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RESEARCH

Twenty-year trend of thyrotoxicosis and thyrotoxic periodic paralysis: a population-based cohort study

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Abstract

Objective: Thyrotoxic periodic paralysis (TPP) is a rare but potentially lethal complication of thyrotoxicosis. Absence of large cohorts limits the conduct of epidemiology studies. We aimed to establish a population-based registry of thyrotoxicosis and TPP in Hong Kong and evaluate their trend.

Methods: We developed algorithms to identify thyrotoxicosis and TPP cases from a representative electronic medical database in Hong Kong. Of the potential cases (thyrotoxicosis:83,184; TPP:999), we reviewed clinical notes and laboratory test records of 200 randomly selected cases. Population-based registries of thyrotoxicosis and TPP were subsequently established. Their standardized incidence rate, TPP-associated hospitalization rate, length of stay (LOS), and trends from 2002 to 2021 were evaluated.

Results: Positive predictive values for thyrotoxicosis and TPP were 0.86–0.97, respectively, enabling establishment of population-based cohorts of incident thyrotoxicosis (n = 77,856) and TPP (n = 994). Age- and sex-standardized incidence rate (per 100,000 person-years) of thyrotoxicosis increased from 41.31 in 2002 to 69.51 in 2021 (average annual percentage change: 4.77%), with a similar trend observed in both sexes. TPP patients were predominantly male (93.66%). In 2002 and 2021, the age-standardized incidence rate (per 100,000 person-years) of TPP in males was 1.43 and 1.18, respectively, while that in females was 0.11 and 0.13, without a significant trend observed. TPP-associated hospitalization rate (90.91–100%) and median LOS (2–3 days) were steady across the two decades.

Conclusion: This is the first study establishing a TPP cohort based on validated clinical data from an electronic medical database. It is important to keep monitoring the increasing incidence rate of thyrotoxicosis.

Keywords: thyrotoxic periodic paralysis; thyrotoxicosis; electronic medical records; validation; trend

Introduction

Thyrotoxic periodic paralysis (TPP) is a rare complication of thyrotoxicosis, mainly due to Graves' disease (GD). TPP is characterized by recurrent hypokalemia, episodic muscle weakness, and paralysis (1), which is potentially fatal in serious attacks with life-threatening cardiopulmonary complications, such as ventricular

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arrhythmia and total paralysis of respiratory and bulbar muscles (1). Although TPP primarily affects Asian males, an increasing number of TPP cases have been reported in Western countries, such as Europe and the Americas, following migration and heightened awareness of TPP (2). Widely known as a channelopathy, several studies reported that mutations in genes encoding potassium inwardly rectifying (Kir) channels (including Kir2.2 and Kir2.6) (3, 4, 5, 6, 7, 8), voltage-dependent calcium channels (9), and voltage-gated sodium channels (10), were associated with TPP. Amid the vast number of case reports on TPP, only a few cohorts of limited sample size (11, 12, 13, 14, 15, 16) have been available to date for epidemiology studies. While investigation of incidence could provide insights for future guidelines in managing TPP, its temporal trend has never been studied.

Attributed to the rarity of the complication, initiating such epidemiology studies is laborious due to the difficulty in patient recruitment and establishment of cohorts with considerable sample size. Even in the presence of electronic medical databases, there is no well-defined specific diagnosis coding for TPP in official systems, such as the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), increasing the challenges of identifying individuals with TPP. In this study, we developed a novel algorithm to identify TPP cases from a representative electronic medical database in Hong Kong, validated the algorithm, identified the cohort of individuals with TPP, and evaluated its epidemiology across 20 years from 2002 to 2021. Thyrotoxicosis was also examined for comparison with TPP.

Methods

Data source and study design

The Clinical Data Analysis and Reporting System (CDARS) is a representative electronic medical database in Hong Kong managed by the Hong Kong Hospital Authority (HA), a public healthcare service provider managing 43 hospitals and institutions and 123 outpatient clinics, serving >80% of hospital admissions in Hong Kong. This centralized database captures anonymized records of demographics, admission, drug prescriptions, diagnoses (in ICD-9-CM), laboratory tests, and deaths of all public healthcare service users since 1993. In this population-based retrospective cohort study, individuals with thyrotoxicosis or TPP were identified by specific diagnosis codes and algorithms, respectively. Demographic, drug prescription, and admission records of this population-based cohort were retrieved from CDARS. Individuals with missing data were excluded from analysis.

Potential case identification for validation of data from CDARS

As the diagnosis coding of ICD-9-CM 242.xx has been commonly adopted to indicate thyrotoxicosis with or without goiter in the clinical setting (17, 18), it was used to identify potential thyrotoxicosis cases from CDARS. Since a specific ICD-9-CM diagnosis code for TPP is unavailable, a novel algorithm was designed to identify potential TPP cases: individuals with i) thyrotoxicosis (ICD-9-CM: 242.xx), ii) periodic paralysis (ICD-9-CM: 359.3), and iii) hypokalemia as indicated by low blood potassium level (<3.5 mmol/liter) in laboratory test records, which occurred within 30 calendar days of each other. To validate the accuracy of the diagnosis codes and algorithm, 100 potential thyrotoxicosis and 100 potential TPP cases were randomly selected for inspection.

Validation of data from CDARS for thyrotoxicosis and TPP

Thyrotoxicosis may not be diagnosed solely by biochemical tests of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) (Supplementary Methods (see section on Supplementary materials given at the end of the article)), so the clinical notes of physicians were also reviewed for validation in addition to laboratory test records. The ICD-9-CM diagnosis code of 242.xx was regarded as a true positive of thyrotoxicosis if the laboratory test records met the criteria of elevated FT4 and reduced TSH levels, or the physician documented in the clinical notes 'thyrotoxicosis' and a management strategy of radioactive iodine (RAI) therapy, thyroidectomy, or anti-thyroid drugs (ATD). The mixed use of ICD-9-CM diagnosis codes (242.xx (thyrotoxicosis) and 359.3 (periodic paralysis)) and low blood potassium level in laboratory test records (<3.5 mmol/liter) in CDARS was considered a true positive of TPP if the physician documented in the clinical notes 'TPP' or the three concurrent symptoms (Supplementary Methods). The positive predictive value (PPV) was calculated as the number of true positives divided by the total number of true positives and false positives (false positives were defined as cases identified by the clinical data in CDARS, but neither documented in the physician's clinical notes (for both thyrotoxicosis and TPP) nor had supporting laboratory tests (for thyrotoxicosis)). The 95% confidence interval (CI) of PPV was estimated with the binomial distribution.

Statistical analysis

Incidence

The annual crude incidence rate was the number of new cases (excluding recurrent cases) divided by the mid-year population of Hong Kong in a calendar year. The annual population estimates, in total, by sex, and by age

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group, were retrieved from the Census and Statistics Department, the Government of the Hong Kong Special Administrative Region (19). By direct standardization, the crude rate was adjusted with reference to the age and sex distribution of the United Nations population in 2012 to derive the age- and sex-standardized incidence rates (20). Since more male thyrotoxicosis patients had TPP with reference to female patients, the age-standardized incidence rate of TPP in both sexes was calculated. The incidence rate in the nine age groups was also examined separately (<10, ≥10–19, ≥20–29, ≥30–39, ≥40–49, ≥50–59, ≥60–69, ≥70–79, and ≥80).

TPP-associated hospitalization rate and LOS

TPP-associated hospitalization was defined as the hospital admission within the period spanning the test date of low blood potassium and the diagnosis dates of thyrotoxicosis and periodic paralysis, as laboratory tests and diagnoses could be done on different dates. The annual hospitalization rate was calculated by dividing the number of TPP-associated hospitalizations by the total number of individuals with TPP in a calendar year. The LOS of each hospitalization referred to the total number of hospitalized bed-days from admission until discharge, excluding overlapping time during transfers between hospitals. Sex-stratified analysis was performed.

Trend analysis

Linear regression was employed to examine whether a linear trend was observed from 2002 to 2021 for crude incidence, age- and sex-standardized incidence for both thyrotoxicosis and TPP, the proportion of TPP patients among thyrotoxicosis patients, as well as TPP-associated hospitalization rate and median LOS. Any changes in trend were evaluated by the joinpoint regression model (21, 22). The annual percent change (APC) for each linear segment and the average annual percent change (AAPC) over the whole study period from 2002 to 2021 were estimated. The optimal model with a maximum of three joinpoints was selected based on weighted Bayesian information criteria.

Ethics approval

This study is in compliance with the Declaration of Helsinki, approved by the institutional review boards of the University of Hong Kong and the HA Hong Kong West Cluster (reference: UW 22–502 and 22–563) and the Hong Kong Polytechnic University (reference: HSEARS20220321008). The requirement for informed consent was waived as this study did not involve patient recruitment and only utilized anonymized records available from CDARS.

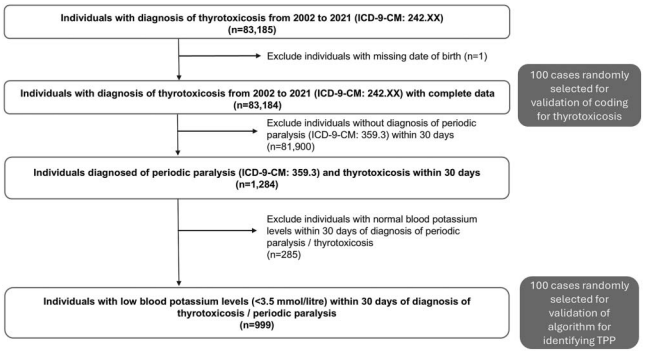

Figure 1

Flowchart in identifying individuals with thyrotoxicosis and TPP in Hong Kong during 2002–2021.

Results

Validation of diagnosis code and algorithm for thyrotoxicosis and TPP cases in CDARS

We identified 83,184 potential thyrotoxicosis cases (ICD-9-CM: 242.xx) from 2002 to 2021 from CDARS, including the recurrent ones. Of the 100 randomly selected potential cases, a total of 86 individuals with the ICD-9-CM diagnosis code of 242.xx were true positives of thyrotoxicosis, yielding a PPV of 0.86 (95% CI: 0.79–0.93). Of the 83,184 thyrotoxicosis cases, 999 had diagnoses of periodic paralysis (ICD-9-CM: 359.3) and low blood potassium test records within 30 days, constituting the potential TPP cases (including the recurrent ones; Fig. 1). Of the 100 randomly selected potential TPP cases, 97 were true positives. The algorithm for identifying TPP had a PPV of 0.97 (95% CI: 0.94–1).

Epidemiology of thyrotoxicosis and TPP

Based on the validated data in CDARS, 77,856 public healthcare users were diagnosed with incident thyrotoxicosis (18,451 males and 59,405 females) during 2002–2021. A total of 994 individuals (931 males (5.05% of male thyrotoxic patients) and 63 females (0.11% of female thyrotoxic patients)) had incident TPP during this period (Table 1). Their baseline characteristics are illustrated in Table 1. Individuals with TPP were predominantly male (93.66%), while over three-quarters of thyrotoxic patients (without TPP) were female (77.17%). Most individuals (69.32%) experienced incident TPP at a younger age <40, whereas the onset of thyrotoxicosis (without TPP history) peaked at the age ≥30–59. Regarding treatment within 30 days of the first diagnosis (Table 1), over 80% individuals with incident thyrotoxicosis were prescribed carbimazole, while propylthiouracil (~10%), radioactive iodine therapy (~5%), and thyroidectomy (~2%) were alternative options. For patients with incident TPP, in

Table 1 Baseline characteristics of the public healthcare users with incident thyrotoxicosis or TPP in Hong Kong during 2002–2021. For both age and age-group at first incidence, $P < 0.001$ was considered statistically significant between male and female among patients with thyrotoxicosis (including TPP cases), patients with thyrotoxicosis (excluding individuals with TPP), and patients with TPP.

	Thyrotoxicosis (including individuals with TPP)			Thyrotoxicosis (excluding individuals with TPP)			TPP		
	All	Male	Female	All	Male	Female	All	Male	Female
n	77,856	18,451 (23.7%)	59,405 (76.3%)	76,902	17,557 (22.83%)	59,345 (77.17%)	994[‡]	931 (93.66%)	63 (6.34%)
Age[*]	48.73 ± 18.47	50.85 ± 17.99	48.07 ± 18.56	48.9 ± 18.47	51.69 ± 17.9	48.08 ± 18.56	35.2 ± 11.02	34.84 ± 10.24	40.6 ± 18.48
Age-groups[†]									
<10	312 (0.4%)	108 (0.59%)	204 (0.34%)	311 (0.4%)	108 (0.62%)	203 (0.34%)	0 (0%)	0 (0%)	0 (0%)
10–19	3,165 (4.07%)	585 (3.17%)	2,580 (4.34%)	3,114 (4.05%)	538 (3.06%)	2,576 (4.34%)	44 (4.43%)	39 (4.19%)	5 (7.94%)
20–29	9,156 (11.76%)	1,841 (9.98%)	7,315 (12.31%)	8,866 (11.53%)	1,568 (8.93%)	7,298 (12.3%)	299 (30.08%)	282 (30.29%)	17 (26.98%)
30–39	14,428 (18.53%)	2,842 (15.4%)	11,586 (19.5%)	14,097 (18.33%)	2,523 (14.37%)	11,574 (19.5%)	346 (34.81%)	333 (35.77%)	13 (20.63%)
40–49	15,748 (20.23%)	3,505 (19.0%)	12,243 (20.61%)	15,552 (20.22%)	3,320 (18.91%)	12,232 (20.61%)	216 (21.73%)	204 (21.91%)	12 (19.05%)
50–59	14,937 (19.11%)	3,689 (20.0%)	11,248 (18.93%)	14,872 (19.34%)	3,630 (20.68%)	11,242 (18.94%)	66 (6.64%)	60 (6.44%)	6 (9.52%)
60–69	9,150 (11.75%)	2,961 (16.05%)	6,189 (10.42%)	9,135 (11.88%)	2,950 (16.8%)	6,185 (10.42%)	16 (1.61%)	12 (1.29%)	4 (6.35%)
70–79	5,680 (7.3%)	1,860 (10.08%)	3,820 (6.43%)	5,677 (7.38%)	1,860 (10.59%)	3,817 (6.43%)	5 (0.5%)	1 (0.11%)	4 (6.35%)
≥80	5,280 (6.78%)	1,060 (5.74%)	4,220 (7.1%)	5,278 (6.86%)	1,060 (6.04%)	4,218 (7.11%)	2 (0.2%)	0 (0%)	2 (3.17%)
Thyrotoxicosis treatment[§]	55,706	13,917	41,789	54,792	13,055	41,737	946	892	54
Anti-thyroid drugs									
Carbimazole	45,554 (81.44%)	11,827 (84.98%)	33,727 (80.71%)	44,745 (81.66%)	11,056 (84.69%)	33,689 (80.72%)	836 (89.13%)	795 (89.13%)	41 (75.9%)
Methimazole	144 (0.26%)	43 (0.31%)	101 (0.24%)	143 (0.26%)	41 (0.31%)	102 (0.24%)	1 (0.11%)	1 (0.11%)	0 (0%)
Propylthiouracil	5,514 (10.08%)	889 (6.39%)	4,625 (11.07%)	5,431 (9.91%)	820 (6.28%)	4,611 (11.05%)	95 (9.42%)	84 (9.42%)	11 (20.37%)
RAI therapy	3,145 (5.75%)	898 (6.45%)	2,247 (5.38%)	3,125 (5.7%)	879 (6.73%)	2,246 (5.38%)	12 (1.27%)	11 (1.23%)	1 (1.85%)
Thyroidectomy	1,349 (2.47%)	260 (1.87%)	1,089 (2.61%)	1,348 (2.46%)	259 (1.98%)	1,089 (2.61%)	2 (0.21%)	1 (0.11%)	1 (1.85%)

[*]Age at first incidence was compared between male and female using a *t*-test. [†]Age-group at first incidence was compared between male and female using a chi-square test. [‡]Includes 40 individuals with prior thyrotoxicosis since the establishment of CDARS in 1993. [§]Thyrotoxicosis treatment within 30 days of the index date.
RAI, radioactive iodine.

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Table 2 Linear and joinpoint regression analysis of the proportion of TPP patients among thyrotoxic patients, stratified by sex.

	Linear regression	Joinpoint regression						
Sample/segment	*P*-value	Period	Annual % change	95% CI	*P*-value	Average annual % change	95% CI	*P*-value
Whole sample	0.014					−5.958*	−9.691 to −2.632	0.008
1		2002–2016	0.28	−2.862–7.739	0.785			
2		2016–2021	−21.436*	−48.877 to −9.21	<0.001			
Male	0.02					−5.856*	−9.179 to −3.06	0.003
1		2002–2016	0.741	−2.236–6.114	0.604			
2		2016–2021	−22.12*	−43.163 to −10.906	<0.001			
Female								
1	0.48	2002–2021	−3.407	−9.883–3.383	0.302	NA†	NA†	NA†

*The annual percent change or/and average annual percent change was significantly different from 0 ($P < 0.05$). †As the optimal model did not consist of any joinpoint, the average annual percent change was not reported.

addition to non-selective β-blockers and potassium, they had a similar treatment pattern against thyrotoxicosis as thyrotoxic patients.

An overall decreasing trend was observed for the proportion of thyrotoxic patients with TPP in the whole sample (*P* for linear trend = 0.014; AAPC −5.958%; 95% CI: −9.691 to −2.632; *P* = 0.008) and males (*P* for linear trend = 0.02; AAPC −5.856%; 95% CI: −9.179 to −3.06; *P* = 0.003). One joinpoint was identified during the study period. The proportion of patients with TPP remained steady from 2002 to 2016, followed by a decreasing trend from 2016 to 2021 (whole sample: APC −21.436%; 95% CI: −48.877 to −9.21; *P* < 0.001; male: APC −22.12%; 95% CI: −43.163 to −10.906; *P* < 0.001). The proportion of female thyrotoxic patients with TPP was stable throughout 2002–2021 (Supplementary Fig. 1; Table 2).

Trend in incidence of thyrotoxicosis and TPP

The number of incident thyrotoxicosis cases was 3,333 in 2002 and increased to 6,598 in 2021. The crude incidence rate (per 100,000 person-years) was 49.42 in 2002 and 89.01 in 2021 in the whole sample (Table 3 and Supplementary Fig. 2), with an increasing trend indicated by linear (*P* = 0.012; Table 3) and joinpoint (AAPC 5.229%; 95% CI: 0.9–8.455; *P* = 0.018; Table 4) regression. One joinpoint was

Table 3 Incidence rate of thyrotoxicosis (TCT) and TPP during 2002–2021 (per 100,000 person-years) in the whole sample (WS), male, and female.

	Crude incidence in WS		Age- and sex-SI in WS		Age-SI, by sex			
					TCT		TPP	
Year	TCT	TPP	TCT	TPP	Male	Female	Male	Female
2002	49.421	0.801	41.31	0.719	20.462	61.14	1.428	0.105
2003	43.368	0.654	35.616	0.584	18.221	52.025	1.133	0.122
2004	41.645	0.693	34.354	0.589	17.964	49.642	1.207	0.057
2005	35.417	0.675	29.703	0.631	14.87	43.275	1.354	0.022
2006	31.179	0.54	25.77	0.508	12.925	37.445	1.078	0.041
2007	35.727	0.752	29.577	0.692	14.452	43.053	1.405	0.11
2008	53.163	0.69	42.985	0.624	20.623	62.809	1.293	0.091
2009	60.22	0.918	48.864	0.845	22.852	71.96	1.876	0.04
2010	58.74	0.598	47.007	0.585	21.72	69.211	1.252	0.044
2011	51.954	0.99	41.91	0.988	20.177	60.789	2.17	0.044
2012	48.041	0.769	39.634	0.715	19.277	57.162	1.578	0.036
2013	44.854	0.585	36.209	0.564	17.566	52.23	1.153	0.117
2014	41.635	0.692	33.369	0.649	15.051	48.966	1.38	0.098
2015	44.382	0.782	36.772	0.83	18.765	52.186	1.743	0.13
2016	43.358	0.859	35.194	0.924	18.398	49.422	1.982	0.093
2017	43.405	0.73	35.933	0.785	16.773	52.288	1.572	0.153
2018	42.428	0.564	34.025	0.623	17.234	48.027	1.313	0.08
2019	137.389	0.519	101.738	0.573	48.486	146.396	1.23	0.071
2020	89.467	0.655	69.362	0.732	33.947	98.966	1.6	0.021
2021	89.005	0.526	69.506	0.604	33.946	99.547	1.181	0.132
P-value*	0.012	0.31	0.013	0.445	0.014	0.018	0.401	0.453

SI, standardized incidence.
**P*-values for linear trend.

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Table 4 Joinpoint regression analysis of the crude and standardized incidence rate of thyrotoxicosis and TPP in the whole sample, male, and female.

IR/sample/disease condition/segment	Period	Annual % change	95% CI	*P*-value	Average annual % change	95% CI	*P*-value
Crude							
Whole sample							
Thyrotoxicosis					5.229*	0.9–8.455	0.018
1	2002–2017	0.763	−17.474–15.066	0.96			
2	2017–2021	23.814*	1.983–78.696	0.033			
TPP							
1	2002–2021	−0.82	−2.686–1.044	0.349	NA†	NA†	NA†
Male							
Thyrotoxicosis					5.341*	1.364–8.175	0.007
1	2002–2017	0.699	−14.022–4.396	0.995			
2	2017–2021	24.735*	3.619–75.569	0.016			
TPP					NA†	NA†	NA†
1	2002–2021	−0.569	−2.546–1.419	0.549			
Female							
Thyrotoxicosis					5.005*	0.517–8.539	0.028
1	2002–2017	0.558	−18.488–18.3	0.859			
2	2017–2021	23.506*	1.1–79.652	0.041			
TPP							
1	2002–2021	−0.283	−6.158–5.857	0.933	NA†	NA†	NA†
SIR							
Whole sample‡							
Thyrotoxicosis					4.766*	0.798–7.686	0.018
1	2002–2017	0.586	−16.056–9.187	0.912			
2	2017–2021	22.047*	2.126–70.825	0.03			
TPP							
1	2002–2021	0.572	−1.205–2.355	0.51	NA†	NA†	NA†
Male§							
Thyrotoxicosis					4.669*	1.116–7.305	0.012
1	2002–2017	0.338	−12.088–3.358	0.881			
2	2017–2021	22.643*	3.445–69.388	0.01			
TPP							
1	2002–2021	0.708	−1.15–2.589	0.437	NA†	NA†	NA†
Female§							
Thyrotoxicosis					4.609*	0.564–7.605	0.025
1	2002–2017	0.417	−16.925–10.562	0.837			
2	2017–2021	21.95*	1.737–72.364	0.034			
TPP							
1	2002–2021	1.302	−4.579–7.318	0.657	NA†	NA†	NA†

*The annual percent change/average annual percent change was significantly different from 0 ($P < 0.05$). †As the optimal model did not consist of any joinpoint, the average annual percent change was not reported. ‡Age- and sex-standardized incidence rate. §Age-standardized incidence rate.
SIR, standardized incidence rate.

identified in 2017, indicating the crude incidence was stable from 2002 to 2017, and an increasing trend was seen from 2017 to 2021 (APC 23.814%; 95% CI: 1.983–78.696; P = 0.033; Table 4). The age- and sex-standardized incidence rate (per 100,000 person-years) of thyrotoxicosis also increased from 41.31 in 2002 to 69.51 in 2021, with a rising trend demonstrated by linear (P = 0.013) and joinpoint regression (AAPC 4.766%; 95% CI: 0.798–7.686; P = 0.018; Tables 3 and 4 and Supplementary Fig. 2). Similarly, one joinpoint was identified in 2017, with steady incidence before 2017 but incidence increased sharply afterward (APC 22.047%; 95% CI: 2.126–70.825; P = 0.03).

Conversely, there were 54 and 39 incident TPP cases in 2002 and 2021, respectively in the whole sample, resulting in a crude incidence (per 100,000 person-years) of 0.8 and 0.53 (Table 3). The age- and sex-standardized incidence rate (per 100,000 person-years) in the whole sample was stable from 2002 (0.72) to 2021 (0.6; Tables 3 and 4 and Supplementary Fig. 2). As there were significant age and sex differences between individuals with thyrotoxicosis and TPP, age- and sex-stratified analyses were also conducted, with similar trends observed (Tables 3 and 4, Supplementary Results, Supplementary Tables 1 and 2 and Supplementary Figs 3 and 4).

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TPP-associated hospitalization and LOS

Of the 994 patients with incident TPP, 962 (96.78%) had associated hospital admissions during 2002–2021. The TPP-associated hospitalization rate was stable in the whole sample (96.3% in 2002 and 94.87% in 2021), as well as in males and females across these two decades (Supplementary Table 3, Supplementary Fig. 5). The median LOS in the whole sample and in males ranged from 2 to 3 days across 2002–2021 and remained steady across the 20 years (Supplementary Table 4, Supplementary Fig. 6). Although the median LOS in females had a wide range (1–8 days), mainly due to the few TPP cases, it also remained stable across the study period (Supplementary Table 4, Supplementary Fig. 6).

Discussion

To our knowledge, this is the first study that established a TPP cohort using a validated novel algorithm from an electronic medical database. It is also the first population-based study of TPP evaluating the incidence, hospitalization rate, LOS, and their trend across 20 years. We validated the diagnosis code and established a population-based thyrotoxicosis cohort as a reference for TPP patients. Although the standardized incidence of thyrotoxicosis increased yearly by an average of 4.77% from 2002 to 2021, the incidence of TPP was stable over the two decades. TPP-associated hospitalization rate and median LOS remained steady during this period.

In our population-based study, 1.2% thyrotoxic patients experienced TPP. More male (5.05%) than female thyrotoxic patients (0.11%) had incident TPP during 2002–2021. The proportion of thyrotoxic patients with TPP during 2002–2021 in Hong Kong was close to a study among the Japanese in 1985–1989, in which TPP occurred in 1.1, 4.3, and 0.04% of all, male, and female thyrotoxic patients, respectively (13). Nevertheless, the proportion of thyrotoxic patients who had incident TPP in this study was lower than the figures reported by two studies conducted in the 1950–1960s among Japanese (11) and southern Chinese in Hong Kong (12), in which incident TPP occurred in 1.83–1.9% of thyrotoxic patients, while 8.2–13% male and 0.17–0.4% female thyrotoxic patients experienced TPP. One plausible reason for the reduced occurrence of TPP among thyrotoxic patients in Hong Kong from the 1960s to 2000s is the reduced exposure to precipitating factors of TPP, such as the shift from a high-carbohydrate diet to a more westernized diet, with decreased rice consumption by 2.4 times from 1967 to 2006 (23). Similarly, the decreasing trend of the proportion of TPP patients among all and male thyrotoxic patients from 2002 to 2021 could also be due to the change in dietary pattern, particularly the reduced intake of carbohydrates (24, 25). Reduced exposure to other unknown or established precipitating factors of TPP toward the end of the study, such as less strenuous exercise attributed to the social distancing measures during the COVID-19 pandemic (26, 27), may also explain the decreased proportion of TPP cases among thyrotoxic patients. Such a decreasing trend was not observed in females, probably due to the small number of cases.

Our study demonstrated that the standardized incidence rate of TPP was stable in Hong Kong during 2002–2021, in the range of 0.51–0.99 per 100,000 person-years. This implies the increasing incidence of thyrotoxicosis was offset by the aforementioned drop in the proportion of TPP cases among thyrotoxic patients. The rate of TPP-associated hospital admission (90.91–100%) was steady across two decades. Similarly, the median LOS (2–3 days) was also stable, even though there was an overall decrease in the LOS of inpatients in public hospitals in Hong Kong (28), indicating the possibility that the minimum LOS had been reached among TPP patients without unnecessary delay.

It was previously reported that most patients with TPP had an early onset at the age of 20–40 (1). This aligns with the present study, in which over 65% patients with TPP had the first onset at the age ≥20–40 (Table 1), although this proportion was lower than that of a single-center study in Taiwan (80%) (14). In this study, approximately 4% patients had the first incident TPP at the age ≥10–20 (Table 1), with the youngest patient experiencing the first TPP at the age of 11, who was among the youngest adolescents with TPP in published case reports (29, 30, 31). In addition, the first onset of TPP in males occurred at a significantly younger age than in females (Table 1).

We found that the standardized incidence rate of thyrotoxicosis (per 100,000 person-years) in Hong Kong increased from 41.31 in 2002 to 69.51 in 2021 (Tables 3 and 4). While the Hong Kong population had insufficient iodine intake (32), its incidence rate was comparable to other iodine-deficient regions, ranging from 5.5 to 92.9 per 100,000 person-years (33). In South Korea, an iodine-sufficient East Asian country, the average age-standardized incidence of hyperthyroidism (per 100,000 person-years) from 2003 to 2018 was 42.23 in men and 105.13 in women, respectively, which was stable during the study period, but data were only available until 2018 (34). In a population-based cohort study of >22 million individuals in the United Kingdom (UK), the standardized incidence rate of GD (per 100,000 person-years) was reported to increase from 33.6 in 2000–2002 to 66 in 2017–2019, by more than 2-fold (35). As GD is the major cause of thyrotoxicosis, its rising trend in the UK aligned with the growing incidence of thyrotoxicosis in Hong Kong during 2002–2021. Notably, the incidence rate of thyrotoxicosis in Hong Kong peaked at 101.74 per 100,000 person-years in 2019, and it remained high in 2020–2021 at >69 per 100,000 person-years, when compared to the incidence rate before 2019 (<49 per 100,000 person-years; Table 3). A plausible reason

could be the major social unrest during 2019, during which the population had five and six times higher prevalence of probable depression (11.2%) and suspected post-traumatic stress disorder (PTSD; 12.8%), respectively when compared to 2014 (36). Moreover, the first case of COVID-19 in Hong Kong was recorded in January 2020, and the pandemic did not end before this study. Amid unforeseen circumstances and broad effects of the pandemic, the prevalence of PTSD in Hong Kong during 2020–2021 was reported to be 12.4% (37). Depression and emotional stress could affect the onset and clinical course of GD by triggering autoimmunity directly, and indirectly via the sympathoadrenal and endocrine systems (38, 39), possibly explaining the high incidence of thyrotoxicosis during 2019–2021 in Hong Kong. Increased risk of GD (40, 41), thyrotoxicosis (42), and subacute thyroiditis (43, 44) was reported in patients infected with SARS-CoV-2, despite the presence of contradictory findings (45). It remains unknown whether the possible physiological effects of SARS-CoV-2 infection, the psychological stress induced by the pandemic, or both, may have elevated the incidence of thyrotoxicosis during 2020–2021. Despite several case reports recording the occurrence of GD following COVID-19 vaccination, large-scale cohort studies suggested COVID-19 vaccination was not linked to an elevated risk of thyroid dysfunction, including GD (46). Future studies are required to examine whether the incidence remains high in the post-pandemic era.

Our current study has important clinical implications. Validating the diagnosis code and algorithm for thyrotoxicosis and TPP, respectively, in CDARS facilitates the establishment of a 20-year population-based registry in Hong Kong. Examining the trend of incidence is made feasible, which is essential for public health surveillance. The current study revealed an increasing trend in the incidence of thyrotoxicosis from 2002 to 2021 in Hong Kong. To reduce the possible burden on the healthcare system and the patients, it is necessary to inform health-related public policy to continuously monitor the trend in the post-pandemic era for optimal management. Furthermore, as the pathogenesis of TPP remains unclear, the establishment of a population-based registry enables future identification of novel precipitating factors of TPP.

This study has several strengths. First, we have established the first and only population-based registry of TPP, with a sample size close to 1,000. Second, the study period is long, enabling us to examine the trend across two decades. Third, CDARS is a representative electronic medical database covering all public healthcare service users in Hong Kong. Clinical data from CDARS are less subject to the selection bias as seen in claims databases. In identifying TPP cases in the present study, we utilized laboratory test records in CDARS that most claims databases lack. There are also limitations. Patients who attended private healthcare institutions were not covered by CDARS, leading to possible underestimation of incidence rates for both thyrotoxicosis and TPP. Nevertheless, this would unlikely affect the finding on temporal trends. In validating the diagnosis code and algorithm for thyrotoxicosis and TPP in CDARS, it was labor-intensive to examine all the clinical notes and/or laboratory records for all cases of thyrotoxicosis and TPP, so the negative predictive value was not evaluated. Although high PPVs were attained in CDARS for the diagnosis code of thyrotoxicosis and the algorithm in identifying TPP, their generalizability in other populations, especially those linked to electronic medical databases with different disease coding systems (such as ICD-10-CM), remains unclear. Moreover, we did not examine the relationship of TSH, FT4, and potassium levels with TPP development. The underlying causes of thyrotoxicosis were not evaluated in this study due to the absence of a specific ICD-9-CM code for GD, which is the most common cause of thyrotoxicosis. Future investigations with different study designs are warranted.

In conclusion, the present study utilized a validated population-based registry, revealing an increasing trend in the incidence rate of thyrotoxicosis, while the incidence rate of TPP was stable in Hong Kong during 2002–2021. It is important to keep monitoring the incidence rate after 2021 in the post-pandemic era, especially for thyrotoxicosis due to its increasing trend. Based on the established population-based cohorts, future studies that focus on the identification of precipitating factors for TPP are warranted to improve the management strategies for this complication.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/ETJ-25-0220.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the work reported.

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Author contribution statement

GHL and CLC contributed to the conceptualization. GHL contributed to funding acquisition, formal data analysis, project administration, and writing of the manuscript. CMT and RSL contributed to data validation and verification. GHL, KCT, and CLC contributed to the resources. All authors contributed to the data interpretation, critical revision of the manuscript for important intellectual content, and approved the final manuscript.

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