Risk of Acute Kidney Injury and Long-Term Outcome in Patients With Acetaminophen Intoxication

A Nationwide Population-Based Retrospective Cohort Study

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Abstract: Acetaminophen (APAP) intoxication is a common cause of hepatic toxicity and life-threatening hepatic failure. However, few studies have investigated the possible association between APAP intoxication and acute kidney injury (AKI). We constructed a retrospective cohort study to clarify the relationship between APAP intoxication and the risk of AKI.

We identified patients with APAP intoxication and selected a comparison cohort that was 1:4 frequency matched according to age, sex, and year of APAP intoxication diagnosis from the Taiwan National Health Insurance Research Database from 1998 to 2010. We analyzed the risks of AKI for patients with APAP intoxication by using Cox proportional hazards regression models.

In this study, 2914 patients with APAP intoxication and 11,656 controls were included. The overall risks of developing AKI were 2.41-fold in the patients with APAP intoxication compared with the comparison cohort. After we excluded APAP intoxication patients with coexisting AKI and hepatic failure/hepatitis, the overall risks of developing AKI were still 2.22-fold in the patients with APAP intoxication. There were 2 patients who had end-stage renal disease (ESRD) following APAP intoxication-related AKI. Limitations include retrospective review, selection bias, and absence of data on detail medications used, laboratory investigations and dosage of APAP intoxication.

Our long-term cohort study results showed that AKI is a possible adverse effect among patients with APAP intoxication, regardless of whether patients have presented with hepatic toxicity. However, additional studies are necessary to clarify whether such patients can progress to ESRD.

INTRODUCTION

Acetaminophen (APAP) is a common analgesic and antipyretic medication widely prescribed worldwide. It is typically available as a single-component formula or in combination with other synergic prescribed drugs. Although medical practitioners generally consider it a safer medication with fewer adverse effects than those of other medications, life-threatening hepatic toxicity is a well-recognized adverse complication in patients with large dose ingestion. In the United States and many other countries, APAP intoxication is the major etiology of drug overdose- and intoxication-related hepatic failure. In the past decade, the incidence rate of acute liver failure related to APAP intoxication has risen dramatically and become a major public health concern. According to the 2012 National Poison Data System report, products containing APAP alone or APAP with other drugs were the 4th and 6th leading cause of substance poisoning, respectively. In addition, APAP-related hepatic failure is the leading cause of acute liver injury in the United States, with an incidence rate of approximately 300,000 hospitalized cases annually. Generally, clinical manifestations after APAP intoxication are classified into 4 stages based on the period since ingestion. Most cases with hepatitis or hepatic encephalopathy are within 72 to 96 hr (stage III) after APAP administration. Other than hepatic toxicity, clinical manifestations caused by APAP intoxication are frequently mild or nonspecific. Relative to the well-recognized fatal hepatic toxicity, APAP-related nephrotoxicity is a less common adverse effect and is generally reported in a single case report or a controlled study with a small sample size. Among all patients with APAP intoxication, the prevalence rate of APAP-related renal function impairment has been estimated at <2% of all patients. Most cases (53%) coexist with hepatic failure and acute kidney injury (AKI). Other cases of renal toxicity have mild liver involvement or no hepatic toxicity features. However, based on a review of the literature, few case reports confirm the effects of APAP toxicity on the nephritic function. In addition, among current small-scale studies, no Chinese or Asian population-based study has been found in serial literature.
To obtain sufficient statistical power, we used a large-scale database and investigated the correlation between APAP poisoning and the subsequent development of AKI.

METHODS

Data Source

The National Health Insurance (NHI) program in Taiwan is a compulsory single-payer program initiated in 1995 that currently covers almost the entire population (99.9%) of Taiwan. The Bureau of the National Health Insurance and the National Health Research Institute (NHRI) of Taiwan established the National Health Insurance Research Database (NHIRD) and currently maintain it. The National Health Insurance Administration deletes all identifiers of individual patients before data are transferred to the NHIRD. For this study, we used a subset of the NHIRD healthcare data including files of inpatient claims and the Registry of Beneficiaries. Diagnostic codes in the NHIRD are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The Institutional Review Board of China Medical University (CMU-REC-101-012) exempted this study from informed consent.

Sampled Participants

Adults with newly diagnosed APAP intoxication (ICD-9-CM code 965.4) were identified from the inpatient claims between 2000 and 2010 as the APAP poisoning cohort. We used the date of the first admission for APAP intoxication as the index date. We excluded patients with a history of chronic kidney disease (CKD) (ICD-9-CM codes 580–589) or end-stage renal disease (ESRD) (ICD-9-CM code 585) before the index date and those with incomplete medical information. We included all remaining patients in the entire NHIRD without a history of APAP intoxication. The comparison cohort, comprising patients who had no history of CKD or ESRD, were frequency matched with the APAP intoxication cohort at a ratio of 1:4 for age (every 5 years), sex, and index year of diagnosis, using the same exclusion criteria.

Outcome

The main outcome of APAP intoxication was hospitalization with a new diagnosis of AKI (ICD-9-CM codes 584) during the follow-up. The duration of follow-up was estimated from the index date until AKI occurred, withdrawal from the insurance system, or the end of 2011. We analyzed the AKI patients with either coexisting hepatitis (ICD-9-CM codes 573.3) or hepatic failure (ICD-9-CM code 585) before the index date and those with incomplete medical information. We excluded patients with a history of chronic kidney disease (CAD) (ICD-9 codes 410–414), stroke (ICD-9 codes 430–438), and alcoholism (ICD-9 codes 291, 303, 305.0, 790.3, and V11.3).

Statistical Analysis

We compared the distributions of categorical demographic characteristics and comorbidities between the APAP intoxication and comparison cohorts. We examined the differences using the chi-square test for categorical variables and used Student t-test to measure and examine the mean ages and follow-up periods. We calculated the overall incidence density rates and age-, sex-, and comorbidity-specific rates of AKI (per 10,000 person-years). We used univariable and multivariable Cox proportion hazard regression models to examine the effect of APAP intoxication on the risk of AKI, shown as a hazard ratio (HR) with a 95% confidence interval (CI). The multivariable models were simultaneously adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, CAD, stroke, and alcoholism. Stratified by age, sex, comorbidity, and follow-up time, the relative risk of AKI development in patients with APAP intoxication, compared with the comparison cohort, was analyzed using the Cox models. The cumulative incidence curves of AKI for the 2 cohorts were compared using the Kaplan–Meier method and log-rank test. All data analyses were conducted using SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc., Cary, NC). Two-tailed P < 0.05 was considered significant.

RESULTS

Table 1 lists the demographic characteristics and comorbidities of the patients in the APAP poisoning and comparison cohorts. The distributions of age and sex for the study patients were similar between the 2 cohorts. The 2 cohorts had mean

| TABLE 1. Demographic Characteristics and Comorbidities in Cohorts With and Without Acetaminophen Poisoning |
|---------------------------------|--------|----------------|-----|
| Acetaminophen Poisoning         | No (N = 11,656) | Yes, (N = 2914) | P Value |
| Age, y                         | 0.99   |                 |      |
| ≤34                            | 8592 (73.7)  | 2148 (73.7)    |      |
| 35–64                          | 2748 (23.6)  | 687 (23.6)     |      |
| 65+                            | 316 (2.71)   | 79 (2.71)      |      |
| Mean ± SD                      | 31.7 (11.9)  | 31.7 (11.5)    | 0.86 |
| Sex                            | 0.99   |                 |      |
| Female                         | 8874 (75.4)  | 2196 (75.4)    |      |
| Male                           | 2872 (24.6)  | 718 (24.6)     |      |
| Comorbidity                    |        |                 |      |
| Diabetes                       | 107 (0.92)   | 68 (2.33)      | <0.001 |
| Hypertension                   | 153 (1.31)   | 112 (3.84)     | <0.001 |
| Hyperlipidemia                 | 47 (0.40)    | 51 (1.75)      | <0.001 |
| COPD                           | 60 (0.51)    | 36 (1.24)      | <0.001 |
| CAD                            | 68 (0.58)    | 45 (1.54)      | <0.001 |
| Stroke                         | 60 (0.51)    | 43 (1.48)      | <0.001 |
| Alcoholism                     | 13 (0.11)    | 81 (2.78)      | <0.001 |

Chi-squared test.
CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; SD = standard deviation.
* t-test.

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FIGURE 1. Cumulative incidence of acute kidney injury among patients with and without acetaminophen intoxication.

Ages of 31.7 (standard deviation [SD] = 11.5) and 31.7 (SD = 11.9) years. Approximately 73.7% of the participants were younger than 34 years. Women outnumbered men in both cohorts (75.4% vs 24.6%). Patients with APAP intoxication had a higher prevalence of comorbidity than that of the comparison cohort (all $P < 0.001$). The mean follow-up duration was 6.42 ± 3.49 years for the APAP intoxication cohort and 6.35 ± 3.50 years for the comparison cohort. The Kaplan–Meier graph in Figure 1 illustrates that the cumulative incidence of AKI was higher in the APAP intoxication cohort than in the comparison cohort (log-rank test $P < 0.001$).

The overall incidence of AKI was 2.69-fold higher in the APAP intoxication cohort than in the comparison cohort (10.20 and 3.78 per 10,000 person-years, respectively; Table 2). After adjustment for age, sex, and comorbidity, patients with APAP intoxication were associated with an increased risk of AKI compared with those without APAP intoxication (adjusted HR [aHR] = 2.41, 95% CI = 1.31–4.44). Compared with patients ages 34 years and younger, the risk of AKI development was 2.44-fold higher in those ages 35 to 64 years (95% CI = 1.10–5.42), and 30.6-fold higher in those ages 65 years and older (95% CI = 12.7–73.5). The AKI incidence was greater in male patients and increased with comorbidity. We observed a significantly higher risk of AKI in patients with diabetes (aHR = 4.54, 95% CI = 2.01–10.30) and in patients with alcoholism (aHR = 5.02, 95% CI = 1.46–17.20). The AKI incidence increased with age in both cohorts (Table 3). The age-specific APAP intoxication cohort to comparison cohort relative risk of AKI was significant for the group ages ≤ 34 years (aHR = 3.51, 95% CI = 1.09–11.30). The sex-specific APAP intoxication cohort to comparison cohort relative risk of AKI was significant for women (aHR = 3.90, 95% CI = 1.59–9.54). Regarding the follow-up duration of 2 years, the APAP intoxication cohort to comparison cohort had a significantly higher risk of AKI (aHR = 3.48, 95% CI = 1.24–9.76). In addition, 2 patients with coexisting hepatic injury and AKI were recognized (1 patient had hepatic failure and the other had hepatitis). The post-AKI follow-up results showed that 2 patients (10.6%) progressed to ESRD and required hemodialysis management.

**DISCUSSION**

APAP is an immediate-release antipyretic and analgesic medication with a maximum recommended therapeutic daily dose of 4 g for adults. Generally, toxicity results from 7.5 to 10.0 g for an adult dose. Most APAP (approximately 90%) is metabolized in the liver to a nontoxic product and excreted in urine. The remainder is metabolized by the hepatic cytochrome P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) to the toxic intermediate, N-acetyl-p-benzoquinoneimine (NAPQI). The major pathophysiology of large dose APAP-related systemic toxicity results from the balance between NAPQI and baseline glutathione levels in the whole body. When normal APAP metabolism pathways are saturated, more NAPQI is manufactured via the cytochrome P450 enzymes. Hepatic injury and other organic toxicity are recognized once tissue glutathione stores are exhausted by NAPQI. In the literatures, 2 possible mechanisms of APAP-related renal toxicity are postulated. First, large amounts of APAP and NAPQI are excreted into the kidney, and coexisting hepatic and renal toxicities can be attributed to these toxic metabolites. These toxic metabolites contribute to subendothelial damage and tubular ischemic change and then progress to acute tubular necrosis. Second, direct nephrotoxicity can result from oxidative stress and an insufficient amount of renal glutathione. Regardless of whether patients had experienced hepatic toxicity, AKI is a possible result of APAP intoxication. In addition to baseline glutathione values in the liver and kidneys, several other clinical factors also play essential roles in enhancing APAP-related toxicity. These factors include starvation, acute or chronic alcohol ingestion, concurrent administration of other drugs, underlying comorbidities, and nutritional status. Chronic alcohol abuse which sometimes reduces organic glutathione levels in the kidneys or liver and lead to subsequent renal toxicities.

In our study, we analyzed traditional risk factors for AKI, such as age, sex, and multiple comorbidities. AKI incidence was relatively higher in older patients and in those with alcoholism or diabetes than young cases. The overall incidence of AKI was 2.41-fold higher in the APAP intoxication cohort than those without APAP after adjustment for these traditional risk factors. However, in age-specific APAP intoxication cohort to comparison cohort, our results showed a 3.51-fold increased risk in younger patients (ages ≤ 34 years) and female patients with APAP intoxication compared with those without. The possible explanation could be considered as larger cases in the younger patients and female patients in this study. In addition, we analyzed the relationship between hepatic injury and renal toxicity in these patients with APAP intoxication. Two patients had coexisting hepatic injury and AKI. One presented with hepatic failure and AKI, and the other had hepatitis and AKI. This risk was still increased 2.22-fold in the patients of the APAP intoxication cohort without hepatic failure, compared with the control group (aHR = 2.22 [95% CI = 1.17–4.22]). In APAP intoxication patients, regardless of whether they presented with hepatic toxicity, had a higher incidence rate of AKI than that of the general population. With a mean follow-up period of 6.42 years, the risk of AKI development in patients with APAP poisoning appeared primarily within the first 2 follow-up years, and the incidence of AKI declined after the
first 2 years. Therefore, APAP toxicity is an independent risk factor for developing AKI regardless of whether underlying comorbidities or hepatic toxicity are present.

Generally, most cases with APAP intoxication-related AKI are reversible and self-limited. The serum creatinine and urea nitrogen can return to previous baseline levels within 1 to 4 weeks. In our study, there were 19 cases of APAP intoxication and AKI, 2 cases presenting with ESRD (10.5%), and none with CKD. Because there was no detail etiologies of ESRD in our patients retrieved from the NHIRD, the possible causes or predisposing factors could be clarified in future registry studies.

This study has several limitations. First, the NHIRD does not contain detailed information regarding patients’ current use of medications, such as nonsteroidal anti-inflammatory agents and aspirin, which are potential confounding factors that might have influenced the primary study outcomes. Second, this study used a health insurance claims database that lacked detailed information on certain general characteristics, including obesity and body mass index, and smoking, exercise, and dietary habits. Third, the NHIRD uses ICD-9-CM codes that do not reflect certain detailed information regarding patients with APAP intoxication, including laboratory values of blood urea nitrogen and serum creatinine levels, detailed dosage of APAP intoxication and severity markers such as pathological results of AKI. Fourth, the evidence of retrospective cohort studies is lower in statistical quality. Large-scale registry studies are necessary to provide more detailed information and evidence. Fifth, based on our method, indeed, there were some detection biases in study group and selection bias in control group. In control group, a higher number of chronic comorbidities were observed in patients with APAP intoxication than in the control patients. However, our study does not provide strong evidence differentiating the relationship between APAP intoxication and AKI according to the relationship between comorbidities and AKI, particularly in patients with diabetes. These could be as potential confounding factors in our presented study. Finally, our study investigated only the general population of Taiwan. Differences may exist between the population examined in our study and other interethnic, geographical, and epidemiological distributions.

### Table 2. Incidence and Hazard Ratio for Acute Kidney Injury and Acute Kidney Injury-Associated Risk Factor

| Variables       | Event | PY  | Rate   | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-----------------|-------|-----|--------|-------------------|----------------------|
| Acetaminophen poisoning | No    | 28  | 74,052 | 3.78              | 1.00                 |
|                 | Yes   | 19  | 18,696 | 10.2              | 2.69 (1.50, 4.82)**  |
| Age, y          |       |     |        |                   |                      |
| ≤34             | 13    | 70,080 | 1.86 | 1.00              |                      |
| 35–64           | 12    | 21,095 | 5.69 | 3.07 (1.40, 6.72)**|                      |
| 65+             | 22    | 1572  | 139.9 | 77.2 (38.5, 154.7)***| 30.6 (12.7, 73.5)***|
| Sex             |       |     |        |                   |                      |
| Female          | 22    | 70,012 | 3.14 | 1.00              |                      |
| Male            | 25    | 22,736 | 11.0 | 3.52 (1.98, 6.24)***| 1.83 (0.99, 3.39)    |
| Diabetes        |       |     |        |                   |                      |
| No              | 35    | 91,991 | 3.80 | 1.00              |                      |
| Yes             | 12    | 758   | 158.4 | 41.2 (21.3, 79.7)***| 4.54 (2.01, 10.30)***|
| Hypertension    |       |     |        |                   |                      |
| No              | 32    | 91,651 | 3.49 | 1.00              |                      |
| Yes             | 15    | 1098  | 136.6 | 39.4 (21.2, 73.4)***| 1.93 (0.77, 4.82)    |
| Hyperlipidemia  |       |     |        |                   |                      |
| No              | 43    | 92,332 | 4.66 | 1.00              |                      |
| Yes             | 4     | 417   | 96.0  | 20.6 (7.36, 57.6)***| 1.03 (0.28, 3.74)    |
| COPD            |       |     |        |                   |                      |
| No              | 43    | 92,329 | 4.66 | 1.00              |                      |
| Yes             | 4     | 419   | 95.4  | 19.5 (6.97, 54.3)***| 0.91 (0.25, 3.29)    |
| CAD             |       |     |        |                   |                      |
| No              | 43    | 92,286 | 4.66 | 1.00              |                      |
| Yes             | 4     | 463   | 86.4  | 18.5 (6.60, 51.80)***| 0.69 (0.09, 5.38)    |
| Stroke          |       |     |        |                   |                      |
| No              | 38    | 92,319 | 4.12 | 1.00              |                      |
| Yes             | 9     | 429   | 210.0 | 51.4 (24.7, 107.3)***| 2.52 (0.96, 6.59)    |
| Alcoholism      |       |     |        |                   |                      |
| No              | 43    | 92,282 | 4.66 | 1.00              |                      |
| Yes             | 4     | 467   | 85.7  | 18.0 (6.46, 50.20)***| 5.02 (1.46, 17.2)***|

Rate = incidence rate, per 10,000 person-years, Crude HR = relative hazard ratio, Adjusted HR = multivariable analysis including age, sex, and comorbidity of diabetes, hypertension, hyperlipidemia, COPD, CAD, stroke, and alcoholism.

| CAD | coronary artery disease; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; PY = person-years.

* P < 0.05.
** P < 0.01.
*** P < 0.001.
This is the first nationwide population-based cohort study to investigate the risk between APAP intoxication and AKI by using a large database and adjusting for traditional AKI risk factors including diabetes, hypertension, hyperlipidemia, COPD, CAD, and stroke. And the main contribution of our study is its use of a population-based database, which contains data on a high number of patients with APAP intoxication, to investigate the risk between APAP intoxication and AKI. Higher incidence rates of AKI were also determined in patients with previous APAP intoxication exhibiting a 2.41-fold risk of developing AKI compared with the general population. Although the detailed pathophysiologic mechanism between APAP intoxication and AKI may require further examination, we recommend that physicians consider the possibility of AKI in patients with APAP intoxication. Future studies might assist physicians in developing strategies for preventing AKI.

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**TABLE 3. Incidence of Acute Kidney Injury by Age, Sex, Comorbidity, and Follow-Up Time and Cox Model Measured Hazards Ratio for Patients With Acetaminophen Poisoning Compared Those Without Acetaminophen Poisoning**

| Comorbidity | No | Event PY Rate | Yes | Event PY Rate | Crude HR (95% CI) | Adjusted HR (95% CI) |
|-------------|----|---------------|-----|---------------|--------------------|----------------------|
|             |    | Age, y        |     |               |                    |                      |
|             | 6  | ≤34           | 7   | 45,791       | 4.87               | 4.51 (1.52, 13.40)**  |
|             | 6  | 35–64         | 6   | 40,589       | 14.8               | 4.19 (1.31, 13.00)*   |
|             | 16 | 65+           | 6   | 259          | 231.5              | 1.78 (0.70, 4.55)     |
| Sex         |    |               |     |               |                    |                      |
|             | 11 | Female        | 11  | 14,278       | 7.70               | 3.93 (1.70, 9.07)**   |
|             | 17 | Male          | 8   | 4418         | 18.1               | 1.95 (0.84, 4.51)     |
| Comorbidity |    |               |     |               |                    |                      |
|             | 15 | No            | 7   | 17,375       | 4.03               | 1.94 (0.79, 4.77)     |
|             | 13 | Yes           | 12  | 1322         | 90.8               | 1.00 (0.46, 2.19)     |
| Follow-up time, y | 7 |   |               |     |               |                      |
|             | 8  | ≤2            | 9   | 5324         | 16.9               | 4.53 (1.75, 11.70)**  |
|             | 20 | >2            | 10  | 13,772       | 7.48               | 1.97 (0.92, 4.20)     |

Rate = incidence rate, per 10,000 person-years, Crude HR = relative hazard ratio, Adjusted HR = multivariable analysis including age, sex, and comorbidity of diabetes, hypertension, hyperlipidemia, COPD, CAD, stroke, and alcoholism.

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