Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

• The hepatotoxicity concerns of antithyroid drugs (ATDs), consisting of propylthiouracil (PTU), methimazole (MMI) and its prodrug carbimazole (CBM), have been raised primarily based on case reports and spontaneous reporting.
• Precise estimates of incidence rates and comparative risks of hepatotoxicity by individual ATDs are accordingly lacking.

WHAT THIS STUDY ADDS

• This study quantifies the incidence rates of hepatotoxicity associated with ATDs and observes that hepatitis is the most frequently occurring hepatotoxicity in both PTU and MMI/CBM users.
• Compared with PTU, MMI/CBM are associated in a dose-dependent manner with an increased risk for hepatitis while the risks are similar for acute liver failure and cholestasis.

AIMS

The evidence of hepatotoxicity of antithyroid drugs (ATDs) is limited to case reports or spontaneous reporting. This study aimed to quantify the incidence and comparative risks of hepatotoxicity for methimazole (MMI)/carbimazole (CBM) vs. propylthiouracil (PTU) in a population-based manner.

METHODS

We conducted a cohort study of hyperthyroidism patients initially receiving MMI/CBM or PTU between 1 January 2004 and 31 December 2008 using the Taiwan National Health Insurance Research Database. The examined hepatotoxicity consisted of cholestasis, non-infectious hepatitis, acute liver failure and liver transplant, with the incidences and relative risks being quantified by Poisson exact methods and Cox proportional hazard models, respectively.

RESULTS

The study cohort comprised 71 379 ATD initiators, with a median follow-up of 196 days. MMI/CBM vs. PTU users had a higher hepatitis incidence rate (3.17/1000 vs. 1.19/1000 person-years) but a lower incidence of acute liver failure (0.32/1000 vs. 0.68/1000 person-years). The relative risk analysis indicated that any use of MMI/CBM was associated with a 2.89-fold (95% CI 1.81, 4.60) increased hepatitis risk compared with PTU, with the risk increasing to 5.08-fold for high dose MMI/CBM (95% CI 3.15, 8.18). However, any MMI/CBM use vs. PTU was not related to an increased risk of cholestasis (adjusted hazard ratio [HR] 1.14, 95% CI 0.40, 3.72) or acute liver failure (adjusted HR 0.54, 95% CI 0.24, 1.22).

CONCLUSIONS

MMI/CBM and PTU exert dissimilar incidence rates of hepatotoxicity. Compared to PTU, MMI/CBM are associated in a dose-dependent manner with an increased risk for hepatitis while the risks are similar for acute liver failure and cholestasis.

Introduction

Antithyroid drugs (ATDs) are the mainstay treatment for hyperthyroidism and include propylthiouracil (PTU), methimazole (MMI) and its prodrug carbimazole (CBM) [1]. However, concerns have been raised about hepatotoxicity by ATDs [2, 3] due to numerous reported PTU-induced [4–6] and MMI/CBM-induced hepatotoxic cases [7, 8]. Additionally, PTU was reported to cause 23 liver transplants from 1990 to 2007 in the US and was ranked as the third most common cause of drug-induced liver failure requiring transplants [3, 9]. Thirty-four cases of PTU-induced severe or fatal liver injury were also identified by analyzing the US Adverse Event Reporting System (AERS) database, which outnumbered the MMI-related hepatotoxic cases by approximately seven-fold [10]. Consequently, the US Food and Drug Administration (FDA) issued a boxed warning of PTU-induced severe hepatotoxicity in April 2010 [10].

To date, previous studies evaluating ATD-induced hepatotoxicity were primarily limited to case reports [4–8, 11–13], retrospective chart reviews [14, 15] and small sample clinical studies [16, 17], which only observed few hepatic adverse events. Accordingly, population-based estimates of incidences of hepatotoxicity by ATDs are lacking. An inspection of previous reports [4–6, 11, 12] seemed to indicate differential hepatotoxicity profiles for the individual ATDs: severe hepatocellular necrosis related to PTU *vs.* relatively mild cholestatic liver injury by MMI. However, several case reports claimed that MMI/CBM could cause severe liver failure or hepatitis [7, 8, 13]. Though analyses of the AERS data revealed a higher reporting rate of severe hepatotoxicity with PTU than MMI in children and adolescents [18], few hepatotoxic events precluded a robust assessment of relative hepatotoxic safety of ATDs in adults. Accordingly, it is still uncertain as to whether PTU and MMI/CBM carry different hepatotoxicity risks in the present clinical setting. We, therefore, conducted an observational cohort study to assess the incidence for individual ATDs and to evaluate the relative risks of hepatotoxicity associated with PTU and MMI/CBM in all hyperthyroidism patients.

Methods

Data source

This was a retrospective population-based cohort study analyzing the data retrieved from the National Health Insurance Research Database (NHIRD) between 1 January 2004 and 31 December 2008 in Taiwan. The NHIRD contains comprehensive information on demographic characteristics, records of prescription drugs and medical services from inpatient, outpatient and emergency care under a universal health insurance programme enrolling up to 99% of Taiwan inhabitants by 2009 [19]. Additionally,

the analyzed database has been widely used for studying drug safety, including drug-induced hepatotoxicity [20, 21]. All patients' identifiers in NHIRD are double encrypted to ensure patient confidentiality. Therefore, this study was exempt from review by the Institutional Review Board when it was performed. The study complies with the current laws of Taiwan where it was performed. The access to and analyses of the database were approved by the National Health Research Institutes (NHRI; registered number: 99154).

Study cohort

All patients diagnosed with hyperthyroidism (International Classification of Diseases, Ninth Revision, Clinical Modifications [ICD-9-CM] codes 242.xx, 775.3) and initiating an ATD between 1 January 2005 and 30 June 2008 were eligible to be part of the study cohort. The date of the initial ATD treatment, without any ATD prescription record in the previous year, marked the cohort entry date. Patients were further excluded if they had less than 1 year continuous NHI enrolment, any record of thyroidectomy, iodine-131 therapy or thyroid cancer or any previous diagnosis of examined hepatotoxicity or underlying liver diseases (see details in Table S1) during the year preceding cohort entry.

We followed the study cohort, categorized into MMI/CBM or PTU users, from the entry date until an ATD discontinuation, combination with or switch to a different ATD, occurrence of hospitalized hepatotoxic outcomes or 31 December 2008, whichever came first. Discontinuation of ATD treatment was defined as > 90 days elapsed between the calculated end date and the subsequent start date of ATD prescriptions. We extended an additional follow-up period of 90 days after the end of the last ATD prescription for any discontinued ATD therapy to observe hepatotoxicity that may occur after discontinued therapy.

Study variables

The hepatotoxic outcomes were identified from inpatient services as any diagnosis of cholestasis (ICD-9-CM code 576.8) [22], non-infectious hepatitis (ICD-9-CM code 573.3) [20, 23], acute liver failure (ICD-9-CM code 570) [20, 23] and liver transplant (ICD-9-CM procedure code 50.5) [24]. In order to avoid misclassification of hepatotoxicity and to increase accuracy of the employed codes, only hospitalized hepatotoxic events were analyzed in this study.

We considered several potential confounders including gender, age (< 65, ≥ 65 years) at study entry and presence of pregnancy during the 280 days prior to cohort entry. History of hyperthyroidism and comorbidities potentially related to liver injury, including thyrotoxic storm, diabetes mellitus, heart failure, chronic kidney disease and hyperlipidaemia were also measured in the year preceding cohort entry. Any diagnosis of underlying liver diseases during follow-up was additionally identified. Furthermore, we examined potentially hepatotoxic medi-

cations consisting of antimicrobial agents, non-opioid analgesics, neurological drugs, Chinese herbal medication and miscellaneous hepatotoxic drugs during the 6 months preceding cohort entry. All confounders are detailed in Table S1.

Statistical analysis

The baseline characteristics between PTU and MMI/CBM users were compared using standardized mean differences, calculated as a mean difference or proportion difference of a variable across groups divided by the pooled estimate of the standard deviations [25]. This measure is employed because use of a significant test to compare characteristics between groups with very large numbers of subjects will often lead to the detection of differences that are statistically significant ($P < 0.05$) but not clinically important [26]. Standardized mean differences of greater than 0.1 generally represent a clinically meaningful difference in a variable across groups [25]. Crude incidence rates of the hepatotoxic events per 1000 person-years were calculated for the two groups and stratified by age (<18, 18–64, ≥65 years), gender, duration of continuous use (0–15, 16–30, 31–60, 61–90, 91–180, >180 days) and average daily dose of ATDs (PTU: ≤100, 100–150, >150 mg day^{-1}; MMI/CBM: ≤10, 10–15, >15 mg day^{-1}) by the Poisson exact method. The average daily dose was calculated based on all ATD prescriptions during the 6 months preceding the end of follow-up.

We performed mutually exclusive Cox proportional hazard analyses to estimate the crude and adjusted hazard ratios (HRs) for each hepatotoxicity outcome associated with MMI/CBM relative to PTU. All covariates listed in Table 1 were adjusted for during multivariate analyses. We validated Cox proportional hazards models by confirming that the Schoenfeld residuals were independent of time. A dose–response assessment was further performed by evaluating the comparative hepatotoxicity of low dose MMI/CBM (≤13 mg), low dose PTU (≤138 mg) and high dose MMI/CBM (>13 mg) vs. any use of PTU and high dose PTU (PTU>138 mg), respectively. The cut-off values used for dose categorizations were determined based on the median daily doses of ATD treatments. Moreover, the individual comparative hepatotoxicity of MMI and CBM vs. PTU, respectively, was also assessed.

Sensitivity analysis

Several sensitivity analyses were conducted: (i) excluding hepatotoxic hospitalizations with any diagnosis of viral hepatitis and/or alcoholic hepatitis in the same admission, (ii) redefining a 30 day gap for continuous use of ATDs, (iii) excluding patients who were diagnosed with underlying liver diseases during follow-up, (iv) restricting patients to those without thyrotoxic storms at baseline, (v) excluding subjects with previous hyperthyroidism, (vi) conducting stratified analyses by age and gender and (vii) employing different model selections in separate Cox models, which

Table 1

Baseline and clinical characteristics of PTU and MMI/CBM users

Characteristic	PTU (n = 24 941)	MMI/CBM (n = 46 438)	Standardized difference
Age group (years)			
<65	22 930 (91.9%)	42 637 (91.8%)	0.004
≥65	2011 (8.1%)	3801 (8.2%)	
Female gender	20 378 (81.7%)	35 617 (76.7%)	0.12
Pregnancy	1105 (4.4%)	624 (1.3%)	0.20
Medical comorbidities			
History of hyperthyroidism	2143 (8.6%)	3867 (8.3%)	0.01
Thyrotoxic storm	1426 (5.7%)	2899 (6.2%)	0.02
Heart failure	803 (3.2%)	1346 (2.9%)	0.02
Chronic kidney diseases	170 (0.7%)	250 (0.5%)	0.02
Diabetes	2014 (8.1%)	4018 (8.7%)	0.02
Hyperlipidaemia	1677 (6.7%)	3425 (7.4%)	0.03
Underlying liver diseases*			
In hepatitis outcome	1364 (5.5%)	2305 (5.0%)	0.02
In acute liver failure outcome	1366 (5.5%)	2316 (5.0%)	0.02
In cholestasis outcome	1368 (5.5%)	2318 (5.0%)	0.02
In liver transplant outcome	1370 (5.5%)	2319 (5.0%)	0.02
Hepatotoxic comedications			
Antimicrobial agents	1684 (6.8%)	2838 (6.1%)	0.03
Non-opioid analgesics	9252 (37.1%)	17 107 (36.8%)	0.005
Neurological drugs	1378 (5.5%)	2461 (5.3%)	0.01
Other hepatotoxic drugs	1920 (7.7%)	3578 (7.7%)	<0.001
Chinese herbs	1832 (7.4%)	3343 (7.2%)	0.006

CBM, carbimazole; MMI, methimazole; PTU, propylthiouracil. *Any diagnosis of underlying liver diseases was recorded during follow-up for the outcomes of hepatitis, acute liver failures, cholestasis and liver transplant, respectively.

adjusted for variables with a standardized mean difference over 0.1 (model 1), as well as controlled for covariates with univariate P values < 0.05 (model 2). Data cleaning was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) and statistical analyses were conducted using STATA version 10.1 (STATA, College Station, TX, USA).

Results

The study cohort consisted of 71 379 ATD initiators with hyperthyroidism, of whom 24 941 started on PTU and 46 438 began MMI/CBM treatment (Figure 1). The mean age of the study cohort was 41.3 years and 78.5% were female. We followed patients on PTU for a median of 173 (interquartile range 112–342) days and those treated with MMI/CBM for a median of 208 (119–390) days. Table 1 indicates that the examined characteristics were quite balanced between the two groups, except for the higher proportions of females and pregnancy in PTU users.

Table 2 indicates that the ranking order of the hepatotoxicity incidence rates from highest to lowest was the same across PTU and MMI/CBM users. The incidence of hepatitis was the highest in both groups (PTU: 1.19/1000

person-years; MMI/CBM: 3.17/1000 person-years), followed by acute liver failure and cholestasis. Only one liver transplant case was found in the PTU users.

For the incidence rates stratified by age (Figure 2A), patients aged over 65 years generally had higher hepatotoxicity incidence rates than those with younger ages, with

Table 2

Crude incidence of hepatotoxic events associated with individual antithyroid drugs

Events	Events/PYs	Rate/1000 PYs (95% CI)
PTU (n = 24 941)		
Hepatitis	21/17 683	1.19 (0.74, 1.82)
Acute liver failure	12/17 683	0.68 (0.35, 1.19)
Cholestasis	4/17 685	0.23 (0.06, 0.58)
Liver transplant	1/17 688	0.06 (0.01, 0.32)
MMI/CBM (n = 46 438)		
Hepatitis	118/37 273	3.17 (2.62, 3.79)
Acute liver failure	12/37 308	0.32 (0.17, 0.56)
Cholestasis	9/37 307	0.24 (0.11, 0.46)
Liver transplant	0/37 310	NA

CBM, carbimazole; CI, confidence interval; MMI, methimazole; NA, not applicable; PTU, propylthiouracil; PYs, person-years.
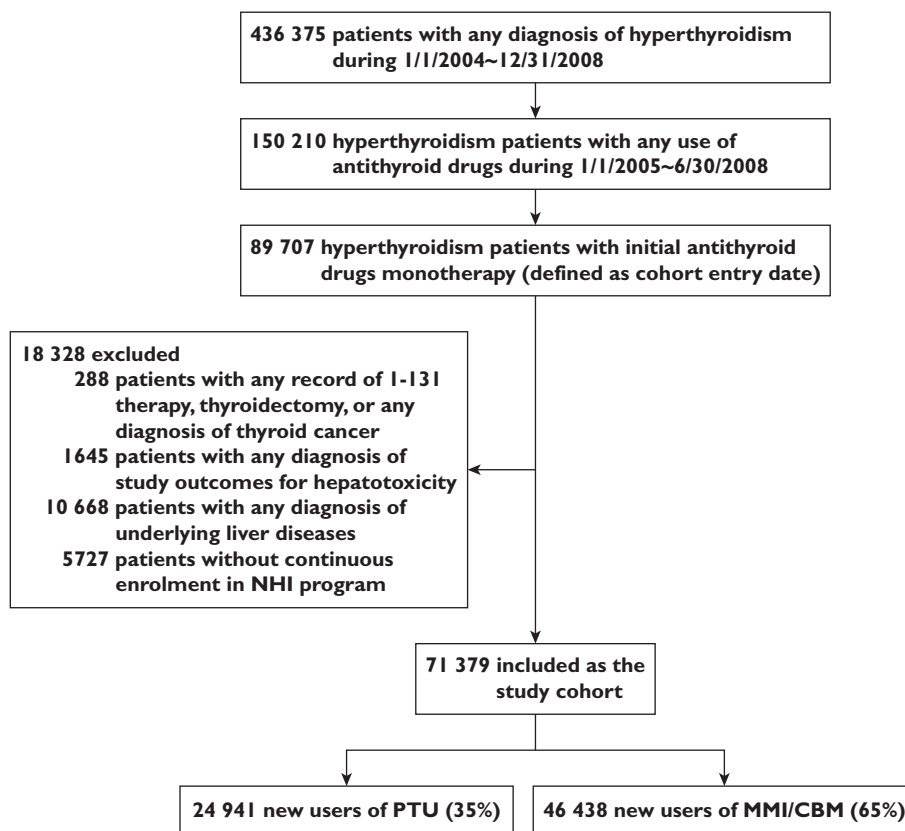
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┌─────────────────────────────────────────────┐
│ 436 375 patients with any diagnosis of        │
│   hyperthyroidism during 1/1/2004~12/31/2008   │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ 150 210 hyperthyroidism patients with any use  │
│   of antithyroid drugs during 1/1/2005~6/30/2008│
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┌─────────────────────────────────────────────┐
│ 89 707 hyperthyroidism patients with initial   │
│   antithyroid drugs monotherapy (defined as     │
│   cohort entry date)                            │
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│ 18 328 excluded                                │
│    288 patients with any record of I-131       │
│        therapy, thyroidectomy, or any          │
│        diagnosis of thyroid cancer             │
│   1645 patients with any diagnosis of          │
│        study outcomes for hepatotoxicity       │
│  10 668 patients with any diagnosis of         │
│        underlying liver diseases               │
│   5727 patients without continuous             │
│        enrolment in NHI program                │
└─────────────────────────────────────────────┘
                      ↓
┌─────────────────────────────────────────────┐
│ 71 379 included as the study cohort            │
└─────────────────────────────────────────────┘
           ↓                      ↓
┌──────────────────────┐  ┌──────────────────────┐
│ 24 941 new users of  │  │ 46 438 new users of  │
│   PTU (35%)          │  │   MMI/CBM (65%)      │
└──────────────────────┘  └──────────────────────┘
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Figure 1

Study flow diagram. NHI, National Health Insurance; PTU, propylthiouracil; MMI, methimazole; CBM, carbimazole
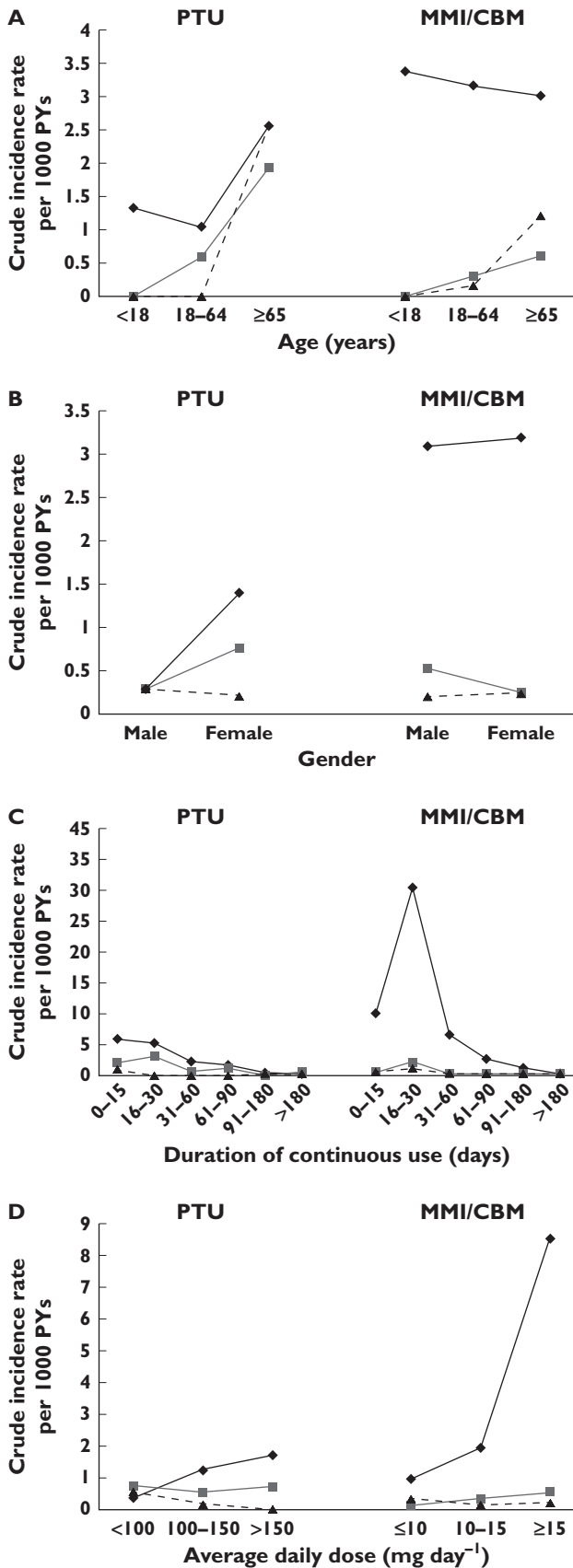
the exception of hepatitis incidence among MMI/CBM users aged <65 years old. Figure 2B indicates that the hepatotoxicity seemed to be more gender sensitive in PTU users than that in MMI/CBM users. Particularly, a 4.8-fold increased incidence rate of hepatitis was observed in females compared with males among PTU users. Additionally, the hepatotoxicity incidence rates peaked within 30 days of continuous treatment of both ATDs and tended to decline afterwards (Figure 2C). The incidence of hepatitis appeared to be the most ATD dose-sensitive, especially during MMI/CBM treatment (Figure 2D).

Table 3 indicates that any MMI/CBM use was associated with a 2.89-fold increased risk of hepatitis compared with any PTU use (95% confidence interval [CI], 1.81, 4.60) after adjustment of all potential confounders. Conversely, any use of MMI/CBM *vs.* PTU was not related to an increased risk of acute liver failure (adjusted HR 0.54, 95% CI 0.24, 1.22) or risk of cholestasis (adjusted HR 1.14, 95% CI 0.40, 3.72). The full multivariate models analyzing risk of hepatotoxicity associated with MMI/CBM *vs.* PTU are shown in Table S2.

As shown in Figure 3A, high dose MMI/CBM was associated with a 5.08-fold (95% CI 3.15, 8.18) increased risk of hepatitis compared with any use of PTU, whereas the risk was absent for use of low dose MMI/CBM (adjusted HR 1.15, 95% CI 0.64, 2.04). Notably, even compared with high dose PTU, high dose MMI/CBM was consistently associated with an increased hepatitis risk (adjusted HR 3.55, 95% CI 2.05, 6.13) (Figure 3B).

Table 4 presents the relative risks of hepatotoxicity of individual MMI or CBM *vs.* PTU. Compared with PTU, MMI still incurred an increased risk of hepatitis (adjusted HR 3.54, 95% CI 2.21, 5.65). Nevertheless, CBM was not associated with the hepatitis risk (adjusted HR 1.04, 95% CI 0.50, 2.16).

The main findings remained robust during the majority of the sensitivity analyses (Figure 4). Notably, the risk of acute liver failure was significantly reduced (adjusted HR 0.34, 95% CI 0.12, 0.98, *P* = 0.045) in MMI/CBM *vs.* PTU users by excluding patients with underlying liver diseases during follow-up.

Discussion

Analyzing the administrative health records of 23 million Taiwan inhabitants, we revealed the similarities and dissimilarities of hepatotoxicity profiles of ATDs. The inci-

Table 3

Relative risk of hepatotoxicity associated with MMI/CBM compared with PTU

	Number of users	Number of events	Crude HR (95% CI)	Adjusted HR (95% CI)*
Hepatitis				
PTU	24 941	21	1.00	1.00
MMI/CBM	46 438	118	2.91 (1.83, 4.63)	2.89 (1.81, 4.60)†
Acute liver failure				
PTU	24 941	12	1.00	1.00
MMI/CBM	46 438	12	0.50 (0.22, 1.10)	0.54 (0.24, 1.22)
Cholestasis				
PTU	24 941	4	1.00	1.00
MMI/CBM	46 438	9	1.10 (0.34, 3.59)	1.14 (0.40, 3.72)

CBM, carbimazole; CI, confidence interval; HR, hazard ratio; MMI, methimazole; PTU, propylthiouracil. *Adjusted for all variables listed in Table 1, with the exceptions of history of hyperthyroidism, hyperlipidaemia and use of neurological drugs for the outcome of acute liver failure as well as presence of pregnancy and chronic kidney diseases for the cholestasis outcome due to small sample size. †$P < 0.05$.

dence rates of the examined hepatotoxicity peaked in the first 30 days of treatment and ranked consistently for both PTU and MMI/CBM, with hepatitis being the most frequently occurring outcome. Nevertheless, MMI/CBM and PTU exert dissimilar hepatotoxicity incidence profiles. MMI/CBM users had a higher hepatitis incidence but a lower incidence rate of acute liver failure than PTU users. The comparative risks of ATDs varied by types of hepatotoxicity. MMI/CBM vs. PTU was associated with a dose-dependent increased hepatitis risk but was not related to the risk of cholestasis or acute liver failure. Our findings contribute significantly to the current literature limited to scattered case reports and spontaneous reporting.
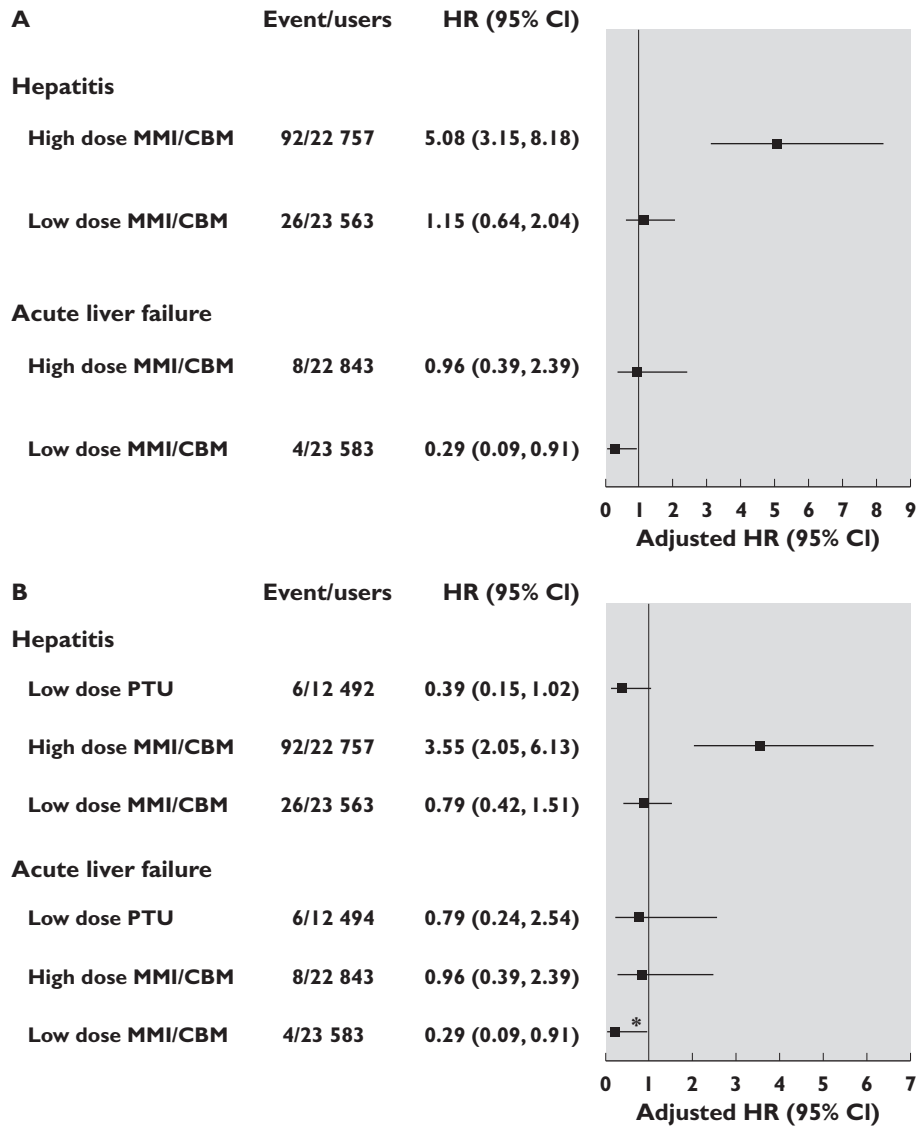
Our estimated incidence rate of PTU-related hepatitis (equal to 0.08%) is smaller than what has been estimated in Asian populations, ranging from 1.0 to 1.2% [14, 16]. The inconsistent findings might result from restriction of hepatotoxicity to hospitalized hepatotoxic events in our study or inclusion of any liver injury case with transaminase elevation in previous studies [14, 16]. MMI/CBM was surprisingly observed to induce more hepatitis events than cholestasis, the reported major type of MMI-associated hepatotoxicity [11, 12]. Prolonged cholestasis may progress to further development of hepatocellular insufficiency [27], but the extent to which delayed treatment of cholestasis led to our observed hepatitis by MMI/CBM is unclear. Additionally, our finding on the incidence rate of ATD-related hepatotoxicity peaking in the first 30 days of treatment extends the previous findings [4, 11].

Our observed hepatotoxicity profiles were dissimilar to those reported by Rivkees & Szarfman [18]. They reported MMI incurred a higher rate (0.09% vs. 0.04%) of composite mild liver injury (including increased hepatic enzymes, jaundice and cholestasis) but a lower rate (0.05% vs. 0.17%) of composite severe liver injury (including hepatitis, acute liver failure and liver transplant) than PTU with analyses of the AERS database [18]. These discrepant findings might result from identification of composite hepatotoxic out-

comes or over-reporting of healthcare professionals' perception of PTU-induced hepatitis and MMI-induced cholestasis in the AERS database.

Additionally, two randomized controlled trials conducted in Japan reported a much higher hepatotoxicity rate with PTU than MMI use. Otsuka et al. [28] reported a higher proportion of hepatotoxic events in patients receiving PTU 300 mg day^{-1} than in those treated with MMI 30 mg day^{-1} or 15 mg day^{-1} (PTU: 25.8% vs. MMI: 8.7 and 9.0%) among 449 patients with Grave's disease. Inclusion of asymptomatic hepatotoxicity and existence of imbalanced baseline characteristics, such as gender, might contribute to their discrepant findings from ours. Notably, a 15% higher proportion of females in the PTU group than in MMI group (15 mg day^{-1}) probably contributed to the conflicting results by Otsuka et al. [28], given that there is an approximately five-fold increased hepatitis rate in females than in males among PTU users (Figure 2B). These abovementioned reasons could also contribute to the discrepant data reported by Nakamura et al. due to the overlap between the two trials [28, 29].

ATD-induced hepatotoxicity might be affected by different dose levels. We observed a dose sensitive incidence rate of hepatitis associated with ATDs, especially for MMI/CBM. Additionally, only high dose MMI/CBM was observed to increase the risk of hepatitis even compared with high dose PTU. These data indicate a dose-dependent hepatitis by MMI/CBM. Furthermore, our findings of MMI and its prodrug CBM differing in their relative hepatitis risk might result from dose effects. MMI and CBM are commonly used at the same doses in the clinical setting. However, a 65% serum MMI concentrations only is reached via delivering the same dose of CBM [30], probably causing the observed null association between CBM use and hepatitis risk. On the other hand, Werner et al. [31] reported that high dose PTU (728 ± 216 mg day^{-1}) but not low dose PTU could incur a higher risk of hepatotoxicity than MMI prescribed either at low doses (23 ± 11 mg day^{-1}) or high doses (60 ±

A	Event/users	HR (95% CI)	
Hepatitis			
High dose MMI/CBM	92/22 757	5.08 (3.15, 8.18)	
Low dose MMI/CBM	26/23 563	1.15 (0.64, 2.04)	
Acute liver failure			
High dose MMI/CBM	8/22 843	0.96 (0.39, 2.39)	
Low dose MMI/CBM	4/23 583	0.29 (0.09, 0.91)	

B	Event/users	HR (95% CI)	
Hepatitis			
Low dose PTU	6/12 492	0.39 (0.15, 1.02)	
High dose MMI/CBM	92/22 757	3.55 (2.05, 6.13)	
Low dose MMI/CBM	26/23 563	0.79 (0.42, 1.51)	
Acute liver failure			
Low dose PTU	6/12 494	0.79 (0.24, 2.54)	
High dose MMI/CBM	8/22 843	0.96 (0.39, 2.39)	
Low dose MMI/CBM	4/23 583	0.29 (0.09, 0.91)	*

Figure 3

Risk of hepatotoxicity associated with use of high or low dose MMI/CBM compared with any use of PTU (A) and high dose PTU (B). High dose MMI/CBM: MMI equivalent dose >13 mg day^{-1}; low dose MMI/CBM: MMI equivalent dose ≤13 mg day^{-1}. The cholestasis outcome was not analyzed due to the small sample size. *$P < 0.05$. PTU, propylthiouracil; MMI, methimazole; CBM, carbimazole; HR, hazard ratio; CI, confidence interval

Table 4

Relative risk of hepatotoxicity associated with individual MMI or CBM compared with PTU

	Events/PTU users	Events/MMI users†	Events/CBM users†	MMI vs. PTU Adjusted HR (95% CI)*	CBM vs. PTU Adjusted HR (95% CI)*
Hepatitis	21/24 941	107/34 361	11/12 077	3.54 (2.21, 5.65)‡	1.04 (0.50, 2.16)
Acute liver failure	12/24 941	9/34 361	3/12 077	0.55 (0.23, 1.32)	0.53 (0.15, 1.88)
Cholestasis	4/24 941	6/34 361	3/12 077	1.04 (0.29, 3.72)	1.41 (0.31, 6.33)

CBM, carbimazole; CI, confidence interval; HR, hazard ratio; MMI, methimazole; PTU, propylthiouracil. *Adjusted for all variables listed in Table 1, with the exceptions of history of hyperthyroidism, hyperlipidaemia and use of neurological drugs for the outcome of acute liver failure as well as presence of pregnancy and chronic kidney diseases for the cholestasis outcome due to small sample size. †The censorship of switch between use of MMI and CBM was considered during analyses of hepatotoxicity risk from individual MMI or CBM. ‡$P < 0.05$.
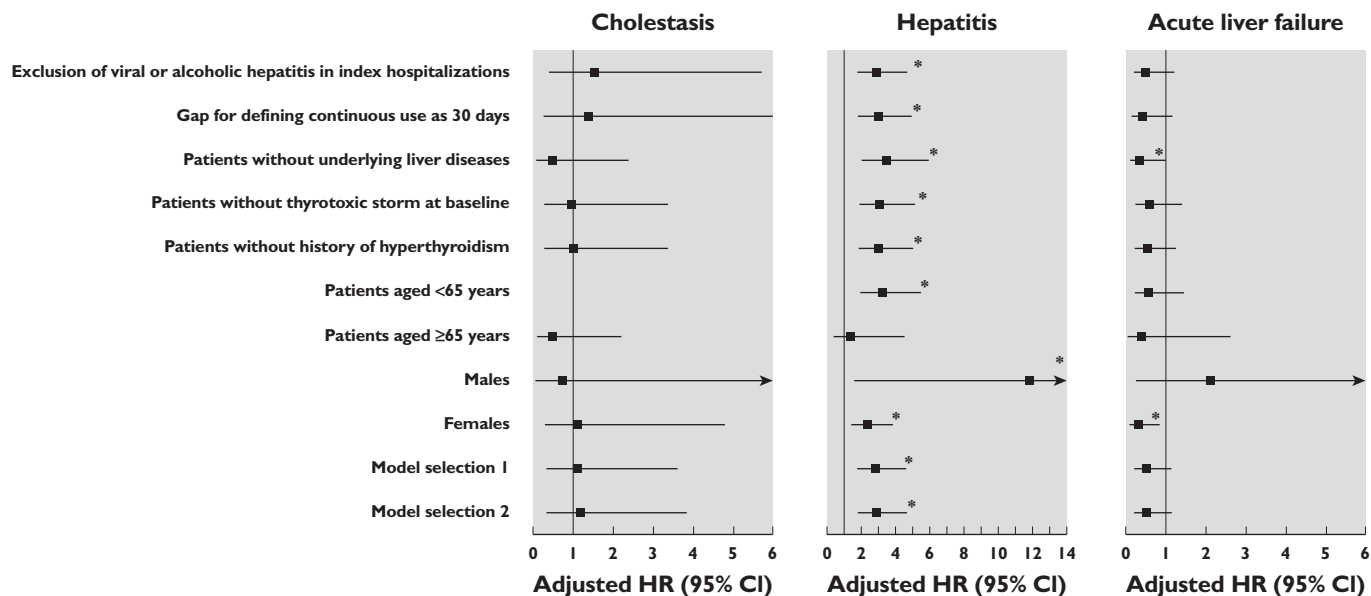
Figure 4

Risk of hepatotoxicity associated with MMI/CBM as compared with PTU in the sensitivity analyses. *P < 0.05. HR, hazard ratio; CI, confidence interval

20 mg day^{-1}). Notably, their observed daily doses of ATDs were much higher than our observed doses (median daily dose of PTU = 138 mg day^{-1}; MMI = 13 mg day^{-1}), which fall in the range of the suggested maintenance daily doses of ATDs [1]. Accordingly, the dose findings of Werner et al. [31] might not be generalizable to the present clinical setting.

After excluding patients who were diagnosed with underlying liver diseases during follow-up, PTU was found to increase statistically the acute liver failure risk as compared with MMI/CBM in our study, which is consistent with reports of severe hapatotoxicity related to PTU [3–6, 32]. Collectively, there are more than 30 case reports of PTU-related severe liver failure [4–6, 32] and accumulating death reports from PTU use [32]. Our data also provide additional evidence supporting severe hepatotoxicity resulting from PTU use.

Our results are probably generalizable to other ethnic groups based on the following reasons. First, the characteristics of our study cohort, such as the female : male ratio and age distribution are similar to patients with hyperthyroidism observed in other countries [33]. Second, case reports of ATD-related hepatotoxicity were observed in a diversity of populations [6, 7, 13] rather than limited to a Taiwanese population [34, 35]. Third, the examined hepatotoxicity was restricted to hospitalized events, which represent severe hepatotoxicity that is less prone to coding misclassification. Fourth, MMI was observed as the most frequently prescribed ATD, consistent with the ATD prescribing pattern in Western countries [36].

Our study has several unique attributes. This is the first population-based cohort study to quantify the incidence

of hepatotoxicity and delineate hepatotoxicity profiles by ATDs. Additionally, the confounding of hepatic comorbidities was minimized by exclusion of patients with underlying liver diseases. Furthermore, we analyzed the data before the warning of PTU-related hepatotoxicity by the FDA, avoiding the effect of the changed ATD prescribing on our findings. Moreover, our study was not threatened by immortal time bias [37] because we followed up all MMI/CBM or PTU users right after the first prescription, without a wait period during which ATD use was defined, and the hepatotoxicity consequently could not occur. Finally, the observed dose–response relationship further enhances the causal inference of hepatotoxic risks in relation to ATD use.

Several limitations merit emphasis. First, although the employed ICD-9-CM codes have been widely used to evaluate drug-induced liver injury [20, 24], error in hepatotoxicity ascertainment in the NHIRD is possible due to lack of rigorous performance evaluation of the codes in the Taiwanese population. To reduce coding error, we restricted the hepatotoxicity outcomes to the hospitalized events because each diagnosis coding made in inpatient settings is based on results of laboratory data and clinical findings, and is under strict regulation from the National Health Insurance Administration in Taiwan. We also explored a more complex operational definition of hepatotoxicity, in which hepatotoxic cases were defined as those who discontinued an ATD therapy or switched to a different ATD within 7 days after hospital admission for hepatotoxicity. Approximately 90% of the originally identified hepatotoxic cases met this definition and restriction of hepatotoxic events to these cases led to similar findings

(details in Table S3). These data seem to support the validity of our identified hepatotoxic cases associated with ATDs. Second, our findings might be biased from other possible causes of hepatotoxicity such as alcoholic hepatitis and hepatitis B virus (HBV) infection [38, 39]. We did exclude patients with alcoholic hepatitis or viral hepatitis measured both at the baseline and during the follow-up period. We further examined the extent to which alcoholic hepatitis or HBV infection contributed to the observed hepatotoxicity. Only one and three patients were observed to have such diseases for cholestasis and acute liver failure outcome, respectively. Exclusion of these patients from the analyses led to the consistent findings. On the other hand, people with HBV infection may not know about their HBV status, and these patients would not be identified from the database. However, the undiagnosed HBV is not likely to be disproportionately distributed between PTU and MMI/CBM users, potentially causing an underestimate of the relative risk of hepatotoxicity from ATD use. Third, confounding by indication bias might pose another threat because patients treated with MMI/CBM could have milder hyperthyroidism [32] and experience better outcomes than those treated with PTU. In this study, we adopted a new user design and analyzed over 90% of patients first diagnosed with hyperthyroidism as well as obtaining robust results while excluding patients with previous thyrotoxic storms. Additionally, the well-balanced characteristics between MMI/CBM and PTU users in Table 1 further precluded the possibility of such bias. Fourth, we excluded patients with underlying liver diseases during the follow-up period in the sensitivity analysis, which might be biased due to violation of the intention-to-treat principle. Nevertheless, a similar proportion of patients were excluded from both ATD treatments (5.5% in PTU and 5.0% in MMI/CBM users), and therefore the potential bias was minimized. Fifth, misclassification of MMI/CBM *vs.* PTU users could occur. However, it is believed to be non-differential and might bias our results towards to the null.

In conclusion, PTU and MMI/CBM exert different comparative hepatotoxicity risks. Our findings suggest that healthcare professionals should not only be vigilant for any symptom related to acute liver failure during PTU treatment, but also be cautious in MMI/CBM-induced hepatitis, especially for those receiving a higher dose of MMI/CBM. Notably, given that PTU is not currently recommended as the first choice of ATD treatment and an increasing population receiving MMI is expected, our observed increased risk of hepatitis by MMI/CBM warrants caution.

Authorship

All authors had access to the data and played a role in writing this manuscript.

Competing Interests

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1
Diagnosis codes of diseases or procedures in the exclusion criteria, medical comorbidities and individual drugs of comedications in potential confounders

Table S2
Full results from multivariate Cox proportional hazard analyses of hepatotoxicity associated with MMI/CBM compared with PTU

Table S3
Adjusted hazard ratios for risk of hepatotoxicity associated with MMI/CBM *vs.* PTU using an operational definition of hepatotoxicity as hepatotoxicity cases with discontinued ATD therapy or switch to another ATD within 7 days after hospital admission for hepatotoxic events