Social Psychiatry and Psychiatric Epidemiology (2019) 54:121–130
https://doi.org/10.1007/s00127-018-1587-x

ORIGINAL PAPER

Excessive mortality and causes of death among patients with personality disorder with comorbid psychiatric disorders

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Received: 3 March 2018 / Accepted: 20 August 2018 / Published online: 27 August 2018

Abstract

Purpose Excessive mortality has been seen in patients with personality disorder (PD), but it has not been well-studied when patients also have other psychiatric comorbidities. This study investigated the mortality rates and causes of death in an Asian cohort with PD.

Method We enrolled patients ≥ 18 years of age with PD as defined by DSM-IV criteria ($N = 1172$), who had been admitted to a psychiatric service center in northern Taiwan between 1985 and 2008. By linking with the national mortality database (1985–2008), cases of mortality ($n = 156$, 13.3%) were obtained. We calculated the standardized mortality ratios (SMRs) to estimate the mortality gap between patients with PD and the general population. Stratified analyses of mortality rates by Axis I psychiatric comorbidity and sex were performed.

Results Borderline PD ($n = 391$, 33.4%) was the dominant disorder among the subjects. The SMRs for all-cause mortality of PD alone, PD comorbid with non-substance use disorder(non-SUD), and PD comorbid with SUD were 4.46 (95% CI 1.94–6.98), 7.42 (5.99–8.85), and 15.96 (11.07–20.85), respectively. Among the causes of death, the SMR for suicide was the highest (46.92, 95% CI 34.29–59.56). The SMR for suicide in PD patients with comorbid SUD was unusually high (74.23, 95% CI 33.88-114.58). Women had a significant increase in suicide with an SMR of 59.00 (95% CI 37.89–80.11). Men had significant increase in SMRs for cardiovascular disease and gastrointestinal disease.

Conclusions We found significant synergistic effects of PD and SUD on mortality risk. A personality assessment should be mandatory in all clinical settings to prevent premature death and detect SUD early.

Keywords Cause of death · Comorbidity · Personality disorder · Standard mortality ratio · Substance use disorder

Introduction

Personality disorder (PD) is a common but challenging psychiatric disorder in various clinical settings. The prevalence of PD in the general population ranges from 6 to 13% [1, 2]. PD plays a predisposing role for other psychiatric disorders and is frequently comorbid with other clinical syndromes. Approximately, 50% of all psychiatric patients have PD [3]. The response of patients with PD to treatment is highly variable, and treatment is often ineffective. Thus, PD tends to take a chronic course, and treatment outcomes are controversial [4–6].

The clinical diagnosis of PD is currently based on the Diagnostic Statistical Manual (DSM-5) of the American

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00127-018-1587-x) contains supplementary material, which is available to authorized users.

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Psychiatric Association [7] and the International Classification of Diseases (ICD-10) of the World Health Organization [8]. There are some nomenclature differences between the two systems. For example, the schizotypal PD of DSM-5 is not listed in the ICD-10. The antisocial PD of DSM-5 is categorized as an emotionally unstable PD in the ICD-10 and subsequently subclassified as an impulsive and borderline type. Based on the clinical utility and symptoms, PDs are usually grouped into three clusters in the DSM-IV: Cluster A is characterized by odd and eccentric behaviors; cluster B, by dramatic and erratic behaviors, and cluster C, by anxious, and fearful behaviors [9].

Patients with PD are sometimes hospitalized because of severe interpersonal difficulties, impulse control problems, or mood disturbances. It is well-known that individuals with PD alone have higher overall mortality rate than the general population [10–13]. People with PD were more likely to die from suicide [14–17], homicide, or accidental death [18, 19]. However, among people with PD, few studies have measured mortality using standardized mortality ratios (SMRs), and all of these studies were conducted in Western countries. The SMR is the mortality ratio of the specified population relative to the general population. Two decades ago, Black et al. [20] investigated SMRs among people with PD in Iowa, USA, but the study sample was limited to antisocial PD and had a small sample size. In the recent decade, only a few studies in Europe [9, 21, 22] have estimated SMRs among people with PD, and studies conducted in the Asian population are exceedingly rare. For instance, a study conducted in the UK [21] using a large psychiatric case registry showed an all-cause SMR of 4.2, and the SMRs for men and women were 3.5 and 5.0, respectively. A Norwegian study [22] based on a hospital case registry showed the SMRs for men and women were 5.0 and 6.1, respectively. A Swedish study [9] using national population registries showed that the SMRs for men and women were 4.3 and 2.9, respectively.

Patients experiencing PD have higher rates of comorbid mental disorders; among them, substance use disorders (SUDs) are very common [23]. Most empirical research is on comorbidity with borderline PD, and according to a systematic review, about 38–57% of borderline PD patients have at least one SUD diagnosis [24]. Furthermore, some studies show the possible aggravation of PD symptoms by SUD such that patients with PD and SUD may have higher levels of psychosocial impairment, more severe psychopathology, and increased rates of suicidal behaviors, which present a considerable challenge for mental health service providers [25]. To the best of our knowledge, very few, if any, studies have compared the mortality rate between patients with PD who had or did not have another comorbid psychiatric disorder, especially SUD. Whether a synergistic effect for PD and comorbid disorders (such as SUD) exists deserves investigation, with mortality as the marker.

In this study, we aimed to investigate the mortality rates and causes of death in specific populations by the follow-up of an Asian cohort with PD that had been admitted to a psychiatric hospital in northern Taiwan. Furthermore, we estimated the mortality rates and stratified them according to axis I psychiatric comorbidity features. The distribution of causes of death by gender also was investigated.

Method

Study population

The source of participants was the Taipei City Psychiatric Center (TCPC), a psychiatric service center serving northern Taiwan. The methodology used is described extensively elsewhere and has been used in prior studies of mortality in SUDs [26–29], suicide in bipolar disorder [30], suicide in schizophrenia [31], and inpatient suicides [32].

All adult patients admitted to Taipei City Psychiatric Center (TCPC) for acute care from January 1, 1985, through December 31, 2008, were included in this retrospective cohort study. The study flow is described in Fig. 1. Study inclusion criteria were as follows: (1) a psychiatric discharge diagnosis of PD made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition Revised (DSM-III-R) and Fourth Edition [33, 34], or ICD-9-CM [35]; and (2) persistence of PD diagnosis during the study period. Discharge and comorbidity diagnoses were made by a senior psychiatrist who reviewed several types of clinical information on each inpatient during each admission, including a comprehensive evaluation by a multidisciplinary therapy team. The administrative system applied ICD-9-CM codes in hospitals and the death certification system in Taiwan. Patients with a consistent diagnosis of PD (ICD-9 code of 301.**) between 1985 and 2008 ($N = 1172$) were enrolled as the study cohort. This study was approved by the Institutional Review Board of the Committee on Human Subjects of Taipei City Hospital, Taipei, Taiwan. Patient consent was not sought because of the retrospective nature of the study, and patient records were de-identified before selection.

Mortality and causes of death

As each Taiwanese citizen has a unique national identification (ID) number, nationwide mortality registration including the ID is maintained by the Ministry of Health and Social Welfare. The number of people who migrated from the island is negligible. National ID numbers are routinely recorded on admission to the TCPC, so the mortality status of these patients can be accurately ascertained via record linkage.

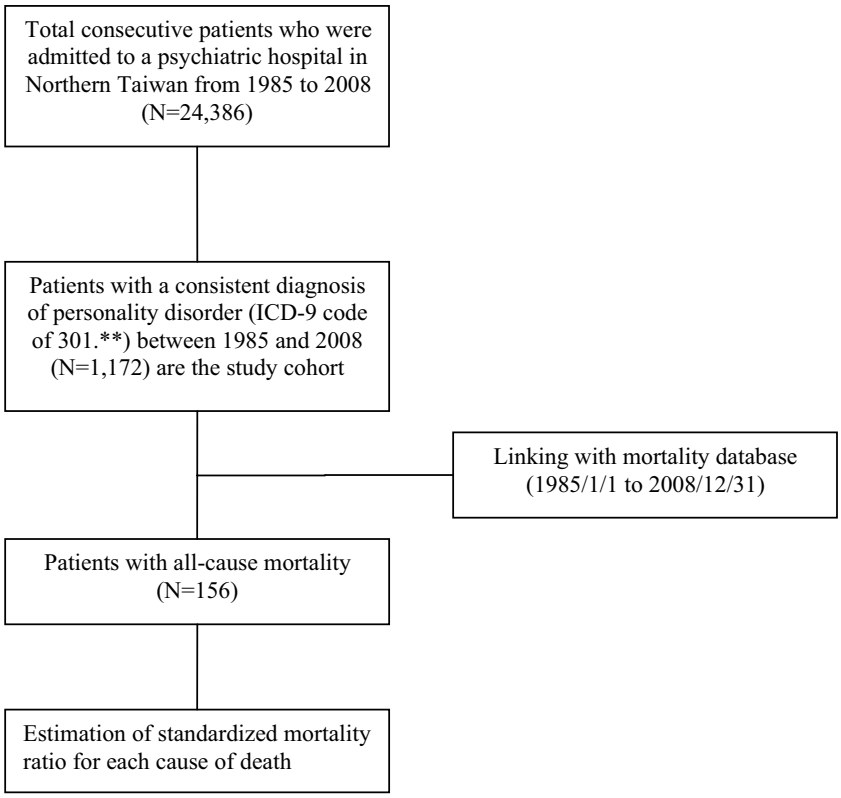

Fig. 1 Study flow diagram

We searched for deceased subjects by matching national IDs with computerized data files from the Ministry of Health and Social Welfare Death Certification System issued for the years 1985–2008. The mortality status ascertained in this way can be considered as complete, with detailed information including mortality status, demographic variables, and the cause of death and the role of the person who made the death verdict. For each patient who died, the cause of death was classified as either natural or unnatural based on the information provided by the Death Certification System. Deaths due to suicide (ICD-9-CM code E950-959), accidents (ICD-9-CM code E800-949), and homicide (ICD-9-CM code E960-989) were categorized as unnatural deaths. All remaining causes of death were considered as natural causes. In Taiwan, in case of sudden death, the coroner and prosecutor have a statutory responsibility to investigate all deaths in which the death was unexpected, unnatural, violent, or resulted from an accident or injury that suggested a possibility of homicide.

Statistical analysis

The survival (contributed) time for each subject was calculated from the index discharge to the end of the study (e.g., until censored or December 31, 2008). Univariate Cox proportional hazards analyses were conducted to estimate the hazard ratios for associations between the mortality and sex, age, and length of stay at the index admission. We calculated the crude mortality rates for various causes of death as the incident cases divided by the contributed person-years for men and women, respectively. Differences in incidence of specific causes of death among men and women were estimated using Gehan's generalized Wilcoxon test [36] and life table survival analysis.

We then estimated the SMR as the ratio of observed deaths in the PD group to expected deaths in the general population in Taiwan [37]. The formula of SMR is calculated as (observed deaths/expected deaths). SMRs were calculated for the PD cohort during the follow-up period, using the number of deaths obtained from the Death Certification System as the numerator and the expected number of deaths as the denominator. Following a method used in a prior study [38], the denominator was first estimated by 5 year age bands, with sex-specific mean mortality rates from the general population of Taiwan in a corresponding year multiplied by the contributed person-years in the at-risk period experienced by patients with PD in each age and sex category, and then the values in each age and sex group were added to obtain the total number of expected deaths.

Each SMR was calculated by dividing the number of observed deaths from a given cause by the age-adjusted expected values. SMRs of natural and unnatural causes of death in this inpatient PD cohort are presented as three

subgroups: without axis I comorbidity, comorbid with SUD, and comorbid with non-substance use disorders (non-SUD).

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institutes Inc., Cary, NC, USA). A p value of 0.05 was considered statistically significant.

Results

Mortality in relation to characteristics of study subjects

For the analysis, 1172 eligible patients with PD were recruited (Table 1). The sociodemographic data revealed that women ($N=666$) predominated (men, $N=506$) in the study. However, men had a higher risk of mortality than women did (Hazard ratio = 1.65, $p=0.002$). The 25–44 year age group ($N=714/1172$, 60.9%) was dominant in this group, which also contributed a significant number of deaths ($N=95/156$, 60.9%). The risk of mortality increased incrementally with age. Approximately, half of the PD patients ($N=534/1172$, 45.6%) were only hospitalized for 2 weeks, but the duration of hospital stay did not affect the number of mortalities.

Mortality in relation to PD subcategory and psychiatric comorbidity

Table 2 shows the distribution of PDs, including paranoid PD ($N=22$, 1.9%); schizoid PD ($N=42$, 3.9%); explosive PD ($N=4$, 0.3%); compulsive PD ($N=30$, 2.6%); histrionic PD ($N=94$, 8.0%); dependent PD ($N=22$, 1.9%); antisocial PD ($N=160$, 13.7%); borderline PD ($N=391$, 33.4%); and others or unspecified PD (301.9) ($N=407$, 34.7%). Borderline PD predominated among the study subjects. However, the numbers of deaths in the different personality subcategories did not differ significantly ($\chi^2=8.52$, $df=8$, $p=0.385$).

The results showed no significant differences in mortality between the types of PDs. Thus, we analyzed the incidence and SMR using the entire study cohort with PD.

Of the 1172 patients with PD, 92 (7.8%) had no comorbidity, 250 (21.3%) had a comorbid SUD (defined as PD with SUD), and the remaining 830 (70.8%) had a comorbid axis I psychiatric disorder other than SUD (defined as PD with non-SUD). Of the 250 patients in the PD with SUD group, 108 had comorbid alcohol use disorder, 59 had comorbid methamphetamine use disorder, and 83 had other substance use disorders. Of the 830 patients in the PD with non-SUD group, 98 had a comorbid major psychiatric illness (42 had comorbid schizophrenia, 21 had comorbid bipolar disorder, 35 had major depressive disorder); the remaining 732 had a comorbid minor psychiatric illness such as neurotic depression or generalized anxiety disorder or adjustment disorder. The distribution of axis I psychiatric comorbidity (no comorbidity, comorbid with SUD, comorbid with non-SUD disorders) between the patients who died and those who lived showed no statistically significant difference ($X^2=2.66$, $df=2$, $p=0.265$).

Incidence of causes of death among men and women

Of the 1172 patients, 156 died during the study period from January 1, 1985, through December 31, 2008. Table 3 shows that the total mortality rate among men was significantly higher than that among women ($p=0.021$). However, the

Table 1 Characteristics of patients with personality disorder at the index admission who died and of those who lived during the study period (1985–2008)

Characteristic	Total ($N=1172$) N (%)	Died ($N=156$) N (%)	Hazard ratio[a]	95% CI	p value
Sex					
Female	666 (56.8)	66 (42.3)	Reference		
Male	506 (43.2)	90 (57.7)	1.65	1.20–2.27	0.002
Age, years					
< 25	302 (25.8)	27 (17.3)	Reference		
25–44	714 (60.9)	95 (60.9)	1.71	1.12–2.63	0.014
45–64	138 (11.8)	29 (18.6)	3.02	1.78–5.11	< 0.001
≥ 65	18 (1.5)	5 (3.2)	5.08	1.95–13.24	< 0.001
Length of stay, days					
< 15	534 (45.6)	67 (43.0)	Reference		
15–29	223 (19.0)	30 (19.2)	1.00	0.65–1.54	0.988
30–44	140 (11.9)	22 (14.1)	1.13	0.70–1.83	0.624
45–59	84 (7.2)	10 (6.4)	0.79	0.41–1.54	0.490
≥ 60	191 (16.3)	27 (17.3)	0.83	0.53–1.31	0.430

[a]By univariate Cox proportional hazards model

Table 2 Clinical diagnosis of personality disorder and axis I psychiatric comorbidity between those who died and those who lived during the study period

Characteristic	Living ($N=1016$) N (%)	Died ($N=156$) N (%)	Total ($N=1172$) N (%)
Cluster A personality disorder[a]			
Paranoid (301.0)	18 (1.8)	4 (2.6)	22 (1.9)
Schizoid (301.2)	37 (3.6)	5 (3.2)	42 (3.9)
Cluster B personality disorder[a]			
Explosive (301.3)	4 (0.4)	0 (0.0)	4 (0.3)
Borderline (301.83)	338 (33.3)	53 (34.0)	391 (33.4)
Histrionic (301.5)	83 (8.2)	11 (7.1)	94 (8.0)
Antisocial (301.7)	131 (12.9)	29 (18.6)	160 (13.7)
Cluster C personality disorder[a]			
Dependent (301.6)	17 (1.7)	5 (3.2)	22 (1.9)
Compulsive (301.4)	28 (2.8)	2 (1.3)	30 (2.6)
Others or unspecified personality disorder (301.9)	360 (35.5)	47 (30.1)	407 (34.7)
Axis I psychiatric comorbidity			
No comorbidity	80 (7.9)	12 (7.7)	92 (7.9)
Comorbid with substance use disorders*	209 (20.6)	41 (26.3)	250 (21.3)
Comorbid with non-substance use disorders[†]	727 (71.6)	103 (66.0)	830 (70.8)

No significance differences among personality categories between those died and those who lived during the study period. $\chi^2=8.52$, $df=8$, $p=0.385$

No significance difference in the distribution of axis I psychiatric comorbidities between those who died and those who lived during the study period. $\chi^2=2.66$, $df=2$, $p=0.265$

*Including alcohol use disorder, methamphetamine use disorder, opioid use disorder, and other substance use disorders

[†]Including schizophrenia, bipolar disorder, major depression disorder, other depressive disorders, and other psychotic disorders

[a]ICD-9-CM code in the parentheses

rate of unnatural deaths among men did not differ from that among women ($p=0.726$). The majority (56.4%, 88/156) of the patients died unnatural deaths, especially, suicide, which comprised 59.1% (52/88) of unnatural deaths.

A substantial portion (43.6%, 68/156) of the subjects died from natural deaths, especially cardiovascular disease, which comprised 27.9% (19/68) of natural deaths. Among those who died, men had a higher natural death rate than women did, especially due to cardiovascular and gastrointestinal diseases.

SMRs among study subjects with PD

Table 4 shows that the SMR for all-cause death is 8.80 in the PD cohort, which indicates a significant health gap relative to the general population. The SMR of PD alone is 4.46, but it is 15.96 in the PD with SUD group and 7.42 in the PD with non-SUD group.

The analysis of SMRs by sex for each category of cause of death is shown in e-Table 1. Table 4 shows only those categories with SMRs significantly different from 1.0, which includes accidental death, suicide, cardiovascular disease, and gastrointestinal disease.

Suicide had the highest SMR among the causes of death relative to the general population, especially in the PD with SUD group (SMR = 74.23, 95% CI 33.88-114.58). Women had a significant increase in suicide, with an SMR of 59.00 (95% CI 37.89–80.11) (Supplemental e-Table 2). Other than unnatural deaths, patients with PD also had an increased SMR (5.64, 95% CI 4.30–6.99) for natural deaths compared with the general population. Moreover, men had significant increase in SMRs for cardiovascular disease (SMR = 8.37, 95% CI 3.99–12.76) and gastrointestinal disease (SMR = 6.28, 95% CI 1.63–10.93).

Discussion

The main finding of the study is the high risk of mortality among patients with PD who had comorbid SUD. We found that the SMR (4.46) of patients with PD alone ($N=92$) is similar to that reported in the literature [9, 22]. However, the total SMR is 16-fold higher among the patients with PD and SUD and sevenfold higher among the patients with PD and non-SUD than in the general population (Table 4). These findings suggest that patients with PD and SUD are

Table 3 Crude incidence of cause of death among the inpatients with personality disorder by sex

Characteristic	Men ($N=506$) (PY = 4306.9)		Women ($N=666$) (PY = 5124.1)		Total ($N=1172$) (PY = 9430.99)		p value
Cause of death	No. of deaths	Incidence[a]	No. of deaths	Incidence[a]	No. of deaths	Incidence[a]	
Total mortality	90	2089.7	66	1288.04	156	1654.12	0.021*
Unnatural death	40	928.7	48	936.76	88	933.09	0.726
Accident	11	255.4	13	253.71	24	254.48	0.907
Suicide	22	510.8	30	585.47	52	551.37	0.353
Homicide	1	23.2	0	0.00	1	10.60	0.254
Undetermined for unnatural deaths	6	139.3	5	97.58	11	116.64	0.610
Natural death	50	1160.9	18	351.28	68	721.03	< 0.001
Cancer	7	162.5	2	39.03	9	95.43	0.078
Endocrine or Metabolic	1	23.2	1	19.52	2	21.21	0.955
Neurological	0	0.0	1	19.52	1	10.60	0.381
Cardiovascular	14	325.1	5	97.58	19	201.46	0.052
Respiratory	3	69.7	1	19.52	4	42.41	0.170
Gastrointestinal	7	162.5	1	19.52	8	84.83	0.013
Genitourinary	1	23.2	0	0.00	1	10.60	0.328
Skin	0	0.0	0	0.00	0	0.00	–
Bone	0	0.0	0	0.00	0	0.00	–
Others	5	116.1	5	97.58	10	106.03	0.444
Undetermined for natural deaths	12	278.6	2	39.03	14	148.45	0.008

PY person-years

The significance of asterisk is defined as $p < 0.05$

[a]Incidence, number per 100,000 person-years. The differences in incidence for specific causes of death between men and women were calculated using the Wilcox (Gehan) statistic by survival life table analysis

exposed to a high risk of mortality. Therefore, a personality assessment is indicated in the clinical setting in consideration of patients' high mortality, especially in those with comorbidity.

Death by suicide

Our study revealed the SMR for suicide was the highest (46.92) among all causes of death. Among the suicide cases, most (57.7%) were women. Among them, SMR was higher than that for men (59.00 vs. 37.04). This high risk of completed suicide is similar to that reported in the literature; for example, Björkenstam et al. [39] studied hospitalized patients with a principal diagnosis of PD and reported the SMR of suicide for women was 55.0 and for men, 35.8. Therefore, it appears that there is no cultural difference regarding the risk of suicide mortality among patients with PD.

Despite our results showing no significant difference in the incidence of suicide between men and women (Table 3), women had a significantly higher SMR for suicide death than men in our study, which is consistent with the results of prior studies [9, 39]. Importantly, this finding implies that the health gap regarding suicide between patients with PD and the general community is wider for women than for men.

A community study in Taiwan has shown that SUDs and severe depression, can be intermingled among people with emotionally unstable PD [15], which could precipitate the risk of suicide mortality.

The present study showed significant synergistic effects of PD and SUD on the risk of suicide mortality. The suicide risk among our patients PD and SUD is 74-fold higher than in the general population. To our knowledge, similar data have rarely been reported in the literature, and only recently a Swedish study [40] reported that patients with PD and SUD had a 48-fold higher suicide risk than in the general population.

The relationship between SUD and premature death is frequently discussed [41, 42]. The SMR for suicide due to SUDs alone is approximately 4- to 16-fold higher than in the general population [10, 26]. Having any SUD is associated with an increased risk of suicide mortality when compared with persons having no SUD [43]. Our previous study [27] of methamphetamine user mortality revealed the SMR among women (8.69) is higher than among men (5.75) for all-cause SMR (6.02 overall). In addition, the SMR of PD patients with heroin use disorder is 7.9-fold higher for

Table 4 Standardized mortality ratios (SMRs) of inpatients with personality disorder who were admitted between 1985 and 2008, with linking to the mortality database in Taiwan (1985–2008), stratified by three subgroups (without Axis I comorbidity, comorbid with substance use disorders, and comorbid with non-substance use disorders)

	Without axis I comorbidity ($N=93$)			Comorbid with substance use disorders ($N=250$)			Comorbid with non-substance use disorders ($N=829$)			Total ($N=1172$)		
	O	*E*	SMR (95% CI)	*O*	*E*	SMR (95% CI)	*O*	*E*	SMR (95% CI)	*O*	*E*	SMR (95% CI)
Total	12	2.69	4.46 (1.94–6.98)	41	2.57	15.96 (11.07–20.85)	103	13.88	7.42 (5.99–8.85)	156	17.73	8.80 (7.42–10.18)
Unnatural death	5	0.88	5.68 (0.70-10.66)	27	0.98	27.51 (17.14–37.89)	56	4.38	12.8 (9.44–16.15)	88	5.68	15.49 (12.25–18.73)
Accidental death*	0	0.68	–	11	0.74	14.9 (6.09–23.70)	13	3.33	3.91 (1.78–6.03)	24	4.28	5.60 (3.36–7.84)
Suicide*	5	0.15	34.5 (4.26–64.73)	13	0.18	74.23 (33.88-114.58)	34	0.76	44.65 (29.64–59.65)	53	1.13	46.92 (34.29–59.56)
Natural death	7	1.81	3.87 (1.00-6.74)	14	1.59	8.83 (4.21–13.46)	47	9.50	4.95 (3.53–6.37)	68	12.05	5.64 (4.3–6.99)
Cardiovascular*	1	0.43	2.32 (-2.23-6.87)	4	0.32	12.59 (0.25–24.93)	14	2.17	6.46 (3.07–9.84)	19	2.73	6.96 (3.83–10.09)
Gastrointestinal*	1	0.19	5.16 (-4.96-15.28)	3	0.22	13.54 (-1.78-28.87)	4	1.14	3.52 (0.07–6.98)	8	1.14	5.67 (1.74–9.6)

O observed, *E* expected

*Cause of death with SMR significantly different from 1.0 ($p<0.05$) in any of the three groups

all-cause mortality compared to that of the general population, and the SMR for suicide mortality was 16.2 [29].

Excessive mortality in PD patients with SUD

The findings of this study showed a higher SMR for all-cause mortality in PD patients with SUD than in those with non-SUD comorbidity or those without any comorbidity.

The complexity of PD, SUD, and premature death is difficult to interpret. The etiology of PD is not well-known, and biological factors (likely genetic factors) and environmental factors possibly contribute equally. People with PD are ego-syntonic and use various pathological defense mechanisms for coping [3]. They experience problems with coping skills and find it hard to adapt to family relationships in daily life. They have interpersonal difficulty and impulse control problems. It appears that the availability of substances seems to provide sanctuary from life's difficulties. Since 1989, substance abuse has become a substantial problem in Taiwan [26]. Recently, heroin, alcohol, methamphetamine, and even ketamine abuse have dramatically increased. This substance abuse may have led to an increase in the number of people with PD and SUD subsequently resulting in self-perishing outcomes.

Excessive natural deaths

This study showed that the increased risk of mortality in the cohort with PD is not only due to increased rates of suicide, but also that the cohort had a high risk of natural death relative to the general population (SMR = 5.64), especially for cardiovascular and gastrointestinal diseases.

There are several explanations for these results. First, the increased risk may be explained by alcohol or drug use [21]. Our findings add to evidence showing a significantly higher risk if patients have comorbid SUDs than in those without axis I comorbidity. These results imply that comorbid SUDs have a strong potentiating effect on the SMR for natural causes. Additionally, people with alcohol dependence are well-known to have a higher risk of natural death, including cardiovascular and gastrointestinal deaths [26, 44]. Methamphetamine-dependent patients also have a higher risk of natural death, especially death due to cardiovascular events [45].

Second, patients with PD without any psychiatric comorbidity still showed a significant risk of natural death, which indicates that PD is inherently associated with poorer health consequences and less healthy lifestyles [46].

Third, similar to patients with mental disorders [47], patients with PD could have barriers to visiting medical facilities when they are physically ill [48].

We also found that higher SMRs for natural causes in men than in women, which is consistent with a Northern

Norway study [22]. The size of the SMR for natural causes in men in this study was even higher than in the Norwegian study (6.75 vs. 2.8). The possible explanations include a substantial portion of men with comorbid SUD (supplemental e-Table 3), which contributes to a higher risk of death from natural causes. Additionally, women are known to be more likely to seek medical help than men, which could result in lower mortality among women.

Limitations

The primary strength of our study was the use of a large psychiatric hospital cohort, covering a variety of PDs to reveal the associated causes of mortalities. The mortality data were drawn from the death certification registry, which is a legal requirement in Taiwan; therefore, missing data is minimal.

There are certain limitations in this study. First, according to a prior study by Moran [49], most patients with PD had no clinical experience in the secondary mental health setting in their lifetime. Thus, we selected the patients with PD from the TCPC indicating that the severity of the illness required admission to a psychiatric center. The patients could have a specific clinical reason for admission to the center, such as suicide risk, aggressive behavior, or another comorbid such as major depression. Therefore, the results of PD cohort in our study may not be generalizable to all the PD patients. Second, although this study employed a national identification system that allows tracking of each suicide event, we might still have missed patients who died of suicide but whose deaths were misclassified due to other causes, for example, "accidental death," which is the most common term used to avoid the potential stigma associated with suicide. Third, a substantial portion of patients with PD had comorbid SUD in this cohort, and 43.2% of them (108/250) were diagnosed with alcohol use disorder. The heterogeneity of the different substances used by PD patients needs further investigation. Fourth, the mortality database ceased to be released after 2009 in Taiwan due to a governmental policy change. Thus, this study was able to follow-up on the mortality status of each subject until December 31 2008, leaving about a 10-year gap until now (2018). This study highlighted an excessive mortality rate in patients with PD, especially those with comorbid SUD. Other studies [50] have shown recent increase in the overall rate of illicit drug use, especially in younger populations. Thus, the current real demands of implementing treatment modalities for patients with PD and SUD could be higher than the demand before the 10-year follow-up period.

Implications

In conclusion, we suggest that it is crucial to identify patients with PD and comorbid SUD, and vice versa, to prevent premature death. Although society is becoming open and diverse, and differences between the sexes is no longer an issue in Taiwan, the care of women with PD and SUD should be reconsidered in a pluralistic point of view because of their ultra-high mortality, especially due to suicide. Men with PD are at high risk of natural death, including cardiovascular and gastrointestinal diseases, which also merit effective intervention.

Acknowledgements The authors thank Yin Chi Chen, BS, with the Department of General Psychiatry, Taipei City Psychiatric Center, Taipei City Hospital, for data management and help with the statistical analyses. Ms. Chen declares that she has no competing interests. The authors thank Formosa Medical Editors for assistance with manuscript preparation.

Author contributions K and CCC conceived and designed the study. CCC acquired the data. K performed the statistical analysis. C provided administrative and material support. CCC, WYC, and K drafted the manuscript. T and PHC made critical revisions to the manuscript for important intellectual content, and K and CCC supervised the study.

Funding This research was supported by grants from the Ministry of Science and Technology, Taiwan (NSC 102-2628-B-532-001-MY3 and MOST 105-2314-B-532-006-MY3) and Taipei City Hospital (10001-62-005, 10501-62-015, and 10601-62-002). The funding sources had no involvement in the study design, data collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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