Endocrine (2023) 80:619–629
https://doi.org/10.1007/s12020-023-03312-y

ORIGINAL ARTICLE

Prevalence and impact of non-alcoholic fatty liver disease in patients with papillary thyroid carcinoma

Renyi Xiao[1] · Chunjue Ni[2] · Yefeng Cai[1] · Yili Zhou[1] · Xiaohua Gong[3] · Keyue Xie[4] · Jie You[1]

Received: 6 October 2022 / Accepted: 12 January 2023 / Published online: 25 January 2023

Abstract

Purpose Papillary thyroid carcinoma (PTC) is the most common thyroid cancer. Non-alcoholic Fatty Liver Disease (NAFLD) was possibly among the risk factors for thyroid carcinoma. It is uncertain whether NAFLD is associated with the aggressiveness of PTC.

Methods We obtained data on patients with PTC who had undergone surgery at the First Affiliated Hospital of Wenzhou Medical University between January 2020 and February 2022. Pre-and post-operative data were obtained from electronic medical records and analyzed. Patients were split into two groups based on the NAFLD diagnostic criteria and compared using univariate and multivariate analysis through a logistic regression model.

Results In all, 3468 patients with PTC were included in this study, of which 594 (17.1%) were diagnosed with NAFLD. NAFLD was found to be an independent risk factor for lymph node metastasis ($OR = 1.285$ 95% *CI:* 1.052–1.570), incidence of $BRAF^{V600E}$ mutation ($OR = 1.504$, 95% *CI:* 1.148–1.972) and later tumor stage at diagnosis ($OR = 2.310$, 95% *CI:* 1.700–3.139) in PTC. The association mentioned above remained significant in subgroups of patients with Hashimoto's thyroiditis (HT), hypertension, diabetes (DM), high triglyceride (TG) levels, low levels of high-density lipoprotein-cholesterol (HDL-C), and high body mass index (BMI). In subgroup of female rather than male, NAFLD was an independent risk factor for lymph node metastasis ($OR = 1.638$ 95% *CI:* 1.264–2.123), incidence of $BRAF^{V600E}$ mutation ($OR = 1.973$, 95% *CI:* 1.368–2.846) as well as later tumor stage ($OR = 2.825$, 95% *CI:* 1.964–4.063) in PTC. However, NAFLD was not a risk factor for the larger tumor size (>1 cm), extra-thyroidal extension (ETE), or multifocality in PTC.

Conclusion Our cross-sectional study indicated that there is a strong association of NAFLD with higher incidence of lymph node metastasis, higher incidence of $BRAF^{V600E}$ mutation and later TNM stage than non-NAFLD in females with PTC.

Keywords Thyroid carcinoma · PTC · NAFLD · Clinicopathological characteristics · Aggressiveness

Introduction

The prevalence of thyroid cancer has been steadily increasing over the last three decades [1]. Thyroid cancer is more prevalent in females, with approximately three times more female patients than male [2]. Papillary thyroid carcinoma (PTC) accounts for the majority of thyroid cancer. Of late, however, there is strong evidence that overdiagnosis of papillary thyroid microcarcinoma (PTMC) may account for the increase in the incidence of reported thyroid cancer cases [1, 3, 4]. Nevertheless, the prevalence of large cancers and those diagnosed at later stages, where lymph node

These authors contributed equally: Renyi Xiao, Chunjue Ni

These authors jointly supervised this work: Keyue Xie, Jie You

✉ Keyue Xie
ballbe@163.com

✉ Jie You
youjie@wmu.edu.cn

[1] Department of Thyroid Surgery, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

[2] Department of Anesthesiology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

[3] Department of Endocrinology and Metabolism, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang Province, China

[4] Department of Anesthesiology and Pain Research Center, The Affiliated Hospital of Jiaxing University, Jiaxing, China

metastasis occurs, are still on the rise [5]. The effects of metabolic and environmental factors, such as radiation exposure, diabetes mellitus, obesity, and iodine deficiency or excess, on the development of PTC remain unclear [1].

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disease characterized by hepatic macrovesicular [6]. It has had a global prevalence of around 25% in adults over the last four decades, making it the most prevalent chronic liver condition in adults [7]. The presence of NAFLD has been associated with the incidence of chronic kidney disease [8], hypothyroidism [9], thyroid autoimmunity [10], and various types of extrahepatic cancers, such as gastrointestinal tract and uterine cancer [11], colon cancer [12], bladder cancer [13], and thyroid and lung cancer in males [14], as well as metabolic syndrome (MetS) and insulin resistance (IR) [15, 16].

MetS was found associated with the aggressiveness of PTC [17]. And NAFLD is also a reversible metabolic disease like MetS. Although males with NAFLD have a high risk of developing thyroid cancer [14], to the best of our knowledge, there is no data on the correlation between NAFLD occurrence and the severity of PTC. Therefore, we undertook this study to explore the relationship between PTC and NAFLD.

Methods

Study protocol

This study used data from a group of patients with PTC who underwent first-time surgery for tumor removal between January 2020 and February 2022 at the First Affiliated Hospital of Wenzhou Medical University. Patients were excluded if they had a history of excessive alcohol intake and/or viral hepatitis, or were diagnosed with other types of thyroid cancers, such as follicular, medullary, or anaplastic cancers. Information on patients' demographic characteristics, preoperative laboratory tests, imaging, and histological data were obtained from electronic medical records. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University and informed consent was obtained from all patients.

Imaging data

Two sonographers or radiologists performed an ultrasound and/or computed tomography (CT) scans on all patients [a chest CT was necessary for all patients due to the ongoing coronavirus disease-19 (COVID-19) pandemic during that time]. The patients were diagnosed with NAFLD based on specific ultrasonographic features, such as diffusely increased echogenicity of liver parenchyma, hepatomegaly, and vascular blunting [18] and if they had a liver-to-spleen attenuation ratio (L/S) < 1 through images obtained via non-contrast chest CT scan. NAFLD occurrence in the patients included in this study excluded viral hepatitis, liver cirrhosis, liver malfunction or cancer, and excessive alcohol intake as causal agents.

Data collection

Basic information and clinical data of all patients included in this study were collected from electronic medical records. Pre-operative data included details of age, gender, weight and height, history of alcohol consumption, history of type 2 diabetes mellitus (DM), history of hypertension, imaging and laboratory findings just before surgery, and clinicopathologic variables, including levels of thyroglobulin antibody (TgAb), thyroid peroxidase antibody (TPOAb), thyroid-stimulating hormone (TSH), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG). Post-operative data included details of surgical outcomes and clinicopathologic variables mentioned above (values obtained after surgery). Body mass index (BMI in kg/m^2) was calculated by dividing the weight in kilograms (kg) by the square of the height in meters (m).

Diagnoses and definitions

All patients underwent surgical resection according to the guidelines of the 2015 American Thyroid Association for the treatment of differentiated thyroid cancer in adults. The dissection of the central lymph nodes was routinely performed. Preoperative imaging, fine-needle aspiration, and intraoperative exploration were used to determine whether the lateral lymph nodes needed to be dissected. Patients were classified as having either multiple foci (having > 1 tumor in the thyroid tissue) or a solitary focus (only one tumor in the thyroid). The PTC tumor stage was defined based on the guidelines provided by the 8^{th} American Joint Committee on Cancer (AJCC) edition. Information on tumor location, TNM staging, histologic differentiation of tumors, extra-thyroidal extension (ETE), and lymph node metastasis were collected from the pathological analysis reports.

A patient was diagnosed with NAFLD if steatosis was found in >5% of the hepatocytes. The diagnosis was linked to metabolic risk factors as none of the patients had a history of excessive alcohol consumption (≥30 g/day for male and ≥20 g/day for female) or any other chronic liver disease [19]. In our study, we diagnosed NAFLD mainly by examining ultrasound and/or CT images.

Hashimoto's thyroiditis (HT) was diagnosed based on pathological results in our study. A BMI of >25 kg/m^2 was considered to be high. Low HDL-C was defined as levels of

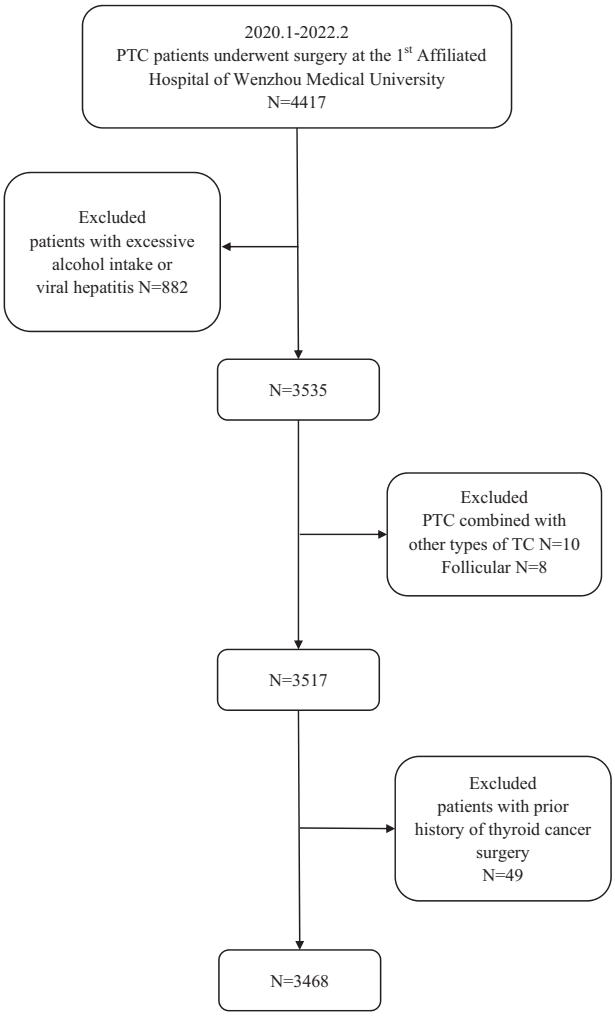

Fig. 1 Flowchart of screened patients. *PTC* papillary thyroid carcinoma, *TC* thyroid carcinoma

HDL-C < 1.16 mmol/L (for male) and <1.29 mmol/L (for female). High LDL-C was defined as levels of LDL-C > 3.10 mmol/L. High TG was defined as levels of TG > 1.70 mmol/L.

Statistical analyses

The software SPSS (version 19.0; SPSS, Chicago, IL, USA) and StataSE (version 16.0; Standard Edition) were used to conduct statistical analyses. All categorical variables were expressed as percentages while continuous variables were represented as mean ± SD. To compare the clinical features of patients with and without NAFLD, we used the chi-square test for categorical variables and the rank-sum test or student's t-test for continuous variables. Both, multivariate and simple binary logistic models were used to examine the relationship between NAFLD and PTC. Variables with *P*-values < 0.05 in the univariate logistic analyses were selected for multivariate analysis when screening for confounding factors. In addition, we investigated the association between NAFLD and clinicopathological characteristics of PTC within subgroups of HT, hypertension, high TG, DM, low HDL-C, high BMI, standard (non-DM & non-hypertension & non-HT & BMI ≤ 25 kg/m^2), female and male. A *P*-value < 0.05 was considered statistically significant for all two-tailed statistical tests.

Results

Baseline characteristics

This study used data from 3468 patients with PTC, of which 2561 (73.8%) were female and 907 (26.2%) were male (Fig. 1). In all, 594 (17.1%) patients were diagnosed with NAFLD. The clinical data, including metabolic and pathological features, of the patients included in this study are listed in Table 1.

As shown in Table 1, the patients diagnosed with NAFLD (NAFLD group) were older ($p = 0.000$) and had higher BMI indices ($p = 0.000$), higher incidence of HT ($p = 0.003$), higher incidence of nodal metastasis ($p = 0.007$), higher incidence of multifocal tumors ($p = 0.037$), higher incidence of hypertension ($p = 0.000$) and DM ($p = 0.000$), higher incidence of $BRAF^{V600E}$ mutation ($p = 0.002$), more advanced tumors at diagnosis (later TNM stages) ($p = 0.000$), lower levels of HDL-C ($p = 0.000$), higher levels of LDL-C ($p = 0.000$), and higher levels of TG ($p = 0.000$) than patients in the non-NAFLD group. In addition, there were more males in the NAFLD group than in the non-NAFLD group ($p = 0.000$). There were no differences between the NAFLD and non-NAFLD groups in the occurrence of tumor subtype (classic versus follicular) ($p = 0.762$). Patients in both groups had similar T stages ($p = 0.870$), the incidence of ETE ($p = 0.132$), and thyroid-stimulating hormone (TSH) levels ($p = 0.764$).

Relationship between NAFLD and clinicopathological features

As demonstrated in Table 2, univariate analysis found that NAFLD was associated with a higher incidence of nodal metastasis (*OR* = 1.312, 95% *CI:* 1.099–1.565), higher incidence of $BRAF^{V600E}$ mutation (*OR* = 1.518, 95% *CI:* 1.167–1.975), later tumor stages (*OR* = 3.409, 95% *CI:* 2.593–4.482), and higher incidence of multifocal diseases (*OR* = 1.232, 95% *CI:* 1.012–1.498) than non-NAFLD. However, tumor sizes were similar between the NAFLD and non-NAFLD groups (*OR* = 1.096, 95% *CI:* 0.890–1.348). In the multivariate analysis, after adjustment for risk factors in each univariate analysis, such as age, gender, BMI, DM, hypertension, HT, HDL-C, LDL-C, and

Table 1 Clinicopathologic characteristics for patients with and without NAFLD

Characteristics	Patients ($N = 3468$)	%	Non-NAFLD ($N = 2874$)	NAFLD ($N = 594$)	*P*
Age (mean ± SD) (year)	45.65 ± 11.79		45.20 ± 11.65	47.88 ± 12.24	0.000
<55	2637	76.0	2246 (78.1%)	391 (65.8%)	0.000
≥55	831	24.0	628 (21.9%)	203 (34.2%)	
BMI (mean ± SD) (kg/m^2)	23.95 ± 3.49		23.38 ± 3.22	26.73 ± 3.43	0.000
≤25	2298	66.3	2087 (72.6%)	211 (35.5%)	0.000
>25	1170	33.7	787 (27.4%)	383 (64.5%)	
Gender					
Female	2561	73.8	2230 (77.6%)	331 (55.7%)	0.000
Male	907	26.2	644 (22.4%)	263 (44.3%)	
Subtype					
Classic variant	3362	96.9	2785 (96.9%)	577 (97.1%)	0.762
Follicular variant	106	3.1	89 (3.1%)	17 (2.9%)	
HT					
No	2758	79.5	2209 (76.9%)	499 (84.0%)	0.003
Yes	710	20.5	615 (21.4%)	95 (16.0%)	
Tumor size (mean ± SD) (cm)	0.87 ± 0.61		0.86 ± 0.61	0.89 ± 0.58	0.242
≤1	2680	77.3	2229 (77.6%)	451 (75.9%)	0.388
>1	788	22.7	645 (22.4%)	143 (24.1%)	
T stage					
T1a	2657	76.6	2209 (76.9%)	448 (75.4%)	0.870
T1b	630	18.2	517 (18.0%)	113 (19.0%)	
T2	120	3.5	99 (3.4%)	21 (3.6%)	
T3–T4	61	1.7	49 (1.7%)	12 (2.0%)	
Lymph node metastasis					
N0	1870	53.9	1583 (55.1%)	287 (48.3%)	0.007
N1a	1362	39.3	1095 (38.1%)	267 (45.0%)	
N1b	236	6.8	196 (6.8%)	40 (6.7%)	
TNM stage					
I	3221	92.9	2722 (94.7%)	499 (84.0%)	0.000
II–III	247	7.1	152 (5.3%)	95 (16.0%)	
Multifocality					
No	2576	74.3	2155 (75.0%)	421 (70.9%)	0.037
Yes	892	25.7	719 (25.0%)	173 (29.1%)	
ETE					0.132
Yes (T3)	15	0.4	14 (0.5%)	1 (0.2%)	
Yes (T4)	36	1.0	26 (0.9%)	10 (1.7%)	
No	3418	98.6	2835 (98.6%)	583 (98.1%)	
TSH (mean ± SD) (mIU/L)	2.08 ± 8.09		2.08 ± 8.62	1.97 ± 2.87	0.764
BRAF ^{V600E} mutation					
No	577	16.7	504 (17.5%)	73 (12.3%)	0.002
Yes	2891	83.3	2370 (82.5%)	521 (87.7%)	
Hypertension					
No	2588	74.6	2246 (78.2%)	342 (57.6%)	0.000
Yes	880	25.4	628 (21.8%)	252 (42.4%)	

Table 1 (continued)

Characteristics	Patients ($N = 3468$)	%	Non-NAFLD ($N = 2874$)	NAFLD ($N = 594$)	*P*
DM					
No	3224	93.0	2730 (95.0%)	494 (83.2%)	0.000
Yes	244	7.0	144 (5.0%)	100 (16.8%)	
HDL-C					
Low	1886	54.4	1453 (50.6%)	433 (72.9%)	0.000
High	1582	45.6	1421 (49.4%)	161 (27.1%)	
LDL-C					
Low	2200	63.4	1871 (65.1%)	329 (55.4%)	0.000
High	1268	36.6	1003 (34.9%)	265 (44.6%)	
TG					
Low	2047	59.0	1861 (64.8%)	186 (31.3%)	0.000
High	1421	41.0	1013 (35.2%)	408 (68.7%)	

Continuous values are summarized as mean ± SD, categorical variables as percentage

NAFLD non-alcoholic fatty liver disease, *SD* standard deviation, *BMI* body mass index, *HT* Hashimoto's thyroiditis, *T stage* tumor stage, *TNM stage* Tumor Node Metastasis stage, *ETE* extra-thyroidal extension, *TSH* thyroid-stimulating hormone, *DM* diabetes, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides

TG, NAFLD still emerged as a risk factor for the development of nodal metastasis ($OR = 1.285$, 95% *CI:* 1.052–1.570) and was associated with a higher incidence of *BRAF* ^{V600E} mutation ($OR = 1.504$, 95% *CI:* 1.148–1.972) and later TNM stage ($OR = 2.310$, 95% *CI:* 1.700–3.139). However, NAFLD was not associated with the incidence of multifocal tumors ($OR = 1.195$, 95% *CI:* 0.972–1.469).

Subgroup analyses associated with NAFLD

We further analyzed the available data to investigate the relationship between the clinicopathological characteristics of PTC and the occurrence of NAFLD. As demonstrated in Fig. 2, we selected nine subgroups, such as HT, hypertension, high TG, DM, low HDL-C, high BMI, standard, female and male. After adjusting for risk factors in each clinicopathological characteristic (Table 3), we discovered that in females and patients with HT, hypertension, high TG levels, low HDL-C levels, and high BMI, NAFLD was still a risk factor for the development of nodal metastasis, incidence of *BRAF* ^{V600E} mutation and later TNM stage. In contrast, NAFLD was not a risk factor for any of the above-mentioned clinicopathological characteristics in males with PTC. Additionally, the analyses revealed that NAFLD was not associated with tumor size in all subgroups. Furthermore, there were no obvious differences in the incidence of multifocal tumors between the non-NAFLD and NAFLD groups in any of the subgroups, except for those in the HT subgroup ($OR = 1.672$, 95% *CI:* 1.052–2.658). In addition, we found that NAFLD was only associated with later TNM stage ($OR = 3.380$, 95% *CI:* 1.656–6.899) in patients without hypertension, HT, DM or overweight (standard group).

Discussion

Currently, only two studies have investigated the association between fatty liver disease and thyroid cancer. One study from China found that males with NAFLD had a higher risk of developing thyroid cancer and that blood levels of alanine transferase in this group were positively associated with the risk of developing thyroid cancer [14]. Another study from China involving 352,911 participants found that the presence of metabolic dysfunction-associated fatty liver disease (MAFLD) was a significant risk factor for the development of thyroid cancer [20]. However, no studies to date have explored the relationship between NAFLD and the clinicopathological characteristics of PTC.

Our study showed that NAFLD may be an independent risk factor associated with the development of lymph node metastasis, incidence of *BRAF* ^{V600E} mutation, and later TNM stage in females with PTC. Despite increased nodal metastasis and a later TNM stage, *BRAF* ^{V600E} mutation was also linked in certain reports to PTC aggressiveness and a worse prognosis [21, 22]. Nevertheless, this study found no significant relationship between NAFLD and tumor size in patients with PTC. The most recent WHO classification of thyroid neoplasms does not include papillary thyroid micro-carcinoma as a subtype of PTC because a subset of these tumors displayed aggressive pathologic characteristics and clinical behaviors, including regional and distant metastasis and structural recurrence after surgery [23–25]. Thus, a small tumor size does not necessarily mean a better prognosis.

Subgroup multivariate analysis indicated that NAFLD was an important risk factor for the development of lymph

Table 2 Univariate and multivariate analyses of the risk factors for clinicopathological features in PTC

Characteristics	Lymph node metastasis (N1 vs N0)	*p*	*BRAF* ^{V600E} mutation (yes vs no)	*p*	TNM stage (II–III vs I)	*p*	Multifocal tumor (yes vs no)	*p*	Tumor size (≤1 cm vs > 1 cm)	*p*
Univariate ORs										
Age (<55 vs ≥55)	2.615 (2.210–3.094)*	0.000	1.324 (1.083–1.618)*	0.006	[a]	-	0.990 (0.828–1.183)	0.909	0.949 (0.786–1.144)	0.581
Gender (male vs female)	2.116 (1.814–2.469)*	0.000	1.373 (1.107–1.704)*	0.004	0.899 (0.665–1.215)	0.490	0.975 (0.819–1.160)	0.771	1.142 (0.956–1.365)	0.142
BMI (>25 vs ≤25)	1.198 (1.041–1.380)*	0.012	1.160 (0.957–1.406)	0.131	1.637 (1.260–2.126)*	0.000	1.174 (1.001–1.377)*	0.048	1.200 (1.017–1.416)*	0.031
HT (no vs yes)	1.172 (0.992–1.384)	0.062	1.978 (1.619–2.416)*	0.000	1.317 (0.932–1.861)	0.118	0.724 (0.604–0.868)*	0.000	0.758 (0.627–0.916)*	0.004
NAFLD (yes vs no)	1.312 (1.099–1.565)*	0.003	1.518 (1.167–1.975)*	0.002	3.409 (2.593–4.482)*	0.000	1.232 (1.012–1.498)*	0.037	1.096 (0.890–1.348)	0.388
DM (yes vs no)	0.730 (0.559–0.953)*	0.021	1.458 (0.984–2.159)	0.060	3.607 (2.545–5.113)*	0.000	1.150 (0.861–1.537)	0.343	1.374 (1.027–1.837)*	0.032
Hypertension (yes vs no)	0.779 (0.667–0.909)*	0.002	1.005 (1.110–1.644)	0.965	3.934 (3.023–5.120)*	0.000	1.157 (0.974–1.375)	0.096	1.000 (0.834–1.201)	0.997
HDL-C (low vs high)	1.172 (1.025–1.341)*	0.020	1.180 (0.986–1.411)	0.070	1.563 (1.194–2.046)*	0.001	1.082 (0.928–1.261)	0.314	1.146 (0.976–1.345)	0.096
TG (high vs low)	1.040 (0.908–1.191)	0.569	1.123 (0.935–1.349)	0.213	1.982 (1.526–2.573)*	0.000	1.061 (0.909–1.238)	0.453	1.093 (0.930–1.284)	0.280
LDL-C (high vs low)	1.055 (0.919–1.212)	0.448	0.991 (0.823–1.193)	0.922	1.218 (0.935–1.585)	0.143	0.967 (0.825–1.133)	0.678	0.759 (0.641–0.898)*	0.001
Multivariate ORs										
Age (<55 vs ≥55)	2.490 (2.074–2.988)*	0.000	1.412 (1.149–1.733)*	0.001	-	-	-	-	-	-
Gender (male vs female)	1.898 (1.612–2.235)*	0.000	1.103 (0.880–1.382)	0.395	-	-	-	-	-	-
BMI (>25 vs ≤25)	1.033 (0.881–1.211)	0.691	-	-	0.941 (0.705–1.255)	0.677	1.145 (0.969–1.355)	0.112	1.232 (1.042–1.457)*	0.015
HT (no vs yes)	-	-	1.947 (1.585–2.391)*	0.000	-	-	0.710 (0.592–0.852) *	0.000	0.747 (0.617–0.904)*	0.003
NAFLD (yes vs no)	1.285 (1.052–1.570)*	0.014	1.504 (1.148–1.972)*	0.003	2.310 (1.700–3.139)*	0.000	1.195 (0.972–1.469)	0.091	-	-
DM (yes vs no)	0.958 (0.715–1.285)	0.776	-	-	1.963 (1.352–2.851)*	0.000	-	-	1.366 (1.019–1.831)*	0.037
Hypertension (yes vs no)	0.903 (0.758–1.077)	0.256	-	-	3.012 (2.278–3.983)*	0.000	-	-	-	-
HDL-C (low vs high)	1.105 (0.958–1.275)	0.169	-	-	1.113 (0.828–1.496)	0.479	-	-	-	-
TG (high vs low)	-	-	-	-	1.306 (0.975–1.750)	0.074	-	-	-	-
LDL-C (high vs low)	-	-	-	-	-	-	-	-	0.749(0.632–0.889)*	0.001

NAFLD non-alcoholic fatty liver disease, *BMI* body mass index, *HT* Hashimoto's thyroiditis, *TNM stage* Tumor Node Metastasis stage, *DM* diabetes, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides

[a]All PTC patients with stage II-III ≥ 55 years old due to no patient with distant metastases observed

*$P < 0.05$ or less

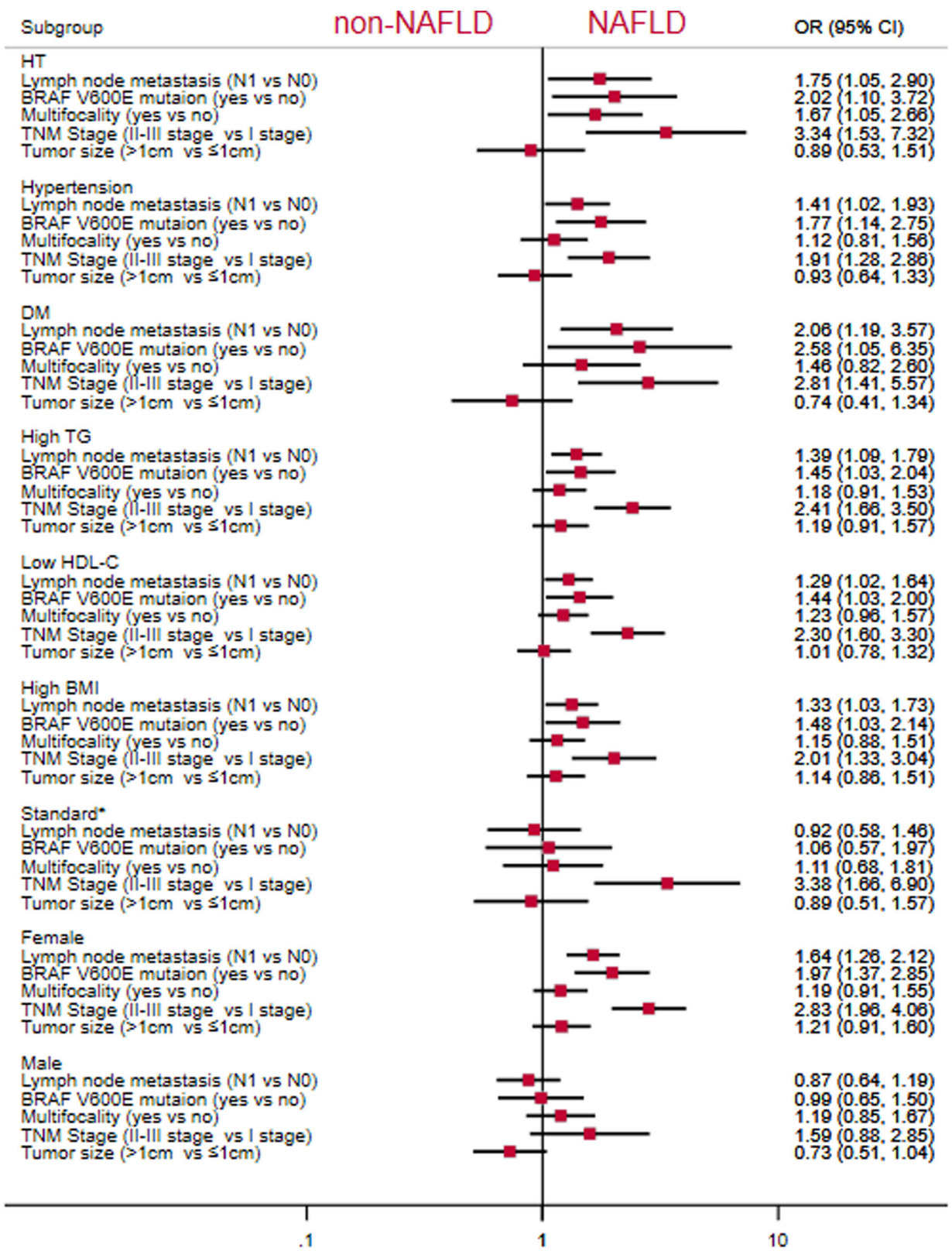

Fig. 2 Multivariate analysis for relationship between NAFLD and clinicopathological features of PTC in 9 subgroups. *NAFLD* non-alcoholic fatty liver disease, *BMI* body mass index, *HT* Hashimoto's thyroiditis, *TNM stage* Tumor Node Metastasis stage, *DM* diabetes, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein Cholesterol, *TG* triglycerides. Standard* subgroup consist of participants without hypertension, HT, DM or overweight. Analyses after adjusted for risk factors in each clinicopathological characteristic (e.g., lymph node metastasis, *BRAF* ^{V600E} mutation, TNM stage, multifocality, tumor size), details of adjustments are shown in Table 3

Table 3 Adjustments for the multivariate analysis in nine subgroups

Variables	Subgroup	Adjustments
Lymph node metastasis (N1 vs N0)	HT	Age, Gender, BMI, DM, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender
Multifocality (yes vs no)		BMI
TNM Stage (II–III stage vs I stage)		BMI, Hypertension, DM, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		BMI, DM, LDL
Lymph node metastasis (N1 vs N0)	Hypertension	Age, Gender, BMI, DM, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II-III stage vs I stage)		BMI, DM, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, DM, LDL
Lymph node metastasis (N1 vs N0)	DM	Age, Gender, BMI, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II-III stage vs I stage)		BMI, Hypertension, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, LDL
Lymph node metastasis (N1 vs N0)	High TG	Age, Gender, BMI, DM, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II-III stage vs I stage)		BMI, Hypertension, DM, HDL
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, DM, LDL
Lymph node metastasis (N1 vs N0)	Low HDL-C	Age, Gender, BMI, DM, Hypertension
BRAF V600E mutaion (yes vs no)		Age, Gender, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II–III stage vs I stage)		BMI, Hypertension, DM, TG
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, DM, LDL
Lymph node metastasis (N1 vs N0)	High BMI	Age, Gender, DM, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender, HT
Multifocality (yes vs no)		HT
TNM Stage (II–III stage vs I stage)		Hypertension, DM, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		HT, DM, LDL
Lymph node metastasis (N1 vs N0)	Standard*	Age, Gender, HDL
BRAF V600E mutaion (yes vs no)		Age, Gender
Multifocality (yes vs no)		HT
TNM Stage (II–III stage vs I stage)		HDL, TG
Tumor size (>1 cm vs ≤1 cm)		LDL
Lymph node metastasis (N1 vs N0)	Female	Age, BMI, DM, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II–III stage vs I stage)		BMI, Hypertension, DM, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, DM, LDL
Lymph node metastasis (N1 vs N0)	Male	Age, BMI, DM, Hypertension, HDL
BRAF V600E mutaion (yes vs no)		Age, HT
Multifocality (yes vs no)		BMI, HT
TNM Stage (II–III stage vs I stage)		BMI, Hypertension, DM, HDL, TG
Tumor size (>1 cm vs ≤1 cm)		HT, BMI, DM, LDL

NAFLD non-alcoholic fatty liver disease, *BMI* body mass index, *HT* Hashimoto's thyroiditis, *TNM stage* Tumor Node Metastasis stage, *DM* diabetes, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-Density Lipoprotein Cholesterol, *TG* triglycerides

Standard* subgroup consist of participants without hypertension, HT, DM, or overweight

node metastasis, high incidence of *BRAF* ^{V600E} mutation, and development of advanced tumor stage at diagnosis even after accounting for the confounding effects of Hashimoto's thyroiditis, hypertension, diabetes, high BMI, high TG, low HDL-C, and gender. However, further analysis showed that NAFLD was not associated with any aggressive clinicopathological characteristics in males, possibly due to the notably worse prognosis generally associated with male patients with PTC [26, 27].

In the subgroup of patients with HT, the NAFLD group had a significantly higher incidence of multifocal lesions than the non-NAFLD group. Several studies have verified that patients with HT, who develop PTC, have an increased risk of having multifocal tumors [28, 29]. Our results suggested that the occurrence of NAFLD and HT together increases the incidence of multifocal tumors; however, further studies are required to confirm this pattern.

The molecular mechanisms underlying the effects of NAFLD on PTC are not well understood; therefore, variables other than NAFLD may play important roles in the progression of PTC. For example, the pathophysiology of NAFLD is closely associated IR [30], which might promote thyroid cancer cell proliferation through insulin and insulin-like growth factor signaling pathways [31–34]. Furthermore, as NAFLD progresses, the release of leptin may cause pyroptotic cell death in macrophages and hepatocytes via $CD8^+$ T lymphocytes [35], which may in turn support the proliferation and invasiveness of cancers such as thyroid cancer [36]. Patients with PTC have elevated levels of serum leptin and thyroid cancer cells with high levels of leptin receptors are associated with tumor aggressiveness [37, 38]. On the other hand, adiponectin inhibits angiogenic growth and its levels are inversely correlated with fat deposits; therefore, it is unsurprising that both, the development of NAFLD and thyroid cancer growth, are negatively correlated with adiponectin levels [39, 40]. Besides these factors, the production of TSH stimulates thyrocyte proliferation and is positively correlated with the expression of vascular endothelial growth factor. An elevated TSH level is a standalone risk factor for the development of NAFLD [41] and likely plays a role in the onset and progression of thyroid tumors in obese patients [42]. In our study, however, no significant differences in pre-surgical TSH levels between the NAFLD and non-NAFLD groups were apparent.

Inevitably, our study has several limitations. (1) We utilized abdominal ultrasonography and/or CT as non-invasive means for diagnosing NAFLD. However, liver biopsies are the gold standard for this diagnosis because conventional ultrasound and CT scans are not sensitive enough to diagnose mild steatosis, particularly in obese people, and the accuracy of ultrasound is hampered by reader variability [43, 44]. Since we did not diagnose NAFLD via liver biopsies, we may have missed diagnosing patients with early-stage NAFLD. (2) Despite the usually favorable prognosis of patients with PTC after surgical treatment, there are no ongoing follow-up evaluations to check for recurrence or distant metastases. (3) Some potential confounders, such as how long a patient has had NAFLD, smoking, and genetic factors were not considered in this study.

In summary, this study indicates that the presence of NAFLD may be positively associated with aggressiveness of PTC in female patients. However, additional research is required to understand the biochemical pathways that link PTC with NAFLD.

Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Acknowledgements We thank the colleagues of the First Affiliated Hospital of Wenzhou Medical University and Affiliated Hospital of Jiaxing University for their support.

Author contributions R.X. and C.N. performed, analyzed data and wrote the manuscript. Y.C., Y.Z., X.G. organized data. K.X., J.Y. conceived, and directed the study. All authors contributed to the article and approved the submitted version.

Funding The Basic Scientific Research Projects of Wenzhou (Y2020739) supported this work.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval The studies involving human participants were reviewed and approved by ethics committee of the First Affiliated Hospital of Wenzhou Medical University.

Informed consent The participants provided their written informed consent to participate in this study.

References

1. L. Davies et al. American association of clinical endocrinologists and american college of endocrinology disease state clinical review: the increasing incidence of thyroid cancer. Endocr. Pract. **21**(6), 686–696 (2015). https://doi.org/10.4158/ep14466.dscr
2. R. Siegel et al. Cancer statistics, 2022. CA: Cancer J. Clin. **72**(1), 7–33 (2022). https://doi.org/10.3322/caac.21708
3. C. Seib, J. Sosa, Evolving understanding of the epidemiology of thyroid cancer. Endocrinol. Metab. Clin. North Am. **48**(1), 23–35 (2019). https://doi.org/10.1016/j.ecl.2018.10.002
4. S. Xu, Y. Han, The overdiagnosis of thyroid micropapillary carcinoma: the rising incidence, inert biological behavior, and countermeasures. J. Oncol. **2021**, 5544232 (2021). https://doi.org/10.1155/2021/5544232
5. L. Enewold et al. Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005.

Cancer Epidemiol. Biomark. Prev. **18**(3), 784–791 (2009). https://doi.org/10.1158/1055-9965.epi-08-0960
6. A.L. Sberna et al. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with Type 2 diabetes. Diabet. Med. **35**(3), 368–375 (2018). https://doi.org/10.1111/dme.13565
7. Z.M. Younossi et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology **64**(1), 73–84 (2016). https://doi.org/10.1002/hep.28431
8. G. Musso et al. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. PLoS Med. **11**(7), e1001680 (2014). https://doi.org/10.1371/journal.pmed.1001680
9. A. Eshraghian, A.Hamidian Jahromi, Non-alcoholic fatty liver disease and thyroid dysfunction: a systematic review. World J. Gastroenterol. **20**(25), 8102–8109 (2014). https://doi.org/10.3748/wjg.v20.i25.8102
10. Y. Chen et al. The association of non-alcoholic fatty liver disease with thyroid peroxidase and thyroglobulin antibody: a new insight from SPECT-China study. Autoimmunity **51**(5), 238–244 (2018). https://doi.org/10.1080/08916934.2018.1488968
11. A.M. Allen et al. The risk of incident extrahepatic cancers is higher in non-alcoholic fatty liver disease than obesity—a longitudinal cohort study. J. Hepatol. **71**(6), 1229–1236 (2019). https://doi.org/10.1016/j.jhep.2019.08.018
12. V. Wong et al. High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. Gut **60**(6), 829–836 (2011). https://doi.org/10.1136/gut.2011.237974
13. G. Tarantino et al. Association of NAFLD and insulin resistance with non metastatic bladder cancer patients: a cross-sectional retrospective study. J Clin. Med. **10**(2) (2021). https://doi.org/10.3390/jcm10020346
14. Z. Wang et al. Associations between nonalcoholic fatty liver disease and cancers in a large cohort in China. Clin. Gastroenterol. Hepatol. **19**(4), 788–796.e4 (2021). https://doi.org/10.1016/j.cgh.2020.05.009
15. S.W. Lee et al. The association of non-alcoholic fatty liver disease and metabolic syndrome in a Chinese population. Hepatobiliary Pancreat. Dis. Int. **16**(2), 176–180 (2017). https://doi.org/10.1016/s1499-3872(16)60132-7
16. E. Muzurović, D.P. Mikhailidis, C. Mantzoros, Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. Metabolism **119**, 154770 (2021). https://doi.org/10.1016/j.metabol.2021.154770
17. J.L. Song et al. Association between metabolic syndrome and clinicopathological features of papillary thyroid cancer. Endocrine **75**(3), 865–871 (2022). https://doi.org/10.1007/s12020-021-02940-6
18. M. Obika, H. Noguchi, Diagnosis and evaluation of nonalcoholic fatty liver disease. Exp. Diabetes Res. **2012**, 145754 (2012). https://doi.org/10.1155/2012/145754
19. EASL-EASD-EASO. Clinical practice guidelines for the management of non-alcoholic fatty liver disease. Obes. Facts, 2016. **9**(2): 65–90, https://doi.org/10.1159/000443344
20. Z. Liu et al. Metabolic dysfunction-associated fatty liver disease and the risk of 24 specific cancers. Metabolism **127**, 154955 (2022). https://doi.org/10.1016/j.metabol.2021.154955
21. G. Howell et al. Both BRAF V600E mutation and older age (≥65 years) are associated with recurrent papillary thyroid cancer. Ann. Surg Oncol. **18**(13), 3566–3571 (2011). https://doi.org/10.1245/s10434-011-1781-5
22. G.M. Howell et al. Both BRAF V600E mutation and older age (≥65 years) are associated with recurrent papillary thyroid cancer. Ann. Surg. Oncol. **18**(13), 3566–3571 (2011). https://doi.org/10.1245/s10434-011-1781-5
23. F. Yang et al. Survival in papillary thyroid microcarcinoma: a comparative analysis between the 7th and 8th versions of the AJCC/UICC staging system based on the SEER database. Front. Endocrinol. **10**, 10 (2019). https://doi.org/10.3389/fendo.2019.00010
24. W.X. Jin et al. Prediction of central lymph node metastasis in papillary thyroid microcarcinoma according to clinicopathologic factors and thyroid nodule sonographic features: a case-control study. Cancer Manag. Res. **10**, 3237–3243 (2018). https://doi.org/10.2147/cmar.s169741
25. N. Arora et al. Papillary thyroid carcinoma and microcarcinoma: is there a need to distinguish the two? Thyroid **19**(5), 473–477 (2009). https://doi.org/10.1089/thy.2008.0185
26. C. Liu et al. Reevaluating the prognostic significance of male gender for papillary thyroid carcinoma and microcarcinoma: a SEER database analysis. Sci. Rep. **7**(1), 11412 (2017). https://doi.org/10.1038/s41598-017-11788-8
27. J. Ding et al. Male sex is associated with aggressive behaviour and poor prognosis in Chinese papillary thyroid carcinoma. Sci. Rep. **10**(1), 4141 (2020). https://doi.org/10.1038/s41598-020-60199-9
28. F.M. Hanege et al. Hashimoto's thyroiditis in papillary thyroid carcinoma: a 22-year study. Acta Otorhinolaryngol. Ital. **41**(2), 142–145 (2021). https://doi.org/10.14639/0392-100x-n1081
29. S. Dong et al. Indicators of multifocality in papillary thyroid carcinoma concurrent with Hashimoto's thyroiditis. Am. J. Cancer Res. **9**(8), 1786–1795 (2019)
30. S.L. Friedman et al. Mechanisms of NAFLD development and therapeutic strategies. Nat. Med. **24**(7), 908–922 (2018). https://doi.org/10.1038/s41591-018-0104-9
31. A. Ciampolillo, C. De Tullio, F. Giorgino, The IGF-I/IGF-I receptor pathway: implications in the pathophysiology of thyroid cancer. Curr. Med. Chem. **12**(24), 2881–2891 (2005). https://doi.org/10.2174/092986705774454715
32. A.K. Karagiannis et al. IGF-IEc expression is associated with advanced differentiated thyroid cancer. Anticancer Res. **39**(6), 2811–2819 (2019). https://doi.org/10.21873/anticanres.13409
33. S. Hursting et al. Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link. Best. Pract. Res. Clin. Endocrinol. Metab. **22**(4), 659–669 (2008). https://doi.org/10.1016/j.beem.2008.08.009
34. R. Malaguarnera et al. Insulin resistance: any role in the changing epidemiology of thyroid cancer? Front. Endocrinol. **8**, 314 (2017). https://doi.org/10.3389/fendo.2017.00314
35. Q. Zhang et al. Leptin induces NAFLD progression through infiltrated CD8+ T lymphocytes mediating pyroptotic-like cell death of hepatocytes and macrophages. Dig. Liver Dis. **53**(5), 598–605 (2021). https://doi.org/10.1016/j.dld.2020.10.025
36. V. Catalán et al. Adipose tissue immunity and cancer. Front. Physiol. **4**, 275 (2013). https://doi.org/10.3389/fphys.2013.00275
37. M. Akinci et al. Leptin levels in thyroid cancer. Asian J. Surg. **32**(4), 216–223 (2009). https://doi.org/10.1016/s1015-9584(09)60397-3
38. S. Cheng et al. Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. Surgery **147**(6), 847–853 (2010). https://doi.org/10.1016/j.surg.2009.11.004
39. J.M. Hui et al. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? Hepatology **40**(1), 46–54 (2004). https://doi.org/10.1002/hep.20280
40. N. Mitsiades et al. Circulating adiponectin is inversely associated with risk of thyroid cancer: in vivo and in vitro studies. J. Clin. Endocrinol. Metab. **96**(12), E2023–E2028 (2011). https://doi.org/10.1210/jc.2010-1908
41. K. Tahara et al. Thyroid-stimulating hormone is an independent risk factor of non-alcoholic fatty liver disease. JGH Open **4**(3), 400–404 (2020). https://doi.org/10.1002/jgh3.12264

42. M. Marcello et al. Obesity and thyroid cancer. Endocr.-Relat. Cancer **21**(5), T255–T271 (2014). https://doi.org/10.1530/erc-14-0070
43. M. Machado, H. Cortez-Pinto, Non-invasive diagnosis of non-alcoholic fatty liver disease. a critical appraisal. J. Hepatol. **58**(5), 1007–1019 (2013). https://doi.org/10.1016/j.jhep.2012.11.021
44. D.H. Lee, Imaging evaluation of non-alcoholic fatty liver disease: focused on quantification. Clin. Mol. Hepatol. **23**(4), 290–301 (2017). https://doi.org/10.3350/cmh.2017.0042