportions were compared using the Chi-square test or nonparametric test.

Multivariate logistic regression and Cox regression were utilized to analyze the relationship between variables. Receiver operating characteristic (ROC) curves were constructed to determine the diagnostic power of HDL and BMI for the prediction of DTC. The area under the ROC curve (AUC), sensitivity, and false-positive rate

Table 2. Correlations between clinicopathological variables and BMI and HDL by multivariate logistic regression analysis

Variable	BMI, kg/m^2			HDL, mmol/L		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Malignancy (DTC vs. BTN)	1.174	1.051-1.310	0.004	0.581	0.371-0.909	0.018
Capsule invasion (yes vs. no)	1.193	1.057-1.347	0.004	0.187	0.020-1.738	0.141
Multifocality (yes vs. no)	1.208	1.079-1.353	0.001	1.717	0.270-10.913	0.566
Tumor size (≤ 1 cm vs. > 1 cm)	0.956	0.858-1.065	0.413	0.197	0.024-1.621	0.131
Vascular invasion (yes vs. no)	1.115	0.903-1.377	0.313	0.085	0.002-3.783	0.203
Extrathyroidal invasion (yes vs. no)	1.022	0.900-1.161	0.734	0.301	0.028-3.285	0.325
Distant metastasis (yes vs. no)	0.922	0.745-1.142	0.460	0.006	0.000-0.517	0.025
TNM stage (I+II vs. III+IV)	0.996	0.886-1.126	0.945	0.217	0.021-2.283	0.203

BMI, body mass index; HDL, high-density lipoprotein; DTC, differentiated thyroid carcinoma; BTN, benign thyroid nodule; TNM, tumor, node and metastasis.

Table 3. Risk factors of CLNM and LLNM by multivariate logistic regression analysis

Variable	CLNM			LLNM		
	OR	95% CI	*p* value	OR	95% CI	*p* value
BMI, kg/m^2	1.032	0.924-1.152	0.576	0.993	0.858-1.150	0.930
HDL, mmol/L	1.174	0.642-2.147	0.602	0.156	0.010-2.508	0.190
Age, year	0.979	0.945-1.013	0.219	0.969	0.927-1.013	0.167
Tumor size, (≤ 1 cm vs. >1 cm)	3.587	1.181-10.896	0.024	0.510	0.135-1.928	0.321
Capsule invasion (yes vs. no)	1.491	0.644-3.452	0.351	1.075	0.372-3.105	0.894
Multifocality (yes vs. no)	1.300	0.602-2.806	0.420	1.009	0.383-2.659	0.986
Vascular invasion (yes vs. no)	5.220	0.000-8.759	0.998	4.188	0.768-22.841	0.098
Extrathyroidal invasion (yes vs. no)	0.995	0.251-3.949	0.994	1.494	0.313-7.142	0.615
Distant metastasis (yes vs. no)	4.923	0.000-9.471	0.999	18.054	1.817-179.392	0.014
CLNM (yes vs. no)	--	-	-	6.403	0.000-9.132	0.997

BMI, body mass index; HDL, high-density lipoprotein; CLNM, central lymph node metastasis; LLNM, lateral lymph node metastasis.

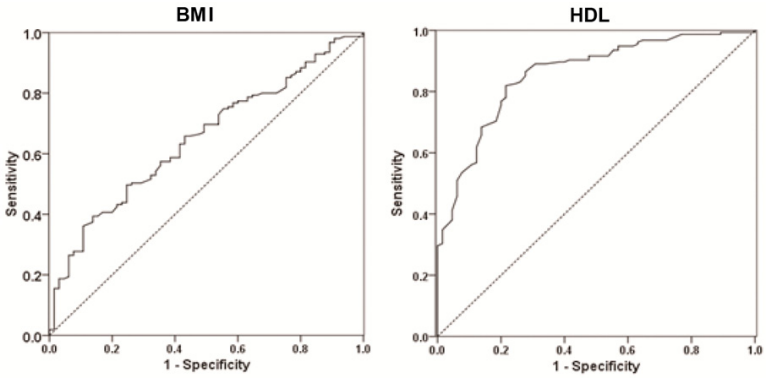

Figure 1. BMI and HDL in the differential diagnosis of DTC from BTN.

(1-specificity) were calculated. The optimal cut-off value was determined based on the Youden index [29]. All statistical tests were two-sided, and statistical significance was determined as $p < 0.05$.

Results

Demographic and clinico-pathological features

In total, 155 patients with DTC (42.08 ± 10.55 years old) and 65 patients with BTN (54.88 ± 10.67 years old) participated in this study. By age stratification, the study included 105 (47.3%) patients aged < 45 years old and 116 (52.7%) patients aged ≥ 45 years old. The patients had a mean tumor size of 1.04 ± 0.57 cm.

For patients with DTC (n = 155), 3 cases were identified as follicular thyroid carcinoma and

Table 4. Diagnostic performance of BMI and HDL for distinguishing DTC from BTN

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	+LR	-LR
BMI	0.649 (0.574-0.725)	0.39	0.86	0.87	0.37	2.79	0.709
HDL	0.857 (0.805-0.910)	0.82	0.75	0.83	0.645	3.28	0.24

BMI, body mass index; HDL, high-density lipoprotein; DTC, differentiated thyroid carcinoma; BTN, benign thyroid nodule; PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio.

152 cases were categorized as papillary thyroid carcinoma. There were 98 (63.2%) patients aged < 45 years old and 57 (36.8%) patients aged ≥ 45 years old. The characteristics of the subjects with DTC, including pathological central lymph node metastasis (CLNM), lateral lymph node metastasis (LLNM), capsule invasion, tumor size (> 1 cm), multifocality, vascular invasion, extrathyroidal invasion, distant metastasis, and advanced TNM stage (III+IV), are shown in **Table 1**. The lung was found to be involved in all patients with distant metastasis. Four-year recurrence occurred in 13 (8.39%) patients.

Relationships of BMI and HDL with clinicopathological variables

Patients with DTC had a higher mean BMI value ($p < 0.001$, **Table 1**) and a lower mean HDL level ($p = 0.020$), as compared to those with BTN. Among patients with DTC, patients with capsule invasion exhibited a higher mean BMI value ($p = 0.001$) and a lower mean HDL level ($p = 0.032$) than those without. In addition, patients with multifocal DTC had a higher mean BMI value than those with a unifocal lesion ($p < 0.001$).

Correlations between clinicopathological variables and BMI and HDL

By multivariate logistic regression analysis, both the BMI (OR, 1.174; 95% CI, 1.051-1.130; $p = 0.004$) and HDL (OR, 0.581; 95% CI, 0.371-0.909; $p = 0.018$) were significantly correlated with DTC occurrence, as shown in **Table 2**. The BMI was found to be significantly correlated with capsule invasion (OR, 1.193; 95% CI, 1.057-1.347; $p = 0.004$) and multifocality (OR, 1.208; 95% CI, 1.079-1.353; $p = 0.001$), while HDL was identified as a risk factor of distant metastasis (OR, 0.006; 95% CI, 0.000-0.517; $p = 0.025$). The multivariate logistic regression still included other variables, such as thyroid-stimulating hormone (TSH), estradiol, total cholesterol, tryglyceride, low-density lipoprotein (LDL), Hashimoto's thyroiditis, and nodular goiter (data not shown).

Risk factors of LNM by multivariate logistic regression analysis

Tumor size (OR, 3.587; 95% CI, 1.181-10.896; $p = 0.024$) and distant metastasis (OR, 18.054; 95% CI, 1.817-179.392; $p = 0.014$) were independent risk factors of CLNM and LLNM, respectively (**Table 3**). Neither BMI nor HDL was an independent risk factor of LNM ($p \geq 0.05$). Other variables, including TSH, estradiol, total cholesterol, tryglyceride, LDL, Hashimoto's thyroiditis, and nodular goiter, were involved in the regression (data not shown).

ROC curves of BMI and HDL for the prediction of DTC

According to the Youden's index, the ROC curves demonstrated that the optimal diagnostic cutoff value of the BMI for DTC was 27.16 kg/m^2 (AUC, 0.649; 95% CI, 0.574-0.725; $p < 0.001$), and the optimal cutoff value of HDL for DTC was 1.37 mmol/L (AUC, 0.857; 95% CI, 0.805-0.910; $p < 0.001$). These results showed that HDL yielded a greater AUC than the BMI (**Figure 1** and **Table 4**).

Clinicopathological features according to BMI and HDL stratification

Based on the optimal diagnostic cutoff values for the BMI (27.16 kg/m^2) and HDL (1.37 mmol/L), patients were categorized into a high-BMI (27.16 kg/m^2) group vs. a low-BMI (< 27.16 kg/m^2) group and a high-HDL (> 1.37 mmol/L) group vs. a low-HDL (≤ 1.37 mmol/L) group, respectively. The proportion of patients with DTC was higher in the high-BMI group and the low-HDL group (both $p < 0.001$, **Table 5**). Patients with a high HDL level were more likely to develop CLNM ($p < 0.05$). Moreover, capsule invasion and multifocal lesions were more commonly observed in patients with a high BMI ($p < 0.05$).

Impact of HDL on the four-year recurrence

The ROC curve was constructed based on the recurrence of DTC within 4 years, with an AUC of 0.730 (95% CI, 0.585-0.875; $p = 0.006$), sensitivity of 0.69, and specificity of 0.75

Table 5. Clinicopathological features according to BMI and HDL stratification

Variable	BMI, kg/m^2			HDL, mmol/L		
	< 27.16	≥ 27.16	*p* value	≤ 1.37	> 1.37	*p* value
Age < 45 years old at DTC diagnosis, n (%)	52 (55.3)	46 (75.4)	0.011	81 (63.3)	17 (63.0)	0.975
Malignancy, n (%)	94 (62.7)	61 (87.1)	< 0.001	128 (88.9)	27 (35.5)	< 0.001
CLNM, n (%)	56 (59.6)	43 (70.5)	0.167	87 (68.0)	12 (44.4)	0.021
No. of CLN removed	4.70 ± 1.64	4.30 ± 1.46	0.05	4.57 ± 1.58	4.17 ± 1.47	0.401
No. of positive CLN	2.11 ± 1.30	1.67 ± 0.87	0.557	1.95 ± 1.17	1.67 ± 0.99	0.419
LLNM, n (%)	20 (21.3)	12 (19.7)	0.809	29 (22.7)	3 (11.1)	0.178
No. of LLN removed	11.95 ± 2.33	11.33 ± 2.23	0.467	11.76 ± 2.29	11.33 ± 2.52	0.763
No. of positive LLN	1.85 ± 1.18	2.00 ± 0.95	0.71	1.83 ± 1.07	2.67 ± 1.15	0.209
Capsule invasion, n (%)	60 (63.8)	49 (80.3)	0.028	92 (71.9)	17 (63.0)	0.357
Multifocality, n (%)	37 (39.4)	39 (63.9)	0.003	62 (48.4)	14 (51.9)	0.747
Tumor size ≤ 1 cm, n (%)	29 (30.9)	21 (34.4)	0.642	45 (35.2)	5 (18.5)	0.093
Extrathyroidal invasion, n (%)	17 (18.1)	14 (23.0)	0.459	26 (20.3)	(18.5)	0.832
Vascular invasion, n (%)	5 (5.3)	6 (9.8)	0.285	8 (6.3)	3 (11.1)	0.630
Distant metastasis, n (%)	5 (5.3)	2 (3.9)	0.840	7 (5.5)	0 (0.0)	0.463
TNM stage III+IV, n (%)	22 (23.4)	11 (18.0)	0.425	30 (23.4)	3 (11.1)	0.155

BMI, body mass index; HDL, high-density lipoprotein; CLN, central lymph node; CLNM, central lymph node metastasis; LLN, lateral lymph node; LLNM; lateral lymph node metastasis; TNM, tumor, node and metastasis.

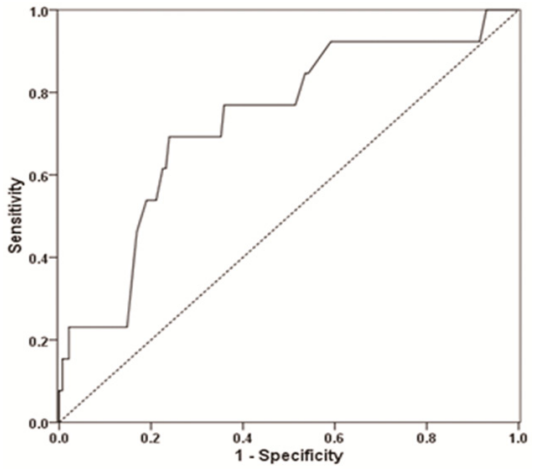

Figure 2. ROC curve for HDL level in predicting recurrence during four-year follow up (AUC = 0.730).

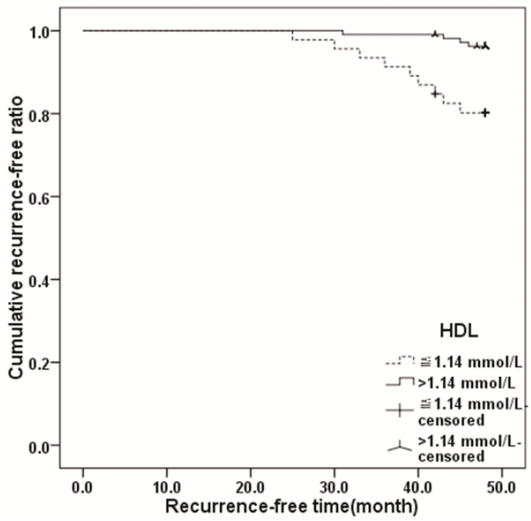

Figure 3. Recurrence-free curve by categorized HDL level in patients with DTC during four-year follow up.

(**Figure 2**). The optimal cutoff value of HDL for predicting the four-year DTC recurrence was 1.14 mmol/L.

We, then, conducted Cox regression analysis to identify risk factors for four-year DTC recurrence, of which a cutoff value of 1.14 mmol/L for HDL was used. A total of 13 patients (8.39%) had DTC recurrence during four years. Nine (19.6%) patients versus four patients (3.7%) experienced DTC recurrence among patients with HDL ≤ 1.14 mmol/L and > 1.14 mmol/L, respectively (p = 0.003). Moreover, patients with HDL ≤ 1.14 mmol/L had a shorter recurrence-free period (45.59 ± 5.25 months) than patients with HDL > 1.14 mmol/L (47.57 ± 1.96, p = 0.016). Patients with HDL ≤ 1.14 mmol/L had a worse clinical outcome than patients with HDL > 1.14 mmol/L (p = 0.001, **Figure 3**).

Univariate Cox proportional hazard regression model analysis revealed that the four-year DTC recurrence was significantly associated

Table 6. Risk factors for four-year DTC recurrence (by univariate and multivariate Cox proportional hazards regression models)

	Univariate analysis		Multivariate analysis	
Variable	HR (95% CI)	*p* value	HR (95% CI)	*p* value
BMI (< 27.16 vs. ≥ 27.16 kg/m^2)	1.891 (0.635-5.627)	0.252		
HDL (≤ 1.14 vs. > 1.14 mmol/L)	0.168 (0.052-0.545)	0.003	0.199(0.059-0.667)	0.009
Age (< 45 years old vs. ≥ 45 years old)	10.223 (2.265-46.132)	0.002	0.000 (0.000-2.013)	0.925
CLNM (yes vs. no)	3.188 (0.707-14.382)	0.132		
LLNM (yes vs. no)	0.686 (0.152-3.094)	0.624		
Capsule invasion (yes vs. no)	2.413 (0.535-10.886)	0.252		
Multifocality (unifocal vs. multifocal)	0.890 (0.299-2.647)	0.834		
Tumor size (≤ 1 cm vs. > 1 cm)	1.280 (0.419-3.912)	0.665		
Vascular invasion (yes vs. no)	4.089 (1.125-14.861)	0.032	1.222 (0.323-4.626)	0.768
Extrathyroidal invasion (yes vs. no)	2.491 (0.815-7.616)	0.104		
Distant metastasis (yes vs. no)	1.863 (0.242-14.330)	0.550		
TNM stage (I+II vs. III+IV)	23.664 (5.240-106.870)	< 0.001	4.255 (0.000-6.196)	0.900

BMI, body mass index; HDL, high-density lipoprotein; CLNM, central lymph node metastasis; LLNM; lateral lymph node metastasis; TNM, tumor, node and metastasis.

with an age ≥ 45 years old (p = 0.002), HDL ≤ 1.14 mmol/L (p = 0.003), the presence of vascular invasion (p = 0.032), and an advanced TNM stage (III+IV) (p < 0.001), as shown in **Table 6**. All variables achieving statistical significance in the univariate analysis were included in the multivariate logistic regression analysis, which demonstrated that the HDL level (≤ 1.14 mmol/L) was an independent risk factor of DTC recurrence (OR, 0.199; 95% CI, 0.059-0.667; p = 0.009, **Table 6**). The covariates included TSH, estradiol, total cholesterol, tryglyceride, LDL, Hashimoto's thyroiditis, and nodular goiter (data not shown).

Discussion

In this study, low HDL level was found to be a risk factor of both DTC and four-year recurrence, while the BMI was positively associated with capsule invasion and multifocality. In addition, HDL was identified as a risk factor of distant metastasis. Although distant metastasis does not frequently occur in DTC, it is the most common cause of thyroid cancer-related mortality [30]. Thus, effective measures should be taken to maintain a reasonable HDL level, such as aerobic exercise [31] and intake of fruits, vegetables [32], and soluble fiber [33] rather than simple carbohydrates [34]. The maintenance or achievement of a normal body weight is necessary to decrease the risk of DTC, capsule invasion, and multifocality. Also, tumor size had a positive correlation with CLNM, while distant metastasis was positively correlated with LLNM, suggesting that special attention should be paid to those patients with positive LNM. However, neither BMI nor HDL was found to be correlated with LNM in this study. These findings provide evidence explaining the important roles of HDL and BMI in carcinogenesis and the prognosis of DTC.

HDL protected against the initiation and four-year recurrence of DTC. The potential underlying mechanism may be related to its ability to downregulate ATP-binding cassette (ABC) A1 and ABCG1 genes, which inhibit thyroid cell proliferation [10]. In obese children, tumor necrosis factor alpha-9 was found to be negatively correlated with BMI, total cholesterol, triglycerides, LDL-cholesterol, and positively correlated with HDL [35], indicating a potentially opposite relationship between HDL and BMI. Since BMI is a cancer-related risk factor, HDL may be a protective factor against carcinogenesis. However, evidence has shown that HDL may promote or initiate carcinogenesis. In addition, studies have demonstrated the significant role of cholesterol and lipoprotein metabolism in the progression of cancer [36]. HDL particles are major suppliers of cholesterol to cancer cells, thus maintaining them at high rates of proliferation [10]. Moreover, scavenger receptor class B type I, as a receptor of HDL, facilitates selective uptake of cholesterol esters

from circulating lipoproteins and mediates cholesterol metabolism, motility, and proliferation of cancer cells [36, 37]. It has been shown that HDL is associated with an increased risk of breast cancer due to its antiapoptotic activity on cancer cells [38]. Inconsistent with these findings, we found that HDL was a protective factor against DTC. These discrepancies may have been due to different study designs and types of diseases. Unfortunately, limited evidence exists regarding the exact role of HDL in the prediction of DTC development and prognosis, although the relevance of HDL has been reported in several other types of cancers with conflicting results [39-41]. To the best of our knowledge, our study is the first to clarify that a low HDL level is not only a risk factor, but also a potential diagnostic marker for the predication of DTC outcomes. Thus, serum HDL levels should be used as a routine indicator for DTC surveillance.

Currently, there is no consensus regarding the influence of BMI on tumor characteristics and behaviors. An increased BMI has been demonstrated to be correlated with LNM, extra-thyroidal invasion, advanced TNM stage [42], and multifocality [27], as well as tumor size [43]. Kim et al. found that an increased BMI predicts a high risk of lymphatic invasion and multiplicity in patients aged ≥ 45 years old with papillary thyroid carcinoma [44]. However, conflicting data have been reported. Choi et al. reported that no correlation exists between BMI and LNM [28]. Another study has shown that the risk of malignancy in thyroid incidentaloma is not increased in overweight or obese adult patients [23]. In this study, a high BMI was able to predict capsule invasion and multifocality in male patients with DTC, but not LNM or four-year recurrence. The differences among studies may be attributed to multiple factors, such as sample size, gender distribution, and types of thyroid cancer.

The underlying mechanisms by which BMI influences DTC remain unknown. The potential pathophysiological mechanisms between obesity and cancers are as follows [16]: (1) obesity frequently occurs along with insulin resistance, under which conditions elevated insulin and insulin-like growth factor-1 (IGF-1) are involved in carcinogenesis by binding to the insulin receptor and IGF-1 receptor. IGF-1 inhibits cell apoptosis and promotes cell proliferation, as well as regulates cancer cell migration and invasion; (2) adipose tissue dysfunction leads to altered serum levels of adipokines, including adiponectin, leptin, and plasminogen activator inhibitor-1 (PAI-1), which are possibly involved in obesity-related carcinogenesis; (3) obesity-induced inflammation has been considered an important link between obesity and cancer. Moreover, genetic mutations and biochemical changes also contribute to the pathogenesis of DTC in overweight and obese populations. In addition, the BRAF (V600E) mutation was found in about 40-86.5% of papillary thyroid cancer patients [45, 46]. Furthermore, BMI has been positively associated with an advanced TNM stage and the BRAFV600E mutation in papillary thyroid cancers [19, 42].

The correlation between LNM and other invasive characteristics of DTC has been investigated. In a study of 1653 patients with papillary thyroid carcinoma, persistent/recurrent disease and distant metastasis are more frequent in patients with LLNM than in patients with CLNM [47]. In our study, no correlation was found between LNM and prognosis. However, correlations were observed between CLNM and tumor size and between LLNM and distant metastasis. Given the poor prognosis of patients with distant metastasis, LLNM should be carefully monitored in DTC patients for the surveillance of distant metastasis.

This study has several strengths. First, to the best of our knowledge, our study is the first to explore the relationship between HDL and invasive characteristics of DTC. In addition, it evaluates the performance of HDL as a marker for diagnosis of DTC and prediction of the prognosis. Second, the eligible patients were consecutively enrolled in this study to avoid a selection bias. Third, only male subjects were enrolled to avoid the influence of gender. However, several limitations of the present study should be noted. First, this study had a relatively small sample size. Second, some efficient indicators, such as waist circumference [35, 48], waist-to-hip ratio [49], skinfold thickness, percentage of body fat, and assessments of intra-abdominal fat [49], were unavailable. Third, the possible mechanism was not investigated due to insufficient data regarding insulin resistance [50], adiponectin [51], leptin [52], and fasting glucose level. Fourth, factors that could have possibly influenced the observed association could

not be entirely ruled out, including androgen and estrogen receptors.

In conclusion, HDL and BMI are both involved in the carcinogenesis of DTC. A low HDL level incurs an increased risk of DTC and four-year recurrence, while a high BMI is associated with capsule invasion and multifocality. However, confirmation of these findings will require further investigation with a larger sample size and a long-term follow up.

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Disclosure of conflict of interest

None.

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