

Bladder pain syndrome/interstitial cystitis is associated with asthma: A case-control study

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Objective: Although asthma and bladder pain syndrome/interstitial cystitis (BPS/IC) are considered to share similar pathophysiological pathways, the relationship between asthma and BPS/IC is uncertain. This case-control study aimed to investigate the relationship between prior asthma and BPS/IC using a large database in Taiwan.

Materials and methods: This study used data from the Taiwan Longitudinal Health Insurance Database 2005. We identified 500 female patients with BPS/IC as cases and 500 propensity score-matched females without BPS/IC as controls. We conducted logistic regressions to estimate the odds ratio (OR) and 95% confidence interval (CI) for prior asthma between cases and controls.

Results: Results indicated that 143 (14.30%) of the total sampled patients had received a prior diagnosis of asthma. Moreover, prior asthma was found in 86 (17.20%) cases and 57 (11.40%) controls. The OR of prior asthma for cases was 1.61 (95%CI: 1.13-2.32) compared to propensity score-matched controls. Additionally, the ORs of prior asthma for females with BPS/IC aged 18-59 and ≥ 60 years were 1.72 (95%CI: 1.11-2.69) and 1.40 (95%CI: 0.74-2.62), respectively, compared to controls.

Conclusions: We concluded that prior asthma was significantly associated with BPS/IC in a female Taiwanese population.

KEYWORDS

allergy, asthma, bladder, bladder pain syndrome, interstitial cystitis

1 | INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic urological condition which frequently occurs in female populations.¹ Suprapubic pain, pelvic pain, urinary urgency, and urinary frequency are all common symptoms in patients with BPS/IC.^{2,3} To date, even though the actual pathophysiology and risk factors for BPS/IC still remain

unclear, this discomforting condition is considered to be associated with multifactorial etiologies.⁴ Recently, growing evidence from laboratory and clinical studies has indicated that mast cells may play an important role in BPS/IC development.^{5,6} They observed that patients with BPS/IC had abnormal mast cell activation and histamine release which were similar to allergic diseases.⁵⁻⁷ Therefore, a few studies postulated that BPS/IC is an allergic disease of the urological system, and some research further revealed that this disease is associated with other allergic diseases.⁸⁻¹¹

Asthma is a complex immunologic and inflammatory disease which is characterized by bronchial hyperresponsiveness and

Hereng-Ching Lin and Li-Ting Kao have equal contributions to this study.

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airflow obstruction, resulting in intermittent dyspnea, coughing, chest tightness, wheezing, etc.^{12,13} This allergic disease is recognized as a multifactorial disease and some pathogeneses, including inheritance, environmental exposure, and immunization, were found to be etiologically involved in asthma.^{12,14} Nowadays, increasing numbers of studies have demonstrated that mast cells and mast cell-produced mediators are strongly implicated in the pathogenesis and development of asthma.^{15–17} The immunologic mechanisms of asthma and many other allergic diseases are similar.^{16–19} Thus, several recent studies explored the relationship between asthma and allergic diseases, such as allergic rhinitis, chronic sinusitis, and atopic dermatitis.^{18,19}

Nevertheless, although both asthma and BPS/IC are considered to be allergic diseases and share analogous pathophysiological pathways, to date, very few studies have attempted to explore the association between these two diseases. Most of the prior literature merely showed that BPS/IC was frequently accompanied by allergies.^{10,20–24} Only three previous Western studies mentioned the association between asthma and BPS/IC.^{22–24} One American research team found that BPS/IC was significantly associated with asthma in a female population.²² Two early studies in the 1990s revealed that patients with BPS/IC had a high prevalence of asthma.^{23,24} However, the causal relationship between asthma and BPS/IC in the early studies was uncertain. The actual association between these two diseases in Asian populations is still unknown. Consequently, the aim of this case-control study was to find the relationship between prior asthma and BPS/IC using a large database in Taiwan.

2 | METHODS

2.1 | Database

This case-control study used data from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The LHID2005 consists of de-identified secondary data on medical records, including inpatient and outpatient claims as well as registry data for one million enrollees randomly selected from the 2005 Registry of Beneficiaries ($n=25.68$ million) of the Taiwanese National Health Insurance (NHI) program. The NHI program has provided affordable and comprehensive health services for almost all Taiwanese residents since 1995. The LHID2005 sample was demonstrated to be representative of the general Taiwanese population, and this database is released to investigators in Taiwan for academic purposes. Additionally, this study was exempted from full review by the Taipei Medical University Institutional Review Board (TMU-JIRB N201709007).

2.2 | Sample selection

This population-based study was designed to include cases and controls. To select cases for this study, we first defined 1233 female patients with a first-time diagnosis of BPS/IC (ICD-9-CM code 595.1, chronic interstitial cystitis) in ambulatory care visits from January 1, 2004 to December 31, 2013. The date on which the cases received their first-time BPS/IC diagnosis was identified as the index date. We then excluded 283 patients aged <18 years in order to limit the study to the adult population. Furthermore, we excluded 450 patients who had only one diagnosis of BPS/IC in ambulatory care claims during the study period in order to increase the diagnostic validity. Finally, 500 female patients with BPS/IC were recruited as cases in this study.

To select controls in this study, we initially excluded males and those subjects with any records of BPS/IC in the LHID2005. We then selected 500 controls (one control per patient with BPS/IC) from the remaining beneficiaries of the LHID2005 using a propensity score-matching methodology. Propensity scores are frequently used to balance sociodemographic characteristics and the health status that are unequally distributed between cases and controls at the baseline. This study calculated a propensity score for each sample subject. In addition, the available sociodemographic characteristics and potential comorbidities were considered in a multivariable logistic regression model to evaluate the odds of being diagnosed with BPS/IC that was associated with their health status on these variables. In this study, the controls were randomly selected by matching patients with BPS/IC in terms of propensity scores and the year of the index date. As for the controls, the date of their first ambulatory care visit during that matched year was identified as the index date.

2.3 | Exposure measurement

In this study, we attempted to estimate the odds of prior asthma in females with BPS/IC compared to those females without BPS/IC. Therefore, we identified asthma cases based on ICD-9-CM codes 493, 493.0, 493.1, and 493.9. In order to increase the accuracy of the asthma diagnosis, we only included those patients who have ever received medications, such as steroid, bronchodilators, or anticholinergics in this study. In addition, we only selected those patients who had received diagnoses of asthma prior to the index date.

2.4 | Statistical analysis

This study used the SAS statistical package (SAS System for Windows, vers. 9.4, SAS Institute, Cary, NC) for data analysis.

An independent *t*-test was used to compare differences in patients' age between cases and controls. Pearson χ^2 tests were conducted to compare differences between cases and controls in terms of monthly income (< NT\$15 841, 15 841-25 000, and $\geq$ 25 001), geographic location (northern, central, eastern, and southern Taiwan), urbanization level (five levels, with one being the most urbanized and five being the least), diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, irritable bowel syndrome, fibromyalgia, endometriosis, chronic fatigue syndrome, tobacco use disorder, and alcohol abuse. We then performed logistic regressions to investigate the association of BPS/IC with prior asthma and displayed the odds ratios (ORs) along with 95% confidence intervals (CIs). A two-sided *P* value of <0.05 was used to evaluate the statistical significance in this study.

3 | RESULTS

Table 1 presents distributions of demographic characteristics and comorbidities among the cases and controls in this study. Of the 1000 total patients (500 cases and 500 controls), the mean age was 48.4 years with a standard deviation of 16.1 years. In addition, the mean ages of the cases and controls were 49.4 ± 15.5 and 47.4 ± 16.7 years, respectively ($P = 0.062$). After matching for propensity scores, the two groups exhibited no differences in monthly income ($P = 0.562$), geographic location ($P > 0.999$), urbanization level ($P = 0.922$), diabetes ($P = 0.808$), hypertension ($P = 0.178$), coronary heart disease ($P > 0.999$), obesity ($P = 0.329$), hyperlipidemia ($P > 0.999$), irritable bowel syndrome ($P > 0.999$), fibromyalgia ($P > 0.999$), endometriosis ($P > 0.999$), chronic fatigue syndrome

TABLE 1 Demographic characteristics of patients with bladder pain syndrome/interstitial cystitis (BPS/IC) and controls ($N = 1000$)

Variable	Patients with BPS/IC ($n = 500$)		Controls ($n = 500$)		<i>P</i> value
	Total no.	%	Total no.	%	
Age, mean (SD)	49.4 (15.5)		47.4 (16.7)		0.062
Monthly income ^a					0.562
$\leq$ NT\$15 840	206	41.2	214	42.8	
NT\$15 841-25 000	188	37.6	172	34.4	
$\geq$ NT\$25 001	106	21.2	114	22.8	
Geographic region					>0.999
Northern	291	58.2	291	58.2	
Central	105	21.0	105	21.0	
South	95	19.0	95	19.0	
Eastern	9	1.8	9	1.8	
Urbanization level					0.922
1 (most urbanized)	192	38.4	179	35.8	
2	132	26.4	134	26.8	
3	69	13.8	74	14.8	
4	62	12.4	63	12.6	
5 (least urbanized)	45	9.0	50	10.0	
Diabetes	95	19.0	92	18.4	0.808
Hypertension	174	34.8	154	30.8	0.178
Coronary heart disease	107	21.4	107	21.4	>0.999
Obesity	11	2.2	16	3.2	0.329
Hyperlipidemia	162	32.4	162	32.4	>0.999
Irritable bowel syndrome	116	23.2	116	23.2	>0.999
Fibromyalgia	254	50.8	254	50.8	>0.999
Endometriosis	48	9.6	48	9.6	>0.999
Chronic fatigue syndrome	21	4.2	21	4.2	>0.999
Tobacco use disorder	4	0.8	5	1.0	0.738
Alcohol abuse	4	0.8	2	0.4	0.413

^aThe average exchange rate in 2017 was US\$1.00 $\approx$ New Taiwan (NT)\$37.77.

TABLE 2 Prevalence, odds ratios (ORs), and 95% confidence intervals (CIs) for asthma among sampled patients

Presence of prior asthma	Total (N = 1000)		Patients with bladder pain syndrome/interstitial cystitis (n = 500)		Controls (n = 500)	
	n, %		n, %		n, %	
Yes	143	14.30	86	17.20	57	11.40
OR (95%CI)	--		1.61** (1.13-2.32)		1.00	

** $P < 0.01$.

($P > 0.999$), tobacco use disorder ($P = 0.738$), or alcohol abuse ($P = 0.413$).

The prevalences of prior asthma between cases and controls are displayed in Table 2. Results indicated that 143 (14.30%) of the total sampled patients had asthma before the index date. In addition, a prior diagnosis of asthma was found in 86 (17.20%) cases and 57 (11.40%) controls. Table 2 also reveals the OR along with the 95%CI for previous asthma among sampled patients. The logistic regression showed that cases were more likely to have asthma (OR: 1.61, 95%CI: 1.13-2.32) than were the propensity score-matched controls.

Table 3 further presents the ORs of prior asthma between controls and cases classified by age group. It shows that ORs of prior asthma for cases aged 18-59 years and ≥ 60 years were 1.72 (95%CI: 1.11-2.69) and 1.40 (95%CI: 0.74-2.62), respectively, compared to the controls.

4 | DISCUSSION

This case-control study found that females with BPS/IC were 1.61-times more likely to have been diagnosed with asthma than were the propensity score-matched controls without BPS/IC. In addition, females with BPS/IC aged 18-60 years had significantly higher odds of prior asthma than those controls without BPS/IC. To date, to the best of our knowledge, only a few studies have mentioned the issue regarding the association between asthma and BPS/IC, although these two diseases supposedly share similar pathological mechanisms.

Some observations in previous studies are consistent with our research, which found an increased odds of prior asthma for patients with BPS/IC compared to those patients without BPS/IC. For instance, a case-control study in the United States recruited 313 females with BPS/IC as cases and 313 females without BPS/IC as controls.²² That study found that cases were 2.1-times more likely to have been diagnosed with asthma (identified by self-reported physician diagnoses) than the controls.²² One early Western study which involved 565 patients with BPS/IC and 171 controls also found that asthma was observed in 8.2% of cases and 4.8% of controls.²³ Another Western questionnaire study in the 1990s which included 2405 patients with BPS/IC found that 10% of the sampled patients had asthma.²⁴ Even though these three prior studies were performed using Western populations and two early studies provided no information regarding the statistical association between asthma and BPS/IC, the elevated prevalences of asthma in patients with BPS/IC in those studies were similar to the findings in our research.

The positive association between prior asthma and BPS/IC might be related to mast cell abnormalities.⁶ Mast cells are recognized to be multifunctional immune cells involved in allergic and late-phase reactions.⁵ They are able to release inflammatory mediators, such as histamine, cytokines, and chemotactic factors, while they are triggered by an allergen that binds to immunoglobulin (Ig)E attached to their FcεRI receptors.²⁵ In patients with asthma, inhalation of an aeroallergen into the respiratory tract may lead to mast cell degranulation, inflammation, elevated vascular permeability, contraction of smooth muscles, and increased mucous

TABLE 3 Prevalence, odds ratios (ORs), and 95% confidence intervals (CIs) for asthma among sampled patients according to age group

Presence of prior asthma	18-59 years old (n = 759)		≥ 60 years old (n = 241)	
	Patients with bladder pain syndrome/interstitial cystitis (n = 376)		Patients with bladder pain syndrome/interstitial cystitis (n = 124)	
	n, %	Controls (n = 383)	n, %	Controls (n = 117)
Yes	57 (15.16)	36 (9.40)	29 (23.39)	21 (17.95)
OR (95%CI)	1.72* (1.11-2.69)	1.00	1.40 (0.74-2.62)	1.00

* $P < 0.05$.

secretion, which further contribute to airway obstruction.^{15,26} Accordingly, mast cells play an essential role in the pathophysiology of asthma.

As for BPS/IC, the actual pathogenesis is still unclear. Urothelial and epithelial dysfunction, mast cell abnormalities, infections, autoimmunity, genetics, etc. are all potential etiologies for this disease.⁴ Recently, increasing biological evidence has highlighted the importance of mast cells following histamine release.^{5,6} It was observed that patients with BPS/IC had an increased mast cell number, mast cell activation, and levels of histamine, or its metabolites.^{27–31} For example, some studies found an increased number of mast cells in the urothelium/submucosa and detrusor of the bladder in patients with BPS/IC.²⁷ Other research also revealed that patients with BPS/IC had an elevated number of mast cells, about 80% of which were activated.²⁸ Additionally, some studies showed that patients with BPS/IC had increased levels of histamine in the bladder wall, elevated methylhistamine (a histamine metabolite) in urine, and a high urine level of tryptase (a specific human mast cell proteinase enzyme).^{29–31} Thus, increasing numbers of studies indicated that BPS/IC is an allergic disease of the urological system.^{8–11} It is plausible that asthma would be associated with BPS/IC, because these two diseases may share similar immune mechanisms regarding mast cells.

However, this study failed to observe a statistical relationship between prior asthma and BPS/IC in elderly patients (≥ 60 years old) (OR: 1.40, 95%CI: 0.74–2.62), even though the difference in prevalences of asthma between cases and controls was relatively large (prior asthma was found in 23.39% of cases and 17.95% of controls). This inconsistent finding might have been due to the small sample size of the elderly population ($n = 241$) in this study. A small sample size of the study population may have contributed to an insufficient statistical power and further have affected the actual connection between asthma and BPS/IC.

A unique strength of this case-control study is the use of a nationwide and representative database in Taiwan with a propensity score-matching design. These factors could avoid a selection bias which commonly occurs in observational studies. Second, this study used medical records to identify the BPS/IC diagnosis and asthma diagnosis rather than depending on patients' recollection. This study strategy could eliminate recall bias that often occurs in case-control studies. Furthermore, this study used the LHID2005 which is representative of the entire Taiwanese population. Consequently, the homogeneity of the selected patients may exempt this study from confounding by ethnicity/race.

However, several limitations still need to be considered. First, the LHID2005 used in this case-control study provides no information regarding patients' lifestyle or individual information, including cigarette smoking, drug

abuse, family history, pollutants, allergen contact, etc. These unmeasured factors might potentially confound the association between prior asthma and BPS/IC. Second, some lab data and spirometry records are not available in LHID2005. Therefore, we could not evaluate the potential influences of those factors. Finally, the database used in this study might not contain all patients with BPS/IC. Several patients with mild symptoms of BPS/IC might not immediately seek medical services covered by the NHI program, because they might feel embarrassed or consider the relevant therapies unnecessary.

In conclusion, this case-control study found that prior asthma was significantly associated with BPS/IC in a Taiwanese female population. Consequently, we suggest that physicians should be alert and suspect BPS/IC with relevant clinical symptoms in patients with a medical history of asthma. In addition, we recommend that physicians should provide instructions to female patients with asthma and advise them to look for medical services as soon as possible if they have urological symptoms. Nevertheless, further large epidemiologic studies are still required to demonstrate the actual association between asthma and BPS/IC in different countries.

CONFLICTS OF INTEREST

None of the authors has any competing interests to disclose.

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