BJS Open, 2022, zrac079
https://doi.org/10.1093/bjsopen/zrac079
Original Article

Attaining biochemical euthyroidism early after total thyroidectomy in Graves' disease may lower long-term morbidity risk

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Abstract

Background: The relationship between good early control of thyroid hormone levels after thyroidectomy for Graves' disease (GD) and subsequent risks of mortality and morbidities is not well known. The aim of this study was to examine the association between thyroid hormone levels within a short interval after surgery and long-term mortality and morbidity risks from a population-based database.

Methods: Patients with GD who underwent complete/total thyroidectomy between 2006 and 2018 were selected from the Hong Kong Hospital Authority clinical management system. All patients were classified into three groups (euthyroidism, hypothyroidism, and hyperthyroidism) according to their thyroid hormone levels at 6, 12, and 24 months after surgery. Cox proportional hazards models were performed to compare the risks of all-cause mortality, cardiovascular disease (CVD), Graves' ophthalmopathy, and cancer.

Results: Over a median follow-up of 68 months with 5709 person-years, 949 patients were included for analysis (euthyroidism, $n = 540$; hypothyroidism, $n = 282$; and hyperthyroidism, $n = 127$). The hypothyroidism group had an increased risk of CVD (HR = 4.20, 95 per cent c.i. 2.37 to 7.44, $P < 0.001$) and the hyperthyroidism group had an increased risk of cancer (HR = 2.14, 95 per cent c.i. 1.55 to 2.97, $P < 0.001$) compared with the euthyroidism group. Compared with patients obtaining euthyroidism both at 6 months and 12 months, the risk of cancer increased in patients who achieved euthyroidism at 6 months but had an abnormal thyroid status at 12 months (HR = 2.33, 95 per cent c.i. 1.51 to 3.61, $P < 0.001$) and in those who had abnormal thyroid status at 6 months but achieved euthyroidism at 12 months (HR = 2.52, 95 per cent c.i. 1.60 to 3.97, $P < 0.001$).

Conclusions: This study showed a higher risk of CVD in postsurgical hypothyroidism and a higher risk of cancer in hyperthyroidism compared with achieving euthyroidism early after thyroidectomy. Patients who were euthyroid at 6 months and 12 months had better outcomes than those achieving euthyroidism only at 6 months or 12 months. Attaining biochemical euthyroidism early after thyroidectomy should become a priority.

Introduction

Graves' disease (GD) is the most prevalent cause of thyrotoxicosis and the prevalence varies from 1 to 1.5 per cent of the general population[1]. Anti-thyroid drugs (ATDs) are an effective initial treatment but persistent or relapsed GD occurs in half of the patients when ATDs are withdrawn. A more definitive treatment such as radioiodine therapy (I-131) or surgery (near-total or total thyroidectomy) is recommended for patients with persistent or relapsed GD[2–4]. One key benefit of surgery over other treatments is the rapid control of hyperthyroidism and this may lead to better patient outcomes over time[5–8]. However, attaining euthyroidism with levothyroxine replacement early after surgery is often difficult because of the long half-life of levothyroxine, narrow therapeutic window, variations in bioavailability and pharmacodynamics, and non-compliance to treatment[9]. One previous study reported the average time of attaining biochemical euthyroidism after surgery to be more than 3 months[10]. Therefore, early monitoring of thyroid hormones, including serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) levels is important after surgery.

Although it has been reported that patients with long-standing mild hypothyroidism or hyperthyroidism may have increased risks of cardiovascular disease (CVD) and cardiac death than individuals who are euthyroid[11–15], the relationship between

Received: April 08, 2022. **Accepted:** April 23, 2022

good early control of thyroid hormone levels after thyroidectomy and subsequent risks of mortality and morbidity is not well known. With more recent studies favouring surgery as the preferred therapy for GD[16], further research evaluating the impact of postoperative thyroid status on the long-term outcomes in patients with GD is essential with the hypothesis that GD patients who could attain biochemical euthyroidism early after surgery may have lower all-cause mortality and morbidity risks over time than those who did not.

This study aimed to estimate the incidence of euthyroidism within a short interval after surgery and to determine the likely association between achieving biochemical euthyroidism early after complete or total thyroidectomy and the outcomes of all-cause mortality, CVD, Graves' ophthalmopathy, and cancer in patients with GD.

Method

Study population

The authorized approval for this present study was obtained from the local institutional review board (UW 17–277). Data were collected from the territory-wide prospectively coded database (the Hong Kong Hospital Authority clinical management system (CMS)), which started in 1998. Connecting all 41 public hospitals and clinics, this electronic database system has a coverage rate of 90 per cent of all inpatient healthcare services in the region. The completeness rates of 100 per cent and 99.98 per cent of patients' demographic and prescription details have been reported in previous research, validating the quality of the CMS dataset[17]. A high positive predictive value also has been confirmed by checking the medical records[18,19]. Given that certain data were not completely certified until 2005, the present study collected data from 1 January 2006 to 31 December 2018. During this interval, those having a diagnosis of GD who underwent total thyroidectomy and received oral levothyroxine replacement afterwards were included. ICD-9-CM diagnosis codes were used to determine the definition of GD, and ICD-9-CM procedure codes were used to identify thyroidectomy. Patients were excluded if they did not receive levothyroxine replacement therapy, had one time, or no test of postoperative thyroid hormones, had other thyroid status, had less than 12 months follow-up after surgery, or were aged under 18 years old.

Data regarding demographic characteristics were extracted including age, sex, BMI, thyroid hormone tests, systolic/diastolic blood pressure, serum triglyceride, serum low-density lipoprotein cholesterol, blood glucose, and estimated glomerular filtration rate. The disease duration of GD (from the diagnosis date of GD to the date of total thyroidectomy), previous treatment records of ATDs and radioactive iodine (RAI), drug dispensation of levothyroxine, comorbidity calculated by the Charlson comorbidity index (CCI), and outcome events of mortality and morbidity were also obtained. Outcome events and treatment procedures were identified using the ICD-9-CM and International Classification of Primary Care, version 2 (ICPC-2) codes (*Table S1*).

Group assignment

With 2–3 months after surgery, patients had their serum TSH and FT4 levels checked and these were repeated 6 months after

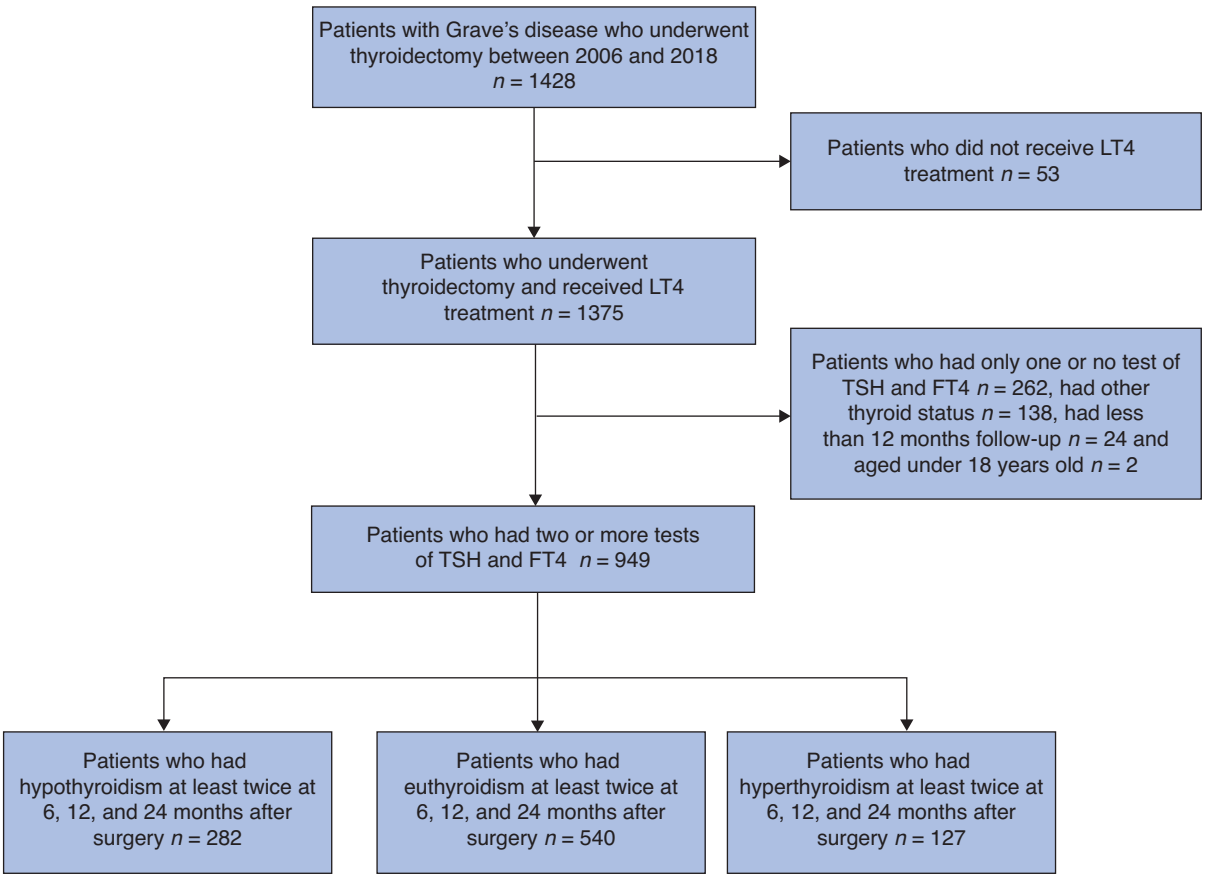

Fig. 1 Flow chart of Graves' disease patients with different thyroid status after thyroidectomy
LT4, levothyroxine; FT4, free thyroxine; TSH, thyroid-stimulating hormone

surgery[20]. Based on the definitions from previous studies[21–23], the identification of thyroid status in this present study was according to the serum TSH level (reference range 0.35–4.78 mIU/l) and FT4 level (reference range 12–23 pmol/l).

Patients with GD after thyroid surgery were categorized into the following groups according to their thyroid status:

- Euthyroidism group, which included patients with normal serum TSH and FT4 levels
- Hypothyroidism group, which included patients with overt hypothyroidism who had a TSH level of more than 4.78 mIU/l with an FT4 level below normal (<12 pmol/l) or those with subclinical hypothyroidism who had a TSH level of more than 4.78 mIU/l and a normal FT4 level (12–23 pmol/l)
- Hyperthyroidism group, which included patients with overt hyperthyroidism who had a TSH level of <0.35 mIU/l with an elevated FT4 level (>23 pmol/l) or those with subclinical hyperthyroidism who had a TSH level of <0.35 mIU/l and a normal FT4 level (12–23 pmol/l).

Given the fluctuation of thyroid hormone levels over time, the thyroid status at three pre-determined time points, including 6, 12, and 24 months was selected to determine the thyroid status in a short interval after surgery. If patients had the same diagnosis two or more times at these three pre-determined time points, they were categorized into the corresponding groups.

The study outcomes included all-cause mortality, CVD, Graves' ophthalmopathy, and primary cancer. The index date of all

Table 1 Baseline characteristics of patients with Graves' disease with different thyroid hormone levels after thyroidectomy

Baseline characteristics	Total ($n = 949$)	Euthyroidism ($n = 540$)	Hypothyroidism ($n = 282$)	Hyperthyroidism ($n = 127$)	P
General information					
Age, (years) mean (s.d.)	41.70 (12.67)	43.04 (12.46)	37.89 (11.79)	44.50 (13.64)	<0.001*
Age group					0.006*
≤60 years	809 (85.2)	451 (83.5)	256 (90.8)	102 (80.3)	
>60 years	140 (14.8)	89 (16.5)	26 (9.2)	25 (19.7)	
Sex ratio (M:F)					<0.001*
Female	727 (76.6)	425 (78.7)	195 (69.1)	107 (84.3)	
Male	222 (23.4)	115 (21.3)	87 (30.9)	20 (15.7)	
Clinical parameters					
Laboratory results, mean (s.d.)					
TSH, mIU/l	3.61 (9.00)	3.56 (8.20)	3.68 (8.40)	3.65 (12.82)	0.983
FT4, pmol/l	15.44 (6.80)	15.13 (6.59)	15.23 (6.50)	17.21 (7.99)	0.007*
BMI, kg/m^2	23.35 (3.96)	23.21 (3.96)	23.73 (4.12)	23.13 (3.51)	0.515
SBP, mmHg	126.79 (17.42)	127.49 (18.02)	124.68 (16.04)	127.87 (17.16)	0.299
DBP, mmHg	74.55 (11.82)	74.85 (11.67)	74.06 (12.61)	74.18 (10.97)	0.802
LDL-C, mmol/l	2.69 (0.91)	2.67 (0.90)	2.74 (0.89)	2.71 (1.03)	0.834
Fasting glucose, mmol/l	1.22 (0.81)	1.21 (0.80)	1.25 (0.95)	1.23 (0.46)	0.924
Triglyceride, mmol/l	5.45 (1.14)	5.48 (1.19)	5.34 (1.03)	5.49 (1.13)	0.556
eGFR, ml/min/1.73 m^2	136.16 (36.79)	135.65 (37.06)	137.08 (35.48)	136.32 (38.70)	0.868
Previous ATD	731 (77.0)	418 (77.4)	217 (77.0)	96 (75.6)	0.908
Previous RAI	86 (9.1)	50 (9.3)	24 (8.5)	12 (9.5)	0.927
Disease status before surgery					
GD duration, (months), mean (s.d.)	34.19 (31.11)	33.67 (30.91)	34.84 (30.94)	34.93 (32.50)	0.840
GD duration					0.636
<24 months	439 (46.3)	257 (47.6)	125 (44.3)	57 (44.9)	
≥24 months	510 (53.7)	283 (52.4)	157 (55.7)	70 (55.1)	
LT4 replacement					
LT4 dose (μg/kg/day), mean (s.d.)	1.57 (0.37)	1.59 (0.34)	1.50 (0.39)	1.69 (0.39)	0.008*
LT4 dose (μg/day)					0.369
≤50	78 (8.2)	41 (7.6)	25 (8.9)	12 (9.4)	
75	120 (12.6)	69 (12.8)	41 (14.5)	10 (7.9)	
100	718 (75.7)	407 (75.4)	210 (74.5)	101 (79.5)	
200	33 (3.5)	23 (4.3)	6 (2.1)	4 (3.1)	
Comorbidities					
CHD	7 (0.7)	5 (0.9)	1 (0.4)	1 (0.8)	0.679
HF	23 (2.4)	19 (3.5)	2 (0.7)	2 (1.6)	0.062
Stroke	10 (1.1)	4 (0.7)	3 (1.1)	3 (2.4)	0.306
AF	42 (4.4)	28 (5.2)	13 (4.6)	1 (0.8)	0.166
DM	44 (4.6)	27 (5.0)	9 (3.2)	8 (6.3)	0.327
HT	72 (7.6)	45 (8.3)	13 (4.6)	14 (11.0)	0.052
Ophthalmopathy	400 (42.2)	244 (45.2)	96 (34.0)	60 (47.2)	0.004*
Cancer	31 (3.3)	13 (2.4)	9 (3.2)	9 (7.1)	0.037*
CCI†, mean (s.d.)	1.10 (1.38)	1.18 (1.40)	0.83 (1.24)	1.39 (1.51)	<0.001*
CCI†					<0.001*
1	663 (69.9)	361 (66.9)	225 (79.8)	77 (60.6)	
2	171 (18.0)	112 (20.7)	31 (11.0)	28 (22.0)	
3	43 (4.5)	23 (4.3)	10 (3.5)	10 (7.9)	
4 or above	72 (7.6)	44 (8.1)	16 (5.7)	12 (9.4)	

Values are *n* (%) unless otherwise indicated. TSH, thyroid-stimulating hormone; FT4, free thyroxine; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; LT4, levothyroxine; ATD, anti-thyroid drug; RAI, radioactive iodine; CHD, coronary heart disease; HF, heart failure; AF, atrial fibrillation; DM, diabetes; HT, hypertension; CCI, Charlson comorbidity index. *Significant difference ($P < 0.05$) between groups by univariable linear regression or binary logistic regression. †The calculation of CCI does not include acquired immune deficiency syndrome.

patients with GD included in the analysis was determined as the date of complete or total thyroidectomy. Patients were followed from the index date and censored at the date of death, outcome events, and the last health service utilization, whichever came first.

Statistical analyses

The baseline characteristics of all patients were summarized with descriptive statistics. Multiple imputation was applied to address the missing data[24]. The incidence rate of each outcome event was calculated using the number of event cases divided by the person-years. Multivariable Cox proportional hazards models were conducted with multiply imputed data sets to determine the association between thyroid status after thyroid surgery and the outcome events. Estimation models performed in the comparisons across three groups were adjusted for variables at baseline. Results estimated from the Cox hazards models were shown as HRs and their 95 per cent confidence intervals (c.i.). Kaplan–Meier survival curves were plotted to study the survival probabilities of each outcome event by groups over an interval of 10-year follow-up.

Sensitivity analyses were performed to test the robustness of the findings from primary analyses. The risk comparisons were conducted across groups by censoring the follow-up interval at 5 or 10 years after surgery. To compare the impact of achieving euthyroidism early on the long-term outcomes, sensitivity analyses were compared according to thyroid status at 6 months, 12 months, and at both 6 and 12 months. The first analysis compared abnormal thyroid status and euthyroidism at both 6 months and 12 months, and the second analysis compared achieving euthyroidism only at 6 months or 12 months and obtaining persistently normal thyroid status.

Statistical analyses were performed with STATA version 16.0, (StataCorp, College Station, Texas, USA). *P* values <0.05 were indicated to be significant.

Results

Figure 1 shows the flow of patients in this study. Between 2006 and 2018, 949 eligible patients were included in the analysis of the study; 540 (56.9 per cent) were in the euthyroidism group, 282

Table 2 Cumulative incidence and incidence rate of all-cause mortality, cardiovascular diseases, Graves' ophthalmopathy, and cancer for Graves' disease patients with different thyroid status after thyroidectomy

Event	Cumulative incidence		Crude incidence rate (cases/1000 person-years)			Median follow-up interval (months)
	Cases with event	Rate (%)	Estimate	95% c.i.*	Person-years	
Total (*n* = 949)						
All-cause mortality	10	1.1	1.75	(0.84, 3.22)	5709	68
CVD	19	2.1	3.38	(2.04, 5.28)	5619	67
Ophthalmopathy	89	16.2	16.92	(13.59, 20.82)	5260	65
Cancer	51	5.6	9.35	(6.96, 12.29)	5455	65
Euthyroidism (*n* = 540)						
All-cause mortality	6	1.1	1.96	(0.72, 4.26)	3064	64
CVD	10	2.0	3.32	(1.59, 6.10)	3014	64
Ophthalmopathy	47	15.9	16.45	(12.09, 21.88)	2857	58
Cancer	26	4.9	8.86	(5.79, 12.99)	2933	60
Hypothyroidism (*n* = 282)						
All-cause mortality	3	1.1	1.59	(0.33, 4.66)	1883	78
CVD	8	2.9	4.33	(1.87, 8.53)	1848	74
Ophthalmopathy	29	15.6	16.98	(11.37, 24.38)	1708	73
Cancer	14	5.1	7.70	(4.21, 12.93)	1817	74
Hyperthyroidism (*n* = 127)						
All-cause mortality	1	0.8	1.31	(0.03, 7.30)	763	72
CVD	1	0.8	1.32	(0.03, 7.36)	757	73
Ophthalmopathy	13	19.4	18.70	(9.96, 31.97)	695	72
Cancer	11	9.3	15.60	(7.79, 27.92)	705	68

CVD, cardiovascular disease. *95 per cent c.i. of incidence rates were constructed by Poisson distribution.

Table 3 Hazard ratios of all-cause mortality, cardiovascular diseases, Graves' ophthalmopathy, and cancer according to thyroid status

Event	Hypothyroidism *versus* euthyroidism			Hyperthyroidism *versus* euthyroidism		
	HR	95% c.i.	P	HR	95% c.i.	P
Primary analysis*						
All-cause mortality	1.71	(0.86, 3.40)	0.125	0.41	(0.13, 1.25)	0.116
CVD	4.20	(2.37, 7.44)	<0.001†	0.84	(0.29, 2.43)	0.745
Ophthalmopathy	1.05	(0.84, 1.30)	0.682	0.99	(0.75, 1.31)	0.938
Cancer	1.16	(0.86, 1.57)	0.332	2.14	(1.55, 2.97)	<0.001†

CVD, cardiovascular disease;. *Primary model is adjusted for age, sex, BMI, thyroid-stimulating hormone, free thyroxine, low-density lipoprotein cholesterol, systolic/diastolic blood pressure, fasting glucose, triglyceride, estimated glomerular filtration rate, history of cardiovascular disease, diabetes, and hypertension, previous treatment with anti-thyroid drugs and radioiodine therapy, levothyroxine dosage, Graves' disease duration, and Charlson comorbidity index. †Significant at 0.05 level by multivariable Cox proportional hazard regression model.

(29.7 per cent) were in the hypothyroidism group, and 127 (13.4 per cent) were in the hyperthyroidism group respectively. There was no difference in all baseline variables between the patients excluded and those included in this present study (*Table S2*).

Table 1 displays the baseline characteristics of patients with GD undergoing total thyroidectomy. The mean(s.d.) age of all study participants was 41.70(12.67) years, and 809 (85.3 per cent) were aged under 60 years. Their mean disease duration of GD before undergoing thyroidectomy was 34.19 months. The mean(s.d.) dose of levothyroxine was higher in the hyperthyroidism group at 1.69(0.39) μg/kg/day than that in the euthyroidism group (1.59(0.34) μg/kg/day) and hypothyroidism (1.50(0.39) μg/kg/day) group. The proportion of patients with hyperthyroidism using a 100 μg/day dosage of levothyroxine was 82.1 per cent; higher than that in those with euthyroidism (78.7 per cent) and hypothyroidism (76.1 per cent). Of the cohort, 731 (77.0 per cent) had pre-treatment with ATDs and 86 (9.1 per cent) received RAI therapy. No difference in the proportions having pre-treatment with ATDs and RAI was found across the groups.

Table 2 presents the incidence rate of primary outcome events in participants over the follow-up interval. With a total follow-up of 5709 person-years, all individuals in the study had a median follow-up of 68 months. Patients in the hypothyroidism group had a higher incidence rate of CVD (euthyroidism *versus* hypothyroidism *versus* hyperthyroidism, 3.32 *versus* 4.33 *versus* 1.32 per 1000 person-years). The incidence rate of cancer was higher in the hyperthyroidism group (euthyroidism *versus* hypothyroidism *versus* hyperthyroidism, 8.86 *versus* 7.70 *versus* 15.60 per 1000 person-years) than in the euthyroidism and hypothyroidism group. The individuals in the hyperthyroidism group had a slightly higher incidence rate of ophthalmopathy (euthyroidism *versus* hypothyroidism *versus* hyperthyroidism, 16.45 *versus* 16.98 *versus* 18.70 per 1000 person-years).

Table 3 shows the risk comparisons of outcome events estimated by multivariable Cox proportional hazard models. Compared with those obtaining euthyroidism shortly after thyroidectomy, patients in the hypothyroidism group were at an increased risk of CVD (HR = 4.20, 95 per cent c.i. 2.37 to 7.44, $P < 0.001$) and patients in the hyperthyroidism group had a higher risk of cancer (HR = 2.14, 95 per cent c.i. 1.55 to 2.97, $P < 0.001$). No significant difference was observed in all-cause mortality and Graves' ophthalmopathy across the three groups.

Figure 2 shows the Kaplan–Meier curves over a 10-year follow-up interval in patients with GD by different thyroid status within a short interval after thyroidectomy. Compared with individuals who achieved euthyroidism shortly after surgery, the survival curves showed that a greater risk of CVD was observed in patients who were hypothyroid, whereas a higher risk of cancer was found in patients who were

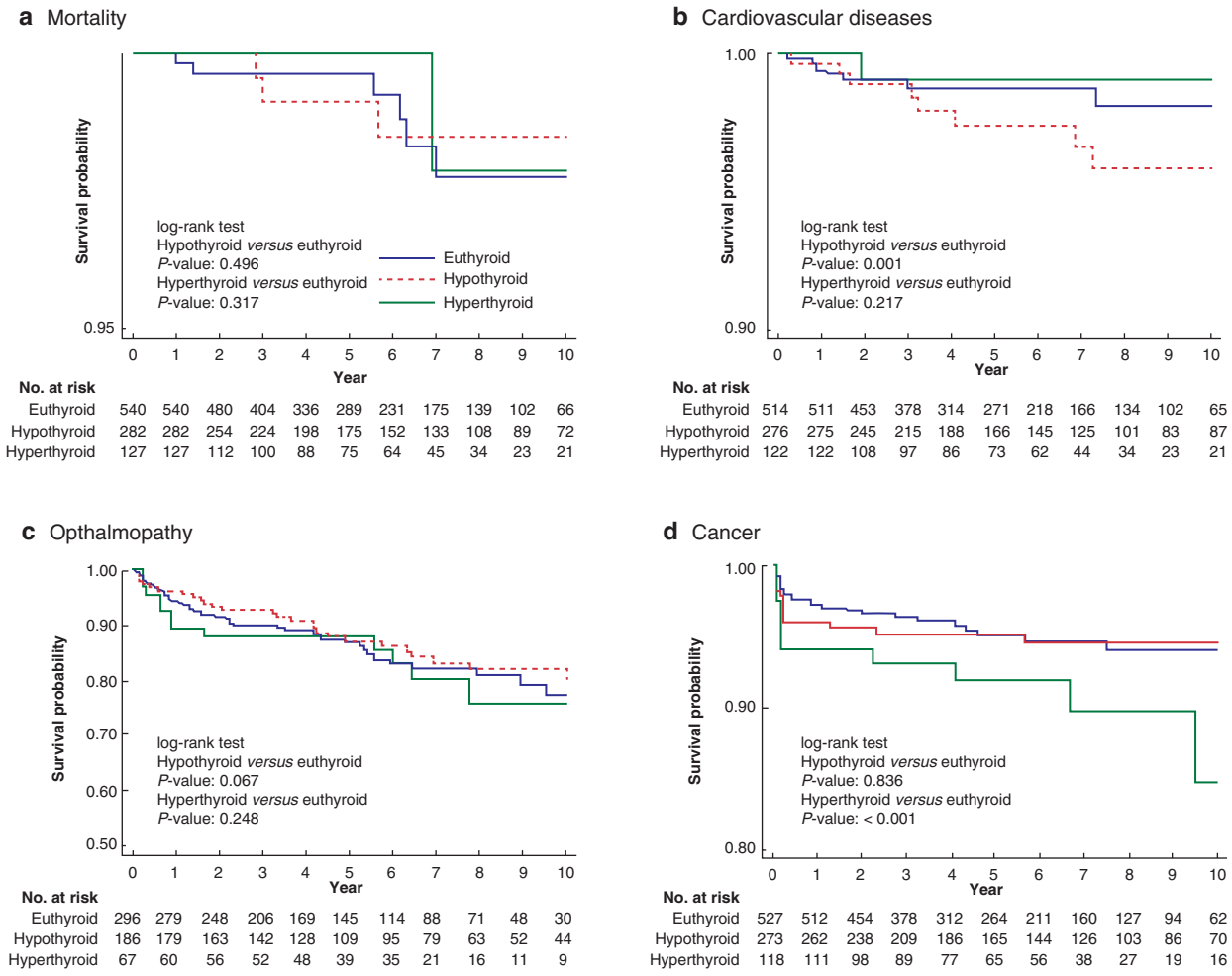

Fig. 2 Kaplan–Meier curves in patients with Graves' disease with different thyroid status after thyroidectomy
a All-cause mortality. **b** Cardiovascular diseases. **c** Graves' ophthalmopathy. **d** Cancer.

hyperthyroid. Similar distributions of survival curves were observed in the other estimations of all-cause mortality and ophthalmopathy across groups.

Table S3 indicates the results of patients assigned to three groups according to their thyroid status at 6 months, 12 months, and both at 6 and 12 months after surgery. Results from the sensitivity analyses were consistent with those from the primary analysis. Compared with euthyroid patients at 6 months, increased risks of CVD (HR = 2.83, 95 per cent c.i. 1.48 to 5.38, $P = 0.002$) and cancer (HR = 1.62, 95 per cent c.i. 1.17 to 2.23, $P = 0.003$) were observed in hypothyroid patients and a higher risk of cancer (HR = 1.83, 95 per cent c.i. 1.23 to 2.71, $P = 0.003$) was found in hyperthyroid patients. Patients who were hypothyroid at 12 months after surgery were at an increased risk of CVD (HR = 4.24, 95 per cent c.i. 1.75 to 10.26, $P = 0.001$). The comparisons also showed a greater risk of cancer (HR = 2.33, 95 per cent c.i. 1.63 to 3.33, $P < 0.001$) in patients with hyperthyroidism than in those with euthyroidism at 12 months. Moreover, compared with patients who achieved euthyroidism both at 6 months and at 12 months, the risk of cancer increased in patients who only achieved euthyroidism at 6 months combined with abnormal thyroid status at 12 months (HR = 2.33, 95 per cent c.i. 1.51 to 3.61, $P < 0.001$) and in those who were at abnormal thyroid status at 6 months but achieved euthyroidism at 12 months (HR = 2.52, 95 per cent c.i. 1.60 to 3.97, $P < 0.001$).

Table S4 presents the sensitivity analyses performed by estimation models censoring the interval at 5-year and 10-year follow-ups. Most of the sensitivity analyses were in line with the main estimations. Compared with the euthyroidism group, hypothyroidism was associated with a higher risk of CVD, and hyperthyroidism was associated with a higher risk of cancer at the 5-year and 10-year follow-ups. A higher risk of all-cause mortality (HR = 3.32, 95 per cent c.i. 1.06 to 10.25, $P = 0.039$) was identified in patients with hypothyroidism than in euthyroid individuals at the 5-year follow-up.

Discussion

In line with the initial hypothesis, the present study shows that individuals who attained biochemical euthyroidism early after their complete or total thyroidectomy for GD had lower subsequent risks of morbidity than those who did not.

To account for possible fluctuations in thyroid hormone levels shortly after surgery, this study screened the thyroid hormone levels over three pre-determined time points (6, 12, and 24 months) after thyroid surgery to determine patients who were truly euthyroid in the postoperative interval. From these results, patients who were hypothyroid were at a higher risk of CVD, whereas those who were hyperthyroid were at a higher risk of cancer than those who were euthyroid at 6 months or 12 months. Furthermore, relative to patients who attained euthyroidism both at 6 months and at 12 months, the risk of cancer increased among those who had not persistently achieved normal thyroid status.

There was no significant difference in all-cause mortality among patients who were hypothyroid or hyperthyroid and those individuals who achieved euthyroidism early after thyroidectomy. Consistent with this study, previous findings from other studies did not support that hypothyroidism or hyperthyroidism increases the risk of mortality[25,26]. A retrospective cohort study of 2730 patients with a 4-year follow-up by Rodondi *et al.* found that subclinical hypothyroidism was not associated with an increased risk of total mortality[25]. In a large prospective cohort study estimating the association between baseline thyroid status and death, Cappola *et al.* also showed no difference in all-cause mortality between the subclinical hyperthyroidism group and euthyroidism group[26]. Contrary to these findings, the retrospective cohort study by Selmer *et al.* reported that overt and subclinical hyperthyroidism was associated with a higher risk of all-cause mortality[27] and Mitchell *et al.* found that patients with hypothyroidism and hyperthyroidism had increased mortality risk compared with those who had normal thyroid status[28]; however, these studies relying solely on serum TSH levels may not reliably reflect the true underlying thyroid status. Therefore, the current findings may provide more robust evidence to explain the impact of thyroid dysfunction on the subsequent risk of mortality.

Given that hypothyroidism or hyperthyroidism is usually accompanied by impaired cardiac contractility, systolic or diastolic dysfunction, and systemic vascular resistance[29], clinical assessment is needed for the association between thyroid status after thyroid surgery and cardiovascular morbidities. From a meta-analysis involving 1 898 314 participants, Ning *et al.* found higher risks of ischaemic heart disease and cardiac mortality in patients with hypothyroidism than those with euthyroidism[30]. In agreement with this, the present study shows a higher CVD risk in the hypothyroidism group compared with the euthyroidism group. This finding is also aligned with an individual analysis of 55 287 participants, where subclinical hypothyroid patients who had higher TSH levels (10.00 mIU/l or greater) had increased risks of coronary heart disease events and related death compared with euthyroid individuals[11]. It has been reported that low-density lipoprotein is increased in overt and subclinical hypothyroidism, and 90 per cent of patients with overt hypothyroidism had hypercholesterolemia[31–33]. The increased lipid levels might contribute to explaining the higher risk of CVD associated with hypothyroidism.

Some studies did not support the association between cardiovascular morbidities and thyroid status. Martin *et al.* estimated the cross-sectional impact of thyroid status on cardiovascular events and did not find increased risks of stroke or myocardial infarction with abnormal thyroid status[34]. Previous studies by Cappola *et al.* and Imaizumi *et al.* showed no impact of subclinical hypothyroidism on cerebrovascular disease[26,35]. Given the controversial data from articles, studies with strict criteria and convincing results are therefore merited. The survival analyses in the population-based cohort of the present study adjusted for many risk factors related to cardiovascular events (BMI, blood pressure, serum lipid levels, fasting glucose, and triglyceride), providing strengthened evidence.

Thyroid hormones have been reported to influence both cell multiplication of breast cancer and induce the process of angiogenesis of some cancer types[36]. Correspondingly, a greater risk of breast cancer has been found in those patients diagnosed with hyperthyroidism than those who were not[37]. In addition to studies indicating a higher cancer risk with thyroid dysfunction, the meta-analysis by Krashin *et al.* reported that subclinical and clinical hyperthyroidism increased the risk of several solid tumours, whereas hypothyroidism might reduce aggressiveness or delay the development of cancer[38]. In agreement with these findings, the present study found a higher risk of cancer in hyperthyroid patients but not in hypothyroid individuals. Although previous research has demonstrated the impact of thyroid dysfunction on several cancer types, the present study primarily focused on the overall cancer risk in patients with GD after surgical therapy. The finding that hyperthyroidism was associated with a higher risk of cancer than euthyroidism after surgery has provided complementary evidence for exploring the

risk factors related to thyroid dysfunction for primary cancer in patients with GD.

Thyroid status may also affect the development of ophthalmopathy, although the present study did not support the impact of thyroid dysfunction on the increased risk of this event. Given that limited studies have estimated the impact of thyroid status on thyroid-associated orbitopathy, the research by Eckstein *et al.* showed that euthyroid/hypothyroid patients developed significantly less severe and less active ophthalmopathy symptoms than those with hyperthyroidism[39]. The present study also found a relatively lower incidence rate of ophthalmopathy in euthyroid and hypothyroid patients than in those with hyperthyroidism. Moreover, patients with euthyroid/hypothyroid orbitopathy were found to have less impaired quality of life and working ability than those with hyperthyroid orbitopathy[40]. Therefore, patients undergoing thyroidectomy need to be monitored for the effects of thyroid abnormality on clinical manifestations at follow-up.

There are some limitations to the present study. First, the results may not be generalizable to older patients and those who had not undergone total thyroidectomy and used levothyroxine for the treatment of GD. Second, data on triiodothyronine is not sufficient, resulting in missing some overtly hypothyroid patients to be included in the analysis. Third, given that the group assignment was based on the test results of thyroid hormone levels of TSH and FT4, the change in thyroid hormone levels may lead to misclassification for transient thyroid abnormality. In terms of strengths, this is the first paper to estimate the impact of thyroid status after total thyroidectomy on all-cause mortality and other long-term outcomes. Few large retrospective studies have access to baseline and follow-up data. Risk estimations performed by models for longitudinal effects had adjustments with clinical parameters, disease duration, levothyroxine use, and history of co-morbidities, reducing confounding bias. This study could provide novel evidence for the effects of thyroid status on adverse outcomes among patients with GD undergoing thyroidectomy.

Obtaining euthyroidism shortly after thyroid surgery was associated with a lower risk of CVD compared with hypothyroidism, and a lower risk of cancer than hyperthyroidism in patients with GD undergoing thyroidectomy. Moreover, being euthyroid both at 6 months and at 12 months decreased the risk of cancer than achieving euthyroidism only at 6 months or at 12 months. Therefore, early monitoring and control of thyroid hormone levels after thyroid surgery is recommended as part of GD management.

Funding

This study was funded by the Health and Medical Research Fund Research Fellowship Scheme, Food and Health Bureau, Hong Kong SAR (ref. no. 17181051).

Acknowledgements

We thank the Central Panel on Administrative Assessment of External Data Requests, Hong Kong Hospital Authority Head Office, for the provision of hospital authority data. X.L. and C.K.H.W. contributed equally as first authors.

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Due to ethical concerns, supporting data cannot be made openly available.

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