

Acetaminophen Poisoning and Risk of Acute Pancreatitis

A Population-Based Cohort Study

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Abstract: The aim of this study was to assess whether acetaminophen poisoning is associated with a higher risk of acute pancreatitis.

We conducted a retrospective cohort study by using the longitudinal population-based database of Taiwan's National Health Insurance (NHI) program between 2000 and 2011. The acetaminophen cohort comprised patients aged ≥ 20 years with newly identified acetaminophen poisoning (N = 2958). The comparison cohort comprised randomly selected patients with no history of acetaminophen poisoning. The acetaminophen and comparison cohorts were frequency matched by age, sex, and index year (N = 11,832) at a 1:4 ratio. Each patient was followed up from the index date until the date an acute pancreatitis diagnosis was made, withdrawal from the NHI program, or December 31, 2011. Cox proportional hazard regression models were used to determine the effects of acetaminophen on the risk of acute pancreatitis.

Editor: Okasha Hussein.

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All authors have contributed significantly and are in agreement with the content of the manuscript—Conception/Design: S-JC, C-SL, C-HK; Provision of study materials: C-HK; Collection and/or assembly of data: all authors; Data analysis and interpretation: all authors; Manuscript writing: all authors; Final approval of manuscript: all authors.

This study is supported in part by the Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW104-TDU-B-212-113002); China Medical University Hospital, Academia Sinica Taiwan Biobank, Stroke Biosignature Project (BM104010092); NRPB Stroke Clinical Trial Consortium (MOST 103-2325-B-039-006); Tseng-Lien Lin Foundation, Taichung, Taiwan; Taiwan Brain Disease Foundation, Taipei, Taiwan; Katsuzo and Kiyo Aoshima Memorial Funds, Japan; and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.

No commercial party having a direct or indirect interest in the subject matter of this research will confer a benefit on the authors or on any organization with which the authors are associated. This material has not previously been presented in any form.

The authors have no conflicts of interest to disclose.

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ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001195

The risk of acute pancreatitis was 3.11-fold higher in the acetaminophen cohort than in the comparison cohort (11.2 vs 3.61 per 10,000 person-years), with an adjusted hazard ratio of 2.40 (95% confidence interval, 1.29–4.47). The incidence rate was considerably high in patients who were aged 35 to 49 years, men, those who had comorbidities, and within the first year of follow-up.

Acetaminophen poisoning is associated with an increased risk of acute pancreatitis. Additional prospective studies are necessary to verify how acetaminophen poisoning affects the risk of acute pancreatitis.

(*Medicine* 94(29):e1195)

Abbreviations: CIs = confidence intervals, HRs = hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, IRR = incidence rate ratio, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database.

INTRODUCTION

Acetaminophen (paracetamol, *N*-acetyl-*p*-aminophenol) is the most commonly used analgesic antipyretic. Because of its wide availability and use as a component in hundreds of over-the-counter and prescription medications, acetaminophen has remained one of the leading drugs of intentional and unintentional overdose worldwide.^{1,2} In the United States, acetaminophen overdose accounts for more calls to poison control centers than does the overdose of any other pharmacological substance.³ The age-adjusted rate of overdose-related hospitalizations was 13.9 per 100,000 people between 2000 and 2006 in the United States.⁴ In 2013, the American Association of Poison Control Centers' National Poison Data System reported 131 deaths caused by acetaminophen and products containing acetaminophen.⁵ Acetaminophen poisoning has been primarily related to hepatic toxicity, which is responsible for nearly half of all acute liver failure cases in the United States.³ Acute pancreatitis is among other, less-common extra-hepatic manifestations of acetaminophen poisoning for which few reports exist.⁶

Acute pancreatitis is the acute inflammation of the pancreas of varying severity, characterized clinically by abdominal pain and elevated levels of pancreatic enzymes in the blood. The incidence of first-attack acute pancreatitis ranged from 4 to 45 per 100,000 person-years between 1966 and 2009.^{7,8} The case fatality rate has decreased in the recent years, but still ranges between 3.3% and 6%.^{7,8} Numerous risk factors are known to induce acute pancreatitis, particularly gallstones and chronic alcohol abuse. Drug-induced acute pancreatitis accounts for <2% of cases; however, the incidence may have been underestimated; mild pancreatitis may be subclinical and severe and fulminant attacks may not have been clearly confirmed because of an unidentified history or complex interrelationships with other, more common causes of morbidity.⁹ Diagnosing

drug-induced acute pancreatitis can be challenging; the causes are a lack of clear biological evidence and mechanisms, for example, inadequate criteria for diagnosing acute pancreatitis, failure to preclude common causes, lack of specific clinical appearances of drug reaction, and mixed effects of combined drugs or prescriptions.¹⁰

Positive rechallenge response (ie, when pancreatitis develops during treatment with a drug, resolves upon discontinuing the drug, and returns upon readministration of the drug) has been considered the most reliable evidence of drug-induced acute pancreatitis.¹¹ However, such evidence cannot be easily obtained on the basis of rare incidences of adverse reports. Moreover, ethical concerns prevent such toxicity or rechallenge tests from being conducted on humans. Therefore, we used the longitudinal population-based database of the Taiwan's National Health Insurance (NHI) program to investigate whether patients with acetaminophen poisoning exhibited a higher risk of acute pancreatitis. We assumed that people who had acute poisoning with acetaminophen exhibited a higher risk of acute pancreatitis.

METHODS

Data Source

The NHI program began in March 1, 1995, and currently covers >99% of the Taiwan population of 23.75 million (<http://www.nhi.gov.tw/english/index.aspx>). The National Health Insurance Research Database (NHIRD) was established and is maintained by the National Health Research Institutes and Taiwan National Health Insurance Bureau. The NHIRD contains detailed records of every visit, including outpatient, emergency department, and hospital visits. For this retrospective cohort study, we used a subset of the NHIRD that includes inpatient claims data and registry of beneficiaries. All individual claims records can be linked using encrypted identification numbers. Because of the uncertainty of paracetamol actually obtained from a pharmacy or a hospital, the potential bias from case mix distribution prevents a conclusion drawn from the retrospective hospital registry data only. Therefore, our study mainly focused on the effects of the proved poisoning episodes on acute pancreatitis. This study was approved by the Institutional Review Board of China Medical University and Hospital in Taiwan (CMU-REC-101-012). All diseases included were diagnosed according to the International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9 code), 2001 edition.

Sampled Patients

Patients aged ≥ 20 years who were hospitalized during 2000 and 2011 for newly diagnosed acetaminophen poisoning (ICD-9 code 965.4) were selected as the acetaminophen cohort. The initial admission date of acetaminophen diagnosis was used as the index date. The comparison cohort comprised randomly selected patients with no history of acetaminophen poisoning. The acetaminophen and comparison cohorts were frequency matched by age (every 5 years), sex, and index year at a 1:4 ratio. The index dates for the patients in the comparison cohort were randomly appointed a month and day with the same index year as that of the matched acetaminophen cases. Patients in both the cohorts with a history of acute pancreatitis (ICD-9 code 577.0), chronic pancreatitis (ICD-9 code 577.1), or a malignant neoplasm in the pancreas (ICD-9 code 157) before the index date, <20 years of age, or with incomplete medical information were excluded.

Baseline Variables

We obtained baseline variables, including age, sex, and comorbidities of acute pancreatitis, namely, alcohol-related diseases (ICD-9 codes 291, 303, 305.0, 790.3, and V11.3), biliary stone (ICD-9 code 574), diabetes mellitus (ICD-9 code 250), hepatitis B (ICD-9 codes V02.61, 070.20, 070.22, 070.30, and 070.32), hepatitis C (ICD-9 codes V02.62, 070.41, 070.44, 070.51, and 070.54), hypertriglyceridemia (ICD-9 code 272.1), cardiovascular disease (ICD-9 codes 410–414, 428, 430–438, and 440–448), chronic kidney disease (ICD-9 codes 585–586 and 588.8–588.9), and chronic obstructive pulmonary disease (COPD; ICD-9 codes 491–493 and 496).

Outcome

The main outcome was acute pancreatitis during the follow-up period. The acute pancreatitis is based on the diagnostic codes of the ICD-9-CM in the Taiwan's NHIRD. Previous studies have described the high accuracy and validity of ICD-9-CM diagnoses in the NHIRD.^{8,12} Each patient was followed up from the index date until diagnosis of acute pancreatitis, withdrawal from the NHI program, or December 31, 2011.

Statistical Analysis

Distributions of age, sex, and comorbidities were compared using a χ^2 test for categorical variables and a *t* test for continuous variables between the 2 cohorts. The cumulative incidences of acute pancreatitis were measured using a Kaplan–Meier method and tested for differences using a log-rank test. The incidence density and relative risk of acute pancreatitis for different risk factors was estimated and stratified according to age, sex, comorbidity, and follow-up time. Univariate and multivariate Cox proportional hazard regression models were used to estimate the effects of acetaminophen on the risk of acute pancreatitis, which were indicated using hazard ratios (HRs) with a 95% confidence interval (CI). The age, sex, and comorbidities of alcohol-related disease, hepatitis C, and COPD were adjusted in the multivariate Cox models. All analyses were performed using SAS (Version 9.3; SAS Institute, Cary, NC), with 2-sided *P* values of <0.05 considered statistically significant.

RESULTS

Table 1 presents the demographic characteristics and comorbidities of the acetaminophen (N = 2958) and comparison (N = 11,832) cohorts. Distributions of age and sex were comparable between the 2 cohorts, with a mean age of 32 years. Most patients were aged <35 years (73.1%) and women (75.2%). Comorbidities were higher in the acetaminophen cohort than in the comparison cohort (all *P* < 0.001). The mean follow-up time was 6.34 years in the acetaminophen cohort and 6.33 years in the comparison cohort. The cumulative incidence for acute pancreatitis after a 12-year follow-up was higher in the acetaminophen cohort than in the comparison cohort (log-rank test, *P* < 0.001; Figure 1). Overall, the incidence of acute pancreatitis (Table 2) was 3.11-fold higher in the acetaminophen cohort than in the comparison cohort (11.2 vs 3.61 per 10,000 person-years), with an adjusted HR (aHR) of 2.40 (95% CI, 1.29–4.47). The incidence of acute pancreatitis increased with age and was higher in men than in women. According to a multivariate model, the risk of acute pancreatitis was higher in patients with the comorbidities of alcohol-related diseases (aHR = 6.01; 95% CI, 1.73–20.9), hepatitis C (aHR = 9.00; 95% CI, 2.40–33.8), and COPD (aHR = 4.38; 95% CI, 1.37–14.0). As shown in Table 3, the relative risk of acute pancreatitis

TABLE 1. Comparison of Demographic Characteristics and Comorbidity of Patients Between Acetaminophen Poisoning and Comparison Cohort

Variable	Acetaminophen Poisoning		P Value
	No N = 11,832	Yes N = 2958	
Age, y			0.99
<35	8652 (73.1)	2163 (73.1)	
35–49	2344 (19.8)	586 (19.8)	
≥50	836 (7.07)	209 (7.07)	
Mean ± SD*	32.0 (12.2)	32.0 (11.8)	0.05
Sex			0.99
Female	8892 (75.2)	2223 (75.2)	
Male	2940 (24.9)	735 (24.9)	
Comorbidity			
Alcohol-related disease	6 (0.05)	79 (2.67)	<0.001
Biliary stone	58 (0.49)	44 (1.49)	<0.001
Diabetes mellitus	83 (0.70)	84 (2.84)	<0.001
Hepatitis B	29 (0.25)	55 (1.86)	<0.001
Hepatitis C	14 (0.12)	32 (1.08)	<0.001
Hypertriglyceridemia	8 (0.07)	14 (0.47)	<0.001
Cardiovascular disease	139 (1.17)	104 (3.52)	<0.001
Chronic kidney disease	13 (0.11)	20 (0.68)	<0.001
COPD	72 (0.61)	78 (2.64)	<0.001

COPD = chronic obstructive pulmonary disease. χ^2 test.
* *t* test.

in the acetaminophen cohort was significantly higher in patients aged <35 years (aHR = 2.47; 95% CI, 1.11–5.53) and 35–49 years (aHR = 4.47; 95% CI, 1.40–14.3), according to age-specific stratification; in men (aHR = 3.44; 95% CI, 1.47–8.00); and in those without comorbidity (aHR = 3.59; 95%

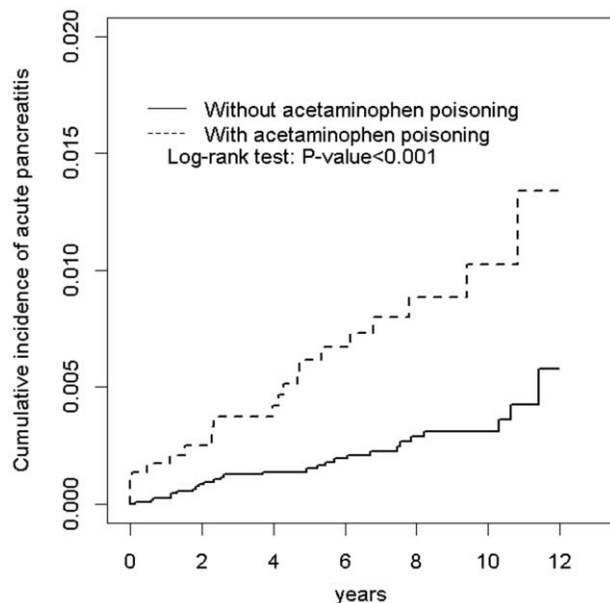


FIGURE 1. Cumulative incidence of acute pancreatitis compared between patients with or without acetaminophen poisoning.

CI, 1.88–6.87). The risk of acute pancreatitis for patients in the acetaminophen cohort was significantly higher within a 1-year follow-up than that for patients in the comparison cohort (aHR = 4.69; 95% CI, 1.01–21.8), and the risk decreased but remained significant after a 1-year follow-up (aHR = 2.12; 95% CI, 1.07–4.23).

DISCUSSION

This is the first nationwide, population-based cohort study to assess how acetaminophen poisoning affects the risk of subsequently developing acute pancreatitis. The results indicate that acute acetaminophen poisoning is associated with a higher risk of subsequently developing acute pancreatitis. Acetaminophen poisoning mostly occurred among patients aged <50 years and in women. The risk of acute pancreatitis was 2.4-fold higher in patients who had acetaminophen poisoning than in those without acetaminophen poisoning and 4-fold higher in the first year of follow-up. The incidence was considerably higher in patients aged 35 to 49 years, men, and those with comorbidities.

Hepatic failure and nephrotoxicity are widely recognized manifestations of an acute acetaminophen overdose and the US Food and Drug Administration has taken measures to limit and monitor exposure to high-dose acetaminophen.¹³ However, other unusual complications of acetaminophen overdose, including acute pancreatitis, myocardial damage, and metabolic acidosis, have been rarely reported. In 1975, Gazzard et al¹⁴ reported necropsy evidence of pancreatitis in 4 of 94 patients who had died of acetaminophen-induced hepatic failure; this evidence suggests that pancreatitis caused by acetaminophen overdose was more prevalent than had been assumed. Nevertheless, knowledge of the correlation between acetaminophen poisoning and acute pancreatitis remains limited because the availability of evidence depends on extrapolation from case reports.^{15–18} Moreover, a retrospective observational study of 814 patients with acetaminophen poisoning revealed that 33 patients exhibited clinically evident pancreatitis and 232 patients exhibited acetaminophen-associated hyperamylasemia.¹⁹ These reports indicate the rarity but potential risk of acute pancreatitis and its direct or indirect relationship with acetaminophen poisoning.

Several mechanisms regarding the pathogenesis of acute pancreatitis have been proposed, such as premature activation of trypsin in acinar cells, intrapancreatic inflammation, and extrapancreatic inflammation.²⁰ However, the exact mechanism of acetaminophen-induced acute pancreatitis remains unknown. Hypotheses regarding acetaminophen-induced acute pancreatitis have suggested intrinsic toxicity and host idiosyncratic reactions.¹⁰ Intrinsic toxicity posits that the metabolites cause damage of pancreas in a cumulative dose effect, reproducible at certain doses and often has a relatively consistent latency. Idiosyncratic reactions are not dose dependent and exhibit a low incidence and varied latency. Certain toxic metabolites or certain intermediary substances causing immunologic reactions, which can be reproduced by rechallenging, might explain the idiosyncratic reactions.¹⁸ Because of the rarity of the complication, idiosyncrasy has been suggested as playing a major role among these potential mechanisms.^{10,18}

Our study indicated that the incidence of acute pancreatitis was considerably high in patients in the acetaminophen cohort aged 35 to 49 years and <35 years; by contrast, for patients in the comparison cohort, the incidence of acute pancreatitis was considerably high in those aged >50 years. Moreover, a 2.5-fold higher risk was exhibited by patients aged <35 years, constituting the group with the highest proportion of acetaminophen

TABLE 2. Incidence and Risk Factors for Acute Pancreatitis

Variable	Event	PY	Rate [#]	Crude HR [†] (95% CI)	Adjusted HR [‡] (95% CI)
Acetaminophen poisoning					
No	27	74,886	3.61	1.00	1.00
Yes	21	18,757	11.2	3.11 (1.76, 5.50)***	2.40 (1.29, 4.47)**
Sex					
Female	24	70,551	3.40	1.00	1.00
Male	24	23,092	10.4	3.08 (1.75, 5.42)***	2.54 (1.41, 4.57)**
Comorbidity					
Alcohol-related disease					
No	45	93,239	4.83	1.00	1.00
Yes	3	404	74.3	15.2 (4.73, 49.1)***	6.01 (1.73, 20.9)**
Biliary stone					
No	47	93,176	5.04	1.00	1.00
Yes	1	466	21.4	4.24 (0.59, 30.8)	—
Diabetes mellitus					
No	48	92,964	5.16	1.00	1.00
Yes	0	679	0.00	—	—
Hepatitis B					
No	47	93,229	5.04	1.00	1.00
Yes	1	414	24.1	4.88 (0.67, 35.4)	—
Hepatitis C					
No	45	93,443	4.82	1.00	1.00
Yes	3	199	150.5	31.0 (9.61, 99.9)***	9.00 (2.40, 33.8)**
Hypertriglyceridemia					
No	48	93,568	5.13	1.00	1.00
Yes	0	75	0.00	—	—
Cardiovascular disease					
No	47	92,645	5.07	1.00	1.00
Yes	1	998	10.0	1.94 (0.27, 14.1)	—
Chronic kidney disease					
No	48	93,538	5.13	1.00	1.00
Yes	0	105	0.00	—	—
COPD					
No	44	92,952	4.73	1.00	1.00
Yes	4	691	57.9	12.3 (4.40, 34.2)***	4.38 (1.37, 14.0)*

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years.

[#] Rate, incidence rate, per 10,000 PY.

[†] Crude HR, relative hazard ratio.

[‡] Adjusted HR: adjusted for age, comorbidities of alcohol-related disease, hepatitis C, and COPD.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

poisoning. These results suggest a strong correlation between acetaminophen poisoning and the occurrence of acute pancreatitis. Furthermore, although patients with comorbidities exhibited a higher incidence of acute pancreatitis in both the acetaminophen and comparison cohorts, those without coexisting comorbidities revealed a significantly higher risk after acetaminophen poisoning, suggesting that acetaminophen poisoning alone exerts a substantial effect on the risk of acute pancreatitis. A high incidence and considerable risk of acute pancreatitis during the first year of follow-up indicate the close association between acute acetaminophen poisoning and acute pancreatitis, suggesting that clinicians should be aware of the higher risk of acute pancreatitis in patients with acetaminophen poisoning.

Men exhibited a higher incidence of acute pancreatitis than did women in both the cohorts, with the risk significantly higher in the acetaminophen cohort (HR = 3.44), suggesting that men

with acetaminophen poisoning exhibited a higher risk of acute pancreatitis than did women. The risk in women was lower (HR = 1.83) after adjusting for coexisting comorbidity, although the trend remained true. A higher incidence of acute pancreatitis in young and middle-aged men compared with women (ie, 58.3 vs 25.2 per 100,000 person-years in 2009) was reported, with a peak male-to-female ratio of 4.02 among patients aged 35 to 44 years.⁸ Although the exact etiology could not be ascertained using the registry database, alcoholic pancreatitis has been reported as the most common cause in middle-aged men, with a peak incidence between 35 and 44 years of age.²¹ This implies that alcohol consumption might exert a synergistic effect in combination with acetaminophen poisoning, which is associated with a higher risk of acute pancreatitis for men. Therefore, we suggest that a quantitative history of recent acetaminophen consumption be obtained from patients with alcoholic pancreatitis.

TABLE 3. Incidence and Hazard Ratio of Acute Pancreatitis by Age, Sex, Comorbidity, and Follow-Up Time Between Patients With and Without Acetaminophen Poisoning

Variables	Acetaminophen Poisoning						Crude HR [†] (95% CI)	Adjusted HR [‡] (95% CI)
	No			Yes				
	Event	PY	Rate [#]	Event	PY	Rate [#]		
Age, y								
<35	15	55,917	2.68	14	14,369	9.74	3.65 (1.76, 7.55) ^{***}	2.47 (1.11, 5.53) [*]
35–49	6	14,749	4.07	6	3480	17.2	4.27 (1.38, 13.2) [*]	4.47 (1.40, 14.3) [*]
≥50	6	4219	14.2	1	908	11.0	0.79 (0.10, 6.58)	0.34 (0.03, 3.63)
Sex								
Female	14	56,182	2.49	10	14,369	6.96	2.80 (1.25, 6.31) [*]	1.83 (0.76, 4.41)
Male	13	18,704	6.95	11	4388	25.1	3.60 (1.61, 8.03) ^{**}	3.44 (1.47, 8.00) ^{**}
Comorbidity								
No	22	73,390	3.00	16	16,993	9.42	3.14 (1.65, 5.98) ^{***}	3.59 (1.88, 6.87) ^{***}
Yes	5	1496	33.4	5	1763	28.4	0.85 (0.25, 2.95)	0.81 (0.23, 2.88)
Follow-up time, y								
≤1	3	11,352	2.64	5	2789	17.9	6.75 (1.61, 28.3) ^{**}	4.69 (1.01, 21.8) [*]
>1	24	63,534	3.78	16	15,967	10.0	2.66 (1.41, 5.00) ^{**}	2.12 (1.07, 4.23) [*]

CI = confidence interval, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, PY = person-years.

[#] Rate, incidence rate, per 10,000 PY.

[†] Crude HR, relative hazard ratio.

[‡] Adjusted HR: adjusted for age, sex, and comorbidities of alcohol-related disease, hepatitis C, and COPD.

^{*} P < 0.05.

^{**} P < 0.01.

^{***} P < 0.001.

This study has several limitations. First, the dose of acetaminophen producing poisoning cannot be ascertained by the hospital registry databank. Because acetaminophen can be easily obtained from any pharmacy without prescription, an acetaminophen-poisoned patient usually has no direct connection or information from a hospital prescription. Moreover, acetaminophen-poisoning cases are usually intentional, the exact dose of poisoning may not be simply referred to their prescriptions if available. Therefore, we chose to select poisoned and hospitalized patients who were believed acetaminophen overdose or at higher risk of abuse as our case group to lower the effects of case mix distribution. Second, the insurance database did not provide the exact etiologies and the severity of acute pancreatitis. Lack of the level of hyperamylasemia is one of the limitations although we did not include its related diagnostic code of 790.5 as our outcome. Therefore, despite controlling numerous confounding risk factors, we were unable to ascertain the causative relationship between acetaminophen poisoning and severity of acute pancreatitis. Third, lack of the acetaminophen level in blood is an inherent limitation in the observational study from the registry databank. Therefore, we were unable to examine whether acetaminophen-poisoning severity exerted different effects on the risk of acute pancreatitis. Novel biomarkers for the diagnosis and identification of high-risk groups that require efficient investigation or treatment are required. Fourth, information on smoking, alcohol consumption, and socioeconomic status, which are potential confounding factors, was not included in the database. Smoking duration has been related to nongallstone acute pancreatitis and estimated to be more than double the risk of acute pancreatitis in present smokers.^{22,23} In addition, the risk of smoking has been reported to be confounded by alcohol consumption. These potential confounding factors might partially explain the sex

and age discrepancy between acetaminophen poisoning and the risk of acute pancreatitis as well as the remaining risk after a 1-year follow-up period. However, even with these limitations, this study provides valuable information regarding the association between acetaminophen poisoning and the risk of acute pancreatitis.

In conclusion, our study suggests that patients with acute acetaminophen poisoning exhibit a high risk of acute pancreatitis, particularly male patients with comorbidities and within the first year of follow-up. Additional prospective studies are necessary to verify how acetaminophen poisoning affects the risk of acute pancreatitis. Clinicians should be aware of the higher risk of acute pancreatitis in this particular group.

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