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Chinese herbal medicine reduces acute hepatitis exacerbation in patients with hepatitis B virus infection: A case-control study in Taiwan

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ABSTRACT

Objectives: Little information is available about the impact of Chinese herbal medicine (CHM) treatment on acute exacerbation of hepatitis. This study aimed to assess the risk of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma in HBV patients with and without CHM use.

Design and setting: This population-based case-control study used data from the Taiwan Longitudinal Health Insurance Database from 2000 to 2013. Newly diagnosed HBV patients had acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma as the case group, while another patients had no acute exacerbation of hepatitis and cirrhosis and hepatoma as the control group. To correct the differences in sociodemographic factors and Western medication use between the two groups, propensity score matching was used at a 1:1 ratio, and resulted in a comparison of 1306 and 805 patients per group, respectively.

Main outcome measures: Occurrence of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma.

Results: Overall rate of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma was 7.9% and 4.8%, respectively. Patients receiving CHM had a significantly lower risk of acute exacerbation of hepatitis (adjusted odds ratio [aOR] =0.20, 95% confidence interval [95%CI]: 0.13–0.31) and subsequent cirrhosis and hepatoma (aOR = 0.29, 95%CI: 0.18–0.49) than those not receiving CHM after adjusting for relevant covariates. However, no dose-dependent relationship was exhibited for either incidence of acute exacerbation of hepatitis and cirrhosis and hepatoma.

Conclusion: These findings highlight that the use of CHM was associated with a significantly reduced risk of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma in patients with HBV. Future research could further explore the benefit of CHM therapies for treatment of acute hepatitis exacerbation.

1. Introduction

Hepatitis B virus (HBV) infection is still a major worldwide health problem with an estimated 292 million hepatitis B surface antigen (HBsAg)-positive individuals chronically infected in 2016, which represents a global prevalence of 3.9%. [1] In Taiwan, the estimated prevalence of HBsAg-positive subjects was 13.7% (approximately 2.5 million people).[2] Chronic HBV infection can cause acute and chronic hepatitis and even lead to cirrhosis, hepatocellular carcinoma, and death. In addition, the occurrence of acute exacerbation during the course of chronic HBV infection is common and causes acceleration of disease progression.[3] Antiviral therapies, including interferon and nucleos(t)ide analogues, are widely recommended for treatment, and have been shown to reduce the acute exacerbation of chronic HBV infection

Abbreviations: ALT, alanine aminotransferase; aOR, adjusted odds ratio; ATC, anatomical therapeutic chemical; CAM, complementary and alternative medicine; CHM, Chinese herbal medicine; CI, confidence interval; HBeAg, Hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; LHID, Longitudinal Health Insurance Database; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; OR, odds ratio; PSM, propensity score matching; TCM, traditional Chinese medicine; TWD, Taiwan dollars; WHO, World Health Organization

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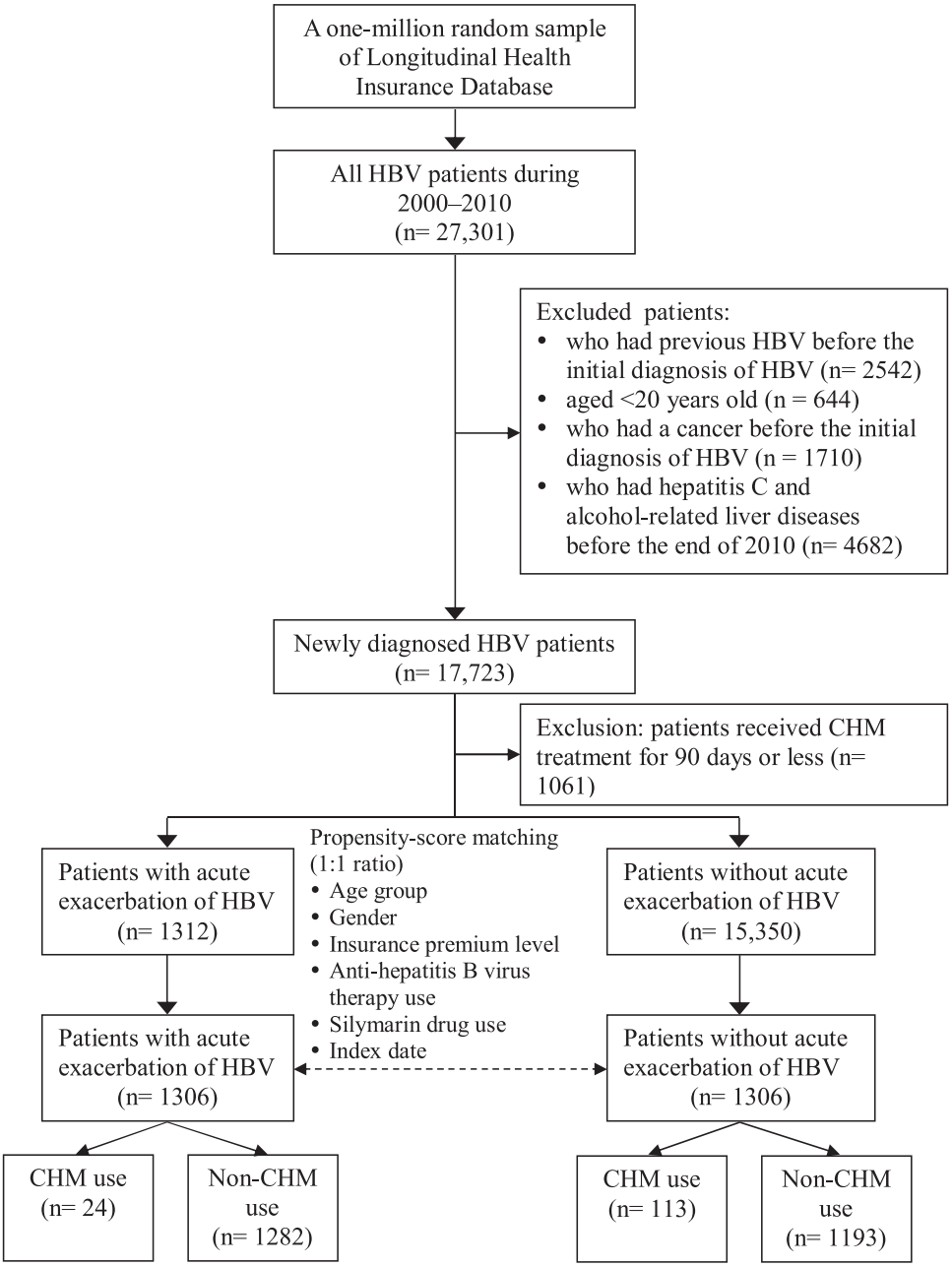

Fig. 1. Flow diagram of subjects selection for acute exacerbation of hepatitis. Abbreviation: CHM, Chinese herbal medicine; HBV, hepatitis B virus.

and delay disease progression.[4–6] Additionally, a meta-analysis study indicated that silymarin may have potential therapeutic effect in the treatment of chronic HBV infection.[7] Furthermore, the use of complementary and alternative medicine (CAM) for therapeutic purposes by chronic disease patients is also becoming more common.[8,9]

Traditional Chinese medicine (TCM) is a CAM that has been widely applied in treating chronic diseases in China and East Asian countries for thousands of years.[9] In Western countries, TCM has become increasingly accepted in recent years.[10] TCM has been reimbursed by the Taiwan's National Health Insurance (NHI) program since 1996. In addition, Chinese herbal medicine (CHM) is an important category of TCM that has been used for the treatment of liver diseases including chronic HBV infection.[11,12] In China, CHM accounted for 30–50% of the total medicine consumed for chronic HBV treatment.[13] In addition, approximately 27.6% of Taiwanese patients used CHM for treatment of chronic hepatitis.[14] Patients use CHM as a complementary or alternative treatment to anti-HBV drugs owing to its lower cost, fewer side effects, and/or a limited effect from Western medicine treatments.[12]

Previous literature reported that CHM alone and combined with Western medicine, may be an effective and safe therapeutic option for the treatment of chronic HBV infection.[9,11] However, to date, no study has evaluated the effect of CHM therapy on acute exacerbation of chronic HBV infection. Therefore, this study aimed to assess whether the addition of CHM affected the risk of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma in HBV patients.

2. Materials and methods

2.1. Data source

The NHI program in Taiwan was implemented in March 1995, and

covers nearly 99% of the 23 million population. This retrospective case-control study used the Longitudinal Health Insurance Database (LHID) with 1 million beneficiaries who were randomly selected from the Taiwan's National Health Insurance Research Database (NHIRD). No significant difference in age, gender or average insured payroll-related premiums existed between the LHID sample group and all NHIRD enrolees. All identification numbers of enrolees and medical institutions were encrypted, transformed, and maintained by Taiwan's National Health Research Institutes. Encrypted identifiers allowed for linkages across databases. Diagnostic codes were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coding system. In addition, the study protocol was approved by the Institutional Review Board of Taichung Veterans General Hospital (IRB No. CE13152B-4), and patient informed consent was not required for the retrospective study.

2.2. Study patients

In order to increase the accuracy of disease diagnosis, we identified 27,301 patients with HBV who had at least three outpatient visits or at least one inpatient admission of ICD-9-CM codes (070.2, 070.3 or V02.61) from 1 January 2000 to 31 December 2010. Patients less than 20 years of age, and those who had a previous diagnosis of HBV were excluded. We excluded patients who had a cancer (140–239) diagnosis before the initial diagnosis of HBV. In addition, those with a diagnosis of hepatitis C virus (070.41, 070.44, 070.51, 070.54, 070.7, and V02.62) and alcohol-related liver diseases (291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3) before the end of 2010 were also excluded. Then, after the initial diagnosis, all newly diagnosed HBV patients were followed for at least 3 years or until the occurrence of an acute HBV infection event. The occurrence of an acute HBV infection was defined as the first admission to the emergency department or inpatient admission for treatment of acute exacerbation of hepatitis during the follow-up period, which was identified from the LHID claims data. The index date was defined as the date of first diagnosis of acute hepatitis exacerbation. Of these, 1312 patients experienced acute exacerbation of hepatitis and were defined as the case group.

Control group was identified as 15,350 patients who did not have acute exacerbation of hepatitis. The index date for control group was defined as the date of first disease diagnosis. To reduce the differences in the characteristics between the case and control groups, a propensity score matching (PSM) was used at a 1:1 ratio, and 2612 patients were enrolled in this study (1306 patients per group). A flow diagram of study selection is shown in Fig. 1.

Besides, based on the previous literature [9] the occurrence of cirrhosis (571.2, 571.5, or 571.6) or hepatoma (155) was evaluated as the secondary endpoint. All HBV patients were followed for at least 3 years or until the occurrence of a cirrhosis or hepatoma event, of which 805 patients had a cirrhosis or hepatoma (case group). These cirrhosis and hepatoma events that occurred after the date of acute exacerbation of hepatitis were identified during the follow-up period. Control group was identified as 15,857 patients who did not have cirrhosis and hepatoma. In order to reduce the difference between the two groups, a PSM approach was performed at a 1:1 ratio, and 1610 patients were enrolled in this study (805 patients per group) (Fig. A.1 in Supplementary materials).

2.3. Chinese herbal medicine exposure

The primary independent variable of interest was patients' use of CHM for treating HBV infection. According to the NHI program guidelines, Chinese herbal prescriptions were only provided for outpatient care by TCM physicians.[15] The cumulative number of CHM treatment days was calculated as the total CHM treatment days within the first year after the patient's HBV diagnosis. CHM use was defined as patients who received CHM treatment for more than 90 days within a year after their HBV diagnosis, whereas those who never visited TCM physicians were defined as non−CHM use. However, in order to compare the effect of CHM treatment on acute exacerbation of hepatitis as well as cirrhosis and hepatoma between the case and control groups can be performed accurately, patients who treated CHM for 90 days or less were excluded.

2.4. Covariates

Patient's age at diagnosis with HBV infection (20–44, 45–64, and ≥65 years), gender, monthly insurance premium, urbanization level, comorbidities, antiviral therapies and silymarin use were included as covariates in the analysis.

The monthly insurance premium of an individual was determined by his/her work salary, and premiums were categorized into five groups (≥Taiwan dollars (TWD) 45,801, 28,801–45,800, 15,841–28,800, < 15,840, and dependents). The dependent group members did not have a fixed salary, such as students, housewives, and dependent on family members. In addition, the level of urbanization was categorized into three groups (urban, suburban, and rural) according to population density (people/km^2), medical resources, age, and education of the people in these areas.

The co-existing comorbidities of the HBV patients were determined by the following ICD-9-CM codes: diabetes mellitus (250), hypertension (401–405), hyperlipidaemia (272), heart failure (428), stroke (430–438), non-alcoholic fatty liver disease (571.8), chronic kidney disease (585), and thyroid disorders (240–242 and 244–246). In addition, several antiviral therapies including interferons (interferon-alfa and pegylated interferon-alfa) and nucleos(t)ide analogues (lamivudine, adefovir, entecavir, telbivudine, and tenofovir) have been approved for treating HBV infection.[16] These therapies were classified based on the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) system of medications (ATC codes L03AB04, L03AB05, L03AB07, L03AB08, L03AB09, J05AF05, J05AF07, J05AF08, J05AF10, and J05AF11). Silymarin (A05BA03), which was a common therapeutic modality for treatment of liver diseases[17] was also included in this study.

2.5. Statistical analysis

Differences in the distribution of characteristics between the case and control groups were examined using Chi-square or Fisher's exact tests for categorical variables, and student's *t*-test for continuous variables. In addition, in order to reduce selection bias and accurately measure the association between CHM use and risk of acute exacerbation of hepatitis and cirrhosis and hepatoma, we used a PSM approach to balance observed confounders between the two groups. Patients were matched using a multivariable logistic regression model that included age, gender, insurance premium, and use of anti-HBV therapies and silymarin, as well as index date.

Then, multivariable logistic regression analyses were performed to assess the association of CHM use with the risk of acute exacerbation of hepatitis and cirrhosis and hepatoma. In addition, we tested the association of the cumulative days of CHM use with risk of acute exacerbation and cirrhosis and hepatoma. Odds ratios (OR) with 95% confidence interval (95% CI) were calculated. The level of statistical significance was set at p less than 0.05. All statistical analyses were conducted using the SAS version 9.4 software (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline patient characteristics before and after matching

Baseline characteristics of patients before and after PSM for acute exacerbation of hepatitis and cirrhosis and hepatoma are shown in

Table 1
Characteristics of patients with hepatitis B virus before and after propensity score matching for acute exacerbation of hepatitis.

Characteristics	Before matching					After matching				
	Acute exacerbation (n = 1312)		No acute exacerbation (n = 15,350)		p	Acute exacerbation (n = 1306)		No acute exacerbation (n = 1306)		p
	n	(%)	n	(%)		n	(%)	n	(%)	
Age at diagnosed HBV, years					< 0.001					0.989
20–44	381	(29.0)	8796	(57.3)		381	(29.2)	381	(29.2)	
45–64	611	(46.6)	5184	(33.8)		609	(46.6)	606	(46.4)	
≥65	320	(24.4)	1370	(8.9)		316	(24.2)	319	(24.4)	
Mean (SD)	53.1	(15.2)	43.0	(14.3)	< 0.001	49.4	(17.0)	48.6	(15.9)	0.497
Gender					< 0.001					1.000
Female	381	(29.0)	6019	(39.2)		381	(29.2)	382	(29.2)	
Male	931	(71.0)	9331	(60.8)		925	(70.8)	924	(70.8)	
Monthly insurance premium (TWD)					< 0.001					0.995
≥45,801	82	(6.2)	1144	(7.4)		82	(6.3)	80	(6.1)	
28,801–45,800	199	(15.2)	2293	(14.9)		199	(15.2)	203	(15.5)	
15,841–28,800	586	(44.7)	5663	(36.9)		586	(44.9)	591	(45.3)	
< 15,840	218	(16.6)	2327	(15.2)		214	(16.4)	214	(16.4)	
Dependent	227	(17.3)	3923	(25.6)		225	(17.2)	218	(16.7)	
Urbanization level					0.154					0.328
Urban	818	(62.4)	9773	(63.7)		813	(62.3)	834	(63.8)	
Sub-urban	154	(11.7)	1945	(12.7)		153	(11.7)	164	(12.6)	
Rural	340	(25.9)	3632	(23.6)		340	(26.0)	308	(23.6)	
Comorbidity										
Diabetes mellitus	158	(12.0)	824	(5.4)	< 0.001	156	(11.9)	117	(9.0)	0.015
Hypertension	142	(10.8)	887	(5.8)	< 0.001	140	(10.7)	119	(9.1)	0.190
Hyperlipidaemia	33	(2.5)	786	(5.1)	< 0.001	33	(2.5)	59	(4.5)	0.008
Heart failure	8	(0.6)	39	(0.3)	0.029	8	(0.6)	4	(0.3)	0.387
Stroke	16	(1.2)	76	(0.5)	0.003	16	(1.2)	12	(0.9)	0.569
Nonalcoholic fatty liver disease	18	(1.4)	227	(1.5)	0.905	18	(1.4)	14	(1.1)	0.594
Chronic kidney disease	25	(1.9)	77	(0.5)	< 0.001	25	(1.9)	13	(1.0)	0.071
Thyroid disorders	6	(0.5)	124	(0.8)	0.192	6	(0.5)	8	(0.6)	0.790
Western medication use for HBV treatment										
Anti-HBV therapies	387	(29.5)	1026	(6.7)	< 0.001	381	(29.2)	377	(28.9)	0.897
Silymarin	866	(66.0)	7439	(48.5)	< 0.001j	860	(65.9)	874	(66.9)	0.590

CHM, Chinese herbal medicine; HBV, hepatitis B virus; SD, standard deviation; TWD, Taiwan dollars.
Data are presented as n (%) or mean ± SD.

Table 1 and Table A.1 in Supplementary materials. Among the 16,662 eligible patients with HBV infection, 1312 (7.9%) and 805 (4.8%) had occurrence of acute exacerbation of hepatitis and cirrhosis and hepatoma during the study period, respectively. Among these, 1.8% and 2.5% of patients with acute exacerbation of hepatitis and cirrhosis and hepatoma who used CHM in comparison with 9.7% and 9.4% of patients without acute exacerbation of hepatitis and cirrhosis and hepatoma used CHM ($p < 0.001$). Before PSM, a comparison of characteristics of the unmatched HBV patients showed significant differences in a number of variables including age at diagnosis with HBV infection, gender, monthly insurance premium, and Western medication use for HBV treatment. In addition, the percentage of certain comorbidities, such as diabetes mellitus, hypertension, heart failure, stroke, and chronic kidney disease were significantly higher among patients with acute exacerbation than in those without acute exacerbation.

After PSM, patients with acute exacerbation of hepatitis and cirrhosis and hepatoma still had a significantly lower proportion of CHM use compared with those without acute exacerbation of hepatitis (1.8% vs 8.6%, $p < 0.001$) and cirrhosis and hepatoma (2.5% vs 8.1%, $p < 0.001$), respectively. However, the patient's characteristics were well matched in both groups with respect to age, gender, monthly insurance premium, and urbanization level, as well as use of anti-HBV therapies and silymarin. Meanwhile, a greater percentage of diabetes mellitus (11.9% vs 9%, $p = 0.015$) and hyperlipidaemia (2.5% vs 4.5%, $p = 0.008$) was observed among patients with acute exacerbation than among those without acute exacerbation (Table 1).

3.2. Association of CHM use with acute exacerbation and cirrhosis and hepatoma

HBV patients with CHM use than those who did not had a significantly lower proportion of having acute exacerbation of hepatitis (17.5% vs 51.8%, $p < 0.001$) and cirrhosis and hepatoma (23.5% vs 51.5%, $p < 0.001$), respectively (Table 2).

Table 2
Occurrence of acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma in patients between with and without Chinese herbal medicine use after propensity score matching.

Variable	No. of patients	Acute exacerbation of hepatitis			No. of patients	Cirrhosis and hepatoma		
		n	(%)	p		n	(%)	p
CHM use				< 0.001				< 0.001
No	2475	1282	(51.8)		1525	785	(51.5)	
Yes	137	24	(17.5)		85	20	(23.5)	

CHM, Chinese herbal medicine.

Table 3
Multivariable analyses of risk for acute exacerbation of hepatitis and subsequent cirrhosis and hepatoma among patients with Chinese herbal medicine use compared with among those without Chinese herbal medicine use.

Variables	Acute exacerbation of hepatitis			Cirrhosis and hepatoma		
	OR	(95% CI)	p	OR	(95% CI)	p
CHM use						
No	1.00			1.00		
Yes	0.20	(0.13–0.31)	< 0.001	0.29	(0.18–0.49)	< 0.001
Age at diagnosed hepatitis B, years						
20–44	1.00			1.00		
45–64	0.92	(0.71–1.21)	0.957	0.95	(0.68–1.32)	0.992
≥65	0.84	(0.55–1.29)	0.440	0.90	(0.52–1.55)	0.709
Gender						
Female	1.00			1.00		
Male	1.01	(0.83–1.22)	0.951	0.99	(0.75–1.32)	0.967
Monthly insurance premium (TWD)						
≥45,801	1.04	(0.73–1.47)	0.901	1.08	(0.72–1.64)	0.788
28,801–45,800	1.00	(0.79–1.28)	0.872	1.04	(0.77–1.39)	0.994
15,841–28,800	1.00			1.00		
< 15,840	1.01	(0.81–1.27)	0.942	1.01	(0.75–1.35)	0.802
Dependent	1.05	(0.83–1.32)	0.797	1.06	(0.74–1.54)	0.860
Urbanization level						
Urban	1.00			1.00		
Sub-urban	0.96	(0.75–1.23)	0.413	1.23	(0.90–1.67)	0.432
Rural	1.13	(0.93–1.36)	0.171	1.19	(0.94–1.50)	0.597
Comorbidity						
Diabetes mellitus	1.46	(1.11–1.90)	0.006	1.16	(0.83–1.62)	0.396
Hypertension	1.12	(0.86–1.47)	0.403	0.78	(0.54–1.13)	0.184
Hyperlipidaemia	0.51	(0.33–0.80)	0.003	0.43	(0.24–0.77)	0.005
Heart failure	1.73	(0.51–5.79)	0.378	2.78	(0.28–27.11)	0.378
Stroke	1.36	(0.63–2.93)	0.430	0.21	(0.04–0.95)	0.043
Nonalcoholic fatty liver disease	1.23	(0.60–2.50)	0.578	0.46	(0.16–1.38)	0.168
Chronic kidney disease	1.91	(0.96–3.79)	0.064	2.33	(0.88–6.17)	0.088
Thyroid disorders	0.72	(0.24–2.12)	0.546	1.11	(0.26–4.72)	0.885
Western medication use for HBV treatment						
Anti-HBV therapies						
No	1.00			1.00		
Yes	1.00	(0.62–1.59)	0.985	0.94	(0.60–1.48)	0.796
Silymarin						
No	1.00			1.00		
Yes	0.93	(0.78–1.11)	0.411	0.96	(0.68–1.36)	0.839

CHM, Chinese herbal medicine; CI, confidence interval; HBV, hepatitis B virus; OR, odds ratio; TWD, Taiwan dollars.

Multivariable analyses showed that compared with non−CHM use patients, HBV patients with CHM use were associated with a significantly reduced risk of acute exacerbation of hepatitis (OR = 0.20; 95% CI: 0.13–0.31) and cirrhosis and hepatoma (OR = 0.29; 95% CI: 0.18–0.49) after adjustment for age, gender, monthly insurance premium, urbanization level, and comorbidities, as well as use of anti-HBV therapy and silymarin (Table 3). In addition, a significant increased risk of acute exacerbation was observed in patients with diabetes mellitus. However, a lower risk of acute exacerbation and cirrhosis and hepatoma was observed in those with hyperlipidaemia.

Otherwise, there was very little or no dose-dependent relationship between the cumulative number of CHM use days and risk of acute exacerbation and subsequent cirrhosis and hepatoma after adjustment (Table 4).

4. Discussion

This is the first population-based case-control study to evaluate the association between CHM use and the risk of acute exacerbation of hepatitis in HBV patients. We found that HBV patients who received CHM had a significantly lower risk of acute exacerbation of hepatitis and cirrhosis and hepatoma than those who did not, even after adjusting for sociodemographic characteristics, comorbid conditions, and Western medication use for HBV treatment. These results are similar to those of previous studies [9,15,19] and they confirm that CHM therapy has a potential effect on the reduction of acute exacerbation of hepatitis and

Table 4
Multivariable analyses of risk of acute exacerbation and subsequent cirrhosis and hepatoma associated with the cumulative use of Chinese herbal medicine among patients with hepatitis B virus.

	No. of patients with CHM use	Acute exacerbation of hepatitis		Multivariable model[a]			No. of patients with CHM use	Cirrhosis and hepatoma		Multivariable model[a]		
		n	(%)	Beta	(95% CI)	p		n	(%)	Beta	(95% CI)	p
No. days of CHM use	137	24	(17.5)	−0.005	(-0.010–-0.001)	0.043	85	20	(23.5)	−0.002	(-0.007–0.003)	0.416

CHM, Chinese herbal medicine; CI, confidence interval.
[a] Adjusted for age, gender, monthly insurance premium, urbanization level, all comorbidities, as well as use of anti-HBV therapy and silymarin as compared with patients without acute exacerbation.

cirrhosis and hepatoma.

Although current clinical guidelines do not recommend the use of CAM as a complementary treatment for patients with chronic HBV infection, CHM has been commonly applied worldwide for treating various diseases.[8,9,11,12] Previous studies reported that the overall prevalence of Taiwan's NHI covered TCM use in outpatient settings for treating liver-related diseases ranged from 23.5% of liver cancer patients[15] to 55.4% of those with liver cirrhosis.[18] The addition of CHM may relieve symptoms and reduce the progression of liver diseases.[9] However, a lower percentage of CHM use (5.3%) was observed in the present study. This difference may be due to a different definition of the CHM use or due to a different study samples that the majority of HBV patients were primarily treated with Western medicine. After that, the CHM might be mostly used after western medicine therapy. In addition, CHM treatment was advised in the management of complicated diseases with limited therapeutic options.[19] Before this study, very little evidence existed to support the use of CHM for the reduction of acute exacerbation of hepatitis among patients with HBV infection. [20]

The therapeutic efficacy and safety of CHM products for HBV treatment have been investigated by several clinical trials. Combination therapy with CHM and interferon or lamivudine significantly exhibited anti-HBV activities, and enhanced HBsAg and Hepatitis B e antigen (HBeAg) expression [21,22] accordingly decreased the rate of cirrhosis and hepatocellular carcinoma (HCC). CHM use may have similar beneficial effects on improving liver function, alleviating clinical symptoms, and preventing liver cancer recurrence and metastasis.[21,23]

A previous review reported that patients with a history of chronic HBV infection experienced spontaneous acute exacerbation with an annual incidence of 10–30%.[20] European Association for the Study of the Liver (EASL) 2017 guidelines revealed the incidence of cirrhosis of them ranges from 8 to 20% [5] and the annual risk of HCC in cirrhosis patients estimated to be 2–5%.[24] However, because this study excluded HBV patients with previous medical conditions, such as hepatitis C virus infection and alcohol-related liver diseases, as well as cancers at the initial diagnosis of HBV, the rate of acute exacerbation of hepatitis and cirrhosis and hepatoma may have been underestimated. We suggest that patients with complicated hepatitis may be associated with a higher risk of acute exacerbation and cirrhosis and hepatoma.

Additionally, HBV patients with several comorbidities, including diabetes mellitus, hypertension, stroke, and chronic kidney disease were associated with an increased risk of acute exacerbation of hepatitis. Patients with multiple comorbid conditions that compromise the immune system may have an increased risk of infection and adverse health outcomes.[9,25] Therefore, optimal treatment for HBV patients should take into account their comorbidities.

However, our results indicated that more cumulative days of CHM use was no further dose-dependent decrease in risk of acute exacerbation and cirrhosis and hepatoma. This implies that the beneficial effect was not apparent in HBV patients receiving higher doses of CHM. In addition, previous studies have shown that CHM alleviates the inflammatory response, improves liver function [13,26] and was related to decreased hepatic exacerbation. Other literature reported that certain CHM products containing aristolochic acid may increase the risk of hepatocellular carcinoma in HBV patients.[27] Thus, clinicians should use caution when prescribing CHM products in patients with HBV infection.

The main strengths of this study are the use of a nationally representative sample to select the HBV patients, and the application of PSM to minimize the effect of selection bias between the groups when evaluating the relationship. In addition, the multivariate analysis performed in this study considered the influence of receiving anti-HBV therapies and silymarin in the case and control groups to ensure the accuracy of our results. However, the development of clinical and basic research on the use of CHM in prevention of acute exacerbation of hepatitis needs further investigation.

Several limitations should be considered in the present study. First, data on laboratory testing, such as alanine aminotransferase (ALT), HBeAg, HBsAg, and HBV-DNA levels, were not available. Thus, we were unable to distinguish the phase of HBV infection of the patients. However, we performed PSM analysis to select appropriate matched controls and to reduce the confounding effects of CHM use on acute exacerbation of hepatitis and cirrhosis and hepatoma. Second, information on personal lifestyle variables, such as cigarette smoking, alcohol use, and diet were not collect. These unmeasured factors may partially influence the occurrence of acute exacerbation of hepatitis and cirrhosis and hepatoma. Third, our results may not be generalized to all HBV patients with progressive liver diseases and complex conditions. Future research to expand on our findings by investigating the risk of acute exacerbation of hepatitis and cirrhosis and hepatoma, specifically for patients with complicated liver disease who receive CHM, is needed.

5. Conclusions

This study revealed that there was a significant reduction in the occurrence of acute exacerbation of hepatitis and cirrhosis and hepatoma with the use of CHM when compared with the control group. Although the observational association of CHM use with acute exacerbation of hepatitis and cirrhosis and hepatoma might not be causal, these findings suggest that in addition to the Western medicine for treatment of HBV, CHM therapy may have a benefit for patients with HBV infection. The present results may serve as a reference for clinicians to treat HBV patients' conditions effectively, and they indicate that CHM therapy did have a positive effect for the prevention of acute exacerbation of hepatitis and cirrhosis and hepatoma.

Authors contributions

WLC, CCH and CIT conceived and designed the study. WLC and CCH interpreted the results and drafted the manuscript. CHL and CCH collected the data, analysis, and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2018.11.024.

References

1. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: A modelling study. *Lancet Gastroenterol Hepatol.* 2018;3:383–403.
2. Chen CL, Yang JY, Lin SF, et al. Slow decline of hepatitis B burden in general population: Results from a population-based survey and longitudinal follow-up study in Taiwan. *J Hepatol.* 2015;63:354–363.
3. Wu HL, Kao JH, Chen TC, et al. Serum cytokine/chemokine profiles in acute exacerbation of chronic hepatitis B: Clinical and mechanistic implications. *J Gastroenterol Hepatol.* 2014;29:1629–1636.
4. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology.* 2016;63:261–283.
5. European Association for the Study of the Liver, EASL. Clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67:370–398 2017.
6. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: A 2015 update. *Hepatol Int.* 2016;10:1–98.
7. Wei F, Liu SK, Liu XY, et al. Meta-analysis: Silymarin and its combination therapy for

the treatment of chronic hepatitis B. *Eur J Clin Microbiol Infect Dis.* 2013;32:657–669.
8. Metcalfe A, Williams J, McChesney J, Patten SB, Jetté N. Use of complementary and alternative medicine by those with a chronic disease and the general population–results of a national population based survey. *BMC Complement Altern Med.* 2010;10:58.
9. Tsai TY, Livneh H, Hung TH, Lin IH, Lu MC, Yeh CC. Associations between prescribed Chinese herbal medicine and risk of hepatocellular carcinoma in patients with chronic hepatitis B: A nationwide population-based cohort study. *BMJ Open.* 2017;7:e014571.
10. Dobos GJ, Tan L, Cohen MH, et al. Are national quality standards for traditional Chinese herbal medicine sufficient? Current governmental regulations for traditional Chinese herbal medicine in certain Western countries and China as the Eastern origin country. *Complement Ther Med.* 2005;13:183–190.
11. Wang G, Zhang L, Bonkovsky HL. Chinese medicine for treatment of chronic hepatitis B. *Chin J Integr Med.* 2012;18:253–255.
12. Zhao CQ, Zhou Y, Ping J, Xu LM. Traditional Chinese medicine for treatment of liver diseases: Progress, challenges and opportunities. *J Integr Med.* 2014;12:401–408.
13. McCulloch M, Broffman M, Gao J, Colford Jr JM. Chinese herbal medicine and interferon in the treatment of chronic hepatitis B: A meta-analysis of randomized, controlled trials. *Am J Public Health.* 2002;92:1619–1628.
14. Chen FP, Kung YY, Chen YC, et al. Frequency and pattern of Chinese herbal medicine prescriptions for chronic hepatitis in Taiwan. *J Ethnopharmacol.* 2008;117:84–91.
15. Ting CT, Kuo CJ, Hu HY, Lee YL, Tsai TH. Prescription frequency and patterns of Chinese herbal medicine for liver cancer patients in Taiwan: A cross-sectional analysis of the National Health Insurance Research Database. *BMC Complement Altern Med.* 2017;17:118.
16. Liaw YF. Impact of hepatitis B therapy on the long-term outcome of liver disease. *Liver Int.* 2011;31:117–121.
17. Féher J, Lengyel G. Silymarin in the prevention and treatment of liver diseases and primary liver cancer. *Curr Pharm Biotechnol.* 2012;13:210–217.
18. Chen YL, Lung CC, Huang JY, Nfor ON, Ko PC, Liaw YP. Association between traditional Chinese medicine use and liver cancer in patients with liver cirrhosis: A population-based study. *J Cancer Epidemiol Prev.* 2017;2:1.
19. Dizdar O, Bilgin E, Akin S, Kilickap S, Hayran M. Evaluation of complementary and alternative medicine trials registered in clinicaltrials.gOv database. *J Buon.* 2017;22:530–534.
20. Tsai WL, Sun WC, Cheng JS. Chronic hepatitis B with spontaneous severe acute exacerbation. *Int J Mol Sci.* 2015;16:28126–28145.
21. Qi FH, Wang ZX, Cai PP, et al. Traditional Chinese medicine and related active compounds: A review of their role on hepatitis B virus infection. *Drug Discov Ther.* 2013;7:212–224.
22. Zhang L, Wang G, Hou W, Li P, Dulin A, Bonkovsky HL. Contemporary clinical research of traditional Chinese medicines for chronic hepatitis B in China: An analytical review. *Hepatology.* 2010;51:690–698.
23. Hong M, Li S, Tan HY, Wang N, Tsao SW, Feng Y. Current status of herbal medicines in chronic liver disease therapy: The biological effects, molecular targets and future prospects. *Int J Mol Sci.* 2015;16:28705–28745.
24. Raffetti E, Fattovich G, Donato F. Incidence of hepatocellular carcinoma in untreated subjects with chronic hepatitis B: A systematic review and meta-analysis. *Liver Int.* 2016;36:1239–1251.
25. Mavilia MG, Molina M, Wu GY. The evolving nature of hepatic abscess: A review. *J Clin Transl Hepatol.* 2016;4:158–168.
26. Yang Y, Jiang HY, Shi Y, He JL, Su S, Chen Z. Chinese herbal medicine for carriers of the hepatitis B virus: An updated systematic review and meta-analysis. *Pharmazie.* 2014;69:723–730.
27. Chen CJ, Yang YH, Lin MH, et al. Herbal medicine containing aristolochic acid and the risk of hepatocellular carcinoma in patients with hepatitis B virus infection. *Int J Cancer.* 2018. https://doi.org/10.1002/ijc.31544.