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Association of total cholesterol and atherosclerotic cardiovascular disease in patients with follicular thyroid cancer

A real-world study from Chinese populations

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Abstract

The association between serum total cholesterol (TC) level and incident atherosclerotic cardiovascular disease (ASCVD) in patients with follicular thyroid cancer postthyroidectomy is unknown.

This was a retrospective study and patients (n = 384) were divided into low and high TC groups according to the median TC level. Incidence of composite ASCVD (myocardial infarction, ischemic stroke, and cardiovascular death) was compared between these 2 groups and factors contributing to the association of TC and ASCVD were evaluated.

Patients in the high TC group were older and more likely to have diabetes and have higher C-reactive protein level. After thyroidectomy, serum levels of free triiodothyronine and free thyroxine were lower while thyroid-stimulating hormone level was higher in the high TC group. 31.6% and 39.7% of patients developed hypothyroidism in the low and high TC groups ($P < .05$) postthyroidectomy. The incidence rate of composite ASCVD was higher in the high TC versus low TC groups, with incidence rate ratio of 1.69 (95% confidence interval [CI]: 1.07–2.69), which was mainly driven by a higher incidence rate of myocardial infarction in the high TC group (incidence rate ratio: 2.11 and 95% CI: 1.10–4.20). In unadjusted model, higher TC was associated with 73% higher risk of composite ASCVD. After adjustment for hypothyroidism, the association of higher TC and composite ASCVD was attenuated into insignificance, with hazard ratio of 0.92 and 95% CI: 0.81 to 1.34.

Increased TC level was associated with composite ASCVD, which might be attributed to hypothyroidism postthyroidectomy. The use of levothyroxine might help to prevent hypercholestemia and reduce the incidence of ASCVD.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BMI = body mass index, CI = confidence interval, CRP = C-reactive protein, FT4 = free thyroxine, HR = hazard ratio, IRR = incidence rate ratio, TC = total cholesterol.

Keywords: atherosclerotic cardiovascular disease, follicular thyroid cancer, total cholesterol

1. Introduction

Thyroid cancer has become the leading cause of morbidity and mortality worldwide, although advancements of the diagnosis and management of thyroid cancer have been achieved in the recent decades.[1–5] For instance, among the US populations, the incidence of thyroid cancer increased from 7.1 per 100,000 persons in the year of 2000 to 17.6 per 100,000 persons in the year of 2013.[1] One recent report from Chinese populations showed that the crude incidence rate of thyroid cancer was 7.6 per 100,000 persons, which ranked No. 7 of all cancers in China, and the mortality rate of thyroid cancer was 5.09 per 100,000 persons.[5] These epidemiological data together highlight the need and importance to screen and improve the management of thyroid cancer.

Thyroid gland is an endocrine organ which plays important roles in regulating vital body function including breathing, heart rate, body temperature, among others.[6] Serum cholesterol metabolism is also significantly associated with the thyroid function.[7] For instance, individuals with hypothyroidism commonly have increased serum cholesterol level, while those with hyperthyroidism commonly have reduced serum cholesterol level.[7,8] Total cholesterol (TC) is a well-recognized risk factor for myocardial infarction and ischemic stroke.[9–11] Suh et al[12] reported that the incidence rate of coronary heart disease and ischemic stroke was higher in individuals with thyroid cancer than their counterparts without thyroid cancer. Park et al[13] also reported that individuals with thyroid cancer experienced an increased risk of atherosclerotic cardiovascular diseases (ASCVDs). The underlying mechanisms might be related to hypercholesterolemia, which deserved further elucidation.

Editor: Wen-Jun Tu.

The current study was supported by the Medical and Pharmacological Health Research Project of Hainan Province (No. 2005320672A2001).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Huang G, Lu H, Li M, Lv Q, Chen Q. Association of total cholesterol and atherosclerotic cardiovascular disease in patients with follicular thyroid cancer: a real-world study from Chinese populations. Medicine 2021;100:39(e27310).

Received: 20 October 2020 / Received in final form: 18 August 2021 / Accepted: 6 September 2021

http://dx.doi.org/10.1097/MD.0000000000027310

Herein, we conducted a retrospective study and included patients with documented follicular thyroid cancer undergoing thyroidectomy, and the aims of current study were to: compare the incidence of ASCVD according to serum TC level; evaluate the association of serum TC level and incident ASCVD; explore the factors contributing to the association of serum TC level and incident ASCVD. To our knowledge, this should be the first few studies to evaluate the association of TC and ASCVD in patients with follicular thyroid cancer after thyroidectomy. Findings from the current study might provide novel insights into how to better prevent ASCVD among patients with follicular thyroid cancer in the future.

2. Methods

2.1. Study participants

This was a retrospective study and the current study was approved by the Institution of Review Board of Hainan Western Central Hospital. Written informed consent was waived by the Institution of Review Board of Hainan Western Central Hospital, and the private information of the patients were de-identified. All methods were performed in accordance to the Declaration of Helsinki. Hospitalized patients with documented diagnosis of follicular thyroid cancer from January 2015 to January 2020, which was pathologically confirmed, were screened by studied investigators. The inclusion criteria were as follows: had lipid profiles measurement at baseline and after thyroidectomy; underwent thyroidectomy; without local or remote metastasis; follow-up at our hospital; did not receive chemotherapy or radiation therapy after surgery; and had thyroid hormone assessment after thyroidectomy. The exclusion criteria were as follows: had prior histories of ASCVD; prior diagnosis of familial hypercholesterolemia; received medications that might influence serum TC level (e.g., estrogen, glucocorticoid, anti-psychotics, and others); had a history of alcohol abuse or presence of non-alcoholic fatty liver disease; coexistence of other malignant diseases; and thyroid cancer relapsed.

2.2. Data collection

Data, including demographics (age and gender), anthropometrics (blood pressure, heart rate, and body mass index [BMI]), risk factors (obesity [BMI $\geq$ 28 kg/m^2], underweight [BMI $<$ 18.5 kg/m^2], smoking status, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and family history of ASCVD), laboratory indices (hemoglobin concentration, serum creatinine, fasting plasma glucose, TC, triglyceride, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, thyroid-stimulating hormone, free triiodothyronine, and free thyroxine [FT4], thyroxine-binding globulin, albumin, alanine aminotransferase, and C-reactive protein [CRP]), and medications prescribed at discharge, were extracted from the electronic health record. BMI was calculated using weight in kilograms divided by height in squared meters.[14] Estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula.[15] All the data were entered to the encrypted Excel sheet by 2 independent investigators to ensure the consistency and accuracy of the data. Stage of follicular thyroid cancer was defined based on previous description,[1] and since those with local or remote metastasis was excluded, all participants in the current study were classified as stage I, II, or III.

2.3. Study endpoint

Composite ASCVD, including myocardial infarction, ischemic stroke, and cardiovascular death, were defined as the study endpoint. In specific, the diagnosis of myocardial infarction was based on clinical symptoms (e.g., chest pain), electrocardiogram (e.g., ST-segment elevation or depression), and serum cardiac troponin-I concentration above the 99th percentile of upper normal limit. The diagnosis of ischemic stroke was based on neurological deficits (e.g., partial paralysis or muscle weakness) plus imaging evidence (e.g., computed tomography shows hypodense lesion). Cardiovascular death was the death related to cardiovascular causes. All these events were adjudicated by an independent physician based on the clinical findings and imaging evidence.

2.4. Statistical analysis

Based on the median serum TC level postthyroidectomy, participants were divided into low and high TC groups. Continuous variables were presented as mean and standard deviation or median and interquartile range, and between-group differences were assessed using Student *t* test or Mann–Whitney *U* test as appropriate. Categorical variables were presented as number and percentage and between-group differences were assessed using the chi-squared test or the Fisher exact test as appropriate. Factors associated with serum TC level postthyroidectomy was evaluated using univariable and multivariable linear regression analysis. In specific, factors with a P value $<$ .1 in the univariable analysis was entered to multivariable analyses. Incidence rate of individual and composite ASCVD was compared between these 2 groups, and incidence rate ratio (IRR) was reported. Factors contributing to the association of serum TC level and incident ASCVD was evaluated using the sequential cumulative regression analysis as previously described.[16] Hazard ratio (HR) and associated 95% confidence interval (CI) was reported. All analyses were conducted in the SPSS 23.0 software (IBM SPSS Statistics) and a 2-sided P value $<$ .05 was considered as statistical significance.

3. Results

3.1. Baseline characteristics

From January 2015 to January 2020, a total of 563 patients with documented follicular thyroid cancer were screened and 348 patients were included into the current analysis (Fig. 1). According to the median serum TC level, participants were divided into the low (TC 5.05 $\pm$ 0.32 mmol/L) and high (TC 5.48 $\pm$ 0.41 mmol/L) groups. Baseline characteristics comparisons were shown in Table 1. Compared to the low TC group, patients in the high TC group were older and more likely to have diabetes mellitus (P $<$ .05). Baseline CRP level was also higher in the high TC group (P $<$ .05). There were no significant differences in lipid profiles at baseline between these 2 groups. However, after thyroidectomy, the serum levels of TC and low density lipoprotein-cholesterol were higher in the high TC versus low TC groups (P $<$ .05). Serum levels of free triiodothyronine and FT4 were lower while thyroid-stimulating hormone level was higher in the high TC versus low TC groups (P $<$ .05).

3.2. Medications use at admission and at discharge

As presented in Table 2, there were no between-group differences in the use of anti-platelet drug, statins, anti-hypertensive, and anti-

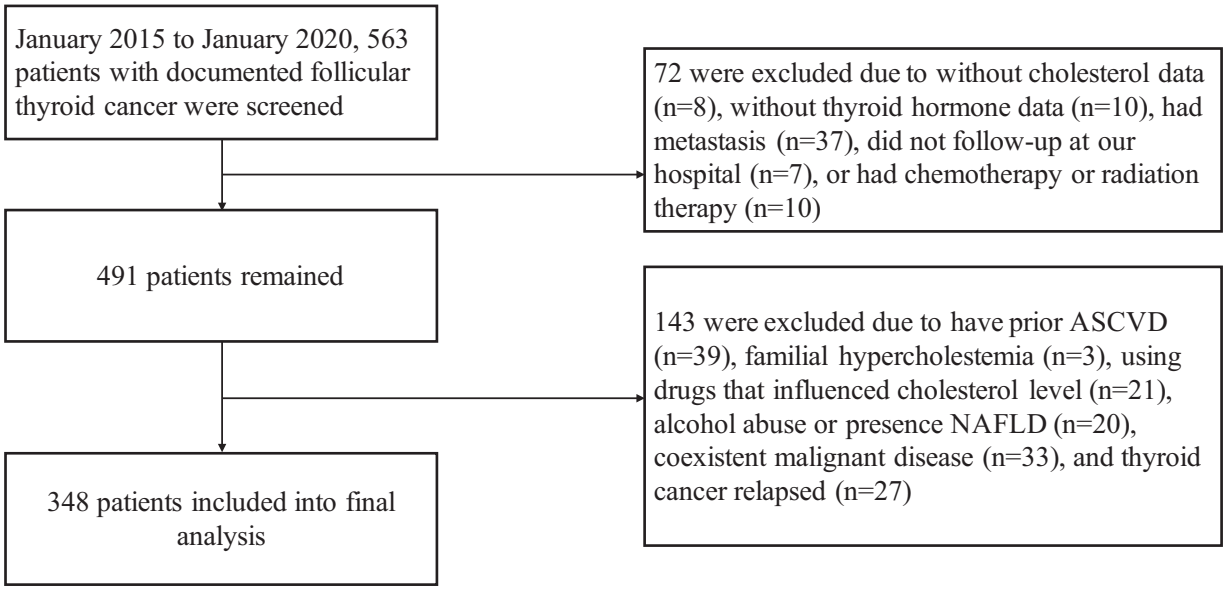

Figure 1. Study flowchart.

Table 1

Baseline characteristics.

Variables	Low TC group (n = 174)	High TC group (n = 174)
Age (years)	52.9 ± 10.8	57.6 ± 13.4†
Men, n (%)	62 (35.6)	65 (37.4)
Systolic blood pressure (mm Hg)	134.5 ± 14.3	135.9 ± 13.1
Diastolic blood pressure (mm Hg)	73.8 ± 10.2	74.2 ± 11.3
Heart rate (beat per minute)	80 ± 13	82 ± 14
Body mass index (kg/m^2)	23.7 ± 5.5	24.0 ± 6.1
Obesity, n (%)	36 (20.7)	39 (22.4)
Underweight, n (%)	15 (8.6)	18 (10.3)
Current smoker, n (%)	40 (23.0)	38 (21.8)
Hypertension, n (%)	82 (47.1)	88 (50.6)
Diabetes mellitus, n (%)	34 (19.5)	51 (29.3)†
Dyslipidemia, n (%)	68 (39.1)	65 (37.4)
Chronic kidney disease, n (%)	13 (7.5)	19 (10.9)
Family history of ASCVD, n (%)	25 (14.4)	28 (16.1)
Hemoglobin (g/dL)	13.9 ± 1.6	14.0 ± 1.8
Total cholesterol (mmol/L) at baseline	4.91 ± 0.25	4.97 ± 0.31
LDL-C (mmol/L) at baseline	2.96 ± 0.20	3.01 ± 0.28
HDL-C (mmol/L) at baseline	1.10 ± 0.04	1.10 ± 0.05
Triglyceride (mmol/L)* at baseline	1.81 (0.74–2.72)	1.83 (0.72–2.80)
Total cholesterol (mmol/L) at follow-up	5.05 ± 0.32	5.48 ± 0.41†
LDL-C (mmol/L) at follow-up	3.07 ± 0.25	3.51 ± 0.37†
HDL-C (mmol/L) at follow-up	1.11 ± 0.05	1.11 ± 0.06
Triglyceride (mmol/L)* at follow-up	1.85 (0.75–2.78)	1.89 (0.78–2.82)
Fasting blood glucose (mmol/L)	6.0 ± 0.7	6.0 ± 0.6
C-reactive protein (mg/dL)	6.3 ± 2.5	8.8 ± 3.4†
Creatinine (μmol/L)	75.4 ± 17.2	78.3 ± 19.6
eGFR (mL/min/1.73 m^2)	76.2 ± 13.3	74.1 ± 11.6
Thyroid-stimulating hormone (μIU/mL)	4.24 ± 0.87	5.19 ± 0.73†
Free triiodothyronine (pmol/L)	5.06 ± 0.63	5.01 ± 0.82†
Free thyroxine (pmol/L)	12.5 ± 2.1	11.2 ± 2.0†
Thyroxine-binding globulin (ng/mL)	37.8 ± 9.3	39.2 ± 10.1
Albumin (g/L)	39.6 ± 11.6	39.3 ± 11.2
Alanine aminotransferase (U/L)*	30.6 (14.2–47.8)	32.8 (15.1–49.4)
Stage I, n (%)	89 (51.1)	86 (49.4)
Stage II, n (%)	63 (36.2)	68 (39.1)
Stage III, n (%)	22 (12.7)	20 (11.5)

ASCVD = atherosclerotic cardiovascular disease, eGFR = estimated glomerular filtration rate, HDL-C = high density lipoprotein-cholesterol, LDL-C = low density lipoprotein-cholesterol, TC = total cholesterol.

* Presented as median (interquartile range).

† $P < .05$ versus low TC group.

diabetic drugs at baseline and at discharge. Notably, 31.6% (n = 55) and 39.7% (n = 69) of participants developed hypothyroidism within 3 months postthyroidectomy in the low and high TC groups ($P < .05$) respectively, and the use of levothyroxine during follow-up was similar between these 2 groups (29.3% vs 28.7%).

3.3. Factors associated with serum TC level after thyroidectomy

As shown in Table 3, in the univariable linear regression analysis, age, BMI, diabetes mellitus, CRP, FT4, baseline TC level, use of levothyroxine, and statin were associated with serum TC level postthyroidectomy. After multivariable adjustment, only diabetes mellitus, FT4, baseline TC level, use of levothyroxine, and statin remained significantly associated with serum TC level postthyroidectomy.

3.4. Incidence rate of ASCVD

Incidence rate of individual and composite ASCVD were shown in Table 4. The incidence rate was 5.1 per 100 person-years in the

Table 2

Medications use at admission and at discharge.

Variables	Low TC group (n = 174)	High TC group (n = 174)
At admission		
Anti-platelet drugs, n (%)	36 (20.7)	39 (22.4)
Statins, n (%)	29 (16.7)	38 (21.8)
Anti-hypertensive drugs, n (%)	61 (35.1)	64 (36.8)
Anti-diabetic drugs, n (%)	24 (13.8)	38 (21.8)
At discharge		
Anti-platelet drugs, n (%)	36 (20.7)	39 (22.4)
Statins, n (%)	32 (18.4)	40 (23.0)
Anti-hypertensive drugs, n (%)	61 (35.1)	64 (36.8)
Anti-diabetic drugs, n (%)	24 (13.8)	38 (21.8)
Levothyroxine, n (%)	51 (29.3)	60 (28.7)

TC = total cholesterol.

Table 3

Factors associated with serum TC level after thyroidectomy.

	Univariable		Multivariable	
	β	*P* value	β	*P* value
Age	0.15	.012	0.08	.25
Male	0.07	.16	–	–
Current smoker	0.09	.23	–	–
Body mass index	0.19	.004	0.11	.06
Diabetes mellitus	0.31	<.0001	0.23	.03
C-reactive protein	0.21	.032	0.15	.08
Thyroid-stimulating hormone	0.10	.13	–	–
Free thyroxine	−0.26	<.0001	−0.20	.009
Baseline TC level	0.21	.019	0.16	.04
Levothyroxine	−0.18	.007	−0.15	.02
Statins	−0.33	<.0001	−0.29	.006

TC = total cholesterol.

overall participants. Compared to the low TC group, the incidence rate of myocardial infarction was higher in the high TC group, with IRR of 2.11 and 95% CI of 1.10 to 4.20. There were no between-group differences in the incidence rate of ischemic stroke and cardiovascular death. The incidence rate of composite ASCVD was higher in the high TC versus low TC groups, with IRR 1.69 (95% CI: 1.07–2.69).

3.5. Factors associated with composite ASCVD

As presented in Figure 2, in unadjusted model, higher TC was associated with 73% higher risk of developing composite ASCVD. After adjustment for age and gender, HR was attenuated to 1.46. With additional adjustment for hypertension, diabetes mellitus, estimated glomerular filtration rate, and CRP, higher TC remained associated with a higher risk of ASCVD. After adjustment for hypothyroidism, the association of higher TC and composite ASCVD was attenuated into insignificance, with HR of 0.92 (95% CI 0.81–1.34). After further adjustment for levothyroxine use, the HR was increased to 0.97 (95% CI 0.93–1.42).

4. Discussion

To the best of our knowledge, the current study should be the first few studies to evaluate the association of serum TC level and incident ASCVD among patients with follicular thyroid cancer undergoing thyroidectomy. There are 3 main findings of the current study. First, the incidence rate of composite ASCVD was significantly higher in individuals with high serum TC level postthyroidectomy. Second, increased TC level was independently associated with an absolute 73% higher risk of composite ASCVD. Third, hypothyroidism seemed to play crucial roles in the association of increased serum TC level and incident ASCVD. These findings together suggest that presence of hypothyroidism might portend an increased risk of ASCVD among patients with follicular thyroid cancer postthyroidectomy, and levothyroxine therapy might help to mitigate the risk associated with hypothyroidism.

Numerous studies have demonstrated that increased serum TC level is associated with cardiovascular events and mortality in the general populations. For example, Jeong et al[17] reported that in a population-based cohort study, compared to the first and second tertiles, the third tertiles level of TC was associated with a 10% higher risk of mortality. Among hypertensive populations, Glazer et al[18] reported that an increased serum TC level was associated with 31% (95% CI: 23%–39%) higher risk of myocardial infarction. Interestingly and importantly, the risk of all-cause and cardiovascular mortality were higher in patients with differentiated thyroid cancer than their counterparts without differentiated thyroid cancer.[19] Consistent to prior report,[19] the current study also showed that patients with follicular thyroid cancer had a high incidence rate of ASCVD, with an incidence rate of 5.1 per 100 person-years among the overall participants. In addition, the incidence rate of ASCVD was significantly higher among patients with high serum TC level. These findings together suggest that the burden of ASCVD in patients with follicular thyroid cancer was high, which might be partly attributed to the increased TC level postthyroidectomy. To confirm this hypothesis, we thereafter evaluated the factors associated with serum TC level and the findings suggested that diabetes mellitus, reduced FT4 and increased baseline TC level were associated with increased TC level, while the use of levothyroxine and statin were associated with reduced TC level postthyroidectomy. These findings had important clinical implications. For instance, maintaining FT4 level at a normal range using levothyroxine therapy might help to prevent hypercholestemia after thyroidectomy, which in turn might reduce the incidence of ASCVD.

It is noted that before adjustment for other potential risk factors, increased TC was associated with an absolute 73% higher hazards of ASCVD. Causal relationship between TC and ASCVD has been substantially demonstrated in the general populations.[20–23] However, the association of TC and ASCVD in patients with follicular thyroid cancer after thyroidectomy has been less well studied. As mentioned above, thyroid gland is a key endocrine organ which regulates cholesterol metabolism. One recent study has shown that serum TC level was markedly

Table 4

Incidence rate of ASCVD (per 100 person-years).

	High TC group		Low TC group			
	Follow-up (years)					*P* value
	781.9		765.2			
Study endpoint	N	Incidence rate	N	Incidence rate	Incidence rate ratio 95% CI	
Myocardial infarction	s	3.6	13	1.7	2.11 (1.10–4.20)	.02
Ischemic stroke	15	1.9	11	1.4	1.33 (0.61–2.99)	.48
Cardiovascular death	7	0.9	5	0.7	1.37 (0.42–4.72)	.61
Composite ASCVD	50	6.4	29	3.8	1.69 (1.07–2.69)	.02

ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, TC = total cholesterol.

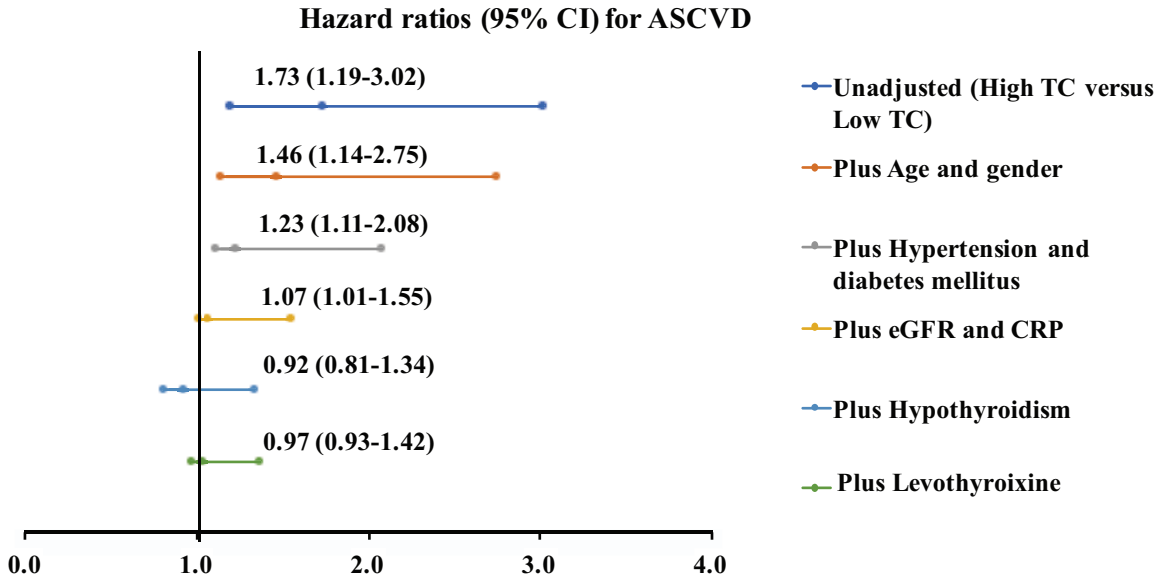

Figure 2. Sequential accumulative regression model. ASCVD = atherosclerotic cardiovascular disease, CI = confidence interval, CRP = C-reactive protein, eGFR = estimated glomerular filtration rate, TC = total cholesterol.

increased in patients with thyroid cancer following thyroidectomy, resulting in hypercholesterolemia.[24] Consistent to prior report,[24] in the current study, after thyroidectomy, serum FT4 level was inversely related to serum TC level and the use of levothyroxine was associated with reduced serum TC level, supporting the notion that hypothyroidism after thyroidectomy was independently associated with serum TC elevation.[24]

We used sequential cumulative regression models to evaluate factors contributing to the association of TC and incident ASCVD. Notably, after gradual adjustment for traditional risk factors, the HR for ASCVD remained statistically significant. With further adjustment for hypothyroidism, the HR was attenuated to statistical insignificance. These findings suggested that the mechanism underlying the association of TC level and incident ASCVD was attributed to hypothyroidism. Notably, after further adjustment for levothyroxine use, the HR was increased slightly, indirectly suggesting that the use of levothyroxine might play a protective role in preventing ASCVD development. Indeed, results from prior studies supported that insufficient levothyroxine replacement after thyroidectomy might contribute to the increased risk of cardiovascular events.[25–27]

There are some limitations of current study. First, this was a retrospective study and findings from the current analysis should not draw any causal relationship. Second, although we have adjusted for potential covariates, undetected and unmeasured covariates might still exist and influence the association of TC and ASCVD. Third, this was a study of Chinese populations and whether these findings can be extrapolated to other ethnic groups was unknown. Fourth, findings from the current analysis should not be applied to patients with local or remote metastasis and also should not be extrapolated to patients with non-follicular thyroid cancer. Last but not the least, we only have collected the serum cholesterol level at baseline after thyroxin usage in hypothyroidism postthyroidectomy group. Therefore, we could not assess the alteration of cholesterol throughout the study. Further studies are needed to evaluate the trajectory of serum cholesterol level after thyroxin usage in these populations.

5. Conclusion

In conclusion, the current study shows that in patients with follicular thyroid cancer, the incidence of ASCVD was high. Increased serum TC level was associated with ASCVD, which might be attributed to hypothyroidism postthyroidectomy. The use of levothyroxine might be helpful to prevent hypercholestemia and reduce the incidence of ASCVD. Further prospective studies are needed to corroborate the current preliminary findings.

Acknowledgment

We appreciate very much for our colleagues who help to adjudicate the clinical outcomes.

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Conceptualization: Guoding Huang.
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