Received: 22 November 2016 | Accepted: 10 November 2017
DOI: 10.1002/nau.23462

ORIGINAL CLINICAL ARTICLE

WILEY Neurourology Urodynamics ICS SUFU

Endometriosis increased the risk of bladder pain syndrome/interstitial cystitis: A population-based study

Chia-Chang Wu MD, PhD[1,2] | **Shiu-Dong Chung MD, PhD**[3,4] | **Herng-Ching Lin PhD**[5]

[1] Department of Urology, Shuang-Ho Hospital, New Taipei City, Taiwan

[2] Department of Urology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3] Division of Urology, Department of Surgery, Far Eastern Memorial Hospital, Ban Ciao, Taipei, Taiwan

[4] Graduate Program in Biomedical Informatics, College of Informatics, Yuan-Ze University, Chung-Li, Taiwan

[5] Research Center of Sleep Medicine, School of Health Care Administration and College of Medicine, Taipei Medical University, Taipei, Taiwan

Correspondence
Shiu-Dong Chung, MD, PhD, Division of Urology, Department of Surgery, Far Eastern Memorial Hospital, Ban Ciao, Taipei, Taiwan, 21, Sec. 2, Nan-Ya South Road, Ban Ciao, New Taipei 220, Taiwan.
Email: chungshiudong@gmail.com

Objective: Previous studies have suggested an association between bladder pain syndrome/interstitial cystitis (BPS/IC) and endometriosis. However, no nation-wide population study has yet reported an association between them. In this study, we examined the risk of BPS/IC among subjects with endometriosis during a 3-year follow-up in Taiwan using a population-based dataset.

Study Design: This study comprised 9191 subjects with endometriosis, and 27 573 subjects randomly selected as controls. We individually followed-up each subject ($n = 36\,764$) for a 3-year period to identify subjects subsequently diagnosed with BPS/IC. A Cox proportional hazards regression model was employed to estimate the risk of subsequent BPS/IC following a diagnosis of endometriosis.

Results: Incidences of BPS/IC during the 3-year follow-up period was 0.2% and 0.05% for subjects with and without endometriosis, respectively. The hazard ratio for developing BPS/IC over a 3-year period for subjects with endometriosis compared to subjects without endometriosis was 4.43 (95% CI: 2.13-9.23). After adjusting for co-morbidities like diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraines, sicca syndrome, allergies, endometriosis, asthma, tobacco use, and alcohol abuse, the Cox proportional hazards regressions revealed that the hazard ratio for BPS/IC among subjects with endometriosis was 3.74 (95% CI = 1.76-7.94, $P < 0.001$) compared to that in controls.

Conclusions: This study provides epidemiological evidence of an association between endometriosis and a subsequent diagnosis of BPS/IC.

KEYWORDS
bladder, endometriosis, interstital cystitis, pelvic pain

1 | INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic pain syndrome of unknown etiology and its successful treatment has been a challenge.[1]

It is characterized by suprapubic pain and may be accompanied by lower urinary tract symptoms including urgency, frequency, and nocturia.[2]

The most common of BPS/IC is constant or intermittent chronic pelvic pain (CPP), for more than 6 months in the

Mickey Karram led the peer-review process as the Associate Editor responsible for the paper.

suprapubic or abdominal region. It is estimated that about 9 million women in the United States suffer from CPP and it is one of the commonest complaints in the urologic or gynecologic clinics.[3]

Endometriosis is diagnosed in up to 80% of patients with CPP.[3] Chung et al[4] described the high prevalence and association between BPS/IC and endometriosis, and took these two conditions as the evil twins of CPP.

In this study, we aimed to determine the risk of BPS/IC among women with endometriosis compared to the general population during a 3-year period following the diagnosis. To the best of our knowledge, this is the largest nationwide population-based study, investigating the relationship between endometriosis and subsequent risk of developing BPS/IC.

2 | METHODS

2.1 | Database

The subjects included in this retrospective cohort study were retrieved from the "Longitudinal Health Insurance Database (LHID2000)." The LHID2000 is complied from medical claim records of the Taiwan National Health Insurance (NHI) program which was rolled out in 1995. The LHID2000 consists of original medical claims and registration files for 1 000 000 subscribers under the Taiwan NHI program, subjects were randomly selected from all the subscribers listed in the 2000 Registry of Beneficiaries ($n = 23.72$ million). Each year, the Taiwan National Health Research Institute collects data from the NHI program and sorts it into the LHID2000. The Taiwan National Health Research Institute as well as some researchers have confirmed the validity of data form the NHI program,[5,6] and multiple research papers based on the LHID2000 dataset have been published in international peer-reviewed journals.[7]

This study was exempt from complete review by the Institutional Review Board of Taipei Medical University because the LHID2000 consists of identity-protected secondary data released to the public for research purposes.

2.2 | Study sample

This study included study cohort and control cohorts. For the study cohort, we selected 9213 female subjects aged between 18 and 50 years, who had been diagnosed with endometriosis (ICD-9-CM code 617.0-617.9 except 617.6) during their ambulatory care visits (including outpatient departments of hospitals and clinics) from January 1, 2001 to December 31, 2006. The study population was limited to the above age group as endometriosis occurs in menstruating women. Since administrative datasets are often criticized for their diagnostic validity, this study only included subjects who had at least one diagnosis of endometriosis by a certified obstetrician/gynecologist. We considered the first ambulatory care visit when the subjects was first diagnosed with endometriosis as the index dates. Furthermore, we excluded subjects who had a history of BPS/IC (ICD-9-CM code 595.1) prior to the index date ($n = 22$). Finally, 9191 subjects with endometriosis were included in the study cohort.

The control cohort was selected from the remaining beneficiaries of LHID2000. We randomly selected 27 573 subjects for comparison (three for every subject with endometriosis) to match the study subjects in terms of age group distribution (18-24, 25-29, 30 = 34, 35-39, 40-44, and 45-49), (0, NT$1-NT$15 840, NT$15 841-NT$25 000, ≥NT $25 001) (US$1 = NT$33 in 2007), geographic location (Northern, Central, Eastern, and Southern Taiwan), and index year. NT$15 840 was chosen as the first income level cutoff point as it is the minimum government-stipulated wage for full-time employees in Taiwan. While for subject with endometriosis, the index dates were the year in which the subjects were first diagnosed with endometriosis, for comparison subjects the index dates were simply a matched year in which they had availed a medical consultation. We also ensured that none of the selected comparison subjects had been ever received a diagnosis of endometriosis since the start of NHI program. In addition, we ensured that none of the comparison subjects had ever been diagnosed with BPS/IC prior to the index date.

In total, 36 764 subjects were included in this study. We followed-up each subject individually for 3 years from their index date to identify patients who were diagnosed with BPS/IC during the follow-up period. Since the diagnosis of BPS/IC is a diagnosis of exclusion, its assessment generally includes a number of parameters. Other than reviewing the patient's medical history and performing a complete pelvic examination, a urine test was performed to check for infection, as well as a hydrodistention test coupled with cystoscopy, and a potassium sensitivity test (PST) to check for increased pain and/or urgency on addition of potassium chloride. To further ensure diagnostic accuracy of subjects in this study, we further confirmed that the prescribed medication included Cystistat (hyaluronic acid). This is because the standardized process of NHI, coverage for this treatment is exclusively reserved for patients diagnosed with BPS/IC. Therefore, it is unlikely that anyone without a clear diagnosis of BPS/IC would be eligible for this treatment.

2.3 | Statistical analysis

This study used the SAS system (SAS System for Windows, Version 8.2, SAS Institute Inc, Cary, NC) to conduct all the statistical analyses performed in this study. The Kaplan-Meier method and log-rank test were performed to calculate the 3-year BPS/IC-free survival rate and to compare differences in the risk for BPS/IC between the two cohorts. We also used conditional logistic regression (conditioned on age group, monthly incomes, geographic location, and the index year) to calculate the hazard ratio (HR) with its corresponding

95% confidence interval (CI) for BPS/IC during the 3 year follow-up periods between the two cohorts. In the regression model, we adjusted for medical co-morbidities with BPS/IC based on prior studies.[8,9] These included diabetes, hypertension, coronary heart disease (CHD), obesity, hyperlipidemia, chronic pelvic pain (CPP), irritable bowel syndrome (IBS), fibromyalgia, chronic fatigue syndrome (CFS), depression, panic disorder, migraine, sicca syndrome, allergy, asthma, and overactive bladder. The value of $P \leq 0.05$ was considered statistical significant.

3 | RESULTS

Of the 9191 subjects with endometriosis and 27 573 control subjects, the mean ages were 34.8 years ± 8.5 years. Table 1 shows that after matching for age, monthly income, and geographic region, subjects with endometriosis had a higher prevalence of diabetes than control subjects (4.2% vs 2.3%, $P < 0.001$), hypertension (7.6% vs 4.1%, $P < 0.001$), CHD (2.7% vs 1.4%, $P < 0.001$), obesity (0.9% vs 0.6%, $P = 0.001$), hyperlipidemia (7.4% vs 3.8%, $P < 0.001$),

TABLE 1 Demographic characteristics of subjects with endometriosis and comparison subjects ($n = 36\,764$)

	Subjects with endometriosis ($n = 9191$)		Comparison subjects ($n = 27\,573$)		
Variable	**Total no.**	**%**	**Total no.**	**%**	***P*-value**
Age (years)					1.000
18-24	978	10.6	2934	10.6	
25-29	1281	13.9	3843	13.9	
30-34	1555	16.9	4665	16.9	
35-39	1844	20.1	5532	20.1	
40-44	2009	21.9	6027	21.9	
45-49	1524	16.6	4584	16.6	
Monthly income					1.000
0	2627	28.6	7881	28.6	
NT$1∼15 840	1684	18.3	5052	18.3	
NT$15 841∼25 000	3202	34.8	9606	34.8	
≥NT$25 001	1678	18.3	5034	18.3	
Geographic region					1.000
Northern	4517	49.2	13 551	49.2	
Central	1628	17.7	4884	17.7	
Eastern	2831	30.1	8493	30.1	
Southern	215	2.3	645	2.3	
Diabetes	385	4.2	606	2.3	<0.001
Hypertension	700	7.6	1071	4.1	<0.001
Coronary heart disease	251	2.7	360	1.4	<0.001
Obesity	79	0.9	144	0.6	0.001
Hyperlipidemia	683	7.4	978	3.8	<0.001
Chronic pelvic pain	2786	30.3	4659	17.9	<0.001
Irritable bowel syndrome	488	5.3	687	2.6	<0.001
Fibromyalgia	1689	18.4	3681	14.1	<0.001
Chronic fatigue syndrome	50	0.5	99	0.4	0.037
Depression	523	5.7	879	3.4	<0.001
Panic disorder	63	0.7	123	0.5	<0.001
Migraine	398	4.3	672	2.6	0.015
Sicca syndrome	109	1.2	192	0.7	<0.001
Allergy	105	1.1	282	1.1	0.633
Asthma	361	3.9	828	3.2	0.001
Overactive bladder	395	4.3	409	1.6	<0.001

CPP (30.3% vs 17.9%, $P < 0.001$), IBS (5.3% vs 2.6%, $P < 0.001$), fibromyalgia (18.4% vs 14.1%, $P < 0.001$), chronic fatigue syndrome (0.5% vs 0.4%, $P = 0.037$), depression (5.7% vs 3.4%, $P < 0.001$), panic disorder (0.7% vs 0.5%, $P < 0.001$), migraine (4.3% vs 2.6%, $P = 0.015$), sicca syndrome (1.2% vs 0.7%, $P < 0.001$), asthma (3.9% vs 3.2%, $P = 0.001$), and overactive bladder (4.3% vs 1.6%; $P < 0.001$).

Table 2 shows the incidence of BPS/IC in the study and control cohorts. We found that, of the 36 764 sampled subjects, 30 subjects (0.09%) were diagnosed with BPS/IC during the 3-year follow-up period, this included 18 (0.20% of the subjects with endometriosis) from the study cohort and 12 (0.05% of comparison subjects) from the control cohort. The Kaplan-Meier method showed that subjects with endometriosis had a significantly lower 3-year BPS/IC-free survival rate compared to control subjects (χ^2 value = 17.941; $P < 0.001$). We presents the results of Kaplan-Meier survival analysis in Figure 1.

Table 2 also shows the HR for BPS/IC. Conditional logistic regression analysis (conditioned on age group, monthly income, geographic region, and the index year) suggested that compared to control subjects, the HR for BPS/IC during the 3-year follow-up period among subjects with endometriosis was 4.43 (95% CI = 2.13-9.23, $P < 0.001$). After adjusting for diabetes, hypertension, CHD, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, CFS, depression, panic disorder, migraine, sicca syndrome, allergy, asthma, and overactive bladder, the HR for BPS/IC among subjects with endometriosis was 3.74 (95% CI = 1.76-7.94, $P < 0.001$).

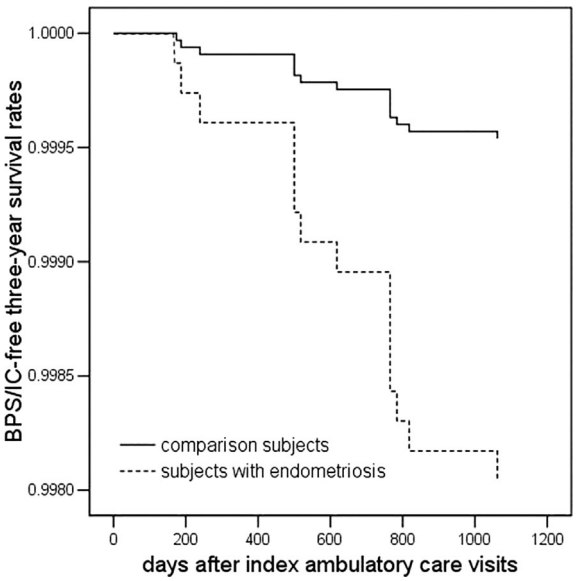

FIGURE 1 Subjects with endometriosis had significantly lower 3-year BPS/IC-free survival rates than comparison subjects

4 | DISCUSSION

Our results suggest that endometriosis is associated with BPS/IC. To the best of our knowledge, this is the first large-scale population-based study that investigated the relationship between endometriosis and BPS/IC. We found that subjects with endometriosis was 4.43-times more likely to develop BPS/IC within 3 years following their diagnosis of endometriosis. Even after adjusting for comorbid conditions associated with BPS/IC, patients with a history of endometriosis had a 3.74-times higher risk for developing BPS/IC than control subjects during the 3-year follow-up period.

Some previously published articles indicated an association between endometriosis and BPS/IC. Chung et al[4] reported that patients who had undergone hysterectomy for pelvic pain but in vain, and a large proportion of patients had interstitial cystitis (IC) in addition to their previously diagnosed endometriosis.

Another study showed that the PST, the most important diagnostic tool for IC, was positive in 81% of women with chronic pelvic pain and appeared to correlate with endometriosis.[10] Women with endometriosis were found to have a high prevalence of autoimmune and atopic conditions, which are similar to BPS/IC. In addition, BPS/IC and endometriosis share common patholomechanisms including inflammatory changes through

TABLE 2 Incidence and hazard ratio for bladder pain syndrome/interstitial cystitis among the sampled patients

Presence of bladder pain syndrome/interstitial cystitis	Total ($n = 36\,764$) n, %		Subjects with endometriosis ($n = 9191$) n, %	
Three-year follow-up period				
Yes	30	0.09	18	0.20
Crude hazard ratio[a] (95%CI)	-		4.43*** (2.13-9.23)	
Adjusted hazard ratio[b] (95%CI)	-		3.74*** (1.76-7.94)	

***$p < 0.001$.

CI = confidence interval.

[a]Hazard ratio was calculated by conditional logistic regression which was conditioned on age group, monthly income, geographic region, and index year.

[b]Adjustments are made for subject's diabetes, hypertension, coronary heart disease, obesity, hyperlipidemia, chronic pelvic pain, irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, depression, panic disorder, migraine, sicca syndrome, allergy, asthma, and overactive bladder.

several potential mediators such as chemokines or cytokines. Recent studies found cytokine mRNAs, including Interleukin (IL)-6 and Tumor Necrosis Factor (TNF)- expressed in the interstitium and urothelium of BPS/IC bladder mucosa.[11,12]

Erickson et al[13] found elevated IL-6 in the urine of patients with ulcerative BPS/IC. Chung et al[14] also found higher serum C-reative protein in patients with BPS/IC than normal controls and indicated an association between chronic inflammation of the urinary bladder and BPS/IC. Several cytokines including interleukin-8 (IL-8) and tumor necrosis factor-alpha (TNF-alpha) are elevated in the peritoneal fluid of women with endometriosis compared to those without endometriosis. These findings suggested that endometriosis is a chronic inflammatory disease.[15] Considered together, both diseases are associated with chronic inflammation in the pelvis.

The present study has several limitations. Diagnoses of endometriosis or BPS/IC were identified from a nationwide administrative database through the ICD-9-CM codes released by the Bureau of the NHI.

Therefore, participants who were not coded accurately or did not seek medical care could not be identified. However, the possibility of a non-differential mis-classification might have biased the results towards null hypothesis. Secondly, the severity of endometriosis or BPS/IC could not be determined from the database. Therefore, we were unable to evaluate whether subjects with severe endometriosis had a higher risk of BPS/IC than those with mild endometriosis. On the other hand, a past history of surgery is not available in this analysis; multiple pelvic or abdominal surgeries might be contributing factors for symptoms similar to those of BPS/IC. Third, some information about factors which might have had an effect on the associations detected in this study was not available through the LHID2000, including tobacco use, family history, alcohol and betel consumption, dietary habits, and body mass index. The manifestations of both endometriosis and BPS/IC may have been confounded by these factors. Lastly, since patients with endometriosis are more likely to have frequent outpatient clinic visits, which may lead to early detection of BPS/IC, it is possible that this study suffered from a surveillance bias. However, since BPS/IC is accompanied by both pain and urinary symptoms, and is only diagnosed in the absence of urinary infection or other pathology, it is unlikely that non-endometriosis subjects would have been less likely to seek medical care. Despite these limitations, this study provides epidemiological evidence of a link between endometriosis and subsequent BPS/IC diagnosis. The specific mechanisms which underlie this relationship are still unclear. Further studies are necessary to confirm these findings and explore the underlying pathological mechanisms. In addition, we suggest that clinical practitioners treating subjects with endometriosis be alert for urinary complaints in these patient groups.

5 | CONCLUSIONS

Our findings are strengthened by the use of a nationally representative, population-based survey sample. The large sample size allowed for the adjustment of known and important confounders of BPS/IC. This study suggested an association between endometriosis and BPS/IC.

CONFLICTS OF INTEREST

All authors have no conflict of interest to declare.

ORCID

Shiu-Dong Chung http://orcid.org/0000-0002-1817-6106
Herng-Ching Lin http://orcid.org/0000-0003-4661-959X

REFERENCES

1. Clemens JQ, Rosetti RT, Rosetti MC, et al. Prevalence and incidence of interstitial cystitis in a managed care population. *J Urol*. 2005;173:98–102.
2. Baranowski AP, Abrams P, Berger RE, et al. Urogenital pain—time to accept a new approach to phenotyping and, as a consequence, management. *Eur Urol*. 2008;53:33–36.
3. Carter. Combined hysteroscopic and laparoscopic findings in patients with chronic pelvic pain. *J Am Assoc Gynecol Laparosc*. 1994;2:43–47.
4. Chung MK, Chung RP, Gordon D, Jennings C. The evil twins of chronic pelvic pain syndrome: endometriosis and interstitial cystitis. *JSLS*. 2002;6:311–314.
5. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML. Validation of the national health insurance research database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20:236–242.
6. Kang JH, Chen YH, Lin HC. Comorbidity profiles among patients with ankylosing spondylitis: a nationwide population-based study. *Ann Rheum Dis*. 2010;69:1165–1168.
7. Chen YC, Yeh HY, Wu JC, Haschler I, Chen TJ, Wetter T. Taiwan's national health insurance research database: administrative health care database as study object in bibliometrics. *Scientometrics*. 2011;86:365–380.
8. Warren JW, Wesselmann U, Morozov V, et al. Numbers and types of nonbladder syndromes as risk factors for interstitial cystitis/painful bladder syndrome. *Urology*. 2011;77:313–319.
9. Warren JW, Howard FM, Cross RK, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology*. 2009;73:52–57.
10. Parsons CL, Bullen M, Kahn BS, Stanford DJ, Willems JJ. Gynecologic presentation of interstitial cystitis as detected by intravesical potassium sensitivity. *Obstet Gynecol*. 2001;98:127–132.
11. Ogawa T, Homma T, Igawa Y, et al. CXCR3 binding chemokine and TNFSF14 over expression in bladder urothelium of patients with ulcerative interstitial cystitis. *J Urol*. 2010;183:1206–1212.
12. Lotz M, Villiger P, Hugli T, Koziol J, Zuraw BL. Interleukin-6 and interstitial cystitis. *J Urol*. 1994;152:869–873.
13. Erickson DR, Belchis DA. Dabbs DJ. Inflammatory cell types and clinical features of interstitial cystitis. *J Urol*. 1997;158:790–793.

14. Chung SD, Liu HT, Lin H, Kuo HC. Elevation of serum c-reactive protein in patients with OAB and IC/BPS implies chronic inflammation in the urinary bladder. *Neurourol Urodyn*. 2011;30:417–420.
15. Sakamoto Y, Harada T, Horie S, et al. Tumor necrosis factor-alpha-induced interleukin-8 (IL-8) expression in endometriotic stromal cells, probably through nuclear factor-kappa B activation: gonadotropin-releasing hormone agonist treatment reduced IL-8 expression. *J Clin Endocrinol Metab*. 2003;88:730–735.

How to cite this article: Wu C-C, Chung S-D, Lin H-C. Endometriosis increased the risk of bladder pain syndrome/interstitial cystitis: A population-based study. *Neurourology and Urodynamics*. 2017;1–6. https://doi.org/10.1002/nau.23462