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Analysis of the Influence of hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

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4 Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine
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6 Therapy among Patients with Differentiated Thyroid Cancer

7 Yanhui Ji¹, Zhaowei Meng¹, Wei Zheng¹, Cailan Wu², Jian Tan¹, Renfei Wang^{1*}

9
10 1 Department of Nuclear Medicine, Tianjin Medical University General Hospital,
11
12 Tianjin, 300052, China.

13
14 2 Tianjin Fourth Central Hospital, Tianjin, 300140, China.

15
16 Correspondence: Renfei Wang, Email: Roslyn_en@163.com.

17
18 **Abstract**

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20 **Purpose** The present study aimed to investigate the risk factors for hepatic
21
22 dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid
23
24 cancer (DTC). **Methods** We recruited 996 patients (314 males, 682 females; age,
25
26 45.07±12.98 years) who were postoperative of DTC. and divided them into two
27
28 groups: one with hepatic dysfunction and one without. We compared changes in
29
30 baseline data and traced liver function levels and other metabolic profiles between the
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32 groups. **Result** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate
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34 aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most
35
36 common abnormality (the prevalence rate was 47.5%). The percentages of mild and
37
38 moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate
39
40 analyses demonstrated that the most prominent risk factors for hepatic dysfunction
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42 (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine
43
44 discontinuation and free triiodothyronine (FT₃)< 2.01 pmol/L, free thyroxine
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46 (FT₄)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total
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48 cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21
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50 days of THW . Multivariate analyses demonstrated that for males, FT₄<3.80 pmol/L
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52 and TG≥1.28 mmol/L were the most prominent risk factors. Patients with moderate
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54 hepatic dysfunction should be treated with hepatoprotective drugs. **Conclusions**
55
56 Patients with minor hepatic dysfunction and ortholiposis are more likely to recover
57
58 normal liver function. For males, FT₄ and TG levels tended to be associated with
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60 hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to
the level of TG.

Strengths and limitations of this study:

Strengths: 1. in this study, we found that hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, $FT_3 < 2.01$ pmol/L, $FT_4 < 4.78$ pmol/L, $TSH > 78.195$ μ IU/mL, $TC > 5.17$ mmol/L, and $TG > 1.71$ mmol/L. And lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. 2. The results of this study may help nuclear physicians to make clinical treatment strategies of DTC patients.

Limitations: 1. since this was an uncontrolled retrospective study, the DTC patients involved in our study had hepatic dysfunction induced by hypothyroidism. Patients with liver diseases (such as autoimmune liver disease or viral hepatitis) or biliary tract diseases were excluded. However, corresponding testing was not universally performed to exclude these patients. 2. Additionally, we selected cases with complete data to perform our retrospective analysis. The exclusion of a few patients who were lost to follow-up might result in potential bias. 3. We could not collect LDL cholesterol measurements. For these reasons, further rigorous prospective studies are needed to confirm these preliminary findings.

Keywords: thyroid cancer, ^{131}I , high-dose radioiodine therapy, hepatic dysfunction, risk factors

1. Introduction

Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid remnant tissues and microscopic deposits of differentiated thyroid carcinoma after thyroidectomy [1, 2]. As reported, RAI therapy was able to reduce the number of locoregional recurrences and to increase overall survival [3] [4]. In order to stimulate I^{131} uptake into the normal thyroid remnants and metastatic tissues of thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential [5, 6]. The classic method of preparation for RAI therapy is thyroid hormone withdrawal (THW). It usually results in some physical or psychological side effects associated with hypothyroidism [7], such as general edema, constipation, and depression. Evidence indicates that hypothyroidism may affect liver function or structure directly [8, 9]. Therefore, identification of factors resulting in hepatic dysfunction is crucial. In the present study, we collected clinical data from 996 patients with differentiated thyroid cancer (DTC) to investigate risk factors for patients with hepatic dysfunction using a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data used in this study were analyzed anonymously.

2.2. Patients and Public Involvement

The study included 996 patients (314 males, 682 females; age, 45.07 ± 12.98 years)

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3
4 who had undergone RAI therapy at our department from January 2012 to March 2018.
5
6 The patients underwent complete or partial thyroidectomy performed by various
7
8 surgeons. The patients agreed to receive RAI therapy and were informed about the
9
10 traditional preparation method, THW. We used hepatitis virus markers, abdominal
11
12 ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype
13
14 determination for patients with hepatic dysfunction to exclude other apparent causes
15
16 of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract
17
18 disease, chronic cardiac dysfunction and autoimmune liver disease^[10].

19 **2.3. Data collection and grouping**

20
21 All RAI therapy regimens were conducted by the same nuclear medicine department
22
23 following a standard protocol (2015 American Thyroid Association Management
24
25 Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time
26
27 between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence or absence
28
29 of metastases (X_5), the presence or absence of Hashimoto's thyroiditis (X_6), serum
30
31 free triiodothyronine (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin
32
33 (Tg) (X_{10}), antithyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and
34
35 triglycerides (TG) (X_{13}). Meanwhile, liver function test results including aspartate
36
37 aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP),
38
39 gamma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct bilirubin
40
41 (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with
42
43 the following criteria: ALT , AST or $\text{GGT} < 3$ times the upper limit of normal (ULN),
44
45 $\text{ALP} < 2$ times the ULN and/or TBIL and $\text{DBIL} < 2.5$ times the ULN were defined as
46
47 mild hepatic dysfunction; 3 times the $\text{ULN} < \text{ALT}$ or $\text{AST} < 20$ times the ULN , 3 times
48
49 the $\text{ULN} < \text{GGT} < 10$ times the ULN , 2 times the $\text{ULN} < \text{ALP} < 5$ times the ULN and/or
50
51 2.5 times the $\text{ULN} < \text{TBIL}$, and $\text{DBIL} < 5$ times the ULN were defined as moderate
52
53 hepatic dysfunction; and ALT or $\text{AST} \geq 20$ times the ULN , $\text{GGT} \geq 10$ times the ULN ,
54
55 $\text{ALP} \geq 5$ times the ULN and/or TBIL and $\text{DBIL} \geq 5$ times the ULN were defined as
56
57 severe hepatic dysfunction^[10].

58 **2.4. Parameter assessments**

59
60 Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA

CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.5. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate liver function.

2.6. Statistical analysis

A chi square test was used to analyze differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variables with $p < 0.05$, and values < 0.05 were considered statistically significant. The odds ratio (OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for abnormal liver function indices. The most common abnormality was elevated ALT and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate, and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0% (0/315), respectively.

3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established two screen for relevant factors of hepatic dysfunction, and single-factor analysis and binary multivariate logistic regression analysis were performed. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). The results showed that for male patients, the THW time, $\text{FT}_3 < 2.01 \text{ pmol/L}$,

FT₄<4.78 pmol/L, TSH >78.195 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all P<0.01).

Furthermore, we used multivariate logistic regression analysis to screen for relevant factors. In our study, we suggested the following assignments for independent variables: X₁=1 for age≤45 years and X₁=2 for age >45 years; X₂=1 for male sex and X₂=2 for female sex; X₃=1 if the time between total thyroidectomy and ¹³¹I therapy was less than 3 months and X₃=2 if the time between total thyroidectomy and ¹³¹I therapy was more than 3 months; X₄=1, 2, and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; X₅=1 for the presence of metastases and X₅=2 for the absence of metastases; X₆=1 for the presence of Hashimoto's thyroiditis and X₆=2 for the absence of Hashimoto's thyroiditis; X₇=1, 2, 3, and 4 for FT₃ levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; X₈=1, 2, 3, and 4 for FT₄ levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; X₉=1, 2, 3, and 4 for TSH levels lower than 57.01 μIU/mL, 57.01-78.20 μIU/mL, 78.20-101.84 μIU/mL, and higher than 101.84 μIU/mL, respectively; X₁₀=1, 2, 3, and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; X₁₁=1 for TgAb levels lower than 40 IU/mL and X₁₁=2 for TgAb levels higher than 40 IU/mL; X₁₂=1, 2, 3, and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher than 6.27 mmol/L, respectively; and X₁₃=1, 2, 3, and 4 for TG levels lower than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L, respectively. Resultant variable: Y=1 for patients with hepatic dysfunction, and Y=0 for patients without hepatic dysfunction. Forward stepwise regression analysis rejecting trends ultimately revealed that male sex, FT₄<3.80 pmol/L and TG≥1.28 mmol/L were independent risk factors predicting hepatic dysfunction in patients with DTC (Table 2).

3.3. Outcomes of hepatic dysfunction after ¹³¹I therapy

The outcomes of hepatic dysfunction of varying degrees after ¹³¹I therapy are

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2
3
4 displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was
5 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252)
6
7 of patients with mild hepatic dysfunction 1 month after ^{131}I therapy. Moreover, the
8
9 remission rate among patients with moderate and severe hepatic dysfunction was
10
11 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was
12
13 higher than that of moderate dysfunction ($P < 0.001$).
14

15 Remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4.
16
17 The liver function tests of 252 patients with mild hepatic dysfunction were evaluated
18
19 at 1 month after ^{131}I therapy, the results of which returned to normal in 94.34% (50/53)
20
21 of patients who were given hepatoprotective treatment (the treated group). Moreover,
22
23 we found that the remission rate among patients in the untreated group was 88.94%
24
25 (177/199). No remarkable difference in the remission rate was observed between the
26
27 two groups ($P = 0.184$).

28
29 63 patients with moderate hepatic dysfunction were treated with hepatoprotective
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31 therapy, and the remission rates among patients at 1 month, 2 months, and 3 months
32
33 after ^{131}I therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively.
34
35 The time until liver function returned to normal in patients with moderate hepatic
36
37 dysfunction was 1.8 months.

36 37 **3.4. The correlation between serum TG and the remission rate of hepatic 38 39 dysfunction in patients with DTC**

40 A total of 559 patients had elevated serum TG before ^{131}I therapy, including 189
41
42 patients with hepatic dysfunction. All patients were divided into 2 subgroups based on
43
44 their serum TG levels 1 month after ^{131}I therapy, subgroup 1: subjects with a normal
45
46 TG level (141 patients), and subgroup 2: subjects with elevated TG (48 patients).
47
48 Liver function tests results returned to normal in 92.90% (131/141) of the patients in
49
50 subgroup 1. Moreover, the remission rate of the patients in subgroup 2 was 75%
51
52 (36/48) ($\chi^2 = 5.382$, $P = 0.02$).

48 49 **4. Discussion**

50
51 • A complex relationship between the thyroid gland and the liver exists in both
52
53 healthy and disease states[11]. Malik' s research showed that thyroid dysfunction
54
55 may affect liver function, [8]. A relationship has been suggested to exist between
56
57 nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction[12]. Several
58
59 studies conducted in some countries worldwide showed the relationship between
60
61 levels of thyroid hormones and the incidence of NAFLD was inverse [13]. In clinical
62
63 practice, we have found that hepatic dysfunction in DTC patients is common, and
64
65 most of these patients have no obvious symptoms. The mechanism may be related to
66
67 the following factors[11, 14]: (1) hypothyroidism may have features similar to those

of liver disease (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of elevated aspartate aminotransferase from myopathy, coma; (2) hypothyroidism may interact liver structure or function directly; in experimental hypothyroidism, with the decrease of the activity of bilirubin UDP-glucuronyltransferase, bilirubin excretion is reduced; (3) hypothyroidism is related to cholestatic jaundice due to decreased bilirubin and bile excretion^[15]; and (4) severe hypothyroidism is known to cause increased permeability of the vascular endothelium^[16].

Our study demonstrated that 31.6% of DTC patients suffered from different degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury. Additionally, an increase in ALT or AST was the most common abnormal indicator, and the prevalence was 47.5%. The findings are different from previous research data from Gokmen's group whose research showed that hypertriglyceridemia and a higher FT₃/FT₄ ratio are independent risk factors for NAFLD, however, hypothyroidism is not related to the condition directly [17]. However, their research subjects were patients with hypothyroidism, where hypothyroidism was defined only by a TSH level ≥ 4.1 mIU/L, and FT₃ and FT₄ levels were not included. The FT₃ and FT₄ levels of some patients were normal.

To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed 13 related factors, such as age and sex, and found that male sex, a THW time greater than 21 days, FT₃<2.01 pmol/L, FT₄<4.78 pmol/L, TSH>78.195 μ IU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L were risk factors for hepatic dysfunction in the univariate analysis (all P<0.01). Additionally, we found that male sex, FT₄<3.80 pmol/L and TG \geq 1.28 mmol/L were more closely associated with hepatic dysfunction in DTC patients in the multivariate logistic regression analysis (P<0.01). No studies related to our study on the risk factors of hepatic dysfunction for DTC patients were found.

In this study, we found that the remission rate of patients with mild hepatic dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ¹³¹I therapy. Additionally, the remission rate among patients with mild hepatic dysfunction was not significantly different between the treated group and the untreated group. We also found that the FT₄ level is associated with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ¹³¹I therapy was not significantly different between the treated group and the untreated group. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with thyroxine replacement [18, 19].

Additionally, liver is the vital organ for cholesterol metabolism, thyroid hormones play an important role in hepatic lipid metabolism^[8, 13]. Thyroid hormones increase the activity of lipid-lowering liver enzymes which can lead to a reduction in low-density lipoprotein levels [20]. Serum lipids also play an important role in liver function^[19], which coincided with the results of our study. In our study,

1
2
3 hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of
4 the patients, the remission rate in patients with normal TG levels was significantly
5 higher than that in the elevated TG group, and the time until liver dysfunction
6 returned to normal in the patients suffering from hyperlipidemia and hepatic
7 dysfunction was longer than that in the patients suffering from only hyperlipidemia.
8 In other words, lipid-lowering therapy was very important for patients with hepatic
9 dysfunction.

12 **Conclusions**

13
14 Hepatic dysfunction is more likely to occur in male patients and patients with a
15 THW time greater than 21 days, $\text{FT}_3 < 2.01$ pmol/L, $\text{FT}_4 < 4.78$ pmol/L, $\text{TSH} > 78.195$
16 $\mu\text{IU/mL}$, $\text{TC} > 5.17$ mmol/L, and $\text{TG} > 1.71$ mmol/L. Additionally, lipid-lowering
17 therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I
18 therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia,
19 lipid-lowering therapy is recommended, which is expected to shorten the remission
20 time of hepatic dysfunction.

21
22
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26 Yanhui Ji and Renfei Wang; Critical revision of the manuscript: Jian Tan and RenFei
27 Wang. Thanks for the patient advisers.

28
29
30 **Contribution to the Field Statement:** An elevated TSH level is essential to stimulate
31 ^{131}I uptake when patient with DTC undergoes RAI therapy. A number of patients
32 suffer from general edema, constipation and so on, before RAI therapy with THW.
33 Evidence reveals that hypothyroidism may have a direct effect on liver structure or
34 function. We retrospectively collected clinical data from 996 patients with DTC to
35 investigate risk factors of hepatic dysfunction in these patients. Patients with mild
36 hepatic dysfunction and ortholiposis were found to have a higher likelihood of
37 recovering normal liver function. For males, FT_4 and TG levels were more closely
38 related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely
39 associated with the level of TG.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ¹³¹ I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT ₃	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT ₄	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0. 828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		

TgAb	≤40 ^A	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17 ^A	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71 ^A	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

CI=confidence interval, OR=odds ratio, *median, ^AUpper limit of the normal value

Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X ₂	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X ₈ (FT ₄)			62.291	3	0.000		
X ₈ (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X ₈ (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X ₈ (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X ₁₃			15.195	3	0.002		
X ₁₃ (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X ₁₃ (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X ₁₃ (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ¹³¹I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2			14.873
<i>p</i>			0.000

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ¹³¹I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)

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No treatment	199	177 (88.94%)	22 (11.06%)
χ^2			1.765
p			0.184

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Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

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Title page:

Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer

Running title: The Influence of hypothyroidism on the Liver Function in Patients with Differentiated Thyroid Cancer

Yan-hui Ji¹, Wei Zheng¹, Zhaowei Meng¹, Cailan Wu², Jian Tan¹, Ren-fei Wang^{1*}

Department of Nuclear Medicine, Tianjin Medical University General Hospital

*Corresponding Author: Ren-fei Wang, PHD, Department of Nuclear Medicine, Tianjin Medical University General Hospital, Anshan Road 154, Heping district, Tianjin, 300052, P.R. China, E-mail: Roslyn_en@163.com

Yan-hui Ji, Zhaowei Meng, Wei Zheng, Jian Tan, Ren-fei Wang: Department of Nuclear Medicine, Tianjin Medical University General Hospital, Tianjin, China.

Cailan Wu: Department of Nuclear Medicine, Tianjin Fouth Hospital, Tianjin, China.

Key words: thyroid cancer, ¹³¹I, radioiodine therapy, hepatic dysfunction, risk factors.

Conts:4364

Analysis of the Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy among Patients with Differentiated Thyroid Cancer **Abstract**

Purpose The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC). **Methods** We recruited 996 patients (314 males, 682 females; age, 45.07±12.98 years) who were postoperative of DTC, and divided them into two groups: one with hepatic dysfunction and one without. We compared changes in baseline data and traced liver function levels and other metabolic profiles between the groups. **Result** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most common abnormality (the prevalence rate was 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine discontinuation and free triiodothyronine (FT₃)< 2.01 pmol/L, free thyroxine (FT₄)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total cholesterol (TC)>5.17 mmol/L, triglycerides (TG)>1.71 mmol/L and more than 21 days of thyroid hormone withdrawal (THW). Multivariate analyses demonstrated that

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4 for males, $FT_4 < 3.80$ pmol/L and $TG \geq 1.28$ mmol/L were the most prominent risk
5 factors. **Conclusions** Patients with minor hepatic dysfunction and ortholiposis are
6 more likely to recover normal liver function. Patients with moderate hepatic
7 dysfunction should be treated with hepatoprotective drugs. For males, FT_4 and TG
8 levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic
9 dysfunction was closely related to the level of TG.

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15 Strengths and limitations of this study:

16 Strengths: 1. in this study, we found that hepatic dysfunction is more likely to occur
17 in male patients and patients with a THW time greater than 21 days, $FT_3 < 2.01$ pmol/L,
18 $FT_4 < 4.78$ pmol/L, $TSH > 78.195$ μ IU/mL, $TC > 5.17$ mmol/L, and $TG > 1.71$ mmol/L.
19 And lipid-lowering therapy is particularly important for DTC patients with hepatic
20 dysfunction before ^{131}I therapy. 2. The results of this study may help nuclear
21 physicians to make clinical treatment strategies of DTC patients.

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24 Limitations: 1. Since this was an uncontrolled retrospective study, the DTC patients
25 involved in our study had hepatic dysfunction induced by hypothyroidism. Patients
26 with liver diseases (such as autoimmune liver disease or viral hepatitis) or biliary tract
27 diseases were excluded. However, corresponding testing was not universally
28 performed to exclude these patients. 2. Additionally, we selected cases with complete
29 data to perform our retrospective analysis. The exclusion of a few patients who were
30 lost to follow-up might result in potential bias. 3. We could not collect LDL
31 cholesterol measurements. Obesity is a very important metabolic risk factor that
32 contributes to liver and thyroid dysfunction. It would be very helpful if we analysis of
33 the influence of overweight and/or obese on hypothyroidism and Liver Function. For
34 these reasons, further rigorous prospective studies are needed to confirm these
35 preliminary findings.

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41 **Keywords:** thyroid cancer, ^{131}I , high-dose radioiodine therapy, hepatic dysfunction,
42 risk factors

43 1. Introduction

44 Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid
45 remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC)
46 after thyroidectomy [1, 2]. As reported, RAI therapy was able to reduce the number of
47 locoregional recurrences and to increase overall survival of the American Thyroid
48 Association (ATA) intermediate-risk and high risk DTC patients [3] [4]. In order to
49 stimulate I^{131} uptake into the normal thyroid remnants and metastatic tissues of
50 thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated
51 thyroid-stimulating hormone (thyrotropin, TSH) level is essential [5, 6]. The classic
52 method of preparation for RAI therapy is thyroid hormone withdrawal (THW). It
53 usually results in some physical or psychological side effects associated with
54 hypothyroidism [7], such as general edema, constipation, and depression. Evidence
55 indicates that hypothyroidism may affect liver function or structure directly [8, 9].
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Therefore, identification of factors resulting in hepatic dysfunction is crucial. In the present study, we collected clinical data from 996 patients with DTC to investigate risk factors for patients with hepatic dysfunction using a retrospective approach.

2. Materials and methods

2.1. Ethics statement

This study is a retrospective clinical study summarizing and analyzing a large amount of clinical data. The ethics committee of Tianjin Medical University General Hospital waived the need to obtain written informed consent from all patients. All clinical data used in this study were analyzed anonymously.

2.2. Patients and Public Involvement

The study included 996 patients (314 males, 682 females; age, 45.07±12.98 years) who had undergone RAI therapy at our department from January 2012 to March 2018. The patients underwent complete or partial thyroidectomy performed by various surgeons. The patients agreed to receive RAI therapy and were informed about the traditional preparation method, THW. We used hepatitis virus markers, abdominal ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype determination for patients with hepatic dysfunction to exclude other apparent causes of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease, liver steatosis, hyperlipidemia, etc^[10].

2.3. Data collection and grouping

All RAI therapy regimens were conducted by the same nuclear medicine department following a standard protocol (2015 American Thyroid Association Management Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time between surgery and ¹³¹I therapy (X_3), the time of THW (X_4), the presence or absence of metastases (lymph node metastasis or lung metastases), (X_5), the presence or absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT₃) (X_7), free thyroxine (FT₄) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antithyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerides (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct bilirubin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: the upper limit of normal (ULN) <ALT, AST or GGT<3 times ULN, the ULN<ALP<2 times the ULN and/or TBIL and the ULN<DBIL<2.5 times the ULN were defined as

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3 mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times
4 the ULN< GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or
5 2.5 times the ULN <TBIL, and DBIL<5 time the ULN were defined as moderate
6 hepatic dysfunction; and ALT or AST \geq 20 times the ULN, GGT \geq 10 times the ULN,
7 ALP \geq 5 times the ULN and/or TBIL and DBIL \geq 5 times the ULN were defined as
8 severe hepatic dysfunction^[10].
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10 11 **2.4. Parameter assessments**

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13 Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA
14 CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system
15 (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry
16 (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer
17 enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The
18 dosage range of ¹³¹I therapy was 3.7-7.4 GBq.
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25 **2.5. Patient follow-up**

26 We measured the serum levels of thyroid parameters, serum lipids, and liver function
27 indices of the 996 patients at 1, 2, 3, and 4 months after ¹³¹I therapy to evaluate liver
28 function.
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30 **2.6. Statistical analysis**

31 A chi square test was used to analyze differences between ratios. To identify risk
32 factors for hepatic dysfunction, we used a bivariate logistic regression model
33 (univariate analysis) and stepwise logistic regression (multivariate analysis) with a
34 variables with $p < 0.05$, and values < 0.05 were considered statistically significant. The
35 odds ratio(OR) was used to evaluate the risk factor. Statistical analysis was performed
36 using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS,
37 Chicago, IL).
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46 **3. Results**

47 **3.1. Clinical features of hepatic dysfunction**

48 Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most
49 patients with hepatic dysfunction had no obvious clinical symptoms except for
50 abnormal liver function indices. The most common abnormality was elevated ALT
51 and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate,
52 and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0%
53 (0/315), respectively.
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3.2. Risk factors for hepatic dysfunction in DTC patients

In this paper, a binary logistic regression model was established for relevant factors of hepatic dysfunction, and single-factor analysis and binary multivariate logistic regression analysis were performed. Patient characteristics were compared using bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the metastase group, the number of patients with hepatic dysfunction and lymph node metastasis or lung metastases were 508 and 21 respectively; and the number of patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12 (with lung metastases) respectively. The results showed that for male patients, the THW time, $FT_3 < 2.01$ pmol/L, $FT_4 < 4.78$ pmol/L, $TSH > 78.195$ μ IU/mL, $TC > 5.17$ mmol/L, and $TG > 1.71$ mmol/L were closely associated with hepatic dysfunction (odds ratio [OR]: 0.324-3.171, all $P < 0.01$).

Furthermore, we used multivariate logistic regression analysis to screen for relevant factors. In our study, we suggested the following assignments for independent variables: $X_1=1$ for age ≤ 45 years and $X_1=2$ for age > 45 years; $X_2=1$ for male sex and $X_2=2$ for female sex; $X_3=1$ if the time between total thyroidectomy and ^{131}I therapy was less than 3 months and $X_3=2$ if the time between total thyroidectomy and ^{131}I therapy was more than 3 months; $X_4=1, 2,$ and 3 if the THW time was shorter than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; $X_5=1$ for the presence of metastases and $X_5=2$ for the absence of metastases; $X_6=1$ for the presence of Hashimoto's thyroiditis and $X_6=2$ for the absence of Hashimoto's thyroiditis; $X_7=1, 2,$ $3,$ and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L, and higher than 2.37 pmol/L, respectively; $X_8=1, 2, 3,$ and 4 for FT_4 levels lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L, respectively; $X_9=1, 2, 3,$ and 4 for TSH levels lower than 57.01 μ IU/mL, 57.01-78.20 μ IU/mL, 78.20-101.84 μ IU/mL, and higher than 101.84 μ IU/mL, respectively; $X_{10}=1, 2, 3,$ and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; $X_{11}=1$ for TgAb levels lower than 40 IU/mL and $X_{11}=2$ for TgAb levels higher than 40 IU/mL; $X_{12}=1, 2, 3,$ and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher

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4 than 6.27 mmol/L, respectively; and $X_{13}=1, 2, 3,$ and 4 for TG levels lower than 1.28
5 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L,
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7 respectively. Resultant variable: $Y=1$ for patients with hepatic dysfunction, and $Y=0$
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9 for patients without hepatic dysfunction. Forward stepwise regression analysis
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11 rejecting trends ultimately revealed that male sex, $FT_4 < 3.80$ pmol/L and $TG \geq 1.28$
12 mmol/L were independent risk factors predicting hepatic dysfunction in patients with
13
14 DTC (Table 2).
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17 **3.3. Outcomes of hepatic dysfunction after ^{131}I therapy**

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19 The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are
20 displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was
21 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252)
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23 of patients with mild hepatic dysfunction 1 month after ^{131}I therapy. Moreover, the
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25 remission rate among patients with moderate and severe hepatic dysfunction was
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27 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was
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29 higher than that of moderate dysfunction ($P < 0.001$).
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33 Remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in Table 4.
34 The liver function tests of 252 patients with mild hepatic dysfunction were evaluated
35 at 1 month after ^{131}I therapy, the results of which returned to normal in 94.34% (50/53)
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37 of patients who were given hepatoprotective treatment [oral bicyclol tablets, Bicyclol
38 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China, at a total daily
39 dose of 75mg (25mg three times daily), the treated group]. Moreover, we found that
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41 the remission rate among patients in the untreated group was 88.94% (177/199). No
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43 remarkable difference in the remission rate was observed between the two groups
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45 ($P=0.184$).
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48 63 patients with moderate hepatic dysfunction were treated with hepatoprotective
49 therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg three times daily)],
50 and the remission rates among patients at 1 month, 2 months, and 3 months after ^{131}I
51 therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively. The time
52 until liver function returned to normal in patients with moderate hepatic dysfunction
53 was 1.8 months.
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58 **3.4. The correlation between serum TG and the remission rate of hepatic** 59 **dysfunction in patients with DTC** 60

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3 A total of 559 patients had elevated serum TG before ^{131}I therapy, including 189
4 patients with hepatic dysfunction (76 males, 113 females). All patients were divided
5 into 2 subgroups based on their serum TG levels 1 month after ^{131}I therapy, subgroup
6 1: subjects with a normal TG level (141 patients), and subgroup 2: subjects with
7 elevated TG (48 patients). Liver function tests results returned to normal in 92.90%
8 (131/141) of the patients in subgroup 1. Moreover, the remission rate of the patients in
9 subgroup 2 was 75% (36/48) ($\chi^2=5.382$, $P=0.02$). **4. Discussion**

12 A complex relationship between the thyroid gland and the liver exists in both
13 healthy and disease states [11]. Maliks research showed that thyroid dysfunction may
14 affect liver function, [8]. A relationship has been suggested to exist between
15 nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction [12]. Several
16 studies conducted in some countries worldwide showed the relationship between
17 levels of thyroid hormones and the incidence of NAFLD was inverse [13]. In clinical
18 practice, we have found that hepatic dysfunction in DTC patients is common, and
19 most of these patients have no obvious symptoms. The mechanism may be related to
20 the following factors [11, 14]: (1) hypothyroidism may have features similar to those
21 of liver disease (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in
22 the presence of elevated aspartate aminotransferase from myopathy, coma; (2)
23 hypothyroidism may interact liver structure or function directly; in experimental
24 hypothyroidism, with the decrease of the activity of bilirubin
25 UDP-glucuronyltransferase, bilirubin excretion is reduced; (3) hypothyroidism is
26 related to cholestatic jaundice due to decreased bilirubin and bile excretion [15]; and (4)
27 severe hypothyroidism is known to cause increased permeability of the vascular
28 endothelium [16].

31 Our study demonstrated that 31.6% of DTC patients suffered from different
32 degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury.
33 Additionally, an increase in ALT or AST was the most common abnormal indicator,
34 and the prevalence was 47.5%. The findings are different from previous research data
35 from Gokmen's group whose research showed that hypertriglyceridemia and a higher
36 FT_3/FT_4 ratio are independent risk factors for NAFLD, however, hypothyroidism is
37 not related to the condition directly [17]. However, their research subjects were
38 patients with hypothyroidism, where hypothyroidism was defined only by a TSH level
39 ≥ 4.1 mIU/L, and FT_3 and FT_4 levels were not included. The FT_3 and FT_4 levels of
40 some patients were normal.

41 To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed
42 13 related factors, such as age and sex, and found that male sex, a THW time greater
43 than 21 days, $\text{FT}_3 < 2.01$ pmol/L, $\text{FT}_4 < 4.78$ pmol/L, $\text{TSH} > 78.195$ $\mu\text{IU/mL}$, $\text{TC} > 5.17$
44 mmol/L, and $\text{TG} > 1.71$ mmol/L were risk factors for hepatic dysfunction in the
45 univariate analysis (all $P < 0.01$). Additionally, we found that male sex, $\text{FT}_4 < 3.80$
46 pmol/L and $\text{TG} \geq 1.28$ mmol/L were more closely associated with hepatic dysfunction
47 in DTC patients in the multivariate logistic regression analysis ($P < 0.01$). No studies
48 related to our study on the risk factors of hepatic dysfunction for DTC patients were
49 found.

50 In this study, we found that the remission rate of patients with mild hepatic
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dysfunction was significantly higher than that of patients with moderate hepatic dysfunction at 1 month after ^{131}I therapy. Additionally, the remission rate among patients with mild hepatic dysfunction was not significantly different between the treated group and the untreated group. We also found that the FT_4 level is associated with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater impact on liver function. Patients with mild hepatic dysfunction may not be treated with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1 month after ^{131}I therapy was not significantly different between the treated group and the untreated group. Recent studies revealed that with no liver damage, hepatic dysfunction associated with hypothyroidism can be reversed over several weeks with thyroxine replacement [18, 19].

Additionally, liver is the vital organ for cholesterol metabolism, thyroid hormones play an important role in hepatic lipid metabolism[8, 13]. Thyroid hormones increase the activity of lipid-lowering liver enzymes which can lead to a reduction in low-density lipoprotein levels [20]. Serum lipids also play an important role in liver function[19], which coincided with the results of our study. In our study, hepatic function indices returned to normal at 1 month after ^{131}I therapy in 86.34% of the patients, the remission rate in patients with normal TG levels was significantly higher than that in the elevated TG group, and the time until liver dysfunction returned to normal in the patients suffering from hyperlipidemia and hepatic dysfunction was longer than that in the patients suffering from only hyperlipidemia. In other words, lipid-lowering therapy was very important for patients with hepatic dysfunction.

Conclusions

Hepatic dysfunction is more likely to occur in male patients and patients with a THW time greater than 21 days, $\text{FT}_3 < 2.01$ pmol/L, $\text{FT}_4 < 4.78$ pmol/L, $\text{TSH} > 78.195$ $\mu\text{IU/mL}$, $\text{TC} > 5.17$ mmol/L, and $\text{TG} > 1.71$ mmol/L. Additionally, lipid-lowering therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia, lipid-lowering therapy is recommended, which is expected to shorten the remission time of hepatic dysfunction.

Contribution to the Field Statement: An elevated TSH level is essential to stimulate ^{131}I uptake when patient with DTC undergoes RAI therapy. A number of patients suffer from general edema, constipation and so on, before RAI therapy with THW. Evidence reveals that hypothyroidism may have a direct effect on liver structure or function. We retrospectively collected clinical data from 996 patients with DTC to investigate risk factors of hepatic dysfunction in these patients. Patients with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood of recovering normal liver function. For males, FT_4 and TG levels were more closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely associated with the level of TG.

Contributorship Statement: Yanhui Ji and Renfei Wang contributed to the conception and design of the study. Yanhui Ji, Wei Zheng, Jian Tan, and Cailan Wu

assisted with data acquisition. Yanhui Ji , Zhaowei Meng, and Renfei Wang conducted the statistical analyses and drafted the manuscript. Jian Tan, Zhaowei Meng critically revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing interests

There are no competing interests for any author

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Data sharing statement

The datasets used during the present study are available from the corresponding author upon reasonable request.

Ethical Approval statement

The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin Medical University General Hospital (NO. IRB2020-WZ-001). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

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Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors	With hepatic	Without hepatic	B value	OR	95%CI	P
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		dysfunction (n[%])	dysfunction (n[%])		value		
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ¹³¹ I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT ₃	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT ₄	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0.828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40 ^Δ	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17 ^Δ	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71 ^Δ	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

CI=confidence interval, OR=odds ratio, *median; ^ΔUpper limit of the normal value

Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X ₂	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534

X ₈ (FT ₄)			62.291	3	0.000		
X ₈ (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X ₈ (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X ₈ (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X ₁₃			15.195	3	0.002		
X ₁₃ (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X ₁₃ (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X ₁₃ (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ¹³¹I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2			14.873
<i>p</i>			0.000

Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ¹³¹I therapy

Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2			1.765
<i>p</i>			0.184

BMJ Open

A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

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1 **Title page:**

2 A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before
3 Radioiodine Therapy in China: A Comparison Analysis based on Patients with
4 Differentiated Thyroid Cancer

5 Running title: The Influence of hypothyroidism on the Liver Function in Patients with
6 Differentiated Thyroid Cancer

7 Yan-hui Ji¹, Wei Zheng¹, Zhaowei Meng¹, cailan wu², Jian Tan¹, Ren-fei Wang^{1*}

8 Department of Nuclear Medicine, Tianjin Medical University General Hospital

9 *Corresponding Author: Ren-fei Wang, PHD, Department of Nuclear Medicine,

10 Tianjin Medical University General Hospital, Anshan Road 154, Heping district,

11 Tianjin,300052, P.R. China, E-mail:Roslyn_en@163.com

12 Yan-hui Ji, Zhaowei Meng, Wei Zheng, Jian Tan, Ren-fei Wang: Department of Nuclear

13 Medicine, Tianjin Medical University General Hospital, Tianjin,China.

14 Cailan Wu: Department of Nuclear Medicine, Tianjin Fouth Hospital, Tianjin,China.

15 Key words: Endocrine tumours ; Head & neck surgery ; Nuclear Medicine; Thyroid
16 disease

17 Word count:3070

18 **Abstract**

19 **Purpose** The present study aimed to investigate the risk factors for hepatic
20 dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid
21 cancer (DTC). **Methods** We recruited 996 patients (314 males, 682 females; age,
22 45.07±12.98 years) who were postoperative of DTC, and divided them into two
23 groups: one with hepatic dysfunction and one without. We compared changes in
24 baseline data and traced liver function levels and other metabolic profiles between the
25 groups. **Result** Overall, 31.6% of patients had hepatic dysfunction. Higher aspartate
26 aminotransferase (AST) and/or alanine aminotransferase (ALT) was the most
27 common abnormality (the prevalence rate was 47.5%). The percentages of mild and
28 moderate hepatic dysfunction were 80.0% and 20.0%, respectively. Univariate
29 analyses demonstrated that the most prominent risk factors for hepatic dysfunction
30 (odds ratio [OR]=0.324-3.171, P<0.01) were male sex with levothyroxine
31 discontinuation and free triiodothyronine (FT₃)< 2.01 pmol/L, free thyroxine
32 (FT₄)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL, total
33 cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than 21
34 days of thyroid hormone withdrawal (THW) . Multivariate analyses demonstrated that
35 for males, FT₄<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk

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4 36 factors. **Conclusions** Patients with minor hepatic dysfunction and ortholiposis are
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6 37 more likely to recover normal liver function. Patients with moderate hepatic
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8 38 dysfunction should be treated with hepatoprotective drugs. For males, FT₄ and TG
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10 39 levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic
11
12 40 dysfunction was closely related to the level of TG.

13 41 Strengths and limitations of this study:

14 42 Strengths: The results of this study may help nuclear physicians to make clinical
15 43 treatment strategies of DTC patients.

16 44 Limitations: performed to exclude these patients.

17 45 1. We selected cases with complete data to perform our retrospective analysis, the
18 46 exclusion of a few patients who were lost to follow-up might result in potential bias.

19 47 2. We could not collect LDL cholesterol measurements.

20 48 3. Obesity is a important metabolic risk factor of liver and thyroid dysfunction, and it
21 49 would be helpful if we analysis of the influence of it in our study

22 50 For these reasons, further rigorous prospective studies are needed to confirm these
23 51 preliminary findings.

24 52 **Keywords:** thyroid cancer, ¹³¹I, high-dose radioiodine therapy, hepatic dysfunction,
25 53 risk factors

26 54 **1. Introduction**

27 55 Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid
28 56 remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC)
29 57 after thyroidectomy¹. As reported, RAI therapy was able to reduce the number of
30 58 locoregional recurrences and to increase overall survival of the American Thyroid
31 59 Association (ATA) intermediate-risk and high risk DTC patients^{2 3}. In order to
32 60 stimulate I¹³¹ uptake into the normal thyroid remnants and metastatic tissues of
33 61 thyroid carcinoma when DTC patient undergoes RAI therapy, an elevated
34 62 thyroid-stimulating hormone (thyrotropin, TSH) level is essential⁴. The classic method
35 63 of preparation for RAI therapy is thyroid hormone withdrawal (THW). It usually
36 64 results in some physical or psychological side effects associated with hypothyroidism⁵,
37 65 such as general edema, constipation, and depression. Evidence indicates that
38 66 hypothyroidism may affect liver function or structure directly⁶. Therefore,
39 67 identification of factors resulting in hepatic dysfunction is crucial. In the present study,
40 68 we collected clinical data from 996 patients with DTC to investigate risk factors for
41 69 patients with hepatic dysfunction using a retrospective approach.

42 70 **2. Materials and methods**

43 71 **2.1. Ethics statement**

44 72 This study is a retrospective clinical study summarizing and analyzing a large amount
45 73 of clinical data. The ethics committee of Tianjin Medical University General Hospital
46 74 waived the need to obtain written informed consent from all patients. All clinical data

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4 75 used in this study were analyzed anonymously.

5 76 **2.2. Participants or Criteria selection**

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7 77 The study included 996 patients (314 males, 682 females; age, 45.07±12.98 years)
8 78 who had undergone RAI therapy at our department from January 2012 to March 2018.

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10 79 The patients underwent complete or partial thyroidectomy performed by various
11 80 surgeons. The patients agreed to receive RAI therapy and were informed about the
12 81 traditional preparation method, THW. We used hepatitis virus markers, abdominal
13 82 ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype
14 83 determination for patients with hepatic dysfunction to exclude other apparent causes
15 84 of liver damage. Other causes included viral hepatitis, liver cirrhosis or biliary tract
16 85 disease, chronic cardiac dysfunction and autoimmune liver disease,
17 86 liver steatosis, hyperlipidemia, etc⁷.

17 87 **2.3. Data collection and grouping**

18 88 All RAI therapy regimens were conducted by the same nuclear medicine department
19 89 following a standard protocol (2015 American Thyroid Association Management
20 90 Guidelines). Data were recorded, including patient age (named X_1), sex (X_2), the time
21 91 between surgery and ¹³¹I therapy (X_3), the time of THW (X_4), the presence or absence
22 92 of metastases (lymph node metastasis or lung metastases), (X_5), the presence of
23 93 absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine (FT₃) (X_7), free
24 94 thyroxine (FT₄) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antithyroglobulin antibody
25 95 (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerides (TG) (X_{13}). Meanwhile,
26 96 liver function test results including aspartate aminotransferase (AST), alanine
27 97 aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase
28 98 (GGT), total-value bilirubin (TBIL), and direct bilirubin (DBIL) were also collected.
29 99 Hepatic dysfunction was diagnosed in accordance with the following criteria: the
30 100 upper limit of normal (ULN) <ALT, AST or GGT<3 times ULN, the ULN<ALP<2
31 101 times the ULN and/or TBIL and the ULN<DBIL<2.5 times the ULN were defined as
32 102 mild hepatic dysfunction; 3 times the ULN <ALT or AST<20 times the ULN, 3 times
33 103 the ULN<GGT<10 times the ULN, 2 times the ULN<ALP<5 times the ULN and/or
34 104 2.5 times the ULN <TBIL, and DBIL<5 times the ULN were defined as moderate
35 105 hepatic dysfunction; and ALT or AST ≥20 times the ULN, GGT ≥10 times the ULN,
36 106 ALP ≥5 times the ULN and/or TBIL and DBIL ≥5 times the ULN were defined as
37 107 severe hepatic dysfunction⁷.

37 108 **2.4. Parameter assessments**

38 109 Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA
39 110 CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system

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4 111 (Immolute 2000 SIEMENS AG). Liver function indices were measured by colorimetry
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6 112 (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer
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8 113 enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The
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10 114 dosage range of ^{131}I therapy was 3.7-7.4 GBq.

11 115 **2.5. Patient follow-up**

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13 116 We measured the serum levels of thyroid parameters, serum lipids, and liver function
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15 117 indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate liver
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17 118 function.

18 119 **2.6. Statistical analysis**

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20 120 A chi square test was used to analyze differences between ratios. To identify risk
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22 121 factors for hepatic dysfunction, we used a bivariate logistic regression model
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24 122 (univariate analysis) and stepwise logistic regression (multivariate analysis) with a
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26 123 variables with $p < 0.05$, and values < 0.05 were considered statistically significant. The
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28 124 odds ratio (OR) was used to evaluate the risk factor. Statistical analysis was performed
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30 125 using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS,
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32 126 Chicago, IL).

33 127 **3. Results**

34 128 **3.1. Clinical features of hepatic dysfunction**

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36 129 Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most
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38 130 patients with hepatic dysfunction had no obvious clinical symptoms except for
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40 131 abnormal liver function indices. The most common abnormality was elevated ALT
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42 132 and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate,
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44 133 and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0%
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46 134 (0/315), respectively.

47 135 **3.2. Risk factors for hepatic dysfunction in DTC patients**

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49 136 In this paper, a binary logistic regression model was established for relevant factors of
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51 137 hepatic dysfunction, and single-factor analysis and binary multivariate logistic
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53 138 regression analysis were performed. Patient characteristics were compared using
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55 139 bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the
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57 140 metastase group, the number of patients with hepatic dysfunction and lymph node
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59 141 metastasis or lung metastases were 508 and 21 respectively; and the number of

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4 142 patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12
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6 143 (with lung metastases) respectively. The results showed that for male patients, the
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8 144 THW time, $FT_3 < 2.01$ pmol/L, $FT_4 < 4.78$ pmol/L, $TSH > 78.195$ μ IU/mL, $TC > 5.17$
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10 145 mmol/L, and $TG > 1.71$ mmol/L were closely associated with hepatic dysfunction
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12 146 (odds ratio [OR]: 0.324-3.171, all $P < 0.01$).

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14 147 Furthermore, we used multivariate logistic regression analysis to screen for relevant
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16 148 factors. In our study, we suggested the following assignments for independent
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18 149 variables: $X_1 = 1$ for age ≤ 45 years and $X_1 = 2$ for age > 45 years; $X_2 = 1$ for male sex and
19
20 150 $X_2 = 2$ for female sex; $X_3 = 1$ if the time between total thyroidectomy and ^{131}I therapy
21
22 151 was less than 3 months and $X_3 = 2$ if the time between total thyroidectomy and ^{131}I
23
24 152 therapy was more than 3 months; $X_4 = 1, 2,$ and 3 if the THW time was shorter than 3
25
26 153 weeks, 3-4 weeks, and longer than 4 weeks, respectively; $X_5 = 1$ for the presence of
27
28 154 metastases and $X_5 = 2$ for the absence of metastases; $X_6 = 1$ for the presence of
29
30 155 Hashimoto's thyroiditis and $X_6 = 2$ for the absence of Hashimoto's thyroiditis; $X_7 = 1, 2,$
31
32 156 $3,$ and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37 pmol/L,
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34 157 and higher than 2.37 pmol/L, respectively; $X_8 = 1, 2, 3,$ and 4 for FT_4 levels lower than
35
36 158 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79 pmol/L,
37
38 159 respectively; $X_9 = 1, 2, 3,$ and 4 for TSH levels lower than 57.01 μ IU/mL, 57.01-78.20
39
40 160 μ IU/mL, 78.20-101.84 μ IU/mL, and higher than 101.84 μ IU/mL, respectively; $X_{10} = 1,$
41
42 161 $2, 3,$ and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL, 2.64-9.18 ng/mL,
43
44 162 and higher than 9.18 ng/mL, respectively; $X_{11} = 1$ for TgAb levels lower than 40
45
46 163 IU/mL and $X_{11} = 2$ for TgAb levels higher than 40 IU/mL; $X_{12} = 1, 2, 3,$ and 4 for TC
47
48 164 levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L, and higher
49
50 165 than 6.27 mmol/L, respectively; and $X_{13} = 1, 2, 3,$ and 4 for TG levels lower than 1.28
51
52 166 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76 mmol/L,
53
54 167 respectively. Resultant variable: $Y = 1$ for patients with hepatic dysfunction, and $Y = 0$
55
56 168 for patients without hepatic dysfunction. Forward stepwise regression analysis
57
58 169 rejecting trends ultimately revealed that male sex, $FT_4 < 3.80$ pmol/L and $TG \geq 1.28$
59
60 170 mmol/L were independent risk factors predicting hepatic dysfunction in patients with
171 171 DTC (Table 2).

172 **3.3. Outcomes of hepatic dysfunction after ¹³¹I therapy**

173 The outcomes of hepatic dysfunction of varying degrees after ¹³¹I therapy are
174 displayed in Table 3. The remission rate of patients at 1 month after ¹³¹I therapy was
175 86.34% (272/315). Liver function test results returned to normal in 90.07% (227/252)
176 of patients with mild hepatic dysfunction 1 month after ¹³¹I therapy. Moreover, the
177 remission rate among patients with moderate and severe hepatic dysfunction was
178 71.43% (45/63). Additionally, the remission rate of mild hepatic dysfunction was
179 higher than that of moderate dysfunction (P<0.001).

180 Remission of hepatic dysfunction at 1 month after ¹³¹I therapy is shown in Table 4.
181 The liver function tests of 252 patients with mild hepatic dysfunction were evaluated
182 at 1 month after ¹³¹I therapy, the results of which returned to normal in 94.34% (50/53)
183 of patients who were given hepatoprotective treatment [oral bicyclol tablets, Bicyclol
184 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China, at a total daily
185 dose of 75mg (25mg three times daily), the treated group]. Moreover, we found that
186 the remission rate among patients in the untreated group was 88.94% (177/199). No
187 remarkable difference in the remission rate was observed between the two groups
188 (P=0.184).

189 63 patients with moderate hepatic dysfunction were treated with hepatoprotective
190 therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg three times daily)],
191 and the remission rates among patients at 1 month, 2 months, and 3 months after ¹³¹I
192 therapy were 55.6% (35/63), 36.5% (23/63), and 7.9% (5/63) respectively. The time
193 until liver function returned to normal in patients with moderate hepatic dysfunction
194 was 1.8 months.

195 **3.4. The correlation between serum TG and the remission rate of hepatic 196 dysfunction in patients with DTC**

197 A total of 559 patients (218 males, 341 females) had elevated serum TG before ¹³¹I
198 therapy, including 189 patients with hepatic dysfunction (76 males, 113 females). All
199 patients were divided into 2 subgroups based on their serum TG levels 1 month after
200 ¹³¹I therapy, subgroup 1: subjects with a normal TG level (141 patients), and subgroup
201 2: subjects with elevated TG (48 patients). Liver function tests results returned to
202 normal in 92.90% (131/141) of the patients in subgroup 1. Moreover, the remission
203 rate of the patients in subgroup 2 was 75% (36/48) ($\chi^2=5.382$, P=0.02).

204 **4. Discussion**

205 A complex relationship between the thyroid gland and the liver exists in both
206 healthy and disease states⁸. Maliks research showed that thyroid dysfunction may

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2
3 207 affect liver function,⁹. A relationship has been suggested to exist between
4 208 nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction¹⁰. Several studies
5 209 conducted in some countries worldwide showed the relationship between levels of
6 210 thyroid hormones and the incidence of NAFLD was inverse¹¹. In clinical practice, we
7 211 have found that hepatic dysfunction in DTC patients is common, and most of these
8 212 patients have no obvious symptoms. The mechanism may be related to the following
9 213 factors¹²: (1) hypothyroidism may have features similar to those of liver disease
10 214 (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of
11 215 elevated aspartate aminotransferase from myopathy, coma; (2) hypothyroidism may
12 216 interact liver structure or function directly; in experimental hypothyroidism, with the
13 217 decrease of the activity of bilirubin UDP-glucuronyltransferase, bilirubin excretion is
14 218 reduced; (3) hypothyroidism is related to cholestatic jaundice due to decreased
15 219 bilirubin and bile excretion¹³; and (4) severe hypothyroidism is known to cause
16 220 increased permeability of the vascular endothelium¹⁴.

17 221 Our study demonstrated that 31.6% of DTC patients suffered from different
18 222 degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury.
19 223 Additionally, an increase in ALT or AST was the most common abnormal indicator,
20 224 and the prevalence was 47.5%. The findings are different from previous research data
21 225 from Gokmen's group whose research showed that hypertriglyceridemia and a higher
22 226 FT₃/FT₄ ratio are independent risk factors for NAFLD, however, hypothyroidism is
23 227 not related to the condition directly¹⁵. However, their research subjects were patients
24 228 with hypothyroidism, where hypothyroidism was defined only by a TSH level ≥ 4.1
25 229 mIU/L, and FT₃ and FT₄ levels were not included. The FT₃ and FT₄ levels of some
26 230 patients were normal.

27 231 To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed
28 232 13 related factors, such as age and sex, and found that male sex, a THW time greater
29 233 than 21 days, FT₃<2.01 pmol/L, FT₄<4.78 pmol/L, TSH>78.195 μ IU/mL, TC>5.17
30 234 mmol/L, and TG>1.71 mmol/L were risk factors for hepatic dysfunction in the
31 235 univariate analysis (all P<0.01). Additionally, we found that male sex, FT₄<3.80
32 236 pmol/L and TG \geq 1.28 mmol/L were more closely associated with hepatic dysfunction
33 237 in DTC patients in the multivariate logistic regression analysis (P<0.01). No studies
34 238 related to our study on the risk factors of hepatic dysfunction for DTC patients were
35 239 found.

36 240 In this study, we found that the remission rate of patients with mild hepatic
37 241 dysfunction was significantly higher than that of patients with moderate hepatic
38 242 dysfunction at 1 month after ¹³¹I therapy. Additionally, the remission rate among
39 243 patients with mild hepatic dysfunction was not significantly different between the
40 244 treated group and the untreated group. We also found that the FT₄ level is associated
41 245 with hepatic dysfunction, with more severe hypothyroidism corresponding to a greater
42 246 impact on liver function. Patients with mild hepatic dysfunction may not be treated
43 247 with hepatoprotective drugs because the remission rate of hepatic dysfunction at 1
44 248 month after ¹³¹I therapy was not significantly different between the treated group and
45 249 the untreated group. Recent studies revealed that with no liver damage, hepatic
46 250 dysfunction associated with hypothyroidism can be reversed over several weeks with

251 thyroxine replacement ¹⁶.

252 Additionally, liver is the vital organ for cholesterol metabolism, thyroid
253 hormones play an important role in hepatic lipid metabolism¹⁷. Thyroid hormones
254 increase the activity of lipid-lowering liver enzymes which can lead to a reduction in
255 low-density lipoprotein levels ¹⁸. Serum lipids also play an important role in liver
256 function¹⁹, which coincided with the results of our study. In our study, hepatic
257 function indices returned to normal at 1 month after ¹³¹I therapy in 86.34% of the
258 patients, the remission rate in patients with normal TG levels was significantly higher
259 than that in the elevated TG group, and the time until liver dysfunction returned to
260 normal in the patients suffering from hyperlipidemia and hepatic dysfunction was
261 longer than that in the patients suffering from only hyperlipidemia. In other words,
262 lipid-lowering therapy (statins or fenofibrate) was very important for patients with
263 hepatic dysfunction.

264 Obesity is a important metabolic risk factor of liver and thyroid dysfunction, and it
265 would be helpful if we analysis of the influence of it in our study. For these reasons,
266 further rigorous prospective studies are needed to confirm these preliminary findings.

267 **Conclusions**

268 Hepatic dysfunction is more likely to occur in male patients and patients with a
269 THW time greater than 21 days, FT₃<2.01 pmol/L, FT₄<4.78 pmol/L, TSH>78.195
270 μIU/mL, TC>5.17 mmol/L, and TG>1.71 mmol/L. Additionally, lipid-lowering
271 therapy is particularly important for DTC patients with hepatic dysfunction before ¹³¹I
272 therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia,
273 lipid-lowering therapy is recommended, which is expected to shorten the remission
274 time of hepatic dysfunction.

275 **Contribution to the Field Statement:** An elevated TSH level is essential to stimulate
276 ¹³¹I uptake when patient with DTC undergoes RAI therapy. A number of patients
277 suffer from general edema, constipation and so on, before RAI therapy with THW.
278 Evidence reveals that hypothyroidism may have a direct effect on liver structure or
279 function. We retrospectively collected clinical data from 996 patients with DTC to
280 investigate risk factors of hepatic dysfunction in these patients. Patients with mild
281 hepatic dysfunction and ortholiposis were found to have a higher likelihood of
282 recovering normal liver function. For males, FT₄ and TG levels were more closely
283 related to hepatic dysfunction, and the prognosis of hepatic dysfunction was closely
284 associated with the level of TG.

285 **Contributorship Statement:** Yanhui Ji and Renfei Wang contributed to the
286 conception and design of the study. Yanhui Ji, Wei Zheng, Jian Tan, and Cailan Wu
287 assisted with data acquisition. Yanhui Ji, Zhaowei Meng, and Renfei Wang
288 conducted the statistical analyses and drafted the manuscript. Jian Tan, Zhaowei
289 Meng critically revised the manuscript. All authors read and approved the final
290 manuscript and agree to be accountable for all aspects of the research in ensuring that
291 the accuracy or integrity of any part of the work are appropriately investigated and
292 resolved. **Competing interests**

293 There are no competing interests for any author

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297 **Data sharing statement**

298 All data relevant to the study included in the article are uploaded as supplementary
299 information

300 **Ethical Approval statement**

301 The studies involving human participants were reviewed and approved by Ethical Committee of Tianjin
302 Medical University General Hospital (NO. IRB2020-WZ-001). Written informed consent to participate in
303 this study was provided by the participants' legal guardian/next of kin.

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371
372 Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000

	Female	523(76.24%)	163(23.76%)		0.324		
the time between	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
thyroidectomy and ¹³¹ I	>3 months	121(69.14%)	54(30.86%)		1.044		
therapy							
Thyroid hormone	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
withdrawal time	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		
FT ₃	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT ₄	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0. 828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40 ^Δ	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17 ^Δ	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71 ^Δ	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

373 CI=confidence interval, OR=odds ratio, *median; ^ΔUpper limit of the normal value

374 Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic
 375 dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X ₂	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X ₈ (FT ₄)			62.291	3	0.000		
X ₈ (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X ₈ (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X ₈ (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X ₁₃			15.195	3	0.002		

X ₁₃ (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X ₁₃ (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X ₁₃ (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

376

377

Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ¹³¹I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)
Moderate	63	45 (71.43%)	18 (28.57%)
χ^2			14.873
<i>p</i>			0.000

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Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ¹³¹I therapy

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Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2			1.765
<i>p</i>			0.184

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	<p>(a) Indicate the study's design with a commonly used term in the title or the abstract “Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy ” in title indicated the study's design</p> <p>(b) Provide in the abstract an informative and balanced summary of what was done and what was found The purpose “The present study aimed to investigate the risk factors for hepatic dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid cancer (DTC).” In line 19-21, on page 1 of revised manuscript(main document) provide what was done; “Patients with minor hepatic dysfunction and ortholiposis are more likely to recover normal liver function. Patients with moderate hepatic dysfunction should be treated with hepatoprotective drugs. For males, FT₄ and TG levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic dysfunction was closely related to the level of TG.” in Line 36-40 on page 2 of revised manuscript(main document) provide what was we found</p>
Introduction		
Background/rationale	2	<p>Explain the scientific background and rationale for the investigation being reported “When DTC patient undergoes RAI therapy, an elevated thyroid-stimulating hormone (thyrotropin, TSH) level is essential, Evidence indicates that hypothyroidism may affect liver function or structure directly. Therefore, identification of factors resulting in hepatic dysfunction is crucial” is line63-68 on page 2 of revised manuscript(main document)</p>
Objectives	3	<p>State specific objectives, including any prespecified hypotheses The objective is “to investigate risk factors for patients with hepatic dysfunction using a retrospective approach” in line 68-69 on page 2 of revised manuscript(main document)</p>
Methods		
Study design	4	<p>Present key elements of study design early in the paper The key elements of study design is how to determine the “Participants or Criteria selection”, it was showed in line 77-86 on page 3 of revised manuscript(main document)</p>
Setting	5	<p>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection It was showed in line 88-107 on page 3 and 116-118 on page 4 of revised manuscript(main document)</p>
Participants	6	<p>(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants</p>

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It was showed in line 77-107 on page 3 of revised manuscript(main document)

(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed

Case-control study—For matched studies, give matching criteria and the number of controls per case

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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It was showed in 129-203 on page 3-4 of revised manuscript(main document)

Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
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It was showed in 109-114 on page 3-4 of revised manuscript(main document)

Bias	9	Describe any efforts to address potential sources of bias
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It was showed in 264-266 on page 8 of revised manuscript(main document)

Study size	10	Explain how the study size was arrived at
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It was showed in 77-80 on page 3 of revised manuscript(main document)

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
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It was showed in 88-107 on page 3 of revised manuscript(main document)

Statistical methods	12	<i>(a)</i> Describe all statistical methods, including those used to control for confounding
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(b) Describe any methods used to examine subgroups and interactions

(c) Explain how missing data were addressed

(d) Cohort study—If applicable, explain how loss to follow-up was addressed

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(e) Describe any sensitivity analyses

It was showed in 120-126 on page 4 of revised manuscript(main document)

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time It was showed in 128-203 on page4-6 of revised manuscript(main document) <i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure <i>Cross-sectional study</i> —Report numbers of outcome events or summary measures
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results	18	Summarise key results with reference to study objectives In line 231-239 on page 7 of revised manuscript(main document)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias In line 41-51 on page 2 and in line 264-266 on page 8 of revised manuscript(main document)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence in line 221-263 on page 7 and 8 of revised manuscript(main document)
Generalisability	21	Discuss the generalisability (external validity) of the study results in line 275-284 on page 8 of revised manuscript(main document)

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based
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This study was sponsored by the Natural Science Foundation of Tianjin City(Grant No.20JCQNJC01610) **in line 295-296 on page 9 of revised manuscript(main document)**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

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A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before Radioiodine Therapy in China: A Comparison Analysis based on Patients with Differentiated Thyroid Cancer

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1 **Title page:**

2 A Retrospective Study of The Influence of Hypothyroidism on Liver Function Before
3 Radioiodine Therapy in China: A Comparison Analysis based on Patients with
4 Differentiated Thyroid Cancer

5 Running title: The Influence of hypothyroidism on the Liver Function in Patients with
6 Differentiated Thyroid Cancer

7 Yan-hui Ji¹, Wei Zheng¹, Zhaowei Meng¹, cailan wu², Jian Tan¹, Ren-fei Wang^{1*}

8 Department of Nuclear Medicine, Tianjin Medical University General Hospital

9 *Corresponding Author: Ren-fei Wang, PHD, Department of Nuclear Medicine,
10 Tianjin Medical University General Hospital, Anshan Road 154, Heping district,
11 Tianjin,300052, P.R. China, E-mail:Roslyn_en@163.com

12 Yan-hui Ji, Zhaowei Meng, Wei Zheng, Jian Tan, Ren-fei Wang: Department of Nuclear
13 Medicine, Tianjin Medical University General Hospital, Tianjin,China.

14 Cailan Wu: Department of Nuclear Medicine, Tianjin Fouth Hospital, Tianjin,China.

15 Key words: Endocrine tumours ; Head & neck surgery ; Nuclear Medicine; Thyroid
16 disease

17 Word count:3256

18 **Abstract**

19 **Purpose** The aim of present study is to investigate the risk factors for hepatic
20 dysfunction before radioiodine (RAI) therapy in patients with differentiated thyroid
21 cancer (DTC). **Methods** 996 patients (314 males, 682 females; ageof 45.07±12.98
22 years) with postoperative of DTC were recruited and divided into two groups
23 including patients with and without hepatic dysfunction. The changes in baseline
24 data and traced liver function levels together with other metabolic profiles were
25 compared between the two groups. **Result** Overall, 31.6% of patients had hepatic
26 dysfunction. Higher aspartate aminotransferase (AST) and/or alanine
27 aminotransferase (ALT) was the most common abnormality (the prevalence rate was
28 47.5%). The percentages of mild and moderate hepatic dysfunction were 80.0% and
29 20.0%, respectively. Univariate analyses demonstrated that the most prominent risk
30 factors for hepatic dysfunction (odds ratio [OR]=0.324-3.171, P<0.01) were male sex

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4 31 with levothyroxine discontinuation and free triiodothyronine (FT₃)< 2.01 pmol/L, free
5 32 thyroxine (FT₄)<4.78 pmol/L, thyroid-stimulating hormone (TSH)>78.195 μIU/mL,
6 33 total cholesterol (TC)>5.17 mmol/L , triglycerides (TG)>1.71 mmol/L and more than
7 34 21 days of thyroid hormone withdrawal (THW) . Multivariate analyses demonstrated
8 35 that for males, FT₄<3.80 pmol/L and TG≥1.28 mmol/L were the most prominent risk
9 36 factors.. **Conclusions** Patients with minor hepatic dysfunction and ortholiposis are
10 37 more likely to recover to normal liver function. Patients with moderate hepatic
11 38 dysfunction should be treated with hepatoprotective drugs. For males, FT₄ and TG
12 39 levels tended to be associated with hepatic dysfunction, and the prognosis of hepatic
13 40 dysfunction was closely related to the level of TG.

14 41 Strengths and limitations of this study:

15 42 Strengths: The results of this study may help nuclear physicians to make clinical
16 43 treatment strategies of DTC patients.

17 44 Limitations: 1. We selected cases with complete data to perform our retrospective
18 45 analysis,however, the exclusion of a few patients who were lost to follow-up might
19 46 result in potential bias.

20 47 2.We could not collect the result of LDL cholesterol measurements.

21 48 3.Obesity is an important metabolic risk factorof liver and thyroid dysfunction, and
22 49 it would be helpful if we could perform analysis of the influence of it in our study.

23 50 For these reasons, further rigorous prospective studies are needed to confirm these
24 51 preliminary findings.

25 52 **Keywords:** thyroid cancer, ¹³¹I, high-dose radioiodine therapy, hepatic dysfunction,
26 53 risk factors

27 54 1. Introduction

28 55 Radioiodine (RAI) therapy is a very important procedure to ablate normal thyroid
29 56 remnant tissues and microscopic deposits of differentiated thyroid carcinoma (DTC)
30 57 after thyroidectomy ¹. As reported, RAI therapy was able to reduce the number of
31 58 locoregional recurrences and to increase overall survival of the American Thyroid
32 59 Association(ATA) intermediate-risk and high risk DTC patients ^{2 3}. In order to
33 60 stimulate ¹³¹I uptake into the normal thyroid remnants and metastatic tissues of
34 61 thyroid carcinoma for DTC patients undergo RAI therapy, an elevated
35 62 thyroid-stimulating hormone (thyrotropin, TSH) level is essential ⁴. The classic
36 63 method of preparation for RAI therapy is thyroid hormone withdrawal (THW).
37 64 However, the application of THWusually results in some physical or psychological
38 65 side effects associated with hypothyroidism⁵, such as general edema, constipation,
39 66 and depression. Evidences indicate that hypothyroidism may affect liver function or
40 67 structure directly ⁶. Therefore, the identification of factors that may causing hepatic
41 68 dysfunction is rather crucial. In the present study, we collected clinical data from 996
42 69 patients with DTC to investigate the risk factors for patients with hepatic dysfunction

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2
3 70 undergoing a retrospective approach.
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5 71 **2. Materials and methods**

6 72 **2.1. Ethics statement**

7 73 This study is a retrospective clinical study summarizing and analyzing a large amount
8
9 74 of clinical data. The ethics committee of Tianjin Medical University General Hospital
10
11 75 waived the need to obtain written informed consent from all patients. All clinical data
12
13 76 used in this study were analyzed anonymously.
14

15 77 **2.2. Participants or Criteria selection**

16
17 78 The study included 996 patients (314 males, 682 females; age of 45.07 ± 12.98 years)
18
19 79 who had undergone RAI therapy at our department from January 2012 to March 2018.
20
21 80 The patients had undergone complete or partial thyroidectomy performed by various
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23 81 surgeons. The patients agreed to receive RAI therapy and were informed about the
24
25 82 traditional preparation method, THW. We used hepatitis virus markers, abdominal
26
27 83 ultrasonography, echocardiography, and autoantibody and immunoglobulin subtype
28
29 84 determination for patients with hepatic dysfunction to exclude other apparent causes
30
31 85 of liver damage. Other possible causes included viral hepatitis, liver cirrhosis or
32
33 86 biliary tract disease, chronic cardiac dysfunction and autoimmune liver disease,
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35 87 liver steatosis and hyperlipoidemia, etc⁷.
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37 88 **2.3. Patient and Public Involvement statement**

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40 89 This was an uncontrolled retrospective study, patients of this study had underg
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42 90 one RAI therapy at our department, and we recorded and analyzed the data in
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44 91 order to investigate the risk factors for patients with hepatic dysfunction.

45 92 **2.4. Data collection and grouping**All RAI therapy regimens were conducted b
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47 93 y the same nuclear medicine department following a standard protocol (2015 A
48
49 94 merican Thyroid Association Management Guidelines). Relevant data were recor
50
51 95 ded during the RAI therapy, including patient age (named X_1), sex (X_2), the ti
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53 96 me between surgery and ^{131}I therapy (X_3), the time of THW (X_4), the presence
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55 97 or absence of metastases (lymph node metastasis or lung metastases), (X_5), the p
56
57 98 resence of absence of Hashimoto's thyroiditis (X_6), serum free triiodothyronine
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59 99 (FT_3) (X_7), free thyroxine (FT_4) (X_8), TSH (X_9), thyroglobulin (Tg) (X_{10}), antit
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100 hyroglobulin antibody (TgAb) (X_{11}), total cholesterol (TC) (X_{12}), and triglycerid
101
102 es (TG) (X_{13}). Meanwhile, liver function test results including aspartate aminotr
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104 ansferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), g
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106 amma-glutamyl transferase (GGT), total-value bilirubin (TBIL), and direct biliru

bin (DBIL) were also collected. Hepatic dysfunction was diagnosed in accordance with the following criteria: the upper limit of normal (ULN) $<ALT$, AST or $GGT < 3$ times ULN, the $ULN < ALP < 2$ times the ULN and/or $TBIL$ and the $ULN < DBIL < 2.5$ times the ULN were defined as mild hepatic dysfunction; 3 times the ULN $< ALT$ or $AST < 20$ times the ULN, 3 times the $ULN < GGT < 10$ times the ULN, 2 times the $ULN < ALP < 5$ times the ULN and/or 2.5 times the $ULN < TBIL$, and $DBIL < 5$ times the ULN were defined as moderate hepatic dysfunction; and ALT or $AST \geq 20$ times the ULN, $GGT \geq 10$ times the ULN, $ALP \geq 5$ times the ULN and/or $TBIL$ and $DBIL \geq 5$ times the ULN were defined as severe hepatic dysfunction⁷.

2.5. Parameter assessments

Thyroid function tests were measured by chemiluminescence immunoassays (ADVIA CENTAUR XP SIEMENS AG). Tg and TgAb were detected by the Immulite system (Immulite 2000 SIEMENS AG). Liver function indices were measured by colorimetry (Hitachi C7600 Japan). TC and TG levels were checked using an auto-analyzer enzymatically (Hitachi Model 7170 analyzer; Hitachi, Ltd., Tokyo, Japan). The dosage range of ^{131}I therapy was 3.7-7.4 GBq.

2.6. Patient follow-up

We measured the serum levels of thyroid parameters, serum lipids, and liver function indices of the 996 patients at 1, 2, 3, and 4 months after ^{131}I therapy to evaluate their liver function.

2.7. Statistical analysis

A chi square test was used to analyze the differences between ratios. To identify risk factors for hepatic dysfunction, we used a bivariate logistic regression model (univariate analysis) and stepwise logistic regression (multivariate analysis) with a variable with $p < 0.05$, and values < 0.05 were considered statistically significant. The odds ratio (OR) was used to evaluate the risk factor. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 20 (SPSS, Chicago, IL).

3. Results

3.1. Clinical features of hepatic dysfunction

Overall, 31.6% (315/996) of patients with DTC had hepatic dysfunction. Most patients with hepatic dysfunction had no obvious clinical symptoms except for

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4 137 abnormal liver function indices. The most common abnormality was elevated ALT
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6 138 and (or) AST, with a prevalence of 47.5%. The prevalence rates of mild, moderate,
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8 139 and severe hepatic dysfunction were 80.0% (252/315), 20.0% (63/315), and 0%
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10 140 (0/315), respectively.

141 **3.2. Risk factors for hepatic dysfunction in DTC patients**

142 In this paper, a binary logistic regression model was established for relevant factors of
143 hepatic dysfunction. Single-factor analysis and binary multivariate logistic regression
144 analysis were performed as well. Patient characteristics were compared using
145 bivariate logistic univariate regression analysis between the 2 groups (Table 1). In the
146 metastase group, the number of patients with hepatic dysfunction and lymph node
147 metastasis or lung metastases were 508 and 21 respectively; and the number of
148 patients without hepatic dysfunction were 245 (with lymph node metastasis) and 12
149 (with lung metastases) respectively. The results showed that for male patients, the
150 THW time, $FT_3 < 2.01$ pmol/L, $FT_4 < 4.78$ pmol/L, $TSH > 78.195$ μ IU/mL, $TC > 5.17$
151 mmol/L, and $TG > 1.71$ mmol/L were closely associated with hepatic dysfunction
152 (odds ratio [OR]: 0.324-3.171, all $P < 0.01$).

153 Furthermore, the multivariate logistic regression analysis were applied to screen the
154 relevant risk factors. In our study, we suggested the following assignments for
155 independent variables: $X_1 = 1$ for age ≤ 45 years and $X_1 = 2$ for age > 45 years; $X_2 = 1$ for
156 male sex and $X_2 = 2$ for female sex; $X_3 = 1$ if the time between total thyroidectomy and
157 ^{131}I therapy was less than 3 months and $X_3 = 2$ if the time between total thyroidectomy
158 and ^{131}I therapy was more than 3 months; $X_4 = 1, 2,$ and 3 if the THW time was shorter
159 than 3 weeks, 3-4 weeks, and longer than 4 weeks, respectively; $X_5 = 1$ for the
160 presence of metastases and $X_5 = 2$ for the absence of metastases; $X_6 = 1$ for the presence
161 of Hashimoto's thyroiditis and $X_6 = 2$ for the absence of Hashimoto's thyroiditis; $X_7 = 1,$
162 $2, 3,$ and 4 for FT_3 levels lower than 1.60 pmol/L, 1.60-2.01 pmol/L, 2.01-2.37
163 pmol/L, and higher than 2.37 pmol/L, respectively; $X_8 = 1, 2, 3,$ and 4 for FT_4 levels
164 lower than 3.80 pmol/L, 3.80-4.78 pmol/L, 4.78-5.79 pmol/L, and higher than 5.79
165 pmol/L, respectively; $X_9 = 1, 2, 3,$ and 4 for TSH levels lower than 57.01 μ IU/mL,
166 57.01-78.20 μ IU/mL, 78.20-101.84 μ IU/mL, and higher than 101.84 μ IU/mL,

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4 167 respectively; $X_{10}=1, 2, 3,$ and 4 for Tg levels lower than 0.50 ng/mL, 0.50-2.64 ng/mL,
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6 168 2.64-9.18 ng/mL, and higher than 9.18 ng/mL, respectively; $X_{11}=1$ for TgAb levels
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8 169 lower than 40 IU/mL and $X_{11}=2$ for TgAb levels higher than 40 IU/mL; $X_{12}=1, 2, 3,$
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10 170 and 4 for TC levels lower than 5.46 mmol/L, 5.46-6.27 mmol/L, 6.27-7.22 mmol/L,
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12 171 and higher than 6.27 mmol/L, respectively; and $X_{13}=1, 2, 3,$ and 4 for TG levels lower
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14 172 than 1.28 mmol/L, 1.28-1.85 mmol/L, 1.85-2.76 mmol/L, and higher than 2.76
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16 173 mmol/L, respectively. Resultant variable: $Y=1$ for patients with hepatic dysfunction,
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18 174 and $Y=0$ for patients without hepatic dysfunction. Forward stepwise regression
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20 175 analysis rejecting trends ultimately revealed that male sex, $FT_4 < 3.80$ pmol/L and
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22 176 $TG \geq 1.28$ mmol/L were independent risk factors to predict hepatic dysfunction in
23
24 177 patients with DTC (Table 2).

178 **3.3. Outcomes of hepatic dysfunction after ^{131}I therapy**

179 The outcomes of hepatic dysfunction of varying degrees after ^{131}I therapy are
180 displayed in Table 3. The remission rate of patients at 1 month after ^{131}I therapy was
181 86.34% (272/315). Liver function test results revealed that 90.07% (227/252) of
182 patients with mild hepatic dysfunction returned to normal 1 month after ^{131}I therapy.
183 Moreover, the remission rate among patients with moderate and severe hepatic
184 dysfunction was 71.43% (45/63). Additionally, the remission rate of mild hepatic
185 dysfunction was higher than that of moderate dysfunction ($P < 0.001$).

186 The remission of hepatic dysfunction at 1 month after ^{131}I therapy is shown in
187 Table 4. The liver function tests of 252 patients with mild hepatic dysfunction were
188 evaluated at 1 month after ^{131}I therapy, Results showed that the liver function of
189 94.34% (50/53) of patients who were given hepatoprotective treatment [oral bicyclol
190 tablets, Bicyclol 25 mg/tablet, Beijing Union Pharmaceutical Factory, Beijing, China,
191 at a total daily dose of 75mg (25mg three times daily), the treated group] returned to
192 normal after 1 month after ^{131}I therapy. Moreover, the remission rate among patients
193 in the untreated group was found to be 88.94% (177/199). However no remarkable
194 difference in the remission rate was observed between the two groups ($P=0.184$).

195 Other 63 patients with moderate hepatic dysfunction were treated with
196 hepatoprotective therapy [oral bicyclol tablets, at a total daily dose of 150mg (50mg
197 three times daily)], and the remission rates among patients at 1 month, 2 months, and

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4 198 3 months after ^{131}I therapy were 55.56% (35/63), 36.5% (23/63), and 7.94% (5/63)
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6 199 respectively. The average time for liver function returned to normal level in patients
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8 200 with moderate hepatic dysfunction was 1.8 months.

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10 **3.4. The correlation between serum TG and the remission rate of hepatic**
11 **dysfunction in patients with DTC**

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13 203 The number of patients with hyperlipidemia, hyperlipidemia with hepatic dysfunction,
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15 204 and dyslipidemia (hypercholesterolemia + hypertriglyceridemia) were 564, 278 and
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17 205 244 respectively. A total of 559 patients (218 males, 341 females) had elevated serum
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19 206 TG before ^{131}I therapy, including 189 patients with hepatic dysfunction (76 males,
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21 207 113 females). All patients were divided into 2 subgroups based on their serum TG
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23 208 levels 1 month after ^{131}I therapy. Subgroup 1 includes subjects with a normal TG
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25 209 level (141 patients) and subgroup 2 includes subjects with elevated TG (48 patients,
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27 210 21 females, 27 males). In subgroup 2, 15 males and 10 females were treated with
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29 211 statins or fenofibrate for lipid-lowering therapy. The percentage of patients with liver
30
31 212 function returned to normal was 92.90% (131/141) in subgroup 1. Moreover, the
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33 213 remission rate of the patients in subgroup 2 was 75.00% (36/48) ($\chi^2=5.382$, $P=0.02$).
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35 214 In subgroup 2, the remission rate of the patients with lipid-lowering therapy was
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37 215 84.00% (21/25) and 65.21% (15/23).

38
39 **4. Discussion**

40
41 217 A complex relationship between the thyroid gland and the liver exists in both
42
43 218 healthy and disease states⁸. Malik's research showed that thyroid dysfunction may
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45 219 affect liver function⁹. It is suggested that a relationship may exist between
46
47 220 nonalcoholic fatty liver disease (NAFLD) and thyroid dysfunction¹⁰. Several studies
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49 221 conducted in some countries worldwide showed that the relationship between levels
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51 222 of thyroid hormones and the incidence of NAFLD was inverse¹¹. In clinical practice,
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53 223 we have found that hepatic dysfunction in DTC patients is common, and most of these
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55 224 patients have no obvious symptoms. The mechanism may be related to the following
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57 225 factors¹²: (1) hypothyroidism may have features similar to those of liver diseases
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59 226 (pseudo-liver disease; such as myalgias, fatigue and muscle cramps in the presence of
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227 elevated aspartate aminotransferase from myopathy, coma); (2) hypothyroidism may

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4 228 interact with liver structure or function directly, for example, bilirubin excretion is
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6 229 reduced in experimental hypothyroidism with the decrease of the activity of bilirubin
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8 230 UDP-glucuronyltransferase; (3) hypothyroidism is related to cholestatic jaundice due
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10 231 to decreased bilirubin and bile excretion¹³; and (4) severe hypothyroidism is known to
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12 232 cause increased permeability of the vascular endothelium¹⁴.

13
14 233 Our study demonstrated that 31.6% of DTC patients suffered from different
15
16 234 degrees of hepatic dysfunction. All of these patients had mild or moderate liver injury.
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18 235 Additionally, an increase in ALT or AST was the most common abnormal indicator,
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20 236 and the prevalence was 47.5%. The findings are different from previous research data
21
22 237 from Gokmen's group whose research showed that hypertriglyceridemia and a higher
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24 238 FT₃/FT₄ ratio are independent risk factors for NAFLD, however, hypothyroidism is
25
26 239 not related to the condition directly¹⁵. However, their research subjects were patients
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28 240 with hypothyroidism, where hypothyroidism was defined only by a TSH level ≥ 4.1
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30 241 mIU/L, and FT₃ and FT₄ levels were not included. The FT₃ and FT₄ levels of some
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32 242 patients were normal.

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34 243 To explore the risk factors of hepatic dysfunction for DTC patients, we analyzed
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36 244 13 related factors, and found that male sex, a THW time greater than 21 days,
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38 245 FT₃<2.01 pmol/L, FT₄<4.78 pmol/L, TSH>78.195 μ IU/mL, TC>5.17 mmol/L, and
39
40 246 TG>1.71 mmol/L were responsible risk factors for hepatic dysfunction in the
41
42 247 univariate analysis (all P<0.01). Additionally, we found that male sex, FT₄<3.80
43
44 248 pmol/L and TG \geq 1.28 mmol/L were closely associated with hepatic dysfunction in
45
46 249 DTC patients in the multivariate logistic regression analysis (P<0.01). No other
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48 250 studies related to our study on the risk factors of hepatic dysfunction for DTC patients
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50 251 were found.

51
52 252 In this study, we found that the remission rate of patients with mild hepatic
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54 253 dysfunction was significantly higher than that of patients with moderate hepatic
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56 254 dysfunction at 1 month after ¹³¹I therapy. Additionally, no significant differences can
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58 255 be found on the remission rate among patients with mild hepatic dysfunction between
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60 256 the treated and untreated groups. It was also found that the FT₄ level is highly
257 257 associated with hepatic dysfunction, with more severe hypothyroidism corresponding

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4 258 to a greater impact on liver function. Patients with mild hepatic dysfunction may not
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6 259 be treated with hepatoprotective drugs because the remission rate of hepatic
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8 260 dysfunction at 1 month after ^{131}I therapy was not significantly different between the
9
10 261 treated and untreated groups. Recent studies revealed that with no liver damage,
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12 262 hepatic dysfunction associated with hypothyroidism can be reversed over several
13
14 263 weeks with thyroxine replacement ¹⁶.

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16 264 Additionally, liver is the vital organ for cholesterol metabolism and thyroid
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18 265 hormones, which plays an important role in hepatic lipid metabolism¹⁷. Thyroid
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20 266 hormones can increase the activity of lipid-lowering liver enzymes which can cause a
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22 267 reduction in low-density lipoprotein levels ¹⁸. As reported, serum lipids also play an
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24 268 important role in liver function¹⁹, which coincided with the results of our study. In
25
26 269 our study, hepatic function indices returned to normal at 1 month after ^{131}I therapy in
27
28 270 86.34% of the patients, the remission rate in patients with normal TG levels was
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30 271 significantly higher than that in the elevated TG group. In addition, the time until
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32 272 liver dysfunction returned to normal level in the patients suffering from
33
34 273 hyperlipidemia and hepatic dysfunction was longer than that of the patients suffering
35
36 274 from only hepatic dysfunction. In other words, lipid-lowering therapy (statins
37
38 275 or fenofibrate) was very important for patients with hepatic dysfunction.
39
40 276 Obesity is an important metabolic risk factor of liver and thyroid dysfunction, and it
41
42 277 would be helpful if we could analysis of the influence of it in our study. However, due
43
44 278 to the limitations, this part of analysis was not included in the current paper. For this
45
46 279 reason, further rigorous prospective studies are needed to confirm these preliminary
47
48 280 findings.

281 **Conclusions**

50
51 282 Hepatic dysfunction is more likely to occur in male patients and patients with a
52
53 283 THW time greater than 21 days, $\text{FT}_3 < 2.01$ pmol/L, $\text{FT}_4 < 4.78$ pmol/L, $\text{TSH} > 78.195$
54
55 284 $\mu\text{IU/mL}$, $\text{TC} > 5.17$ mmol/L, and $\text{TG} > 1.71$ mmol/L. Additionally, lipid-lowering
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57 285 therapy is particularly important for DTC patients with hepatic dysfunction before ^{131}I
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59 286 therapy. For DTC patients with hepatic dysfunction combined with dyslipidemia,
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287 lipid-lowering therapy is recommended, which is expected to shorten the remission

288 time of hepatic dysfunction.

289 **Contribution to the Field Statement:** An elevated TSH level is essential to stimulate
290 ¹³¹I uptake when patient with DTC undergoes RAI therapy. A number of patients
291 suffer from general edema, constipation and so on, before RAI therapy with THW.
292 Evidence reveals that hypothyroidism may have a direct effect on liver structure or
293 function. We retrospectively collected clinical data from 996 patients with DTC to
294 investigate the relevant risk factors of hepatic dysfunction in these patients. Patients
295 with mild hepatic dysfunction and ortholiposis were found to have a higher likelihood
296 of recovering to normal liver function. For males, FT₄ and TG levels were more
297 closely related to hepatic dysfunction, and the prognosis of hepatic dysfunction was
298 closely associated with the level of TG.

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302 conducted the statistical analyses and drafted the manuscript. Jian Tan, Zhaowei
303 Meng critically revised the manuscript. All authors read and approved the final
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307 **Competing interests**

308 There are no competing interests for any author

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312 **Data sharing statement**

313 All data relevant to the study included in the article are uploaded as supplementary
314 information

314 **Ethical Approval statement**

315 The studies involving human participants were reviewed and approved by Ethical
316 Committee of Tianjin Medical University General Hospital (NO. IRB2020-WZ-001).
317 Written informed consent to participate in this study was provided by the participants'

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4 318 legal guardian/next of kin.

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383 Table 1 Bivariate logistic univariate regression of the factors for DTC patients with hepatic dysfunction

Relevant factors		With hepatic dysfunction (n[%])	Without hepatic dysfunction (n[%])	B value	OR value	95%CI	P
Age	≤45	350(68.50%)	161(31.50%)	-1.011	1	0.744-1.321	0.934
	>45	331(68.25%)	154(31.75%)		1.011		
Sex	Male	158(50.97%)	152(49.03%)	-1.127	1	0.244-0.430	0.000
	Female	523(76.24%)	163(23.76%)		0.324		
the time between thyroidectomy and ¹³¹ I therapy	≤3 months	560(68.20%)	261(31.80%)	0.043	1	0.734-1.486	0.810
	>3 months	121(69.14%)	54(30.86%)		1.044		
Thyroid hormone withdrawal time	≤21 days	372(72.51%)	141(27.49%)	0.396	1	0.517-0.892	0.005
	>21 days	309(63.98%)	174(36.02%)		1.486		
Metastases	Negative	152(72.38%)	58(27.62%)	-0.242	1	0.561-1.100	0.160
	Positive	529(67.30%)	257(32.70%)		0.785		
Hashimoto's thyroiditis	Negative	595(67.85%)	282(32.15%)	-0.211	1	0.529-1.239	0.331
	Positive	86(72.27%)	33(27.73%)		0.810		

FT ₃	<2.01*	316(63.71%)	180(36.29%)	0.432	1	1.177-2.016	0.002
	≥2.01	365(73.00%)	135(27.00%)		1.540		
FT ₄	<4.78*	280(56.34%)	217(43.66%)	1.154	1	2.389-4.209	0.000
	≥4.78	401(80.36%)	98(19.64%)		3.171		
TSH	<78.195*	365(73.29%)	133(26.71%)	-0.458	1	0.483-0. 828	0.001
	≥78.195	316(63.45%)	182(36.55%)		0.633		
Tg	<2.635*	346(69.48%)	152(30.52%)	-0.185	1	0.609-1.134	0.244
	≥2.635	335(67.27%)	163(32.73%)		0.831		
TgAb	≤40 ^Δ	527(66.96%)	260(33.04%)	0.381	1	0.979-1.930	0.067
	>40	154(73.68%)	55(26.32%)		1.374		
TC	≤5.17 ^Δ	129(75.44%)	42(24.56%)	0.758	1	1.615-2.822	0.000
	>5.17	552(66.90%)	273(33.10%)		2.135		
TG	≤1.71 ^Δ	336(77.42%)	98(22.58%)	-0.418	1	0.451-0.960	0.03
	>1.71	344(61.54%)	215(38.46%)		0.658		

384 CI=confidence interval, OR=odds ratio, *median, ^ΔUpper limit of the normal value

385 Table 2 Bivariate logistic multivariate regression analysis of the factors for DTC patients with hepatic
386 dysfunction

Causal variable	B	Standard error	Wald	df	P	EXP (B)	95%CI
X ₂	-0.933	0.156	35.703	1	0.000	0.393	0.290-0.534
X ₈ (FT ₄)			62.291	3	0.000		
X ₈ (2)	-0.347	0.193	3.249	1	0.071	0.707	0.485-1.031
X ₈ (3)	-0.853	0.200	18.146	1	0.000	0.426	0.288-0.631
X ₈ (4)	-1.789	0.239	55.817	1	0.000	0.167	0.105-0.267
X ₁₃			15.195	3	0.002		
X ₁₃ (2)	0.325	0.225	2.072	1	0.150	1.383	0.889-2.152
X ₁₃ (3)	0.643	0.223	8.313	1	0.004	1.901	1.228-2.943
X ₁₃ (4)	0.787	0.219	12.784	1	0.000	2.197	1.429-3.376
Constant	-0.188	0.270	0.484	1	0.487	0.829	

387

388 Table 3 Outcomes of hepatic dysfunction of varying degrees after 1 month of ¹³¹I therapy

Degree	n	Outcomes (n[%])	
		Remission	Nonremission
Mild	252	227 (90.07%)	25 (9.93%)

Moderate	63	45 (71.43%)	18 (28.57%)
χ^2			14.873
p			0.000

389 Table 4 Remission of hepatic dysfunction among patients given different treatments at 1 month after ^{131}I therapy

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Group	n	Outcomes (n[%])	
		Remission	Nonremission
Treatment	53	50 (94.34%)	3 (5.66%)
No treatment	199	177 (88.94%)	22 (11.06%)
χ^2			1.765
p			0.184

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