Suicide and Life-Threatening Behavior

ORIGINAL ARTICLE OPEN ACCESS

All-Cause Mortality and Suicide Mortality in Patients With Tic Disorder: An Entire Population Longitudinal Study in Taiwan

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Received: 17 January 2025 | **Revised:** 3 May 2025 | **Accepted:** 5 May 2025

Funding: The study was supported by a grant from Taipei Veterans General Hospital (V111C-010, V111C-040, V111C-029, V112C-033), Yen Tjing Ling Medical Foundation (CI-109-21, CI-109-22, CI-110-30), Ministry of Science and Technology, Taiwan (MOST110-2314-B-075-026, MOST110-2314-B-075-024-MY3, MOST 109-2314-B-010-050-MY3, MOST111-2314-B-075-014-MY2, MOST 111-2314-B-075-013), Taipei, Taichung, Kaohsiung Veterans General Hospital, Tri-Service General Hospital, Academia Sinica Joint Research Program (VTA112-V1-6-1), Veterans General Hospitals and University System of Taiwan Joint Research Program (VGHUST112-G1-8-1). The funding source had no role in any process of our study.

Keywords: mortality | suicide | tic disorder | time-dependent mortality | Tourette's syndrome

ABSTRACT

Background: Few studies investigate cause-specific mortality in individuals with tic disorders. We aimed to examine all-cause, natural-cause, and unnatural-cause mortality in individuals with tic disorders.

Methods: Using the nationwide database of Taiwan from 2003 to 2017, we identified 50,018 patients with tic disorders and, using a ratio of 1:4, matched unaffected controls based on birth year and sex. Cause-specific mortality (i.e., natural cause, accident, and suicide mortality) and all-cause mortality were assessed between the two cohorts using time-dependent Cox regression models.

Results: After adjusting for demographics, individuals with tic disorders had increased likelihoods (reported as adjusted hazard ratio [aHR] with 95% confidence interval [CI]) of all-cause (1.14, 1.03–1.26), unnatural-cause (including accidents and suicides; 1.78, 1.43–2.23), and suicide mortality (3.09, 2.07–4.59) compared to controls. With additional adjustments for psychiatric comorbidities, the likelihood of all-cause, unnatural-cause, and suicide mortality remained significant. However, we did not find a higher natural cause mortality in patients with tic disorders compared to controls (1.02, 0.91–1.15).

Conclusion: Individuals with tic disorders have a higher likelihood of unnatural causes and suicide mortality after adjusting for demographics, clinical characteristics, and psychiatric comorbidities. Our findings suggest that clinicians should routinely monitor both the physical and mental conditions of patients with tic disorders.

Chih-Sung Liang and Mu-Hong Chen contributed equally to this article as corresponding authors.

1 | Introduction

Tic disorders, including Tourette syndrome, are childhood-onset neurodevelopmental disorders with motor and/or phonic tics lasting more than 1 year, affecting 0.5% to 1% of children and young adults (American Psychiatric Association 2013; Scahill et al. 2014; Scharf et al. 2015). Individuals with tic disorders have poor academic performance, poor interpersonal relationships, and increased physical comorbidities (i.e., autoimmune diseases and asthma) (Fernandez de la Cruz and Mataix-Cols 2020; Singer 2019; Zinner et al. 2012). Severe tic symptoms might interfere with daily activities, cause social ostracism, and lead to low self-esteem (Efron and Dale 2018). Moreover, they are at a higher risk of psychiatric comorbidities than the general population, including attention deficit hyperactivity disorder (ADHD), anxiety and mood disorders, sleep disorders, disruptive behaviors, and obsessive-compulsive disorder (OCD), which impair daily function and outcomes (Fernandez de la Cruz and Mataix-Cols 2020; Hirschtritt et al. 2015; Singer 2019).

Few studies have investigated premature mortality among patients with tic disorders. In cases where ADHD, autism spectrum disorder (ASD), and major depressive disorder (MDD) frequently co-occur, patients with tic disorders may exhibit higher impulsivity, lower cognitive function, poorer self-care quality, and greater recklessness than the general population, potentially leading to a higher risk of premature mortality (Kano et al. 2015; Laursen et al. 2016; Mataix-Cols et al. 2021). A Danish cohort study ($n = 6781$) reported a higher risk of premature death in patients with tic disorders (mortality rate ratio [RR], 2.02; 95% confidence interval [CI], 1.49–2.66) compared to the control. The higher mortality rate remained significant even after excluding those with comorbid ADHD, OCD, or substance use disorders (RR, 2.30; 95% CI, 1.57–3.23) (Meier et al. 2017). A 40-year follow-up Swedish cohort study ($n = 7736$) reported a higher suicide mortality rate (odd ratio [OR], 4.39; 95% CI, 2.89–6.67) and higher suicide attempt rate (OR, 3.86; 95% CI, 3.50–4.26) in individuals with tic disorders compared with controls (de la Fernandez Cruz et al. 2017). After adjusting for psychiatric comorbidities, suicide mortality and suicide attempt rates remain significantly higher in the patient population (de la Fernandez Cruz et al. 2017). Another Swedish cohort study ($n = 3449$) reported a high traffic accident rate among patients with tic disorders, with this study also reporting a higher risk of injury or death in individuals with tic disorders (adjusted hazard ratio [aHR], 1.50; 95% CI, 1.33–1.69) compared to unaffected siblings (Mataix-Cols et al. 2021). However, the risk of traffic injury/death did not remain significant after adjusting for comorbid ADHD, which has already been associated with a higher risk of traffic accidents (Curry et al. 2019; Mataix-Cols et al. 2021). Few studies have investigated natural-cause mortality in patients with tic disorders. A Danish cohort study reported a 1.88-fold increase in natural cause mortality risk in patients with tic disorders, with only 17 deaths (Meier et al. 2017). Individuals with tic disorders are at higher risk of developing obesity, type 2 diabetes mellitus, and circulatory systemic diseases than that of the general population (Brander et al. 2019). These metabolic diseases are associated with a higher mortality risk (Huang et al. 2016; Qin et al. 2020).

Upon integrating the current evidence, tic disorders might be associated with higher unnatural-cause mortality, including suicide and accidental causes, whereas no direct evidence exists on natural-cause mortality risk among individuals with tic disorders. In the current 15-year follow-up study, we investigated all-cause mortality, natural-cause mortality, and unnatural-cause mortality (including accidents and suicides) in individuals with tic disorders using the Taiwan National Health Insurance Research Database (NHIRD). Since tic disorders are predominant in males and are rarely diagnosed in middle-aged to older Taiwanese adults, we will perform age and sex matching to reduce confounding effects (Black et al. 2021; Chou, Hung, et al. 2022). We hypothesize that individuals with tic disorders would have elevated risks of all-cause mortality, natural-cause mortality, and unnatural-cause mortality compared to unaffected individuals.

2 | Methods

2.1 | Data Source

The Taiwan NHIRD, which contains healthcare data for > 99.6% of the entire Taiwanese population, was audited and released by the Health and Welfare Data Science Center of the Ministry of Health and Welfare, Taiwan, for research purposes (Hsu et al. 2023; Huang et al. 2021; Liang et al. 2020). This database includes comprehensive data on insured individuals, including demographics, clinical visits, and disease diagnoses. Individual medical records included in the NHIRD are anonymized to protect patient privacy. In the current study, the Longitudinal Health Insurance Database of the NHIRD—which includes all medical records between 2003 and 2017 of the entire Taiwanese population ($n = 29{,}253{,}529$)—was linked to the National Death Registry, which includes all-cause mortality records between 2003 and 2017 for the entire Taiwanese population for the analyses of mortality risk in patients with tic disorders. The NHIRD has been used in numerous epidemiological studies in Taiwan (Chen et al. 2016; Cheng et al. 2018; Hsu et al. 2023; Tsai et al. 2023). The diagnostic codes used in this study are based on the *International Classification of Diseases, 9th or 10th Revision*, *Clinical Modification* (*ICD-9-CM* [2003–2014] or *ICD-10-CM* [2015–2017]). The Institutional Review Board of Taipei Veterans General Hospital approved the study protocol [2018-07-016 AC] and conformed to the provisions of the Declaration of Helsinki. The study protocol waived the requirement for informed consent because de-identified data were used, and no participants were actively included.

2.2 | Inclusion Criteria for Patients With Tic Disorders and Control Group

Patients with a diagnosis of tic disorders (*ICD-9-CM* codes: 307.2 or *ICD-10-CM* code: F95) given by board-certified neurologists, psychiatrists, and pediatricians at least twice were included in the cohort of people with tic disorder. A 1:4 matched analysis was conducted based on birth year and sex. The control cohort was randomly identified from the entire Taiwanese population after those who had been diagnosed

with tic disorders at any time were eliminated from the database. The urbanization level of residence (levels 1–4, most to least urbanized) was assessed as a proxy for healthcare availability in Taiwan (Liu et al. 2006). A previous NHIRD study reported that those residing in areas with lower urbanization levels tended to utilize outpatient services less than individuals residing in areas with higher levels of urbanization (Lin et al. 2011). The income data in NHIRD were estimated based on the National Health Insurance premium, which was correlated with the individual's income or guardian's income (if the individual was a minor without income). The diagnosis of tic disorders was regarded as a time-dependent variable during the study period. The date of first diagnosis during 2003 to 2017 for tic disorder was the same as the date of enrollment for the cohort of people with tic disorder, and the same applied to their controls (birth date matched). For example, if this case was first diagnosed with tic disorder on January 1, 2005, we would include it in the cohort from that date and begin follow-up. The corresponding control members for this case would also have January 1, 2005, as their enrollment date. Data on all-cause mortality, natural-cause mortality, and unnatural-cause mortality (accident and suicide mortality) were identified during the follow-up period between 2003 and 2017 (from enrollment to December 31, 2017, or until death) from the National Death Registry, which holds information on primary and contributing causes of death and date of death for all citizens (Cho et al. 2024). For patients with tic disorders and matched controls, Charlson Comorbidity Index (CCI) scores were calculated, which comprised 22 physical conditions and which determine the systemic health conditions of all enrolled subjects (Charlson et al. 1987). The physical conditions of the CCI scores, such as liver cirrhosis or leukemia, had to be diagnosed (on at least two instances) by relevant specialists (e.g., gastroenterologists or hematologists). Psychiatric comorbidities—including intellectual disability (*ICD-9-CM* codes: 317, 318, 319; *ICD-10-CM* codes: F70, F71, F72, F73, F78, F79), ASD (*ICD-9-CM* codes: 299; *ICD-10-CM* codes: F84), attention-deficit hyperactivity disorder (*ICD-9-CM* codes: 314; *ICD-10-CM* codes: F90), schizophrenia (*ICD-9-CM* codes: 295; *ICD-10-CM* codes: F20), bipolar disorder (*ICD-9-CM* codes: 296 except 296.2, 296.3, 296.9, and 296.82; *ICD-10-CM* codes: F30, F31), and MDD (*ICD-9-CM* codes: 296.2, 296.3; *ICD-10-CM* codes: F32, F33)—were also assessed, given that they were diagnosed by board-certified psychiatrists at least twice. All psychiatric disorder diagnoses (including tic disorder) and medical condition diagnoses (used for calculating CCI) are obtained from the NHIRD. The "twice-diagnosis method" was used to enhance the validity of the diagnosis (Cho et al. 2024; Hsu et al. 2023; Huang et al. 2021; Liang et al. 2020). For psychiatric diagnoses, we employed diagnoses by board-certified specialists at least twice to further improve the validity.

2.3 | Statistical Analysis

For between-group comparisons, the independent t test was used for continuous variables, while Pearson's χ^2 test was used for nominal variables. Time-dependent Cox regression models with adjustments for sex, birth year, income, level of urbanization, and CCI were used to calculate the HR and the 95% CI of subsequent mortality—including all-cause, natural-cause, and unnatural-cause (accident and suicide) mortality—between patients with tic disorders and the controls. Income reflects the socioeconomic impact on health, the level of urbanization serves as a proxy for healthcare availability and environmental factors, and CCI scores measure comorbidity burden affecting mortality (especially for natural causes). A Cox regression model was also performed with additional adjustment for comorbid psychiatric disorders to assess the independent role of tic disorders on mortality risk. Finally, each subject may experience different age stages (childhood, adolescence, young adulthood, or later adulthood) as he or she grows. For example, a young adult might have a higher risk of motor accidents than a child. Analyses based on age as a time-dependent variable (0–6 [reference group], 7–12, 13–17, 18–29, and 30 years) in the Cox regression models were performed. If an individual was enrolled at 5 years old, and then died at 16 years old, he will be coded as alive in groups (0–6) and (7–12), and coded as deceased in the group (13–17). Such analyses would clarify the effect of age on mortality risk. A two-tailed p value of < 0.05 was considered statistically significant. All data processing and statistical analyses were performed using the Statistical Analysis Software Version 9.1 (SAS Institute, Cary, NC, USA).

3 | Results

We enrolled 50,018 individuals diagnosed with tic disorders and 200,072 age-/sex-matched unaffected individuals, with an evident male predominance (76.51%) (Table 1). A greater proportion of individuals in the cohort of people with tic disorder resided in the urban region ($p < 0.001$) and had a higher income ($p < 0.001$) compared with the matched controls (Table 1). Individuals with tic disorders demonstrated higher CCI scores than matched controls (0: 32.64% vs. 49.24%; 1–2: 58.81% vs. 45.47%; > 2: 8.55% vs. 5.29%; $p < 0.001$) (Table 1). Additionally, a higher proportion of people in the cohort of people with tic disorder had psychiatric comorbidities than controls in all investigated disorders—namely, schizophrenia, bipolar disorder, MDD, ASD, ADHD, and intellectual disabilities (all, $p < 0.001$) (Table 1).

In Model 1 (crude hazard ratio), individuals with tic disorders showed higher risks of all-cause (HR, 1.24; 1.13–1.36), natural cause (HR, 1.19; 1.07–1.32), unnatural cause (HR, 1.48; 1.20–1.82), and suicide mortality (HR, 2.57; 1.79–3.69) compared to controls (Table 2). After adjusting for sex, birth year, income, level of urbanization, and CCI score (Model 2, main outcomes of the current study), individuals with tic disorders had higher risks of all-cause mortality (reported as aHR with 95% CI: 1.14; 1.03–1.26), unnatural cause mortality (aHR, 1.78; 1.43–2.23), and suicide mortality (aHR, 3.09; 2.07–4.59) compared to controls (Table 2). In Model 3 (adjusting for sex, birth year, income, level of urbanization, CCI score, and additionally psychiatric comorbidities), adjusted risks of all-cause (aHR, 1.17; 1.06–1.30), unnatural cause (aHR, 1.62; 1.27–2.07), and suicide mortality (aHR, 1.82; 1.13–2.94) remained elevated for individuals with tic disorders compared to controls (Table 2).

According to Model 2, stratified by sex, male individuals with tic disorders also exhibited elevated all-cause mortality (aHR, 1.15; 1.01–1.31), unnatural cause mortality (aHR, 1.67; 1.29–2.17), and suicide mortality (aHR, 3.23; 1.99–5.24). Female individuals

TABLE 1 | Demographic characteristics of patients with tic disorder or Tourette's syndrome and matched controls.

	Patients with tic disorder or Tourette's syndrome ($n = 50,018$)	Control group $n = 200,072$	p
Birth year (n, %)			> 0.999
–1950	1338 (2.68)	5352 (2.68)	
1951–1960	1031 (2.06)	4124 (2.06)	
1961–1970	1038 (2.08)	4152 (2.08)	
1971–1980	1120 (2.24)	4480 (2.24)	
1981–1990	2691 (5.38)	10,764 (5.38)	
1991–2000	17,377 (34.74)	69,508 (34.74)	
2000—	25,423 (50.83)	101,692 (50.83)	
Male (n, %)	38,267 (76.51)	153,068 (76.51)	> 0.999
Monthly income (n, %)			< 0.001
0–1000 USD	17,703 (35.39)	81,570 (40.77)	
1001–1800 USD	17,494 (34.98)	68,869 (34.42)	
≥ 1801 USD	14,821 (29.63)	49,633 (24.81)	
Level of urbanization (n, %)			< 0.001
1 (urban)	35,442 (70.86)	131,713 (65.83)	
2	10,368 (20.73)	45,746 (22.86)	
3	2859 (5.72)	14,871 (7.43)	
4 (rural)	1349 (2.70)	7742 (3.87)	
CCI (n, %)			< 0.001
0	16,326 (32.64)	98,523 (49.24)	
1–2	29,415 (58.81)	90,966 (45.47)	
> 2	4277 (8.55)	10,583 (5.29)	
Mental comorbidities (n, %)			
Schizophrenia	735 (1.47)	433 (0.22)	< 0.001
Bipolar disorder	773 (1.55)	466 (0.23)	< 0.001
Major depressive disorder	3501 (7.00)	3033 (1.52)	< 0.001
ASD	2566 (5.13)	1636 (0.82)	< 0.001
ADHD	13,041 (26.07)	9284 (4.64)	< 0.001
Intellectual disability	1562 (3.12)	1351 (0.68)	< 0.001

Abbreviations: ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index; USD, United State dollar.

with tic disorders only showed elevated risks of unnatural cause mortality (aHR, 2.24; 1.42–3.54) and suicide mortality (aHR, 2.69; 1.30–5.58) compared to controls (Table 3).

Compared to those of 0–6 years of age, only those ≥ 30 years old were associated with increased risks of all-cause (aHR, 4.38; 3.43–5.59) and natural cause mortality (aHR, 3.14; 2.38–4.15) (Table 4). Those older than 18 years of age (18–29 years and ≥ 30 years) were associated with higher risks of unnatural cause (aHR, 5.53; 3.21–9.52; aHR, 10.2; 5.95–17.50) and accident mortality (aHR, 4.47; 2.31–8.66; aHR, 6.07; 3.04–12.10) (Table 4). Notably, individuals with tic disorders younger than 30 years of age had a decreased risk of all-cause and natural cause mortality compared to those of 0–6 years of age (Table 4).

4 | Discussion

In this cohort study, we presented data on the mortality risk in 50,018 individuals with tic disorders from the entire Taiwanese population. Compared with controls, individuals in the cohort of people with tic disorder had higher comorbid rates of psychiatric disorders and physical conditions (higher CCI scores). In the crude model, individuals with tic disorders

TABLE 2 | Mortality risk between patients with tic disorder or Tourette's syndrome and matched controls with three different adjusted models.

	Event (*n*)	Mortality rate (per 100,000 person-year)	Model 1 HR (95% CI)	Model 2 adjusted HR (95% CI)	Model 3 adjusted HR (95% CI)
All cause					
Patient group	597	89.0	**1.14 (1.03–1.26)**	**1.14 (1.03–1.26)**	**1.17 (1.06–1.30)**
Control group	2983	111.5	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Natural cause					
Patient group	472	70.3	1.02 (0.91–1.15)	1.02 (0.91–1.15)	1.08 (0.96–1.22)
Control group	2474	92.4	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Unnatural cause					
Patient group	125	18.6	**1.78 (1.43–2.23)**	**1.78 (1.43–2.23)**	**1.62 (1.27–2.07)**
Control group	509	19.0	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Accident					
Patient group	55	8.2	1.22 (0.89–1.68)	1.22 (0.89–1.68)	1.34 (0.96–1.89)
Control group	338	12.6	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Suicide					
Patient group	49	7.3	**3.09 (2.07–4.59)**	**3.09 (2.07–4.59)**	**1.82 (1.13–2.94)**
Control group	102	3.8	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)

Note: Model 1: Crude. Model 2: adjusting for sex, birth year, income, level of urbanization, and CCI. Model 3: additionally adjusting for psychiatric comorbidities. Bold type indicates the statistical significance.
Abbreviations: ASD, autism spectrum disorder; CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.

TABLE 3 | Mortality risk between patients with tic disorder or Tourette's syndrome in sex difference.[a]

	All cause	Natural cause	Unnatural cause	Accident	Suicide
Male					
Events patient group (vs. control)	362 (1936)	269 (1522)	93 (414)	42 (286)	35 (69)
Adjusted HR[a] (95% CI) Patient group (vs. control)	**1.15 (1.01–1.31)**	1.03 (0.88–1.20)	**1.67 (1.29–2.17)**	1.12 (0.77–1.61)	**3.23 (1.99–5.24)**
Female					
Events patient group (vs. control)	235 (1047)	203 (952)	32 (95)	13 (52)	14 (33)
Adjusted HR[a] (95% CI) Patient group (vs. control)	1.11 (0.94–1.30)	1.00 (0.84–1.19)	**2.24 (1.42–3.54)**	1.95 (0.97–3.90)	**2.69 (1.30–5.58)**

Note: Bold type indicates the statistical significance.
Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.
[a]Adjusted according to Model 2: adjusting for sex, birth year, income, level of urbanization, and CCI.

had a 1.24-fold higher all-cause mortality, a 1.19-fold higher natural cause mortality, a 1.48-fold higher unnatural cause mortality, and a 2.57-fold higher suicide mortality than the controls. After adjusting for sex, birth year, income, level of urbanization, and CCI scores, individuals with tic disorders had a 1.14-fold higher all-cause mortality, a 1.78-fold higher unnatural cause mortality, and a 3.09-fold higher suicide mortality than controls, while they did not exhibit a higher risk of natural mortality. Additionally, even after adjustment for psychiatric comorbidities, the increased risks of all-cause and unnatural-cause mortality remained comparable to those in the adjusted model (Model 2, without adjustment for

TABLE 4 | Age as a time-dependent variable on the mortality between groups.

	HR[a] (95% CI)				
	All cause	**Natural cause**	**Unnatural cause**	**Accident**	**Suicide**
Age as a time-dependent variable					
0–6 years	1.00 (ref. grp)	1.00 (ref. grp)	1.00 (ref. grp)	1.00 (ref. grp)	1.00 (ref. grp)
7–12 years	**0.22 (0.15–0.32)**	**0.14 (0.09–0.23)**	0.67 (0.35–1.29)	0.76 (0.37–1.58)	na
13–17 years	**0.26 (0.17–0.39)**	**0.09 (0.05–0.17)**	1.49 (0.80–2.78)	1.39 (0.65–2.95)	na
18–29 years	**0.71 (0.52–0.96)**	**0.14 (0.08–0.25)**	**5.53 (3.21–9.52)**	**4.47 (2.31–8.66)**	na
30– years	**4.38 (3.43–5.59)**	**3.14 (2.38–4.15)**	**10.2 (5.95–17.50)**	**6.07 (3.04–12.10)**	na

Note: Bold type indicates the statistical significance.
Abbreviations: CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; na, not available.
[a]Adjusting for group, sex, birth year, income, level of urbanization, and CCI.

psychiatric comorbidities); however, suicide risk decreased from 3.09- to 1.82-fold. In the time-dependent variable analysis (age effect), we found increased risks of all-cause mortality and natural cause mortality in tic disorder patients older than 30 years, and increased risks of unnatural mortality and accident mortality in adult tic disorder patients compared to those of 0–6 years of age.

In our analyses, the suicide mortality risk of individuals with tic disorders was significantly increased in all three models—namely crude—adjusting for demographics, and adjusting for demographics plus psychiatric comorbidities, compared to the controls. In particular, the risk of suicide mortality was much higher (3.09-fold) than that of other causes of mortality, such as natural causes or accidents (1- to 1.7-fold), even after adjusting for psychiatric comorbidities (1.82-fold). When stratified by sex, elevated suicide mortality risk was observed in both sexes. Our results are consistent with the largest study to date, a Swedish cohort study with 7736 patients with tic disorders and 32 patients who died by suicide, which reported a higher risk of suicide mortality in patients with tic disorders than in controls in the unadjusted model; the risk was reduced after adjusting for psychiatric comorbidities but remained substantial (de la Fernandez Cruz et al. 2017). These findings imply that tic disorders have their own impact on increased suicide risk, regardless of other physical or psychiatric comorbidities. The severity of tic symptoms is also correlated with the severity of depression (Marwitz and Pringsheim 2018). A Swedish cohort study also investigated the predictive factors of suicide and showed that persistence of tics beyond young adulthood was the strongest predictor of suicide (de la Fernandez Cruz et al. 2017). Unfortunately, we were unable to assess the severity of tics or depressive symptoms in our study due to the limitations of the NHIRD database. Further studies investigating the severity of tic and depressive symptoms and suicide risk are required to address this issue.

Regarding natural-cause mortality, our study did not find an elevated risk after adjusting for demographics. However, the Danish study reported a 1.88-fold increase in natural-cause mortality risk in patients with tic disorder (Meier et al. 2017). This Danish study had a longer follow-up period than ours (1975 to 2013 vs. 2003 to 2017). Naturally, a longer follow-up period provides a higher chance of capturing natural deaths as individuals age. We have two possible explanations for the non-significant higher natural-cause mortality in the patients with tic disorder in our study. First, the CCI score did not account for diseases that are more prevalent in those with tic disorders—such as Hashimoto thyroiditis, celiac disease (Mataix-Cols et al. 2018), and asthma (Chang et al. 2011)—which would also influence natural-cause mortality. Second, patients with tic disorder might have higher substantial risks of metabolic and cardiovascular disorders, or immune diseases such as diabetes, coronary artery diseases, or asthma (Brander et al. 2019; Fernandez de la Cruz and Mataix-Cols 2020). In addition, unlike malignancies or severe congenital diseases, physical problems (such as diabetes or asthma) take time to cause mortality. Nevertheless, in the age as time variable analysis of our study, a 3.14-fold higher risk of natural-cause mortality was noted among patients aged > 30 years, which reflects the influencing factors of age. On the other hand, we found that patients aged 0–6 years demonstrated a higher risk of natural-cause mortality than those aged 7–12 years, 13–17 years, and 18–29 years. Tic disorders may co-occur with other congenital diseases, such as Wilson's disease, Duchenne's muscular dystrophy, tuberous sclerosis, and Fragile X syndrome (Jankovic and Kwak 2004). This may explain why the 0–6 age group has a relatively higher mortality rate, while those who survive beyond the age of 6 are likely to have fewer severe comorbid congenital diseases.

Similar to natural causes, accidental mortality was not elevated in the general analyses, but was elevated in the adult age group in the time-dependent analysis. Previous epidemiological studies in Taiwan have shown that, when stratified by age, the risk of head injury and accidental trauma increases significantly after reaching adulthood (Chou, Huang, et al. 2022; Hsu et al. 2018). This may be related to the higher likelihood of engaging in hazardous work and the more frequent use of motor vehicles for independent driving or riding after becoming an adult. Furthermore, a previous Swedish cohort study reported that individuals with tic disorder had increased risks of alcohol-related disorders (aHR, 3.45; 3.19–3.72), drug-related disorders (aHR, 6.84; 6.32–7.40), and substance-related deaths (aHR, 2.54; 1.83–3.52) (Virtanen et al. 2021). Mostly, people began to use substances and alcohol since adolescence or young adulthood (Griffin 2010), which might also stand for our findings.

Nevertheless, our findings should be interpreted with caution and have several limitations. First, the diagnoses were obtained from a health database and not from structured diagnostic interviews. The accuracy of psychiatric diagnoses should be validated in further studies. Second, various potential contributing factors—such as drug adherence, psychosocial stress, environment, and lifestyle—could not be assessed in the database. Third, in some analyses, we did not have a sufficiently large sample size, which might have limited the statistical power of certain tests. For example, we included only 49 patients with tic disorders who died by suicide. Nevertheless, our sample size was larger than that of a large Swedish cohort study (de la Fernandez Cruz et al. 2017). Fourth, we used age- and sex-matched individuals as the control group and not their siblings. Comparing with siblings who may share similar environmental factors and some common genetic factors with the cases might help reduce bias. Fifth, left truncation effects would bias the analyses of age as a time-dependent variable. Elderly individuals who were already adults at enrollment can only have been exposed since the later stages of age. On the other hand, with the relatively short follow-up duration, young individuals had not yet reached an age where natural cause mortality would be common during the follow-up period, possibly leading to an underestimation of natural cause mortality. Sixth, psychiatric diagnoses were identified using the ICD-9/ICD-10 codes in the administrative claims, and we could not address those who were underdiagnosed or those who did not seek medical help. Therefore, the prevalence of psychiatric diagnoses could be underestimated. Seventh, although the diagnoses of physical comorbidities calculated in the CCI score, schizophrenia, and major depression had been validated previously, diagnoses of tic disorder and other psychiatric comorbidities had not been validated (Hsieh et al. 2019; Wu et al. 2014). Nevertheless, we employed diagnoses made at least twice by board-certified specialists to improve the validity of our study. Eighth, we did not include OCD and other anxiety disorders as covariates, which have a high co-occurrence with tic disorders. Finally, the generalizability of this study is limited to the Taiwanese population and the healthcare system.

5 | Conclusion

Few studies have investigated all-cause mortality and cause-specific mortality in patients with tic disorders, and our study suggests a higher all-cause mortality risk, unnatural mortality (including accident and suicide) risk, and suicide risk in the tic disorders population than in controls. Especially after reaching adulthood, patients with tic disorders also have increased risks of natural and accidental mortality compared to controls. Our findings suggest that, when individuals with tic disorders enter adulthood, clinicians should carefully monitor their physical condition and mental health and provide education and information accordingly.

Author Contributions

Tien-Wei Hsu: writing – original draft (equal). **Wen-Han Chang:** validation (equal), writing – review and editing (supporting). **Chih-Ming Cheng:** validation (equal), writing – review and editing (supporting). **Shih-Jen Tsai:** supervision (equal), validation (equal), writing – review and editing (equal). **Ya-Mei Bai:** validation (equal), writing – review and editing (supporting). **Ju-Wei Hsu:** validation (equal), writing – review and editing (supporting). **Kai-Lin Huang:** validation (equal), writing – review and editing (supporting). **Tzeng-Ji Chen:** methodology (equal). **Chih-Sung Liang:** investigation (equal), writing – original draft (equal). **Mu-Hong Chen:** conceptualization (equal), formal analysis (equal), writing – review and editing (equal).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The NHIRD was released and audited by the Department of Health and the Bureau of the NHI Program for the purpose of scientific research (https://www.apre.mohw.gov.tw/). The NHIRD can be accessed through a formal application regulated by the Health and Welfare Data Science Center of the Ministry of Health and Welfare of Taiwan.

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