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Relationship Between Acute Benzodiazepine Poisoning and Acute Pancreatitis Risk

A Population-Based Cohort Study

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Abstract: We designed a population-based retrospective cohort study to investigate the association between the event of benzodiazepine (BZD) poisoning and the risk of acute pancreatitis.

In the present study, 12,893 patients with BZD poisoning during 2000 to 2011 were enrolled and matched with 4 comparison patients according to mean age and sex. We determined the cumulative incidences and adjusted hazard ratios of acute pancreatitis.

A significant association was observed between BZD poisoning and acute pancreatitis. After adjustment for potential risk factors, the patients with BZD poisoning had a 5.33-fold increased risk of acute pancreatitis compared with the controls without BZD poisoning (HR = 5.33, 95% CI = 2.26–12.60). The results revealed that acute pancreatitis in patients with BZD poisoning occurred in a follow-up time of ≤ 1 month (HR = 50.0, $P < .001$), and the risk of acute pancreatitis was no different

between the patients with and without BZD poisoning when the follow-up time was > 1 month (HR = 1.07, $P > .05$).

This population-based study revealed the positive correlation between the event of BZD poisoning and an increased risk of acute pancreatitis. The findings warrant further large-scale and in-depth investigation.

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Abbreviations: BZD = benzodiazepine, CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases Ninth Revision Clinical Modification, NHI = Taiwan's National Health Insurance, NHIRD = National Health Insurance Research Database.

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INTRODUCTION

Acute pancreatitis is an inflammatory condition of the pancreas characterized clinically by abdominal pain and elevated levels of pancreatic enzymes: amylase and lipase in the blood.^{1,2}

The incidence of acute pancreatitis in the United States is approximately 17 cases per 100,000 people. Based on the previous data, acute pancreatitis results in 100,000 hospitalizations every year.³ Although gallstones and alcohol cause $> 90\%$ of all cases in adults, medications have been recognized as a potential cause of acute pancreatitis.⁴

Since the first reported case of acute pancreatitis in the 1950s, hundreds of commonly prescribed medications have been reported to induce acute pancreatitis. Even medications are considered a common cause of acute pancreatitis, but the numbers of reported drug-induced acute pancreatitis cases account for only 0.1% to 2% of all cases.^{4,5}

Benzodiazepines (BZDs) are used as sedatives and to treat anxiety, seizure, withdrawal disorder, sleeping disturbance, and agitation. Because of their versatility, BZDs are widely prescribed, and there are nearly 50 kinds of BZDs available worldwide. However, the high incidence of BZD poisoning reflects their universal use and availability.^{6,7} BZD poisoning refers to ingesting the BZD class in quantities greater than those recommended or generally used. The most common symptoms of BZD poisoning include central nervous system depression, impaired balance, and slurred speech. Severe symptoms include coma and respiratory depression. The mainstay of treatment for BZD poisoning is supportive care.

Few case reports were published about BZD use and the risk of acute pancreatitis. The US Food and Drug Administration has reported that since 2001 to 2012, 81 people (0.33%) had acute pancreatitis among 24,300 people taking zolpidem with side effects.⁸ In addition, Lai et al⁹ found these patients actively using zolpidem were at 7-fold increased odds of acute

pancreatitis in Taiwan. Zolpidem is a short-acting non-BZD hypnotic with fewer side effects than BZD, because zolpidem potentiates γ -aminobutyric acid (GABA) by binding only to α subunit. In contrast to zolpidem, BZD has a higher affinity for other subunits of GABA.¹⁰ Therefore, we believed BZDs overdose could also increase risk of acute pancreatitis. In this study, we used data from the Taiwan National Health Insurance Research Database (NHIRD) to investigate whether BZD poisoning increases the risk of acute pancreatitis.

METHODS

Data Source

The Taiwan National Health Insurance (NHI) program integrated 13 insurance programs into a nationwide, single-payer health insurance program implemented in 1995. In 1998, the coverage rate reached 99% of the 23 million Taiwan residents (<http://www.nhi.gov.tw/english/index.aspx>). The Taiwan government appointed the National Health Research Institute to establish and manage the NHIRD, which contains all historical reimbursement claims data, including a registry for beneficiaries, disease records, and medical services; the database is updated each year. Before releasing the data for research purposes, the National Health Research Institute encrypts all personal identification information and provides an anonymous identification number to protect patient privacy. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The Institutional Review Board also specifically waived the consent requirement.

In this study, disease histories were collected from inpatient data. Disease diagnoses in the NHIRD are based on the criteria of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study Population

We applied a population-based retrospective cohort design. Cases of BZD poisoning before 2000 were excluded. The BZD poisoning cohort comprised patients who used BZD-based tranquilizers (ICD-9-CM 969.4) during 2000 to 2011 and were aged >20 years. We appointed the initial date of BZD poisoning as the index date. Each BZD poisoning cohort patient was frequency matched to 4 comparison controls according to age and sex (per 5 years); the controls had no BZD poisoning. The index date for the comparison controls was set by randomly appointing a month and day with the same index year as that of the matched cases. We excluded the individual with the history of the pancreas cancer (ICD-9-CM 157), chronic pancreatitis (ICD-9-CM 577.1), and acute pancreatitis (ICD-9-CM 577.0) before the index date in BZD poisoning cohort and comparison cohort. The outcome of interest was acute pancreatitis. Follow-up was terminated after 3 months or upon withdrawal from the NHI program, acute pancreatitis occurrence, or December 31, 2011.

In addition to demographic factors, we considered the effect of comorbidities on the risk of acute pancreatitis. A history of comorbidities before the index date was collected and included chronic obstructive pulmonary disease (COPD, ICD-9-CM 491–493 and 496), alcohol-related disease (ARD, ICD-9-CM 291, 303, 305.0, 790.3, and V11.3), cardiovascular disease (CVD, ICD-9 410–414, 428, 430–438, and 440–448), gallstone (ICD-9-CM 574), chronic kidney disease (ICD-9-CM 585–586 and 588.8–588.9), diabetes mellitus (DM, ICD-9-CM

250), hepatitis C virus infection (ICD-9-CM V02.62, 070.41, 070.44, 070.51, 070.54), hepatitis B virus infection (HBV, ICD-9-CM V02.61, 070.20, 070.22, 070.30 and 070.32), and hypertriglyceridemia (ICD-9-CM 272.1).

Statistical Analysis

To determine the structure of the study population, we calculated the means and standard deviations for number, percentage, age, age group, sex, and comorbidities. The *t* test and χ^2 test was used to determine the distribution difference for continuous variables and category variables, respectively. The incidence density of acute pancreatitis for each group was calculated as number of acute pancreatitis incidences divided by the sum of follow-up time (per 1000 person-months). The cumulative incidence curves were measured using the Kaplan–Meier method, and the difference in the curves was assessed using the log-rank test. The risk of acute pancreatitis between the BZD poisoning and comparison cohorts was presented as hazard ratios (HRs) and 95% confidence intervals (CIs) by using single variable and multivariate Cox proportional hazards models. In addition, we estimated the acute pancreatitis risk in the BZD poisoning cohort according to different demographic characteristics and comorbidities by conducting a stratified analysis involving the Cox model.

The data management and statistical analysis was performed using SAS 9.4 software (SAS Institute, Cary, NC). The plot of the cumulative curve for acute pancreatitis was drawn using R software. The significance level was set at <0.05 for the 2-sided testing of the *P* value.

RESULTS

This study included a total of 12,893 BZD poisoning patients and 4 times as many comparison controls with similar ages (nearly 53 years) and sex ratios (men: 39.0%) (Table 1). The comorbidities in the BZD poisoning cohort were more prevalent than those in the comparison cohort (all *P* < .001).

The incidence of acute pancreatitis in the comparison cohort was only 0.60 per 10,000 person-months (Table 2), whereas that in the BZD poisoning cohort was nearly 10-fold higher (6.32 per 10,000 person-months). Figure 1 shows that the cumulative incidence curve for the BZD poisoning cohort was significantly greater than that for the comparison cohort (log-rank test, *P* < .001). We observed that ARD, gallstone, DM, HBV, hypertriglyceridemia, and CVD significantly influenced the increased risk of acute pancreatitis and considered model adjustment. After adjustment for potential risk factors, the patients with BZD poisoning had a 5.33-fold increased risk of acute pancreatitis compared with patients without BZD poisoning (HR = 5.33, 95% CI = 2.26–12.60).

Table 3 presents the risk of acute pancreatitis in BZD poisoning patients with different demographic characteristics and comorbidities. Men and patients with BZD poisoning had a significantly increased risk of acute pancreatitis compared with female patients without BZD poisoning (HR = 13.2, *P* < .001), patients in the 3 age levels (HR = 11.8, 10.7, and 3.17, all *P* < .05), and patients with/without comorbidity (HR = 3.50 and 12.9, all *P* < .05). In addition, we estimated the acute pancreatitis risk in patients in the BZD poisoning cohort according to follow-up time. The results revealed that acute pancreatitis in the BZD poisoning patients occurred in a follow-up time of ≤ 1 month (HR = 50.0, *P* < .001), and the risk of acute pancreatitis was no different between the patients with and without BZD poisoning when the follow-up time was >1 month (HR = 1.07, *P* > .05).

TABLE 1. Demographic Characteristics and Comorbidities in Cohorts With and Without BZD Poisoning

Variable	BZD Poisoning		P value*
	No N = 51,572	Yes N = 12,893	
Age, y			0.99
≤34	13,168 (25.5)	3292 (25.5)	
35–49	12,800 (24.8)	3200 (24.8)	
50–64	7,788 (15.1)	1947 (15.1)	
65+	17,816 (34.5)	4454 (34.6)	
Mean ± SD†	52.7 (20.9)	53.2 (21.0)	0.05
Sex			0.99
Female	31,452 (61.0)	7863 (61.0)	
Male	20,120 (39.0)	5030 (39.0)	
Comorbidity			
ARD	68 (0.13)	662 (5.13)	<0.001
Gallstone	1,191 (2.31)	588 (4.56)	<0.001
DM	3,130 (6.07)	2357 (18.3)	<0.001
HBV	251 (0.49)	315 (2.44)	<0.001
HCV	297 (0.58)	395 (3.06)	<0.001
Hypertriglyceridemia	187 (0.36)	197 (1.53)	<0.001
CVD	5,252 (10.2)	3519 (27.3)	<0.001
Chronic kidney disease	491 (0.95)	522 (4.05)	<0.001
COPD	2,138 (4.15)	1500 (11.6)	<0.001

ARD = alcohol-related disease, BZDs = benzodiazepines, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, SD = standard deviation.

* Chi-square test.

† t test.

DISCUSSION

This population-based retrospective cohort study reveals a significant association between BZD poisoning and an increased risk of acute pancreatitis, namely BZD poisoning significantly affects the acute pancreatitis risk. After adjustment for potential confounding factors, patients with BZD poisoning had a 5.33-fold greater acute pancreatitis risk (95% CI = 2.26–12.60) compared with patients without BZD poisoning (Table 2).

The alcohol abuse causes approximately 30% of all acute pancreatitis cases in the United States.¹¹ Alcohol may promote the synthesis by pancreatic acinar cells of the digestive and lysosomal enzymes that is the key to cause acute pancreatitis¹² or the oversensitization of acini to cholecystokinin.¹³ In our study, the patients with BZD poisoning and an alcohol-related disorder had a 11.6-fold increased risk of acute pancreatitis compared with the patients without BZD poisoning (Table 2). Thus, BZD poisoning increased the risk of acute pancreatitis in the patients with alcohol-related disorders.

Hypertriglyceridemia was accounted for 1% to 4% of all acute pancreatitis cases.¹⁴ Serum triglyceride concentrations exceeding 1000 mg/dL (11 mmol/L) can precipitate attacks of acute pancreatitis; however, the pathogenesis of inflammation is still unclear.¹⁵ Acquired hypertriglyceridemia may be secondary to obesity, DM, hypothyroidism, pregnancy, estrogen or tamoxifen therapy, glucocorticoid excess, nephrotic syndrome,

and β-blockers.^{16–18} In our study, patients with BZD poisoning and hyperglyceridemia had a significantly higher risk of acute pancreatitis (adjusted HR = 3.57, 95% CI = 0.96–13.30) than did patients without BZD poisoning. We also noted that people with DM had a higher risk of acute pancreatitis when they had BZD poisoning (adjusted HR = 2.63, 95% CI = 1.12–6.19).

The gallstone is the most common cause of acute pancreatitis in the world, accounting for 35% to 40% of all cases.¹⁹ But only 3% to 7% of patients with gallstones develop biliary pancreatitis.^{20,21} There were 2 mechanisms of biliary pancreatitis: reflux of bile into the pancreatic duct caused by transient obstruction of the ampulla during passage of gallstones,²² or obstruction at the ampulla secondary to stone or edema caused by the passage of gallstone.²³ Our study revealed that the BZD poisoning did not increase the risk of biliary pancreatitis, possibly because the BZD is unrelated to the obstruction of biliary tract.

Although its mechanisms remain unclear, some studies have reported that cigarette smoking is an independent risk factor for acute and chronic pancreatitis.^{24–27} Tobacco smoking is the most common cause of COPD, which is characterized by chronically poor airflow. In our study, BZD poisoning non-significantly increased the risk of pancreatitis in patient with COPD.

Although drug-induced acute pancreatitis is rare, some studies show that incidence is increasing.^{28–31} Drug-induced pancreatitis has no distinguishing clinical features. Therefore, the diagnosis depends on a high level of suspicion and careful drug history review. The time course of developing acute pancreatitis relative to the drug involved. According to Table 3, patients with BZD poisoning exposure had a significantly higher risk of acute pancreatitis within 1 month after the event occurred (adjusted HR = 50.0, 95% CI = 6.39–390.8). However, the risk was nonsignificant >1 month after the event occurred (adjusted HR = 1.07, 95% CI = 0.30–3.90).

We found that female patients with BZD poisoning exposure had a higher risk of acute pancreatitis than did male patients (adjusted HR = 13.2, 95% CI = 3.60–48.5). We noted the same trend in another cohort study: In 2015, a cohort study identified several factors associated with acute pancreatitis and chronic pancreatitis that may be specific to older women.³² Heavy smoking (40+ years vs 0 pack-years) was associated with a 2-fold increased odds ratio (OR) for chronic pancreatitis. For body mass index (≥30 kg/m² vs <25 kg/m²), the ORs were 1.35 (1.07–1.70) for acute pancreatitis (P for trend = .009) and 0.59 (0.37–0.94) for chronic pancreatitis (P for trend = .01). The ORs for acute and chronic pancreatitis were increased for hormone replacement therapy, heart disease, and hypertension.

In Taiwan, the BZD poisoning is always diagnosed at emergent room. We diagnosed the patient as having BZD poisoning based on careful history taking, clinical symptoms, and urine BZD screen. All criteria established, and we key the ICD code to the system. Although we can't measure the doses of BZD, we still believed the diagnosis is correct. On the same way, the doctors diagnosed the patient as having acute pancreatitis based on clinical symptoms, blood examination, and image. After we adjusted for the potential confounding factors, the people with BZD poisoning exposure had a 5.33-fold greater acute pancreatitis risk (95% CI, 2.26–12.6) than people without BZD's poisoning exposure. We believed the result is trusted.

The exact mechanism associated with BZD use and acute pancreatitis cannot be fully shown, so we review some of the research in order to explain the possible mechanisms. Most cases of drug-induced acute pancreatitis may have a peculiar character. Specific reactions to drugs are adverse effects and its

TABLE 2. The Incidence (per 10,000 Person-Months) and Risk Factors for Acute Pancreatitis

Variable	Event	PMs	Rate [#]	Crude HR (95% CI)	Adjusted HR ^{&} (95% CI)
BZD poisoning					
No	9	150,165	0.60	1.00	1.00
Yes	23	34,618	6.32	10.5 (4.84, 22.6) ^{***}	5.33 (2.26, 12.6) ^{***}
Age groups, y					
≤34	6	47,922	1.25	1.00	1.00
35–64	12	74,753	1.61	1.28 (0.48, 3.41)	–
65+	14	63,908	2.19	1.74 (0.67, 4.53)	–
Sex					
Female	18	113,955	1.58	1.00	1.00
Male	14	72,628	1.93	1.22 (0.61, 2.45)	–
Comorbidity					
ARD					
No	23	184,495	1.25	1.00	1.00
Yes	9	2,088	43.1	34.5 (16.0, 74.6) ^{***}	11.6 (4.83, 27.7) ^{***}
Gallstone					
No	29	181,527	1.60	1.00	1.00
Yes	3	5,056	5.93	3.70 (1.13, 12.1) [*]	1.79 (0.50, 6.43)
DM					
No	22	171,023	1.29	1.00	1.00
Yes	10	15,560	6.43	4.96 (2.35, 10.5) ^{***}	2.63 (1.12, 6.19) [*]
HBV					
No	30	184,990	1.62	1.00	1.00
Yes	2	1,592	12.6	7.68 (1.84, 32.1) ^{**}	1.75 (0.38, 8.04)
HCV					
No	31	184,635	1.68	1.00	1.00
Yes	1	1,948	5.13	3.03 (0.41, 22.2)	–
Hypertriglyceridemia					
No	29	185,493	1.56	1.00	1.00
Yes	3	1,090	27.5	17.5 (5.33, 57.4) ^{***}	3.57 (0.96, 13.3)
CVD					
No	23	161,748	1.42	1.00	1.00
Yes	9	24,835	3.62	2.53 (1.17, 5.47) [*]	1.07 (0.45, 2.54)
CKD					
No	31	183,788	1.69	1.00	1.00
Yes	1	2,794	3.58	2.10 (0.29, 15.3)	–
COPD					
No	30	176,292	1.70	1.00	1.00
Yes	2	10,291	1.94	1.13 (0.27, 4.75)	–

ARD = alcohol-related disease, BZDs = benzodiazepines, CKD = chronic kidney disease, COPD = chronic obstructive pulmonary disease, CVD = cardiovascular disease, CI = confidence interval, DM = diabetes mellitus, HBV = hepatitis B virus infection, HCV = hepatitis C virus infection, HR = hazard ratio, PM = person-month.

[#] Rate = incidence rate, per 10,000 person-months.

[&] Adjusted HR: multivariable analysis including comorbidities of ARD, gallstone, DM, HBV, hypertriglyceridemia and CVD.

^{*} $P < .05$.

^{**} $P < .01$.

^{***} $P < .001$.

pharmacodynamic mechanisms are not related to drugs directly. These adverse events may occur, which are usually by the abnormal interaction of the drug or its metabolites, or trigger immune-mediated cytotoxicity between the drug and the pancreas.³³ Although the accurate mechanism of drug-induced acute pancreatitis is not always known, it should have similar pathogenesis. We found that there are several mechanism assumptions that include duct stenosis, direct pancreatic toxicity, the impact of bile flow, immune-mediated toxicity, metabolic effects, and thrombosis.^{34,35}

Some researchers suggested potential mechanisms of drug-induced acute pancreatitis. If acute pancreatitis occurred after

drug used for 4 to 8 weeks, it may be caused by hypersensitivity. If acute pancreatitis happened after several months of drug use, it is caused by accumulation of a toxic metabolite. If acute pancreatitis occurred immediately after drug overdose, it usually caused by its intrinsic toxicity. Following this hypothesis, we think the mechanism of BZD poisoning-induced acute pancreatitis most likely is the intrinsic toxicity or the sphincter of Oddi dysfunction. Tracing the past studies, we found the diazepam and midazolam had no effect on motility of the sphincter of Oddi in human.³⁶ This mechanism seems not the cause of acute pancreatitis by BZD. While there is no direct evidence that BZD has a direct toxicity for pancreas, there are

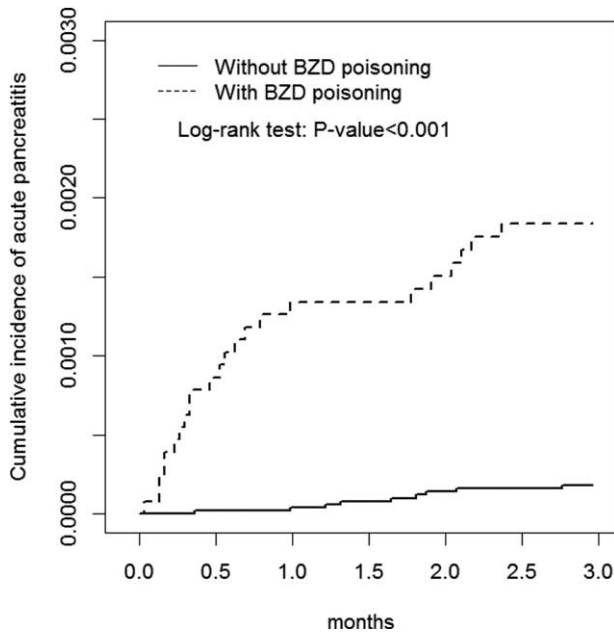


FIGURE 1. Cumulative incidence comparison of acute pancreatitis for patients with (dashed line) or without (solid line) BZD poisoning. BZD = benzodiazepines.

studies that showed that BZDs may be related to acute pancreatitis. The GABA is the major inhibitory neurotransmitter in the central nerve systems. However, they are also found in other sites, for example, pancreatic β cells and immune cells. Some studies have implicated the GABAergic system in immune cell functions, inflammatory conditions, and diseases in peripheral tissues.³⁷

Some researchers identify GABA is related with pancreatic ductal adenocarcinoma. The recent research has investigated the modulation of this autocrine regulatory loop by chronic ethanol and explored the potential prevention of these effects by GABA.³⁸ We also found the use of zolpidem or zopiclone will increase the incidence of acute pancreatitis.^{9,39} Some studies point out the zolpidem is a short-acting agent with half-life of 2.1 to 2.4 hours. Its metabolite is not active, and it does not have an accumulating effect.^{40,41} Although zolpidem and zopiclone is non-BZD class of sleeping pills, but they also are acting on the GABA receptor. Therefore, they think BZDs may have an acute and direct toxic effect on the pancreas, which further precipitates the pancreatic inflammation.

This present study has some limitations. First, we have no information about the amounts and types of BZDs that poisoned patients. We also couldn't obtain some possible risk factors for acute pancreatitis, such as socioeconomic status, smoking habit, body mass index, and family history. Even we can't sure whether the patient has alcohol abuse, pancreatic trauma, gene mutation, or coprescribed drugs in detail. However, this cohort study is national research, because NHIRD covers 99% of the Taiwan population. Compared to BZD poisoning, the gene mutations, pancreatic trauma, and other drug poisoning are relatively rare. We have the enough database to establish the stronger relationship between BZD poisoning and acute pancreatitis than other resource. Second, the evidence derived from a case-control study has lower quality than randomized controlled trials, because a case-control study design adjusted by the relevant confounding factors. Although we carefully study design, including adequate control for confounding factors, a key limitation is that bias could still remain if there are unmeasured or unknown confounders. Third, the diagnoses in NHI claims are used for administrative billing purposes and do not for scientific purposes. Because of the data anonymity, we are unable to contact patients with BZD poisoning

TABLE 3. Incidence of Acute Pancreatitis by Age, Sex, Comorbidity, Follow-up Time, and Cox Model Measured Hazards Ratio for Patients With BZD Poisoning Compared to Those Without BZD Poisoning

Variables	Without BZD poisoning			With BZD poisoning			Crude HR (95% CI)	Adjusted HR ^{&} (95% CI)
	Event	PMs	Rate [#]	Event	PM	Rate [#]		
Age, y								
≤34	1	38,426	0.26	5	9495	5.27	20.2 (2.36, 172.7)**	11.8 (1.20, 116.1)*
35–64	2	60,088	0.33	10	14,665	6.82	20.4 (4.46, 93.0)***	10.7 (2.03, 56.1)**
65+	6	51,651	1.16	8	12,257	6.53	5.58 (1.94, 16.1)**	3.17 (1.00, 10.0)*
Sex								
Female	3	91,552	0.33	15	22,403	6.70	20.3 (5.87, 70.0)***	13.2 (3.60, 48.5)***
Male	6	58,612	1.02	8	14,015	5.71	5.56 (1.93, 16.0)**	1.63 (0.39, 6.79)
Comorbidity								
No	3	125,577	0.24	6	19,564	3.07	12.7 (3.18, 50.9)***	12.9 (3.18, 52.5)***
Yes	6	24,588	2.44	17	16,854	10.1	4.12 (1.62, 10.4)**	3.50 (1.33, 9.22)*
Follow time, mo								
≤1	1	49,267	0.20	16	12,129	13.2	64.9 (8.60, 489.0)***	50.0 (6.39, 390.8)***
>1	8	100,898	0.79	7	24,288	2.88	3.63 (1.31, 10.0)*	1.07 (0.30, 3.90)

BZD = benzodiazepines, CI = confidence interval, HR = hazard ratio, PM = person-months.

[#] Rate, incidence rate, per 10,000 person-months.

[&] Adjusted HR: multivariable analysis including age, sex, and comorbidities of ARD, gallstone, DM, HBV, hypertriglyceridemia, and CVD.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

directly. However, the data on the acute pancreatitis diagnosis and BZD poisoning were highly reliable.

CONCLUSIONS

This population-based, retrospective case-control study revealed that the event of BZD poisoning is significantly associated with an increased risk of acute pancreatitis. Such a risk was significantly greater within 1 month after a BZD poisoning event. Our findings require confirmation through a large, population-based, unbiased study before any definite conclusions can be drawn.

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