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Associations between Comorbidities and Bladder Conditions in Patients with Interstitial Cystitis/Bladder Pain Syndrome

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Abstract

Purpose

To examine the associations among functional somatic disorders, psychiatric disorders, medical diseases, and extravesical inflammatory disorders with bladder conditions in patients diagnosed with interstitial cystitis/bladder pain syndrome (IC/BPS).

Methods

Patients with confirmed IC/BPS were included in this retrospective analysis. Cystoscopic hydrodistention was performed to identify the presence of Hunner's (HIC) and non-Hunner's IC (NHIC) and classify the bladder condition according to maximal bladder capacity (MBC) and glomerulation grade. Treatment outcomes were assessed using the Global Response Assessment scale (GRA). Data on the comorbidities of patients were obtained from chart reviews and classified as functional somatic disorders, psychiatric disorders, autoimmune diseases, or medical diseases. Fifteen urinary biomarkers were examined, including inflammatory proteins, neurogenic proteins, and oxidative stress biomarkers. The associations between bladder condition and urinary biomarker levels were compared between patients with and without comorbidities.

Results

Overall, 389 patients with IC/BPS, including 44 HIC and 345 NHIC, were enrolled in this study. Among the patients, 324 (83.3%) had various comorbidities, while 65 (16.7%) did not. Patients with depression had higher rate of glomerulation grade 2 or 3 and MBC < 760 mL, while patients with insomnia and arrhythmia had higher rate of glomerulation grade 0 or 1 and MBC ≥ 760 mL. Urinary levels of the inflammatory urinary biomarker RANTES and oxidative stress biomarker 8-OHdG were significantly lower in patients with IC/BPS with functional somatic and psychiatric disorders. The other biomarkers did not differ significantly between subgroups. Patients with and without comorbidities had similar GRA scores after long-term treatment (56% vs 56.9%, p = 0.896). Patients with comorbid IC/BPS and depression had GRA 2or 3 (47.5% vs 59.2%) compared with those without depression (p = 0.043).

Conclusion

Patients with IC/BPS have more medical comorbidities, but these were not associated with cystoscopic bladder conditions. In patients with functional somatic and psychiatric disorders, RANTES and 8-OHdG were significantly lower than in those without comorbidities.

Clinical trial registration

Not available

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a complicated bladder disorder characterized by potential bladder inflammation and associations with several functional somatic disorders, psychiatric disorders, autonomic nervous system diseases, and extravesical inflammatory disorders [1]. The proposed pathophysiological mechanisms of IC/BPS include urothelial dysfunction, chronic inflammation, activation of nociceptive afferent pathways, autoimmune processes, autonomic dysfunction, central sensitization, and psychological stress [2]. Patients with IC/BPS tend to have one or more functional somatic disorders, which could exaggerate the bladder symptoms if not properly managed [3]. Furthermore, a certain percentage of women with pelvic floor muscle fasciitis may also present with pelvic pain mimicking bladder pain [4]. These multiple pathophysiologies complicating IC/BPS often render therapies targeting bladder inflammation and urothelial dysfunction insufficient for achieving satisfactory outcomes.

Although functional somatic disorders, psychiatric disorders, medical comorbidities, and extravesical inflammatory diseases may contribute to the clinical presentation of IC/BPS or exacerbate IC/BPS symptoms, no solid evidence has linked these disorders to IC/BPS pathophysiology. Recent clinical investigations indicate that combining cognitive behavioral therapy with bladder therapy could improve IC/BPS symptoms [5]. However, the underlying mechanisms of the therapeutic efficacy are not fully understood [6], and cytoscopic bladder findings remain unchanged post-treatment, suggesting psychological interventions may not alleviate bladder inflammatory conditions [5]. Similarly, another study found that interventions for pelvic floor muscle pain (PFMP) can also influence treatment outcomes for IC/BPS; however, the underlying bladder pathology did not improve [7]. Furthermore, patients with IC/BPS and significant psychosocial comorbidities tend to show greater symptom severity and less favorable treatment outcomes after bladder-targeted therapies [8].

Traditionally, IC/BPS is categorized into two clinical phenotypes, Hunner's IC (HIC) and non-Hunner's IC (NHIC) [1]. Cystoscopic hydrodistention is recommended by the European Association of Urology and Eastern Asian guidelines to identify glomerulations for the diagnosis of NHIC. However, bladder capacity and glomerulation grade are not well recognized indicators of IC/BPS severity [9]. Recent studies have found that a higher glomerulation grade and a smaller maximal bladder capacity (MBC) assessed by cystoscopic hydrodistention are associated with bladder inflammation and may thus influence bladder therapy outcomes. Patients with higher MBC and lower glomerulation grade after hydrodistention presented with more severe medical comorbidities but a significantly higher rate of satisfactory treatment outcomes [10]. Thus, HIC can be identified among patients with bladder pain syndrome using urinary inflammatory, neurogenic, and oxidative stress biomarkers [11, 12]. Although the reproducibility of urinary biomarkers for diagnosis of different NHIC subtypes is not well established, certain candidate urine biomarkers have shown diagnostic and prognostic value in predicting treatment outcomes for IC/BPS [13], including eotaxin, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-

alpha (TNF-α), regulated on activation, normal T-cell expressed and secreted (RANTES), 8-hydroxy-2'-deoxyguanosine (8-OHdG), and 8-isoprostane.

This study evaluated the associations of functional somatic disorders, psychiatric disorders, medical comorbidities, and extravesical inflammatory disorders with bladder conditions in patients diagnosed with IC/BPS. We also investigated treatment outcomes in this cohort receiving long-term bladder therapies.

Materials and Methods

Overall, 389 patients with confirmed by cystoscopic hyudrodistention were included in this retrospective analysis. IC/BPS was classified as HIC or NHIC based on characteristic cystoscopic findings [9]. HIC was diagnosed by cystoscopic visualization of characteristic Hunner's lesions without anesthesia [14], while NHIC was diagnosed by cystoscopic hydrodistention under intravenous general anesthesia and an intravesical pressure of 80 cmH_2O. MBC was measured at the end of infusion, while glomerulation grade was assessed based on the distribution of glomerulation bleeding after bladder pressure was released. Furthermore, all patients underwent videourodynamic studies to exclude bladder outlet obstruction, low bladder compliance, detrusor underactivity, neurogenic lower urinary tract dysfunction, or detrusor overactivity. This retrospective analysis was approved by the Research Ethics Committee of the Tzu Chi Hospital **(IRB: 115-015-B, dated February 05, 2026)**. Informed consent was waived because of the retrospective study design. All study procedures were conducted in accordance with the Declaration of Helsinki.

Patients underwent bladder therapies tailored to the results of the initial cystoscopic hydrodistention, including electrofulguration or laser ablation of Hunner's lesions (for HIC), intravesical hyaluronic acid instillation (for HIC and NHIC), intravesical platelet-rich plasma injection (for HIC and NHIC), intravesical botulinum toxin A injection (for NHIC), and bladder low-energy shock wave therapy (for NHIC) [15]. Patients also underwent pelvic floor muscle examination. The tender points were recorded, and patients with a Visual Analog Pain Score > 5 underwent regular pelvic floor physiotherapy or local triamcinolone or botulinum toxin A injections [15]. Treatment outcomes were assessed by self-reported Global Response Assessment scale (GRA): 0 = no response, 1 = mildly improved, 2 = moderately improved, 3 = markedly improved [16].

Data on the comorbidities of patients were obtained from chart reviews and classified into the following categories: functional somatic disorders (including reflux esophagitis, asthma, arrhythmia, fibromyalgia, dyspepsia, and irritable bowel syndrome, etc.)[17]; autoimmune diseases (including systemic lupus erythematosus, Sjogrene syndrome, and rheumatoid arthritis); PFM pain and lower back pain; and other medical comorbidities (including diabetes mellitus [DM], coronary arterial disease [CAD], chronic heart failure, chronic kidney disease, and chronic obstructive pulmonary disease). Psychiatric disorders, such as depression and insomnia, were also recorded.

Fifteen urinary biomarkers were measured at baseline, including inflammatory proteins, neurogenic proteins, and oxidative stress biomarkers. Midstream urine samples (50 mL) were obtained via spontaneous voiding at full bladder capacity prior to cystoscopic hydrodistension. Immediately after collection, samples were placed on ice, centrifuged at 1,800 rpm for 10 minutes at 4°C, and the supernatant was aliquoted and stored at − 80°C. Before biomarker analysis, samples were thawed and centrifuged again at 12,000 rpm for 15 minutes at 4°C to remove cellular debris [11, 12].

Urinary biomarkers were quantified using multiplex bead-based immunoassays and enzyme-linked immunosorbent assays (ELISAs). [11] Pro-inflammatory and regulatory cytokines/chemokines—including eotaxin, interleukin (IL)-2, IL-6, IL-8, C-X-C motif chemokine ligand 10 (CXCL 10, IP-10), MCP-1, macrophage inflammatory protein-1β (MIP-1β), RANTES, TNF-α, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and total antioxidant capacity (TAC)—were measured using the Milliplex® Human Cytokine/Chemokine Magnetic Bead Panel (Millipore, Darmstadt, Germany). Oxidative stress biomarkers 8-OHdG and 8-isoprostane were measured using commercially available ELISA kits (Biovision, K4160-100; Enzo Life Sciences, DI-900-010, U.S.A.) [18]. 8-Isoprostane levels were normalized to urinary creatinine concentration using a creatinine assay kit (Enzo, ADI-907-030A). Biomarker concentrations were calculated based on median fluorescence intensity or optical density in accordance with manufacturers' protocols.

Baseline demographics, cystoscopic bladder condition, videourodynamic study findings, and urine biomarker, and cystoscopic bladder conditions were compared between patients with and without comorbidities. Furthermore, we also compared cystoscopic bladder conditions between patients with and without individual comorbidities. Finally, we compared urinary biomarker levels between patients with and without functional somatic and psychiatric disorders, autoimmune diseases, and medical diseases.

Continuous variables are expressed as median and ranges, with the *t*-test used for group comparisons. Categorical variables were compared using the chi-square test or Fisher's exact test. Clinical data, videourodynamic findings, and urine biomarker levels were compared between subgroups and controls, as well as between different cystoscopic bladder condition groups using analysis of variance. All statistical tests were two-tailed, with a significance level of $p \leq 0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

In total, 389 patients with IC/BPS, including 44 HIC and 345 NHIC, were enrolled in this study. The patients' demographics and videourodynamic results are shown in Table 1. Among the patients, 324 (83.3%) had comorbidities, while 65 (16.7%) did not. Patients with comorbidities were older, had significantly larger bladder volumes and greater urgency sensation, larger post-void residual volumes, and lower voiding efficiency.

Table 1
Patients' demographics, cystoscopic bladder condition, and videourodynamic study results between interstitial cystitis patients with and without comorbidities

Age	**(A) Co-morbidities (+)**	**(B) Co-morbidities (-)**	**P-value**
	(N = 324)	**(N = 65)**	
	54.53 ± 12.78	**46.28 ± 13.3**	**< 0.001**
Sex (male/female)	47/277	14/51	0.155
duration	10.62 ± 5.98	8.28 ± 4.73	**0.001**
HIC	36 (11.12%)	8 (12.3%)	0.257
GR 0/1, MBC ≥ 760 ml	72 (22.2%)	9 (13.8%)	
GR 2/3, MBC ≥ 760 ml	41 (12.9%)	14 (21.5%)	
GR 0/1, MBC < 760 ml	61 (18.8%)	10 (15.4%)	
GR 2/3, MBC < 760 ml	114 (35.2%)	24 (36.9%)	
First sensation filling	121.16 ± 52.23	113.09 ± 58.03	0.266
Full sensation	190.86 ± 78.32	172 ± 75.82	0.076
Urge sensation	229.48 ± 93.44	201.83 ± 81.34	**0.027**
Compliance	71.39 ± 73.45	61.16 ± 58.56	0.291
Pdet (cmH2O)	20.73 ± 12.6	22.22 ± 14.44	0.398
Qmax (ml/s)	11.38 ± 6.43	10.85 ± 5.43	0.535
Volume (ml)	229 ± 128.15	231.86 ± 107	0.866
PVR (ml)	39.15 ± 77.84	14.81 ± 34.16	**< 0.001**
BCI	77.55 ± 32.91	76.47 ± 27.14	0.804
CBC (ml)	268.03 ± 123.79	246.45 ± 98.85	0.187
cQmax	0.72 ± 0.37	0.7 ± 0.28	0.545
Voiding efficiency	0.86 ± 0.25	0.93 ± 0.17	**0.003**
AG-number	-2.18 ± 19.29	0.51 ± 20.27	0.310

HIC: Hunner's interstitial cystitis, GR: grade of glomerulation, MBC: maximal bladder capacity, GRA: global response assessment, Pdet: detrusor pressure, Qmax: maximum flow rate, PVR: post-void residual, BCI: cladder contractility index, CBC: cystometric bladder capacity, cQmax: corrected Qmax (= Qmax / $Volume^{1/2}$), AG-number: Abrams-Griffiths number (= Pdet − 2 x Qmax)

Eighty patients had glomerulation grade 0 or 1 and MBC ≥ 760 mL, 55 had glomerulation grade 2or 3 and MBC ≥ 760 mL, 72 had glomerulation grade 0 or 1 and MBC < 760 mL, and138 had glomerulation grade

2or 3 and MBC < 760 mL. Furthermore, 324 patients had one or more different comorbidities, including 308 (79.2%) with functional somatic disorders including 154 (39.6%) with gastrointestinal diseases, 110 (28.3%) with PFMP or lower back pain, 16 (4.1%) with asthma, 29 (7.5%) with arrhythmia; 100 with depression (25.7%), 198 with insomnia (50.9%); and 25 (6.4%) with autoimmune disease; and 139 (35.7%) with DM, CAD, or other medical comorbidities. The distribution of patients with and without different comorbidities and the cystoscopic findings are presented in Table 2.

Table 2
The association of comorbidities and cystoscopic hydrodistention results in IC/BPS patients with different cystoscopic hydrodistention bladder condition

			(A)GR 0/1 MBC ≥ 760	(B) GR 2/3 MBC ≥ 760	(C)GR 0/1 MBC < 760	(D) GR 2/3 MBC < 760	(D) HIC	P-value
Total IC/BPS		389	80 (20.6%)	55(14.1%)	72 (18.5%)	138(35.5%)	44 (11.3%)	
FSS, insomnia, depression	(-)	125	21 (16.8%)	23 (18.4%)	20 (16%)	42 (33.6%)	19 (15.2%)	0.141
	(+)	264	59 (22.3%)	32 (12.1%)	52 (19.7%)	96 (36.4%)	25 (9.5%)	
Autoimmune diseases	(-)	364	70 (19.2%)	51 (14%)	67 (18.4%)	135(37.1%)	41 (11.3%)	0.057
	(+)	25	10 (40%)	4 (16%)	5 (20%)	3 (12%)	3 (12%)	
Low back pain PFM pain	(-)	279	48 (17.2%)	38 (13.6%)	52 (18.6%)	109(39.1%)	32 (11.5%)	0.056
	(+)	110	32 (29.1%)	17 (15.5%)	20 (18.2%)	29 (26.4%)	12 (10.9%)	
Medical diseases	(-)	250	52 (18.9%)	44 (16%)	51 (18.5%)	103(37.5%)	25 (9.1%)	0.070
	(+)	139	28 (24.6%)	11 (9.6%)	21 (18.4%)	35 (30.7%)	19 (16.7%)	

IC/BPS: interstitial cystitis/bladder pain syndrome, GR: grade of glomerulation, MBC: maximal bladder capacity, HIC: Hunner's IC, FSS: functional somatic syndrome, PFM: pelvic floor muscle

Comparisons on cystoscopic bladder conditions between patients with and without individual functional somatic disorder, psychiatric disorder, or medical comorbidity revealed slightly significant differences based on specific comorbidities. Patients with depression had a higher prevalence of glomerulation grade 2 or 3 and MBC < 760 mL. Those with insomnia had a higher prevalence of glomerulation grade 0 or 1 and MBC ≥ 760 mL, while those with arrhythmia had a higher prevalence of glomerulation grade 0 or 1 and MBC ≥ 760 mL. No significant differences in bladder conditions were observed among patients

with autoimmune diseases, medical diseases (including DM and CAD), or frequent urinary tract infections (Table 3).

Table 3
The association of individual comorbidity and cystoscopic hydrodistention bladder conditions in IC/BPS patients

	N=	MBC > = 760 GR 0/1	MBC > = 760 GR 2/3	MBC < 760, GR 0/1	MBC < 760, GR 2/3	HIC	P-value
Depression (-)	289	56 (19.4%)	50 (17.3%)	55 (19%)	89 (30.8%)	39(13.5%)	**< 0.001**
Depression (+)	100	24 (24%)	5 (5%)	17 (17%)	49 (49%)	5 (5%)	
Insomnia(-)	191	34 (17.8%)	37 (19.4%)	31(16.2%)	66 (34.6%)	23 (12%)	**0.041**
Insomnia (+)	198	46 (23.2%)	18 (9.1%)	41(20.7%)	72 (36.4%)	21(10.6%)	
GI disease (-)	235	50 (21.3%)	33 (14%)	42(17.9%)	81 (34.5%)	29(12.3%)	0.909
GI disease (+)	154	30 (19.5%)	22 (14.3%)	30(19.5%)	57 (37%)	15 (9.7%)	
PFM/LB pain (-)	291	48 (17.2%)	38 (13.6%)	52 (18.6%)	109(39.1%)	32(11.5%)	0.056
PFM/LB pain (+)	98	32 (29.1%)	17 (15.5%)	20 (18.2%)	29 (26.4%)	12(10.9%)	
Arrythmia (-)	360	68 (18.9%)	53 (14.7%)	65(18.1%)	133(36.9%)	41(11.4%)	**0.024**
Arrythmia (+)	29	12 (41.4%)	2 (6.9%)	7 (24.1%)	5 (17.2%)	3 (10.3%)	
Autoimmune (-)	364	70 (19.2%)	51 (14%)	67(18.4%)	135(37.1%)	41(11.3%)	0.057
Autoimmune (+)	25	10 (40%)	4 (16%)	5 (20%)	3 (12%)	3 (12%)	
DM (-)	341	67 (19.6%)	49 (14.4%)	64(18.8%)	124(36.4%)	37(10.9%)	0.650
DM (+)	48	13 (27.1%)	6 (12.5%)	8 (16.7%)	14 (29.2%)	7 (14.6%)	
CAD (-)	291	55 (18.9%)	46 (15.8%)	52(17.9%)	109(37.5%)	29 (10%)	0.125

GR: grade of glomerulation, MBC: maximal bladder capacity, HIC: Hunner's IC, GI: gastrointestinal, PFM/LB: pelvic floor muscle/ low back, DM: diabetes mellitus, CAD: coronary arterial disease, UTI: urinary tract infection

	N=	MBC > = 760 GR 0/1	MBC > = 760 GR 2/3	MBC < 760, GR 0/1	MBC < 760, GR 2/3	HIC	P-value
CAD (+)	98	25 (25.5%)	9 (9.2%)	20(20.4%)	29 (29.6%)	15(15.3%)	
Frequent UTI (-)	325	65 (20%)	46 (14.2%)	59(18.2%)	120(36.9%)	35(10.8%)	0.713
Frequent UTI (+)	64	15 (23.4%)	9 (14.1%)	13(20.3%)	18 (28.1%)	9 (14.1%)	

GR: grade of glomerulation, MBC: maximal bladder capacity, HIC: Hunner's IC, GI: gastrointestinal, PFM/LB: pelvic floor muscle/ low back, DM: diabetes mellitus, CAD: coronary arterial disease, UTI: urinary tract infection

Urinary biomarkers were compared between patients with IC/BPS and 30 controls **(**Table 4**)**. Regardless of comorbidity status, patients with IC/BPS showed significantly higher urinary levels of MCP-1, 8-OHdG, and 8-isoprostane but significantly lower IL-2 and NGF levels than controls. Urinary levels of RANTES and 8-OHdG were significantly higher in patients with IC/BPS without functional somatic or psychiatric disorders. No significant differences were found in other biomarkers between patients with and without functional somatic or psychiatric disorders. Furthermore, urinary biomarker levels did not vary significantly among patients with and without autoimmune disease, PFMP, lower back pain, or medical diseases.

Table 4
The urinary biomarker levels between IC/BPS patients with and without functional somatic and psychiatric disorders and the controls

	IC /BPS		Control			
	(A) With functional and psychiatric disorders (n = 264)	**(B) Without functional and psychiatric disorders (n = 125)**	**(C) Control (n = 30)**	**P- (A v B)**	**P- (A v C)**	**P- (B v C)**
Eotaxin	8.36 ± 11.0	9.14 ± 10.58	4.98 ± 3.7	0.512	0.097	**< 0.001**
IL-2	0.25 ± 0.12	0.26 ± 0.1	0.83 ± 0.24	0.452	**< 0.001**	**< 0.001**
IL-6	6.48 ± 25.1	9.15 ± 22.6	1.89 ± 3.51	0.312	0.318	**0.001**
IL-8	22.9 ± 41.4	28.9 ± 54.4	22.1 ± 57.0	0.234	0.924	0.546
IP-10	23.6 ± 113.3	53.1 ± 177.5	48.9 ± 193.1	0.091	0.288	0.910
MCP-1	333.5 ± 448.1	413.2 ± 639.4	161.2 ± 132.5	0.157	**< 0.001**	**< 0.001**
MIP-1β	1.73 ± 5.19	2.13 ± 5.04	2.75 ± 2.17	0.477	0.290	0.514
RANTES	6.1 ± 9.66	21.5 ± 85.6	7.19 ± 8.09	**0.047**	0.552	0.362
TNF-α	1.52 ± 1.19	1.59 ± 2.54	0.92 ± 0.64	0.712	**0.007**	0.153
NGF	0.18 ± 0.07	0.17 ± 0.03	0.26 ± 0.08	0.155	**< 0.001**	**< 0.001**
BDNF	0.63 ± 0.76	1.74 ± 10.0	0.66 ± 0.64	0.074	0.805	0.559
PGE2	307 ± 466.8	291.1 ± 259.9	182.2 ± 154.0	0.716	0.146	**0.004**
8-OHdG	58.5 ± 49.2	82.3 ± 71.4	18 ± 13.73	**0.001**	**< 0.001**	**< 0.001**

IC/BPS: interstitial cystitis/bladder pain syndrome, IL: interleukin, IP-10: interferon gamma–inducible protein 10, MCP-1: monocyte chemoattractant protein-1, MIP-1β: macrophage inflammatory protein 1β, RANTES: regulated on activation, normal T cell expressed and secreted, TNF-α: tumor necrosis factor-alpha, NGF: nerve growth factor, BDNF: brain-derived neurotrophic factor, PGE2: prostaglandin E2, 8-OHdG: 8-hydroxy 2-deoxyguanosine, TAC: total antioxidant capacity

	IC /BPS		Control			
	(A) With functional and psychiatric disorders (n = 264)	**(B) Without functional and psychiatric disorders (n = 125)**	**(C) Control (n = 30)**	**P- (A v B)**	**P- (A v C)**	**P- (B v C)**
8-isoprostane	55.2 ± 98.3	61.4 ± 114.1	19.0 ± 16.5	0.584	**0.045**	**0.044**
TAC	959 ± 1034	1090 ± 1446	1078 ± 925	0.306	0.546	0.965

IC/BPS: interstitial cystitis/bladder pain syndrome, IL: interleukin, IP-10: interferon gamma–inducible protein 10, MCP-1: monocyte chemoattractant protein-1, MIP-1β: macrophage inflammatory protein 1β, RANTES: regulated on activation, normal T cell expressed and secreted, TNF-α: tumor necrosis factor-alpha, NGF: nerve growth factor, BDNF: brain-derived neurotrophic factor, PGE2: prostaglandin E2, 8-OHdG: 8-hydroxy 2-deoxyguanosine, TAC: total antioxidant capacity

Bladder therapies administered for IC/BPS included detrusor botulinum toxin injection in 200 patients, platelet-rich plasma injection in 209, and low-energy shock wave therapy in 66. GRA scores did not vary significantly between patients with and without medical comorbidities in any one bladder therapy. Patients with and without comorbidities had similar GRA after long-term follow-up (56% vs 56.9%, p = 0.896). Among functional somatic disorders, psychiatric disorders, and medical comorbidities, only depression was associated with treatment outcome. Fewer patients with IC/BPS patients and comorbid depression had GRA 2 or 3 (47.5% vs 59.2%) than those without depression (p = 0.043). No other medical comorbidities showed a significant difference in GRA between patients with and without the condition.

Discussion

The results of this study revealed that patients with IC/BPS had several comorbidities, commonly comprising functional somatic disorders, psychiatric disorders, autoimmune diseases, and medical diseases. However, these medical comorbidities were not associated with cystoscopic bladder conditions. Among patients with comorbid functional somatic and psychiatric disorders, those with depression had a higher frequency of glomerulation grade 2 or 3 and MBC < 760 mL, suggesting an association between depression and more severe bladder inflammatory conditions. Patients with insomnia and arrhythmia showed a higher prevalence of glomerulation grade 0 or 1 and MBC ≥ 760 mL, suggesting less severe bladder inflammation than patients without these comorbidities. Patients with functional somatic and psychiatric disorders had significantly lower urinary RANTES and 8-OHdG levels than those in patients without comorbidities.

IC/BPS is a heterogeneous syndrome of unknown etiology. Patients with IC/BPS usually present with bladder/pelvic pain, pressure/discomfort associated with urinary frequency, and urgency sensation [1]. The fundamental pathology of IC/BPS is chronic inflammation of the urinary bladder due to autoimmune

processes, urothelial injury, sensory nerve activation, or central sensitization, with extravesical inflammation [19]. Chronic inflammation of the bladder wall activates sensory afferents, resulting in increased bladder sensation, reduced functional bladder capacity, and bladder pain in severe cases [20]. Moreover, IC/BPS frequently overlaps with functional somatic disorders and several psychosomatic conditions, such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and psychological distress further complicates management and outcomes of IC/BPS [21].

No direct evidence has demonstrated that these functional somatic disorders and medical comorbidities can exacerbate bladder condition toward progression to a higher bladder inflammatory grade or less favorable therapeutic outcomes [8]. Patients with the NHIC phenotype may have affective dysregulation and more functional somatic symptoms [22]. Many patients with IC/BPS report bladder pain, a PFMP phenotype, or multiple pain locations outside the pelvis [21]. The UPOINT system has been used to guide IC/BPS management, incorporating domains such as urinary, psychosocial, organ-specific, infection, neurological, and muscular tenderness [23]. Patients with more affected domains usually have more severe symptoms [24]. In this study, although the prevalence of comorbid functional somatic and psychiatric disorders like depression (25.7%), insomnia (50.9%), gastrointestinal disorders (39.6%), PFMP (25.2%), and lower back pain (15.7%) is high, these comorbidities were not significantly correlated with cystoscopic bladder conditions, suggesting the absence of a bidirectional comorbid relationship. However, we found patients with IC/BPS and comorbid depression more frequently had glomerulation grade 2 or 3 and MBC < 760 mL. A higher glomerulation grade and lower MBC have been associated with higher levels of urinary inflammatory biomarkers [10] and more severe bladder inflammation histopathology [25].

IC/BPS is associated with more severe depression, and more than 60% of patients with IC/BPS have moderate anxiety severity [26]. A previous study proposed that psychosocial factors, such as comorbid anxiety, depression, and quality of life issues, may exacerbate IC/BPS symptoms [8]. Therefore, the primary distress of patients with IC/BPS may stem from unfavorable bladder conditions [26]. However, the severity of IC symptoms and depression may be bidirectionally associated. Elevated depressive states can affect bladder sensation, resulting in urothelial dysfunction, increased bladder permeability, bladder inflammation, and cross-organ sensitization between visceral organs [27]. Emotional distress can also exacerbate afferent hypersensitivity and pain processing, causing IC/BPS flares [28]. In this study, patients with depression had higher glomerulation grade and lower MBC, suggesting that depression may worsen urothelial dysfunction and chronic inflammation in IC/BPS bladders. Patients with IC/BPS frequently reported experiencing symptom flares under stress or diet triggers [29]. Such symptom flares may be associated with central sensitization, which leads to bladder pain refractory to conventional bladder therapy [30]. Patients with IC/BPS and more severe depression should be concomitantly managed with psychiatric consultation while undergoing IC/BPS-appropriate medications to achieve better outcomes [15].

In this study, patients with insomnia and arrhythmia frequently had low glomerulation grade and large MBC. This aligns with a population-based study, where patients with IC/BPS had a significantly higher

incidence of anxiety, depression, and insomnia than the matched controls [31]. Insomnia and arrhythmia are linked to sympathetic hyperactivity, which may be activated by chronic inflammation in IC/BPS [32]. Furthermore, patients with sympathetic hyperactivity more frequently present with bladder inflammation and increased bladder sensation despite retaining a normal urothelial structure. Therefore, these patients usually present with a nearly normal bladder urothelium on cystoscopic hydrodistention. Severe autonomic nervous system dysfunction can trigger symptoms in patients with IC/BPS. A study that scored patients with IC/BPS and higher sympathetic hyperactivity symptoms on the Composite Autonomic Symptoms Score questionnaire found that most had NHIC, larger functional bladder capacity, and more comorbid non-urological syndromes [33]. Autonomic nervous system dysfunction is also frequently observed in patients with non-bladder-centric IC/BPS. Thus, while combining cognitive behavioral therapy and bladder therapy may reasonably improve subjective IC/BPS symptoms, it will not alleviate objective bladder conditions [5, 33].

Psychiatric consultation has contributed significantly to decreasing IC symptom indexes; however, it did not improve bladder conditions despite being performed concomitantly with bladder therapy [26]. Psychological stress exacerbates voiding frequency, somatic sensitivity, and urinary bladder inflammation, as demonstrated in mouse models [34]. Thus, cognitive behavioral therapy may help patients with IC/BPS better cope with pain and psychological stress by addressing the cognitive factors that influence pain sensitivity and symptoms. However, it does not mitigate bladder structural abnormalities due to chronic inflammation [35]. In contrast, improving IC symptoms alleviated anxiety and depression in patients with IC/BPS, consequently improving the GRA score. Therefore, psychiatric consultation primarily facilitates stress coping and mitigating the psychological effects of bladder diseases [5]. These results highlight the importance of combining bladder-targeted therapies with psychiatric consultation to achieve optimal outcomes in patients with IC/BPS and comorbid functional somatic disorders, psychiatric disorders, or other medical diseases.

This study has several limitations. First, its retrospective design and reliance on chart reviews for comorbidity data may introduce selection bias, as other patients treated for comorbidities at other institutions would not have been identified. Second, the severity of comorbidities was not graded, which may result in inflated or misinterpreted prevalence rates.

Conclusion

This study found that 83.3% of patients with IC/BPS have comorbid functional somatic disorders, psychiatric disorders, or medical diseases. Overall, no strong association was observed between comorbidities and cystoscopic bladder conditions. However, patients with depression showed worse inflammatory bladder conditions. Patients with insomnia and arrhythmia frequently had a larger MBC and lower glomerulation grade. Nevertheless, long-term treatment outcomes remained modest, with GRA of 56% for both patients with and without comorbidities.

Declarations

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