

# Evaluation of the efficacy of Chinese herbal medicine and acupuncture for the prevention of mental disorders in interstitial cystitis patients

## A nationwide population-based study

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### Abstract

Traditional Chinese medicine (TCM) is commonly used for urinary symptoms in Eastern countries. Since there are few effective treatments available for patients with interstitial cystitis/bladder pain syndrome (IC/BPS), the psychological burden leads to increased healthcare-seeking behavior. Some patients may therefore seek TCM treatment for related urinary symptoms. Due to limited clinical research evaluating the effects of TCM on IC/BPS, we conducted a nationwide population-based cohort study to investigate the relationship between TCM and mental disorders among these patients. The IC/BPS cohort and its matched non-IC/BPS comparison cohort were recruited from the National Health Insurance (NHI) Research Database between 2000 and 2011. Patients with the use of Chinese herbal medicine (CHM) granules or acupuncture over 90 days per year were enrolled as the TCM users. Multivariable Cox proportional hazards models were used to evaluate the hazard ratio (HR) of mental disorders related to interstitial cystitis. The incidence of mental disorders in the 2 cohorts was assessed with Kaplan–Meier curves. A total of 1123 patients with IC/BPS and 4492 matched non-IC/BPS subjects were included in this study. The IC/BPS cohort demonstrated higher incidence rate of mental disorders than the cohort without IC/BPS (adjusted HR: 2.21, 95% confidence interval [CI]: 1.73–2.81). There was no statistically significant difference in the risk of mental disorders between IC/BPS patients with and without CHM granules or acupuncture treatment (adjusted HR: 0.99, 95% CI: 0.58–1.68). Our results indicated that CHM and acupuncture showed insignificant efficacy in the prevention of mental disorders in IC/BPS patients.

**Abbreviations:** CAD = coronary artery disease, CAM = complementary and alternative medicine, CHM = Chinese herbal medicine, CIs = confidence intervals, COPD = chronic obstructive pulmonary disease, HR = hazard ratio, IC/BPS = Interstitial cystitis/bladder pain syndrome, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, TCM = traditional Chinese medicine.

**Keywords:** anxiety, depression, insomnia, interstitial cystitis/bladder pain syndrome, National Health Insurance Research Database, traditional Chinese medicine

### 1. Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a diagnosis that applies to patients with chronic bladder discomfort in the absence of an identifiable etiology.<sup>[1]</sup> It primarily affects women and may be accompanied by voiding problems such as nocturia, urgency, and frequency.<sup>[2]</sup> In the absence of measurable

pathophysiological biomarkers, the diagnosis of IC/BPS is mainly based on patient-reported symptoms. Although IC/BPS is a rare condition affecting around 6.5% of the women in United States,<sup>[3]</sup> the treatment is relatively time-consuming and requires multiple therapeutic modalities.<sup>[4]</sup> Patients with IC/BPS often experience diminished health-related quality of life, which is

Editor: Yi Zhu.

This study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial Center (MOHW109-TDU-B-212-114004), MOST Clinical Trial Consortium for Stroke (MOST 108-2321-B-039-003-), Tseng-Lien Lin Foundation, and China Medical University (DMR-109-085 and CMU108-S-38), Taichung, Taiwan.

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Hung HH, Chen WC, Chen YH, Chiu LT, Chen HY. Evaluation of the efficacy of Chinese herbal medicine and acupuncture for the prevention of mental disorders in interstitial cystitis patients: a nationwide population-based study. *Medicine* 2020;99:30(e21422).

Received: 20 January 2020 / Received in final form: 2 June 2020 / Accepted: 24 June 2020

<http://dx.doi.org/10.1097/MD.00000000000021422>

associated with physical limitations, decreased vitality, increased sleep dysfunction, greater pain, and more problems related to sexual/social functions.<sup>[5–7]</sup> Previous studies have concluded that mental disorders such as anxiety and depression are common problems among women with IC/BPS.<sup>[8,9]</sup> Sleep disturbance is also a common comorbidity among patients with IC/BPS, since IC/BPS is a chronic pain condition that can exacerbate sleep disturbance and vice versa.<sup>[10,11]</sup>

Current management of IC/BPS consists of a stepwise approach involving therapeutic methods based on the severity and the features of patients' symptoms.<sup>[4]</sup> These methods include initial behavior modification, use of analgesics, physical therapy, and oral medications such as amitriptyline, pentosan polysulfate sodium, cimetidine, and antihistamines. In case of failure of the initial treatment approaches, invasive approaches such as bladder hydrodistention, intravesical instillation, intradetrusor injection, and sacral neuromodulation can be considered. Due to sparse data evaluating the efficacy of treatment approaches and poor understanding about the etiology of IC/BPS, no single approach has been proven to be helpful for all patients.<sup>[12,13]</sup>

Since very few effective treatments are available for IC/BPS, many patients seek complementary and alternative medicine (CAM) therapies.<sup>[14]</sup> Traditional Chinese medicine (TCM), including Chinese herbal medicine (CHM) and acupuncture, is a part of CAM that has evolved over thousands of years. Based on clinical presentations, TCM believes that the cause of IC/BPS lies mainly in the bladder and the kidneys. According to the TCM theory, the bladder's main function of transforming and excreting fluids depends on the kidney qi. Qi stagnation and other exacerbating factors including dampness and blood stasis might interfere with the physiological functions of the bladder and lead to urinary problems and bladder discomfort. The therapeutic principles of many herbal formulae are related to nourishment of the bladder and the kidneys, activation of qi and blood, and elimination of dampness. Some of the proven formulae could inhibit the micturition reflex and decrease the bladder sensation via spinal kappa-opioid receptors,<sup>[15]</sup> while some could alleviate the bladder overactivity via modulating the bladder receptors in animal models.<sup>[16]</sup> Acupuncture demonstrated positive effect on bladder volume, suppressed bladder contraction, and changed the firing properties of the micturition center.<sup>[17,18]</sup> Despite these positive effects on urinary symptoms, clinical research regarding the effects of TCM on IC/BPS is scarce. Previous case series were often limited by ambiguous enrollment criteria and short follow-up duration. We therefore conducted a nationwide cohort study to determine whether TCM treatment such as CHM and acupuncture decreases the risk of mental disorders in IC/BPS patients.

## 2. Material and methods

### 2.1. Data source

We conducted a population-based retrospective cohort study using insurance claim data from the Longitudinal Health Insurance Database (LHID2000). LHID is a sub-database from the Taiwan National Health Insurance program (NHI), covering approximately 99% of Taiwan citizens. LHID2000 contains the annual claims data of 1 million NHI enrollees randomly selected from the NHI Research Database. Diseases were coded in accordance with the International Classification of Diseases,

Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved by the Research Ethics Committee of China Medical University and Hospital in Taiwan (CMUH-104-REC2-115 (CR-4)).

### 2.2. Sampled participants

We selected patients aged >18 years old and were diagnosed with interstitial cystitis (ICD-9-CM 595.1) at least 3 times from January 1, 2000 to December 31, 2011 as the interstitial cystitis cohort. The index date of the interstitial cystitis cohort was set as the first date of interstitial cystitis diagnosis. Patient aged >18 years old without interstitial cystitis were randomly selected from the LHID as comparison cohort. Subjects in both cohorts with a history of mental disorders before the index date were excluded. To minimize baseline differences between the 2 cohorts, we performed 1:4 propensity score matching between the interstitial cystitis cohort and the comparison cohort on the basis of the following covariates: age, sex, index year, diabetes mellitus (ICD-9-CM 250), chronic kidney disease (ICD-9-CM 582, 583, 585, 586, and 588), coronary artery disease (CAD, ICD-9-CM 410–414), chronic obstructive pulmonary disease (COPD, ICD-9-CM 491, 492 and 496), cancer (ICD-9-CM 140–208), irritable bowel syndrome (ICD-9-CM 564.1), autoimmune diseases (ICD-9-CM 370.33, 710.0, 710.1, 710.2, 710.3, 710.4, 714, and 720), endometriosis (ICD-9-CM 617), pelvic inflammatory disease (ICD-9-CM 614.9), fibromyalgia (ICD-9-CM 729.0 and 729.1), amitriptyline use, cystitis use, occupation and insurance premium levels by logistic regression model. We further collected the TCM data of study patients during the follow-up period to explore the impact of TCM treatment on the study results. Despite various therapies in TCM, only the prescription records of CHM granules, acupuncture, and manipulative therapy are available in NHI database. We therefore included patients with the use of CHM granules or acupuncture over 90 days per year as the TCM users. Since IC/BPS is a chronic condition, subjects who received short-term use of CHM granules were excluded. And we have excluded subjects diagnosed with mental disorders before the use of CHM granules or acupuncture.

### 2.3. Main outcome measures

The outcome of this study was the diagnosis of mental disorders, which included depressive disorder (ICD-9-CM code 296.2, 296.3, 300.4, and 311), anxiety disorder (ICD-9-CM 300.0, 300.1, 300.2, 300.3, 300.5, 300.6, 300.7, 300.8, and 300.9), and insomnia (ICD-9-CM 307.41, 307.42, 780.52). To improve the accuracy of diagnosis, these mental disorders should be diagnosed by psychiatrist. All of the study patients were followed-up from the index year until being diagnosed with mental disorders, being censored because of the loss to follow-up, withdrawal from insurance, or at the end of 2011.

### 2.4. Statistical analysis

Distributions of demographic characteristics, TCM treatment and comorbidities between the interstitial cystitis cohort and the comparison cohort were analyzed using Chi-square test for categorized variables and *t* test for continuous variables. Multivariable Cox proportional hazards models were used to evaluate the hazard ratio (HR) and 95% confidence intervals

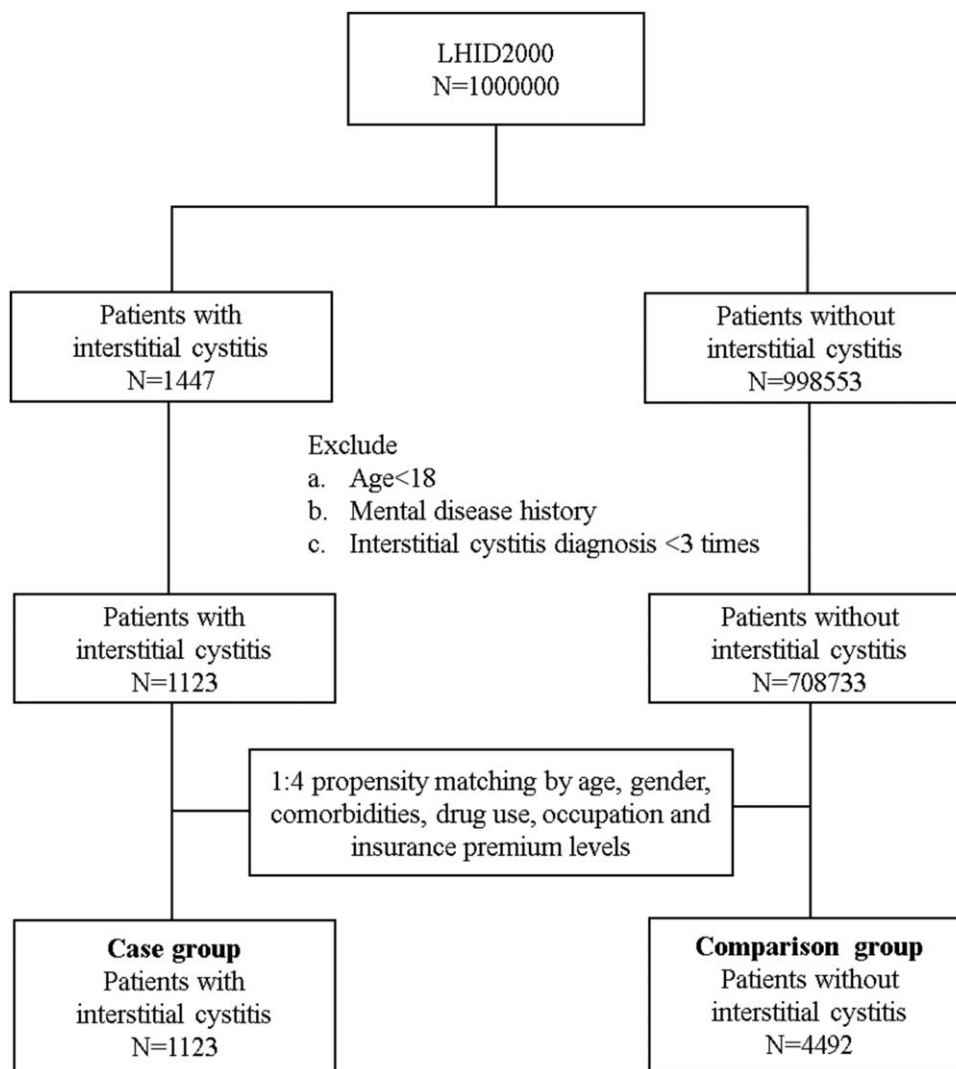


Figure 1. Flow chart for study participants.

(CIs) of mental disorders related to interstitial cystitis. The cumulative incidence of mental disorders in the interstitial cystitis cohort and the comparison cohort was estimated using the Kaplan–Meier method and the difference was evaluated using the log-rank test. Further analysis was performed to assess the effect of TCM treatment on the risk of mental disorders stratified by interstitial cystitis. All analyses were performed using SAS statistical software (version 9.4; SAS Institute, Inc., Cary, NC), and 2-tailed  $P < .05$  was considered statistically significant.

### 3. Results

A total of 1123 patients with IC/BPS and 4492 matched non-IC/BPS subjects were included in this study (Fig. 1). No significant differences were observed in age, sex, comorbidity, drug use, occupation, and insurance premium levels between the IC/BPS group and the non-IC/BPS group (Table 1). The average follow-up duration in the IC/BPS cohort (7.64 years) was shorter than that in the non-IC/BPS cohort (7.98 years) due to the shorter time-

to-events in the IC/BPS cohort. The mean age was 49.25 years and women accounted for 80.14% of the patients in the IC/BPS cohort.

A total of 329 subjects from both the cohorts were subsequently diagnosed with mental disorders (Table 2). The IC/BPS cohort demonstrated higher incidence rate of mental disorders than the non-IC/BPS cohort (adjusted hazard ratio [HR]: 2.21, 95% confidence interval [CI]: 1.73–2.81). Men appeared to have a lower risk of mental disorders than women (HR: 0.65, 95% CI: 0.47–0.89), but there was no significant difference after adjustment. The use of CHM or acupuncture was associated with higher incidence rate of mental disorders (adjusted HR: 2.15, 95% CI: 1.71–2.71). Mental disorders were significantly associated with coronary artery disease (CAD) (adjusted HR: 2.18, 95% CI: 1.23–3.84), cancer (adjusted HR: 1.53, 95% CI: 1.21–1.93), and fibromyalgia (adjusted HR: 1.68, 95% CI: 1.32–2.13). Mental disorders showed inverse association with endometriosis (adjusted HR: 0.59, 95% CI: 0.39–0.96). However, it might be difficult to draw a conclusion from this finding, since only 18 cases were involved.

**Table 1**  
**Baseline demographic characteristics in patients with and without interstitial cystitis.**

Characteristics	Interstitial cystitis		n	%	P-value
	No (n = 4492)	Yes (n = 1123)			
Age, y					.87
<40	1430	31.83	362	32.24	
40–65	1798	40.03	454	40.43	
≥65	1264	28.14	307	27.34	
Mean ± SD	49.67 ± 17.16		49.25 ± 16.92		.47
Gender					.77
Female	3617	80.52	900	80.14	
Male	875	19.48	223	19.86	
TCM					<.0001
No	3324	74.00	949	84.51	
Yes	1168	26.00	174	15.49	
Comorbidity					
Diabetes mellitus	731	16.27	194	17.28	.42
Chronic kidney disease	384	8.55	100	8.90	.70
Coronary artery disease	113	2.52	1090	97.06	.42
COPD	729	16.45	188	16.74	.81
Cancer	1934	43.25	478	42.56	.77
Irritable bowel syndrome	690	15.36	177	15.76	.74
Autoimmune diseases	413	9.19	98	8.73	.62
Endometriosis	293	6.52	72	6.41	.89
Pelvic inflammatory disease	1104	24.58	271	24.13	.75
Fibromyalgia	1378	30.68	352	31.34	.66
Drug use					
Amitriptyline	9	0.20	3	0.29	.66
Cystistat	0	0	2	0.18	.01
Occupation					.98
White collar	2198	48.93	553	49.24	
Blue collar	1962	43.68	487	43.37	
Others	332	7.39	83	7.39	
Insurance premium levels					.66
<15,000	1555	34.62	374	33.3	
15,000–30,000	2320	51.65	587	52.27	
≥30,000	617	13.73	162	14.43	
Follow-up duration, y	7.98 ± 3.76		7.64 ± 4.19		.01

Data shown as n (%) or mean ± SD.

TCM included the use of Chinese herbal medicine granules or acupuncture.

TCM = traditional Chinese medicine, COPD = chronic obstructive pulmonary disease using 1:4 propensity matching.

In the IC/BPS cohort, 106 subjects subsequently developed mental disorders (Table 3). There was no statistically significant difference in the risk of mental disorders between IC/BPS patients with and without CHM granules or acupuncture treatment (adjusted HR: 0.99, 95% CI: 0.58–1.68).

The Kaplan–Meier analysis showed a higher incidence rate of mental disorders in the IC/BPS cohort when compared with the non-IC/BPS cohort (log rank test,  $P < .0001$ ) (Fig. 2). In the IC/BPS cohort, there was no significant difference in the incidence rate of mental disorders between patients with and without CHM granules or acupuncture treatment (Fig. 3).

#### 4. Discussion

Anxiety and depression are stress-related mental disorders that are often correlated with chronic medical illness including IC/BPS.<sup>[9]</sup> Previous studies have revealed a higher prevalence of depression and anxiety in IC/BPS patients.<sup>[19,20]</sup> Chuang et al<sup>[21]</sup> also reported increased healthcare-seeking behavior for anxiety,

depression, and insomnia in patients with IC/BPS. These observations are consistent with our findings, which revealed that the IC/BPS cohort demonstrated a higher incidence rate of mental disorders than the non-IC/BPS cohort (adjusted HR: 2.21, 95% CI: 1.73–2.81).

Due to the difficulties in diagnosis and the lack of a therapeutic response, IC/BPS patients are often underdiagnosed and show poor adherence to treatment.<sup>[22]</sup> Therefore, some patients may seek TCM treatment due to its potential efficacy in related urinary symptoms. Some researches have revealed the effect of some of the Traditional Chinese blended herbal medicines on related lower urinary tract symptoms.<sup>[23,24]</sup> A previous study has also reported that acupuncture is an effective treatment method in IC/BPS patients.<sup>[17]</sup> Therefore, we assumed that the positive effects of CHM and acupuncture might alleviate the psychological burden of patients with IC/BPS and subsequently decrease the risk of mental disorders. However, there was no statistically significant difference in the risk of mental disorders between IC/BPS patients with and without

**Table 2**  
**Hazard ratios and 95% confidence intervals of mental disorders associated with interstitial cystitis.**

Variables	Mental disorders (n = 329)			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PY	IR		
Interstitial cystitis					
No	223	35863	6.22	1 (reference)	1 (reference)
Yes	106	8581	12.35	1.96 (1.55–2.58)***	2.21 (1.73–2.81)**
Age, y					
<40	119	15530	7.66	1 (reference)	1 (reference)
40–65	127	18232	6.97	0.51 (0.71–1.18)	0.75 (0.58–1.08)
≥65	83	10682	7.77	1.04 (0.79–1.38)	0.85 (0.61–1.19)
Gender					
Female	286	36128	7.92	1 (reference)	1 (reference)
Male	43	8317	5.17	0.65 (0.47–0.89)***	0.80 (0.57–1.13)
TCM					
No	193	33719	5.72	1 (reference)	1 (reference)
Yes	136	10726	12.68	2.25 (1.80–2.81)***	2.15 (1.71–2.71)***
Comorbidity (ref = non-comorbidity)					
Diabetes mellitus	53	6196	8.55	1.21 (0.90–1.63)	0.99 (0.72–1.37)
Chronic kidney disease	35	2905	12.05	1.77 (1.24–2.52)**	1.43 (0.99–2.06)
Coronary artery disease	14	821	17.05	2.47 (1.44–4.22)***	2.18 (1.23–3.84)**
COPD	58	5873	9.88	1.46 (1.10–1.94)**	1.18 (0.87–1.62)
Cancer	171	17017	10.05	1.81 (1.45–2.25)***	1.53 (1.21–1.93)**
Irritable bowel syndrome	59	5638	10.46	1.55 (1.17–2.06)**	1.22 (0.91–1.64)
Autoimmune diseases	37	3321	11.14	1.62 (1.12–2.29)**	1.24 (0.87–1.77)
Endometriosis	18	2675	6.73	0.91 (0.57–1.47)	0.59 (0.39–0.96)*
Pelvic inflammatory disease	101	9876	10.23	1.59 (1.25–2.01)***	1.29 (0.99–1.67)
Fibromyalgia	132	11452	11.53	2.03 (1.62–2.53)***	1.68 (1.32–2.13)***

TCM included the use of Chinese herbal medicine granules or acupuncture.

HR adjusted for age, gender, diabetes mellitus, chronic kidney disease, coronary artery disease, COPD, cancer, irritable bowel syndrome, autoimmune diseases, endometriosis, pelvic inflammatory disease, fibromyalgia, amitriptyline, cystistat, occupation and insurance premium levels.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 = person-years, PY = person-years.

\*  $P < .05$ .

\*\*  $P < .01$ .

\*\*\*  $P < .001$ .

CHM granules or acupuncture treatment (adjusted HR: 0.99, 95% CI: 0.58–1.68). Therefore, we speculated that despite evidence showing positive effects of TCM on urinary symptoms, either CHM granules or acupuncture failed to overcome the heavy psychological burdens resulting from IC/BPS or its comorbidities. Though there is a lack of solid evidence, multiple constituents in Traditional Chinese medicine formulae may lead to bladder mucosal irritation and diminish the efficacy of CHM granules in IC/BPS patients. To the best of our knowledge, this is the first study using a nationwide database to investigate the impact of CHM and acupuncture on psychological burdens among IC/BPS patients.

In the present study, mental disorders were significantly associated with CAD (adjusted HR: 2.18, 95% CI: 1.23–3.84). Previous studies have also suggested that CAD may increase the risk of developing mental disorders, mainly depressive, and anxiety states.<sup>[25,26]</sup> CAD is a chronic disease that affects patients' physical and psychological aspects of life. Patients with CAD may experience difficulties in activities of daily living and decreased quality of life, subsequently increasing the risk of mental illnesses.

In the present study, mental disorders were significantly associated cancer (adjusted HR: 1.53, 95% CI: 1.21–1.93). Cancer diagnosis generates a high sense of psychological distress and may lead to anxiety, depression, or both.<sup>[27]</sup> Besides, metastases and cancer-related pain have been associated with higher levels of depression.<sup>[28]</sup>

In the present study, mental disorders were inversely associated with endometriosis (adjusted HR: 0.59, 95% CI: 0.39–0.96). A previous study has also revealed the association between endometriosis and increased risk of anxiety, depression, and other psychiatric disorders.<sup>[29]</sup> However, we speculated that it might be difficult to draw a conclusion based on the findings of the present study due to limited number of cases.

In the present study, mental disorders were also significantly associated with fibromyalgia (adjusted HR: 1.68, 95% CI: 1.32–2.13). One reason for this association may be the fact that fibromyalgia is a chronic disorder characterized by persistent musculoskeletal pain. As reported by a previous study, there is a high prevalence of psychiatric comorbidities in patients with fibromyalgia.<sup>[30]</sup>

There are some limitations to our research. The accuracy of the diagnosis codes (ICD-9-CM) for IC/BPS is unclear due to variations in the diagnostic criteria and the time-consuming process for the exclusion of other possible causes. In the present study, we enrolled patients who had at least 3 times outpatient service claim with the diagnosis of IC/BPS and only the patients diagnosed by urologists or gynecologists were included. Another limitation is the difficulty in evaluating the severity and the disease duration of IC/BPS by using the ICD-9-CM coding alone. Patients who developed higher degree of related symptoms or complications may tend to use the health system more than those with minor illnesses<sup>[31]</sup> and TCM treatment is



**Table 3**  
**Hazard ratios and 95% confidence intervals of mental disorders associated with TCM stratified by interstitial cystitis.**

Variables	Mental disorders (n = 329)			Crude HR (95% CI)	Adjusted HR (95% CI)
	Event	PY	IR		
Interstitial cystitis	106				
TCM					
No	88	7184	12.25	1 (reference)	1 (reference)
Yes	18	1397	12.88	1.07 (0.64–1.78)	0.99 (0.58–1.68)
Age, y					
<40	45	2962	15.19	1 (reference)	1 (reference)
40–65	35	3572	9.80	0.65 (0.42–1.02)	0.54 (0.34–0.86)*
≥65	26	2045	12.71	0.84 (0.51–1.36)	0.58 (0.32–1.05)
Gender					
Female	91	6823	13.34	1 (reference)	1 (reference)
Male	15	1725	8.70	0.63 (0.36–1.09)	0.57 (0.32–1.03)
Comorbidity (ref = non-comorbidity)					
Diabetes mellitus	16	1227	13.04	1.06 (0.62–1.81)	1.01 (0.56–1.81)
Chronic kidney disease	12	607	19.77	1.67 (0.91–3.06)	1.61 (0.85–3.03)
Coronary artery disease	4	177	22.60	1.81 (0.66–4.93)	2.14 (0.71–2.20)
COPD	17	1156	14.71	1.23 (0.73–2.07)	1.25 (0.71–2.20)
Cancer	46	3223	14.27	1.27 (0.86–1.88)	1.18 (0.78–1.78)
Irritable bowel syndrome	20	1097	18.23	1.58 (0.97–2.59)	1.52 (0.92–2.53)
Autoimmune diseases	8	624	12.82	1.04 (0.50–2.15)	0.89 (0.42–1.87)
Endometriosis	5	491	10.18	0.81 (0.33–1.99)	0.58 (0.23–1.29)
Pelvic inflammatory disease	27	1807	14.94	1.27 (0.82–1.98)	1.04 (0.64–1.70)
Fibromyalgia	35	2213	15.82	1.42 (0.94–2.15)	1.39 (0.90–2.14)
Non-Interstitial cystitis	223				
TCM					
No	105	26534	3.96	1 (reference)	1 (reference)
Yes	118	9328	12.65	3.21 (2.47–4.18)***	2.76 (2.10–3.63)***
Age, y					
<40	74	12567	5.89	1 (reference)	1 (reference)
40–65	92	14659	6.28	1.08 (0.79–1.46)	0.87 (0.63–1.20)
≥65	57	8636	6.60	1.17 (0.83–1.65)	1.01 (0.67–1.53)
Gender					
Female	195	29304	6.65	1 (reference)	1 (reference)
Male	28	6559	4.27	0.64 (0.43–0.96)*	0.95 (0.62–1.45)
Comorbidity (ref = non-comorbidity)					
Diabetes mellitus	37	4968	7.45	1.28 (0.90–1.82)	0.99 (0.67–1.45)
Chronic kidney disease	23	2298	10.01	1.79 (1.16–2.76)**	1.40 (0.89–2.20)
Coronary artery disease	10	643	15.55	2.75 (1.46–5.20)**	2.27 (1.17–4.42)***
COPD	41	4716	8.69	1.57 (1.12–2.21)**	1.16 (0.80–1.68)
Cancer	125	13793	9.06	2.14 (1.64–2.80)***	1.68 (1.26–2.24)**
Irritable bowel syndrome	39	4540	8.59	1.53 (1.08–2.17)*	1.06 (0.74–1.53)
Autoimmune diseases	29	2696	10.76	1.93 (1.30–2.86)***	1.35 (0.89–2.03)
Endometriosis	13	2183	5.96	0.97 (0.55–1.70)	0.58 (0.32–1.04)
Pelvic inflammatory disease	74	8068	9.17	1.76 (1.33–2.33)***	1.45 (1.07–1.98)*
Fibromyalgia	97	9238	10.50	2.37 (1.81–3.10)***	1.74 (1.30–2.32)***

TCM included the use of Chinese herbal medicine granules or acupuncture.

HR adjusted for age, gender, diabetes mellitus, chronic kidney disease, coronary artery disease, COPD, cancer, irritable bowel syndrome, autoimmune diseases, endometriosis, pelvic inflammatory disease, fibromyalgia, amitriptyline, cystistat, occupation, and insurance premium levels.

CI = confidence interval, HR = hazard ratio, IR = incidence rate, per 1000 = person-years, PY = person-years.

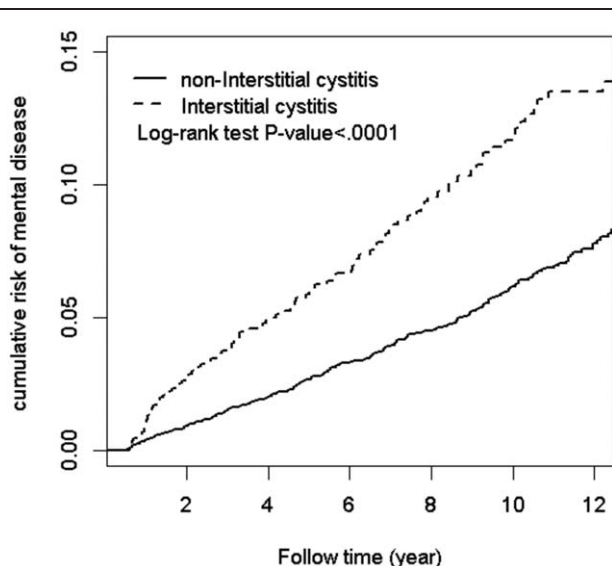
\*  $P < .05$ .

\*\*  $P < .01$ .

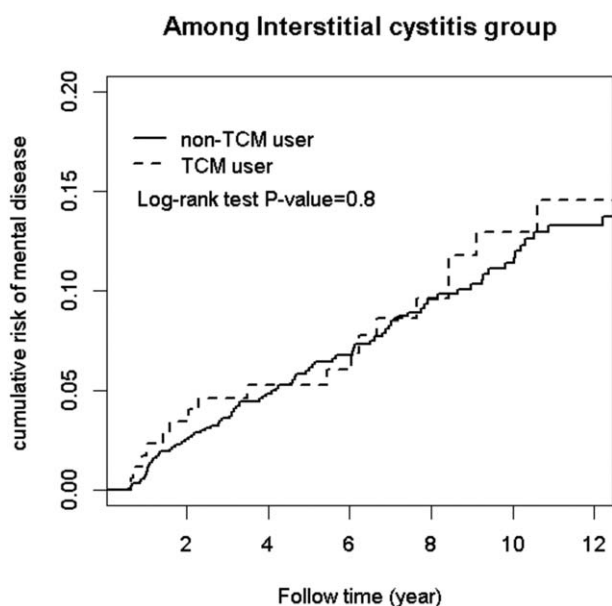
\*\*\*  $P < .001$ .

one of the possible choices. In the present study, we matched several covariates such as age, sex, and comorbidity. However, we still have to interpret the outcome of this study carefully, since the severity of IC/BPS may also influence the psychological burden in IC/BPS patients. Since only the prescription records of CHM granules and acupuncture are available in NHI database,

selection bias may occur during identification of the TCM users. Due to the nature of multiple herb combinations, variations in the prescription and frequent dosage adjustment, there are difficulties to launch a subgroup analysis among TCM users. Other possible confounding factors related to mental disorders such as lifestyle, marital status, obesity, alcohol, smoking, and



**Figure 2.** The estimated cumulative incidence of mental disorders between the cohort and control cohort by Kaplan–Meier analysis.



**Figure 3.** The estimated cumulative incidence of mental disorders between TCM users and non-TCM users by Kaplan–Meier analysis. CHM=Chinese herbal medicine.

family history of mental disease were not available in the NHI program database.

## 5. Conclusions

The results of this large population-based and long-term follow-up study demonstrated that Chinese herbal medicine and acupuncture treatment showed insignificant efficacy in the prevention of mental disorders in IC/BPS patients. Further prospective studies are required to validate the findings of this study.

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