In the Name of God

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Hypoparathyroidism and mortality after total thyroidectomy: A nationwide matched cohort study

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INTRODUCTION

Hypoparathyroidism (hypoPT) following total thyroidectomy (TT) remains common **(0.3%−20%)**, due to unintentional removal or damage to the parathyroid glands or their vascular supply.

Differences in hypoPT definitions is one explanation for differences in risks, however **surgical volume, extent of surgery or differences in reporting** have been shown to affect risks as well.

It is now well-known, that insufficient plasma levels of parathyroid hormone (PTH) are common immediately after TT. For most patients, this is only a transient condition. Only in a minority of patients with postoperative hypoPT, the condition will be a chronic disease. This disease can have severe consequences for the patients.

HypoPT has been found to have a negative impact on **quality of life**, and several studies have shown that hypoPT might affect **mortality**. However, some studies have reported increased mortality solely in nonsurgical hypoPT patients while others found no increased mortality in hypoPT patients at all. Besides suffering surgical complications, these patients will require daily medication and frequent monitoring of serum calcium levels. The condition is also associated with a higher risk of different **morbidities,** including **seizures, cardiovascular disease, infections, neuropsychiatric disorders and kidney complications**.

The latter has been suggested to be associated with **long-term treatment** involving oral calcium and active vitamin D, potentially leading to **kidney stones, nephrocalcinosis and chronic kidney disease** caused by ectopic calcifications in soft tissues.

Whether increased mortality could be attributed to the previously observed higher risk of kidney impairment in hypoPT remains **unknown**. In the present study, we used the Danish health registries to estimate the risk of hypoPT and mortality after TT.

2 | METHODS

This nationwide register-based **cohort study** compared all patients undergoing **first-time total thyroid surgery** between January 1998 and December 2017 and comparing them with a group of matched controls.

2.1 | Data sources

The Danish healthcare system is financed through income tax and is available to all Danish residents free of charge. Registration is mandatory for all hospitals and outpatient clinics in Denmark. The linkage of various registries in the Danish healthcare program is made possible through the use of the personal identification number known as ‘The Central Person Register’, which is required for accessing the healthcare system.

We used **three registries** for the present study.

-The Danish National Patient Registry (DNPR) has information on all hospital admissions and outpatient contacts since 1995. This includes discharge diagnoses, examinations, major treatments and operations.

-The Danish Civil Registration System (CRS) contains data on vital status including date of birth, immigration and death and also provides information on the family structure.

-Finally, we used The Danish National Prescription Registry to obtain data on prescriptions for active vitamin D. This register contains individual-level data on prescriptions filled by Danish residents at community pharmacies since 1994.

2.2 | *Patients*

Using the DNPR, we identified all patients who had thyroid surgery performed during the period 1998−2017 and classified the patients according to the type of thyroid surgery performed (TT in one procedure or in two or more procedures), using procedure codes in the DNPR. Individuals who underwent procedures **less than a TT** (such as hemithyroidectomy) were excluded, as well as **patients on treatment with active vitamin D before the operation, patients under 18 years of age** at the time of their first thyroid surgery and those **who did not survive 12 months after the surgery** (Figure 1).

Patients were classified according to indication for thyroid surgery that is, goiter, thyrotoxicosis or malignancy based on the most recent thyroid diagnosis code before surgery.

To avoid immortal time bias and to ensure that patients who had acquired hypoPT after surgery could be considered as chronic, the **index date was defined as 12 months after surgery.**

Patients who acquired hypoPT after surgery were defined as patients with a filled prescription for active vitamin D (calcitriol or equivalent medication 12 months postoperatively. Active vitamin D is mainly used to treat patients with hypoPT or renal insufficiency.
Further, patients were excluded if they had any preoperative use of active vitamin D. Accordingly, we only defined hypoPT in patients with a new need for long-term use of active vitamin D after TT.

2.3 | Comparison cohort

Individuals in the comparison cohort were identified from the background population which increased from 5,294,860 inhabitants in 1998 to 5,748,769 in 2017.

At the index date, patients in the study population were matched 1:10 with individuals from the background population on **sex, birth year** and **being alive on the index date using the CRS.**

Exclusion criteria for the comparison cohort were previous thyroid surgery, treatment with active vitamin D or having emigrated before the index date.

2.4 | Potential confounders

That is, factors associated with thyroidectomy, hypoPT and outcome (death), included: **age, sex, diabetes, hospital diagnosed hypertension, obesity and cardiovascular, pulmonary and autoimmune diseases**.

We considered both inpatient and outpatient diagnoses, that occurred within the 10-year period before the surgery. By this information, we calculated the **Charlson comorbidity index** (CCI), and the CCI was classified into groups of 0, 1–2 or 3+. The CCI has previously been used with high accuracy to control for confounding by comorbidity in Danish patients. We removed all thyroid cancer diagnoses from the CCI.

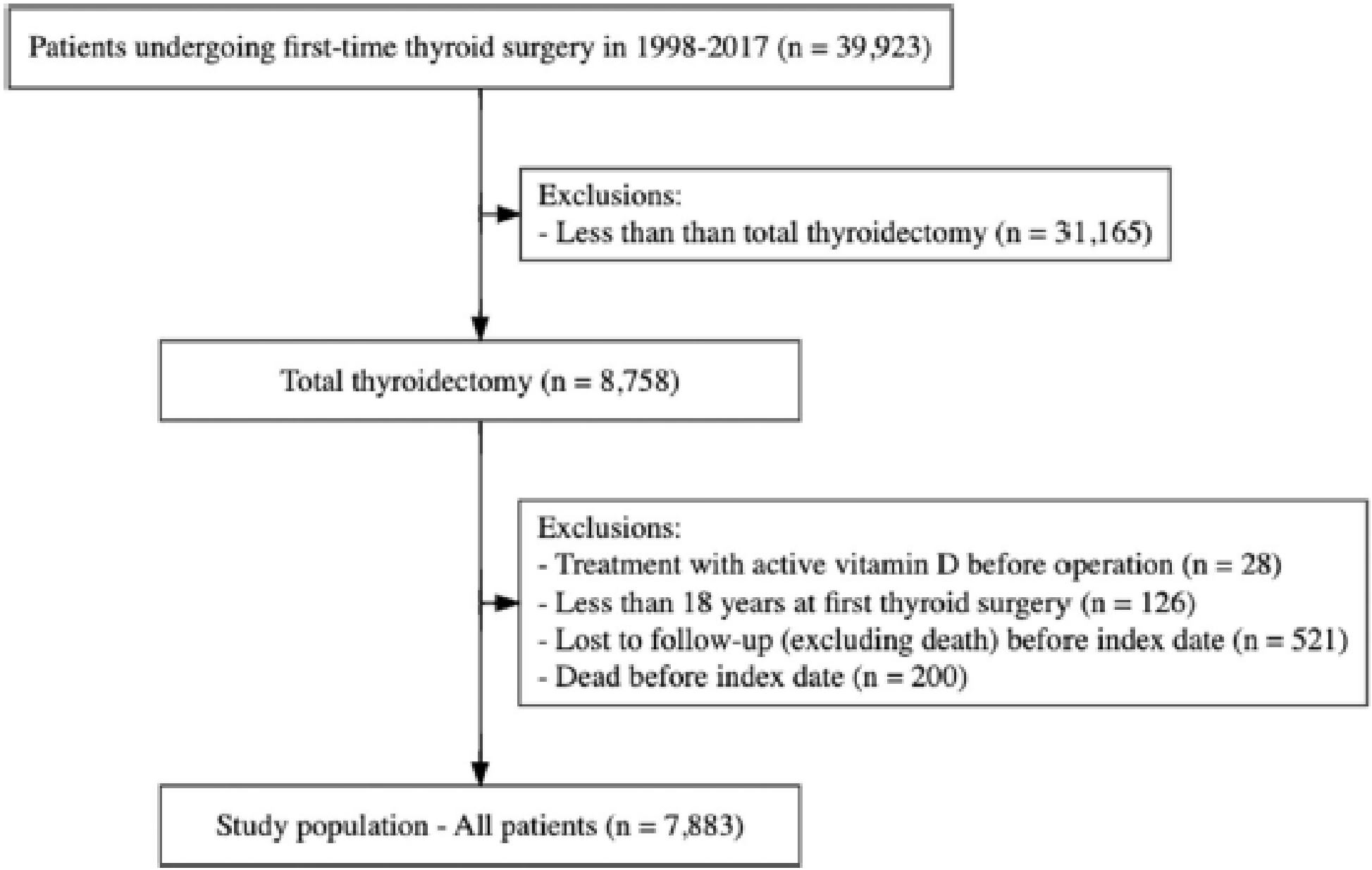
2.5 | Statistics

Patients were grouped according to occurrence of hypoPT 12 months postoperatively. The frequency of hypoPT was calculated for different groups, categorized according to **etiology, sex, age and CCI score.**

We estimated the risk of mortality using the cumulative incidence method for mortality after 1, 5 and 10 years. We compared the hazard ratios (HRs) of death using Cox regression adjusted for potential confounders and stratified by CCI.

After conducting statistical analyses on all patients, we repeated the analyses stratified by **different indications for TT** to evaluate the potential influence on outcome by surgical indication.

Data management and analyses were performed using SAS V.9.4, and final tables and visualizations were made using R V.4.3.1.


Patients undergoing first-time thyroid surgery in 1998-2017 (n = 39,923)
Exclusions:
- Less than than total thyroidectomy (n = 31,165)
Total thyroidectomy (n = 8,758)
Exclusions:
- Treatment with active vitamin D before operation (n = 28)
- Less than 18 years at first thyroid surgery (n = 126)
- Lost to follow-up (excluding death) before index date (n = 521)
- Dead before index date (n = 200)
Study population - All patients (n = 7,883)

3 | RESULTS

We included 7883 patients with TT and 78,830 individuals in the comparison cohort, and excluded a total of 32,040 patients.

Among all patients, **16.6%** (n = 1310) received active vitamin D treatment 12 months postoperatively. The population consisted predominantly of **females (78.6%)** with a median **age of 52.1 years** (interquartile interval: 41.8–63.7).

Most thyroidectomies were performed as a single procedure (78.2%). HypoPT was more frequently observed when TT was performed as a single procedure (Table 1).

The primary indications for TT were **goiter** (44%), **cancer** (28.9%) and **thyrotoxicosis** (25.9%).

The risk of developing hypoPT following surgery was 13%, 18.6% and 20.3% after operation for goiter, cancer or thyrotoxicosis, respectively.

The majority of patients were classified as **CCI group 0 (67.3%)**, whereas the remaining patients were in CCI groups 1−2 (21.7%) or in CCI group 3+ (11%).

The median follow-up time for all patients including the comparison cohort was 7.1 years.

TABLE 1 Descriptive summary of patients undergoing thyroid surgery with and without hypoparathyroidism and a matched comparison cohort 1998–2017 in Denmark.

Characteristic	Study population	Hypoparathyroidism	No hypoparathyroidism	Comparison cohort
Number of patients, *N*	7883	1310	6573	78,830
Type of thyroid procedures, *N* (%)				
Total thyroidectomy in 2+ procedures	1721 (21.8)	110 (8.4)	1611 (24.5)	
Total thyroidectomy in one procedure	6162 (78.2)	1200 (91.6)	4962 (75.5)	
Aetiology, *N* (%)				
Goitre	3465 (44.0)	451 (34.4)	3014 (45.9)	
Cancer	2280 (28.9)	425 (32.4)	1855 (28.2)	
Thyrotoxicosis	2041 (25.9)	414 (31.6)	1627 (24.8)	
Unknown	97 (1.2)	20 (1.5)	77 (1.2)	
Male, *N* (%)	1683 (21.3)	253 (19.3)	1430 (21.8)	16,830 (21.3)
Age, median (IQI)	52.1 (41.8–63.7)	50.0 (39.2–61.9)	52.6 (42.3–64.0)	52.2 (41.7–63.7)
CCI, *N* (%)				
0	5302 (67.3)	856 (65.3)	4446 (67.6)	61,799 (78.4)
1–2	1714 (21.7)	270 (20.6)	1444 (22.0)	13,857 (17.6)
+3	867 (11.0)	184 (14.0)	683 (10.4)	3174 (4.0)

Abbreviations: CCI, Charlson comorbidity index; IQI, interquartile interval.

3.1 | Mortality following TT

The cumulative incidence % (95% CI) of **all-cause mortality after 1 year** for **hypoPT patients was 2.5%** (1.8–3.5), compared with **1.6% (1.3–1.9) in non-hypoPT** patients and **1.3% (1.2–1.4) in the comparison cohort**.

Ten years after the index date, TT patients still had a higher risk of mortality compared with the comparison cohort (Table 2). With increasing number of comorbidities and increasing CCI score, the mortality increased.

TABLE 2 1-, 5- and 10-year risks after total thyroidectomy for all patients, with and without hypoparathyroidism and a matched comparison cohort 1998–2017 in Denmark.

Outcome	Stratification	Strata level	Population	Cumulative incidence % (95% CI)		
				1 year	5 years	10 years
All-cause mortality	All patients		Comparison cohort	1.3 (1.2–1.4)	7.0 (6.8–7.2)	16.3 (16.0–16.6)
			Hypoparathyroidism	2.5 (1.8–3.5)	9.2 (7.6–11.0)	19.6 (16.8–22.5)
			No hypoparathyroidism	1.6 (1.3–1.9)	8.4 (7.6–9.1)	17.8 (16.6–18.9)
	CCI	0	Comparison cohort	0.4 (0.4–0.5)	3.1 (2.9–3.3)	9.0 (8.7–9.3)
			Hypoparathyroidism	1.3 (0.7–2.3)	4.6 (3.2–6.3)	10.5 (8.0–13.5)
			No hypoparathyroidism	0.6 (0.4–0.8)	3.6 (3.0-4.2)	9.8 (8.7–11.0)
		1–2	Comparison cohort	2.1 (1.9–2.4)	13.4 (12.9–14.0)	30.1 (29.2–31.1)
			Hypoparathyroidism	1.9 (0.7–4.2)	13.0 (8.9–18.0)	31.8 (24.1–39.8)
			No hypoparathyroidism	2.1 (1.4–2.9)	11.0 (9.2–12.8)	26.9 (23.9–30.1)
		+3	Comparison cohort	8.5 (7.9–9.1)	32.7 (31.6–33.8)	53.4 (52.1–54.7)
			Hypoparathyroidism	9.0 (5.4–13.8)	25.0 (18.6–32.0)	44.2 (35.0–53.0)
			No hypoparathyroidism	7.1 (5.3–9.2)	34.3 (30.4–38.2)	52.7 (47.9–57.4)

Abbreviation: CCI, Charlson comorbidity index.

We observed **no clear difference** between TT patients and the comparison cohort (Table 2 and Figure 2). The adjusted HR (95% CI) using Cox regression for all-cause mortality was increased to 1.34 (1.15−1.56) and 1.00 (0.93−1.08) with and without hypoPT.

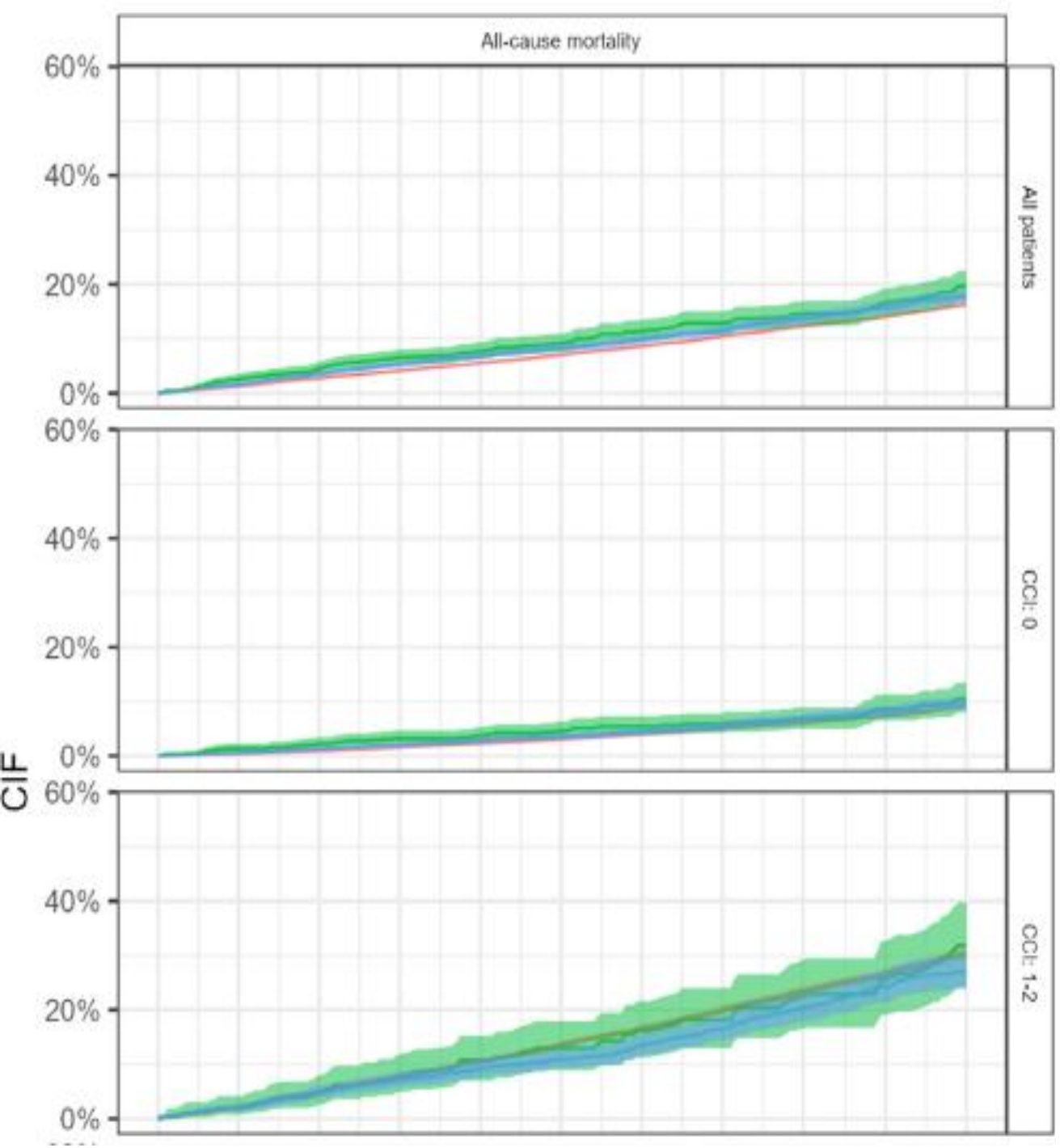


FIGURE 2 Cumulative incidence graph for all-cause mortality for patients undergoing thyroid surgery with and without hypoparathyroidism compared a matched comparison cohort with Charlsons comorbidity index 1998–2017 in Denmark. The 'Index' refers to 12 months from surgery, that is, year 0 is 12 months from surgery. The width of the colours represents 95% confidence intervals.

When stratifying for CCI, only **hypoPT patients without comorbidities (CCI 0) had an increased adjusted HR of 1.35** (1.04–1.76) (Table 3).

TABLE 3 Cox regression of all-cause mortality for all patients after total thyroidectomy with and without hypoparathyroidism compared with a matched comparison cohort 1998–2017 in Denmark.

Outcome	Statification	Strata	Population	Crude HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality	All patients	All patients	Hypoparathyroidism	1.27 (1.09–1.48)	1.34 (1.15–1.56)
			No hypoparathyroidism	1.13 (1.05–1.21)	1.00 (0.93–1.08)
			Comparison cohort	Ref	Ref
	CCI	0	Hypoparathyroidism	1.25 (0.96–1.62)	1.35 (1.04–1.76)
			No hypoparathyroidism	1.11 (0.99–1.26)	1.09 (0.96–1.23)
			Comparison cohort	Ref	Ref
		1–2	Hypoparathyroidism	1.00 (0.76–1.32)	1.08 (0.82–1.42)
			No hypoparathyroidism	0.87 (0.76–0.99)	0.79 (0.70–0.91)
			Comparison cohort	Ref	Ref
		+3	Hypoparathyroidism	0.80 (0.62–1.04)	0.99 (0.77–1.28)
			No hypoparathyroidism	1.00 (0.88–1.13)	0.98 (0.86–1.10)
			Comparison cohort	Ref	Ref

Abbreviation: CCI, Charlson comorbidity index.

3.2 | Mortality by surgical indication

Stratifying patients according to indication revealed a difference between patients with different preoperative indications. In patients having **TT due to goitre or thyrotoxicosis, all-cause mortality by cumulative incidence was comparable to the comparison cohort at all time points**.

In cancer patients, the mortality and adjusted HRs were significantly higher for TT patients than the comparison cohort after 1, 5 and 10 years (Table 4). The highest HR seems to be in hypoPT patients (Table 4).

TABLE 4 Cox regression analysis of all-cause mortality in patients following total thyroidectomy, comparing those with and without hypoparathyroidism. The cohorts were stratified based on surgical indication, with each indication having its corresponding comparison cohort.

Outcome	Statification	Indication	Population	Crude HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality	All patients	Goitre	Hypoparathyroidism	0.99 (0.76–1.30)	0.88 (0.67–1.15)
			No hypoparathyroidism	0.88 (0.78–0.98)	0.75 (0.67–0.84)
			Comparison cohort	Ref	Ref
All-cause mortality	All patients	Thyrotoxicosis	Hypoparathyroidism	0.83 (0.56–1.23)	0.86 (0.57–1.28)
			No hypoparathyroidism	0.97 (0.81–1.16)	0.82 (0.69–0.99)
			Comparison cohort	Ref	Ref
All-cause mortality	All patients	Cancer	Hypoparathyroidism	1.93 (1.55–2.41)	2.48 (1.99–3.10)
			No hypoparathyroidism	1.66 (1.48–1.86)	1.59 (1.42–1.78)
			Comparison cohort	Ref	Ref

4 | DISCUSSION

In this nationwide study, we estimated the risk of all-cause mortality in all Danish TT operations over a 20-year period with long-term follow-up, and was evaluated in relation to a large matched reference cohort.

The frequency of hypoPT, defined as continuous postoperative treatment with active vitamin D was high during this period. This finding may primarily be due to a high frequency of postoperative hypoPT.

Patients with hypoPT did not have increased mortality compared with a reference cohort when TT was performed on benign indications. Mortality risk was found to be increased in thyroid cancer patients. This finding may reflect **a well-known risk of long-term mortality after thyroid cancer operations.**

registry study containing 4899 **benign TT patients, only 5.2%** had permanent hypoPT, and in a Japanese cohort the risk was **15%–20%** after 1 year. The definition of hypoPT varies across different regions of the world, especially regarding the time from surgery to diagnosis of permanent hypoPT.

If hypoPT is defined based on the requirement of active vitamin D **after 6 months, the percentage of hypoPT cases seems to be higher** compared with a 12-month criterion.

In a Spanish study, the time to parathyroid recovery was illustrated. Of all patients with parathyroid recovery, around **70% recovered in the first 6 months**, around **20% recovered in the following 6 months** and **10% recovered more than 1 year** after TT.

Accordingly, our definition/in the present paper/may overestimate the number of hypoPT patients who will develop a chronic condition, but only marginally, as most seem to recover within the 12-month period.

Differences in hypoPT prevalence could also be attributed to **differences in clinical practice** since endocrinologists have different strategies for withdrawing calcium and active vitamin D intake after TT.

This was illustrated in a Swedish study showing hypoPT patients being **overtreated** because attempts to stop treatment were lacking.
A Spanish study showed **15% of hypoPT patients had poor disease control** which may indicate that the treatment can be optimised.

Finally, many different degrees of hypoPT exist including both symptomatic and asymptomatic cases, patients with normal, low or unmeasurable PTH, patients with normal and abnormal absorption from oral intake and patients with various combinations of other comorbidities.

4.2 | Mortality

We found no increased mortality risk in patients developing hypoPT when the indication for TT was benign. For patients undergoing TT due to malignancy, we found an increased risk of mortality compared with our comparison cohort. This is consistent with a **previous Danish study showing no difference in mortality** for patients with hypoPT following surgery due to nonmalignant causes when compared with the background population.

In contrast, a Swedish study demonstrated that in a benign population of TT patients, **age, CCI 2+ and permanent hypoPT were independent risk factors for death**. This was after patients were matched to individuals with similar age and comorbidity according to CCI. Likewise, results from the current study were matched on age and comorbidity.

Although we also found increased mortality in all TT patients, the increased **HR** was primarily **influenced by thyroid cancer.** In benign cases, the mortality was unaffected.
In the population with multiple comorbidities (CCI 1–2, 3+), the all-cause mortality was either comparable or even in some cases reduced compared to the comparison cohort.

This finding is also demonstrated in a study by Salem et al. where patients **above the age of 80 with benign indications** for thyroidectomy have a **reduced mortality risk**.
This could be attributed to **selection bias** since only patients who are healthy enough to undergo surgery are included.

Another contributing factor could be that TT patients have an **increased frequency of medical appointments** following the surgery. To date, no studies have identified any evidence of overall or cause-specific mortality attributable to hypoPT after surgery.

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However, several comorbidities following hypoPT have been identified, such as **bipolar affective disorders, risk of hospitalization due to infections and chronic kidney disease**.

As our cohort had a median follow-up time of 7.1 years, we cannot exclude the possibility that a longer time is needed for more events to occur.

4.3 | Limitations

Several limitations must be considered when interpreting the findings from this study. Due to the retrospective study design, we cannot exclude the **possibility that potential unmeasured confounders** were not accounted for. Furthermore, the biological pathway from developing hypoPT to increased risk of death is not fully understood and it is possible that **an unknown pathological process** is unevenly distributed between cohorts.

Using several databases, some data may be **miscoded or missing**. However, the data is based on mandatory registration, thereby increasing completeness. There is a risk of **misclassification** with our definition of hypoPT. Some patients may only be **treated with calcium supplements**, and consequently, not included in our hypoPT cohort.

Other patients on active vitamin D treatment may only suffer from **transient hypoPT without discontinuing treatment**, possibly leading to a reduced mortality risk in the cohort.
To avoid including patients failing to discontinue treatment in time, we prolonged the index date to 12 months instead of 6 months as per current guidelines.

One **strength** of this study is the ability to link data from all patients from different registries and the ability to include a **large matched comparison cohort**. Another strength is the possibility to include a large number of patients. This leads to **better statistical power** and a low risk of a type 2 error.

In our cohort cancer patients had an increased risk of death compared with other surgical indications. Cancer patients is a broad term, and we were not able to distinguish between different types of cancers. To reduce the inclusion of aggressive subtypes (i.e.,anaplastic, poorly differentiated) patients were excluded if they died before the index day.

We are not able to confirm, if the cause of death in cancer patients is due to thyroid cancer. This is due to the potential misclassification resulting from **differences in reporting causes of death**. Finally, the Danish population is predominantly homogeneous, comprised mainly of individuals of Caucasian descent. Therefore, it is possible that our findings may not be generalizable to populations that exhibit a greater diversity of ethnicities.

5 | *CONCLUSION*

The continuous postoperative treatment of hypoPT with active vitamin D following TT has been a frequent complication in the last 20 years. For patients who underwent TT due to goiter or thyrotoxicosis, postoperative mortality was not affected compared to a comparison cohort, regardless of the presence or absence of hypoPT. However, when the indication for surgery was malignancy, the risk of mortality was higher than in a matched comparison cohort.

THANKS FOR YOUR ATTENTION