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ORIGINAL ARTICLE

Histological evidence supports low anesthetic bladder capacity as a marker of a bladder-centric disease subtype in interstitial cystitis/bladder pain syndrome

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Abstract

Introduction and hypothesis Low anesthetic bladder capacity has been shown to be a biomarker for bladder-centric interstitial cystitis/bladder pain syndrome (IC/BPS). The goal of this study was to determine if histopathological evidence from bladder biopsies supports anesthetic bladder capacity (BC) as a marker to distinguish a bladder-centric IC/BPS subtype.

Methods From a review of our large IC/BPS cohort of patients undergoing hydrodistention, we identified a total of 41 patients with low BC (≤ 400 ml); an additional 41 consecutive patients with BC > 400 ml were selected as the comparator group. The original bladder mucosal biopsy pathology slides were re-reviewed by a single pathologist (blinded to patient information) using a standardized grading scale developed for this study.

Results Histologically, the low BC subjects exhibited higher levels of acute inflammation ($p = 0.0299$), chronic inflammation ($p = 0.0139$), and erosion on microscopy ($p = 0.0155$); however, there was no significant difference in mast cell count between groups ($p = 0.4431$). There was no significant gender difference between the groups; female patients were the majority in both groups (low BC: 94.12%, non-low BC: 100%; $p = 0.1246$). Individuals in the low BC group were older ($p < 0.0001$), had a higher incidence of Hunner's lesions on cystoscopy ($p < 0.0001$), and had significantly higher scores, i.e., more bother symptoms, on two IC/BPS questionnaires (ICPI, $p = 0.0154$; ICSI, $p = 0.0005$).

Conclusions IC/BPS patients with low anesthetic bladder capacity have histological evidence of significantly more acute and chronic inflammation compared with patients with a non-low bladder capacity. These data provide additional evidence to support low bladder capacity as a marker of a distinct bladder-centric IC/BPS phenotype.

Keywords Bladder capacity · Bladder pain syndrome · Histology · Interstitial cystitis · Subtype

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) encompasses a broad spectrum of clinical symptoms, including pelvic pain, pressure, discomfort, and a number of lower urinary tract symptoms. It has been hypothesized that patients diagnosed with IC/BPS display at least two distinct phenotypes: a *bladder-centric disease* state in which pain is confined to the bladder and a *systemic syndrome* where lower urinary tract symptoms and pain are accompanied by systemic symptoms and syndromes such as irritable bowel syndrome, depression, headaches, and fibromyalgia [1]. Due to the clinical heterogeneity and lack of a specific diagnostic test or standardized way to interpret histological findings, the diagnosis of IC/BPS can be difficult to make and thus is usually delayed [2]. Roughly, 3 to 8 million women in the US experience IC/BPS symptoms, yet only 9.7% have been given that diagnosis by a physician [3].

The clinical management of IC/BPS patients has proven to be a formidable challenge. Currently, the American Urological Association (AUA) guidelines for treatment of IC/BPS are mostly based on expert opinion and grade C evidence [4]; therefore, treatment success rates are so variable

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that most clinicians practice a multi-modal, multidisciplinary approach that often necessitates frequent re-evaluation [5, 6]. There is considerable difficulty in finding efficacious treatments for *all* IC/BPS patients due to the heterogeneity of the disease. Having the ability to discriminate between subjects with a bladder-centric versus a systemic phenotype prior to the initiation of treatment may permit a more targeted treatment approach.

Anesthetic bladder capacity represents one clinical feature that may be considered for distinguishing between IC/BPS phenotypes. Low anesthetic bladder capacity (low BC, defined here as ≤ 400 ml) has been reported to represent a more severe form of the disease [7]. In a recent study describing a large cohort of women diagnosed with IC/BPS and exhibiting a wide range of bladder capacities, those with low BC were less likely to report systemic pain symptoms and syndromes than women with non-low bladder capacity [1]. Furthermore, molecular profiling in bladder biopsies from the low BC group revealed significantly different gene expression compared with those with BC > 400 ml [8].

Although not required by the AUA guidelines, many patients being evaluated for IC/BPS undergo cystoscopy with bladder biopsy [4]. In the case series presented here, patients underwent cystoscopy and hydrodistention either when the diagnosis was unclear or when performed for therapeutic indications as a third-line treatment option. When a bladder biopsy is taken, the pathologist reports the histological findings and may note the presence of erosion, fibrosis, inflammation, and mast cell counts. Currently, there is no standardized method for evaluating and reporting these findings, which makes it difficult for a physician to compare the results from one patient to the next—especially when they are generated by many different pathologists, each with their own reporting style.

Previously, the presence of Hunner's lesions (HLs) has been used to denote a more severe phenotype of IC/BPS [9]. In our prior studies, 33–50% of subjects in the low BC group had HL (low BC/HL+) on cystoscopy [1]. There were however a considerable number of IC patients with low BC but without HL (low BC/HL-) who had similar symptomatology to the low BC/HL+ group. Given that subjects with low BC had similar gene expression profiles and had similarly more bladder-centric symptomatology regardless of HL status, we hypothesized that *low anesthetic bladder capacity* may be a more inclusive marker of a severe bladder-centric phenotype.

The goal of this study was to investigate whether there is histopathological support for this hypothesis, as it seems logical that microscopic changes occur that coincide with changes on a macroscopic level. During the diagnostic workup of IC/BPS, a cystoscopy is routinely performed to rule out other disease processes, and cystoscopy with hydrodistention is performed on approximately 50% of patients in our tertiary referral clinic. Identifying a histopathological marker not only for help in diagnosing IC/BPS itself, but also to further classify the bladder-centric phenotype, may provide crucial information that can significantly alter the route of therapy. In addition, histopathological differences may provide insight into the disease process and may provide the groundwork toward developing new treatment options.

Subjects/patients and methods

Subject recruitment

Male and female subjects, at least 18 years of age, who were being treated for IC/BPS and who were scheduled for cystoscopy with hydrodistention (HOD; third-line therapy for IC/BPS, based on the AUA guideline algorithm) have been prospectively enrolled in this IRB-approved protocol (IRB00018552) since 2014. For this retrospective sample selection, our entire patient database ($n = 380$ IC/BPS patients) was reviewed, and 41 subjects were identified as having a low BC (≤ 400 ml). To decrease selection bias, the remaining subjects in the database (BC > 400 ml) were arranged by medical record number, and the first 41 consecutive patients were identified for the comparator group. At the time of enrollment, baseline demographic data were collected for each patient. Patients also completed three validated questionnaires: the Interstitial Cystitis Problem Index (ICPI) [10], the Interstitial Cystitis Symptoms Index (ICSI) [10], and the Pelvic Pain and Urgency/Frequency Patient Symptoms Scale (PUF) [11]. The scores from these questionnaires were retrieved from the electronic medical record (EMR) for the 82 patients selected for this study.

Bladder hydrodistention

Hydrodistention was performed by a single surgeon (RJE) in a standard fashion and according to AUA guidelines. Cystoscopy was performed under general anesthesia, and general descriptions of the bladder, including the presence of Hunner's lesion, were noted prior to distention. Next, the bladder was distended with normal saline to a pressure of 100 cm of water for 5 min. Following hydrodistention the bladder was emptied, the anesthetic bladder capacity was recorded, and the bladder was re-inspected with the cystoscope. Biopsies were obtained using a cold-cup technique. If a Hunner's lesion was identified, a biopsy was obtained from near the lesion; otherwise, biopsies were obtained from the posterior bladder wall above the level of the trigone. Biopsies were sent to the Medical Center Pathology Department (per standard hospital protocol) for formal evaluation.

Standardized histology grading scale

After initially reviewing the pathology reports of the 82 IC/BPS patients, several trends were noted; however, meaningful comparisons could not be made because of the reports having been generated by 25 different pathologists with different reporting styles. As a result, for this study, the original pathology slides were pulled from the Pathology Department archive to be re-reviewed by a single pathologist (GEP) who was blinded to the individual patient information including IC/BPS history and bladder capacity.

In an effort to standardize reporting, the specific histological variables to be scored, i.e., *inflammation*, *erosion*, and *mast cell count,* were defined by the authors (GEP and JSS) before any of the slides had been reviewed. Inflammation was classified as either 'acute' (if neutrophils were present) or 'chronic' (if other inflammatory cells, such as lymphocytes or plasma cells, were present). Inflammation, either acute or chronic, was then graded on a scale as being 'none,' 'mild,' 'moderate,' or 'severe.' Standardized definitions of 'mild,' 'moderate,' and 'severe' inflammation do not currently exist. Therefore, general guidelines were created to define each of the subjective variables prior to review of the slides. The term 'mild' was used if the variable could only be identified after intense examination of the slide under high power (400×). The term 'moderate' was used if the variable was easily visualized on intermediate power (100×), without significant searching. The term 'severe' was used if the variable was immediately obvious using low power (40×) (see Fig. 1 for representative images). Erosion on microscopy was noted as either 'present' or 'absent,' based on the presence of superficial urothelial defects.

Currently, there is no single stain that is used routinely to visualize and count mast cells, and therefore data from the use of three different mast cell stains—(1) mast cell tryptase (MCT), (2) toluidine blue (TB), and (3) c-kit (CD117, here referred to as CK)—are represented in this series. The choice of mast cell stain was made by the original pathologist, based upon personal preference. When the slides were re-reviewed, mast cell count was recorded as the number of mast cells in the highest density area. Cell counts were provided per one high power field (400×, 0.24 mm² per high power field). In addition, the location where the mast cell count was performed was noted as either 'epithelial/lamina propria' or 'detrusor.'

Statistical analysis

Statistical analyses were performed using JMP version 14 (SAS Institute, Cary, NC). Normally distributed continuous data were analyzed using Student's t-test, whereas skewed continuous data were compared using the Wilcoxon signed-rank test. Categorical data (such as inflammation, erosion, and stain types) were analyzed using Pearson's chi-square test or Fisher's exact test if there were ≤ 5 subjects in 20% of cells. The results of the ICPI, ICSI, and PUF questionnaires were considered as ordinal data and were compared between groups using the Mann-Whitney U test. The Kruskal-Wallis test was used to compare non-parametric categorical and ordinal data (histological findings and symptom questionnaires). If a significant association was identified, Wilcoxon tests were used to compare each of the categorical values to identify the pair that differed significantly from the rest. $p < 0.05$ was considered statistically significant.

Results

Of the 82 subjects identified for this study, histology slides for 73 subjects were available to be re-reviewed (the remaining 9 slides were no longer available). Patient demographic information is presented in Table 1. The *low BC* group ($n = 34$) had an average BC of 321 ± 86 ml, and the comparator group ($n = 39$) had an average BC of 896 ± 247 ml. Subjects in the low BC group were significantly older than the comparator group ($p < 0.0001$), and there was no significant gender difference between the groups; female patients were the majority in both groups ($p = 0.1246$). Patients in the low BC group were more likely to have Hunner's lesions (seen on cystoscopy) than those in the comparator group ($p < 0.0001$).

Upon re-review of the slides by a single pathologist, blinded to patient data and using the pre-determined scoring criteria, several differences were noted between the groups (Table 2). The low BC group had more severe acute inflammation ($p = 0.0299$), more severe chronic inflammation ($p = 0.0139$), and more erosion ($p = 0.0155$).

Mast cell counts were also compared between the two groups. As indicated in Table 3, there were three different mast cell stains in use, and the *type* of stain used differed significantly between the groups ($p = 0.0011$). Given that mast cell counts may differ based on which of the three stains are used, the counts were compared overall, as well as within each stain type and within each location. The number of mast cells identified by each stain or by each location did not differ significantly between the two groups, with one exception—when the CK stain was used, the low BC group showed significantly fewer mast cells ($p = 0.0296$). The overall mast cell count, however, was not significantly different between the groups ($p = 0.4431$).

A comparison of the IC/BPS symptom questionnaire scores between the groups showed that the low BC group had significantly higher scores, indicating more severe bladder symptoms, on both the ICPI ($p = 0.0154$) and the ICSI ($p = 0.0005$) (Table 4). There was also a significant association between the ICPI scores and the level of chronic inflammation ($p = 0.0464$) as well as the presence of erosion on microscopy ($p = 0.0120$). Those with 'no chronic inflammation' had

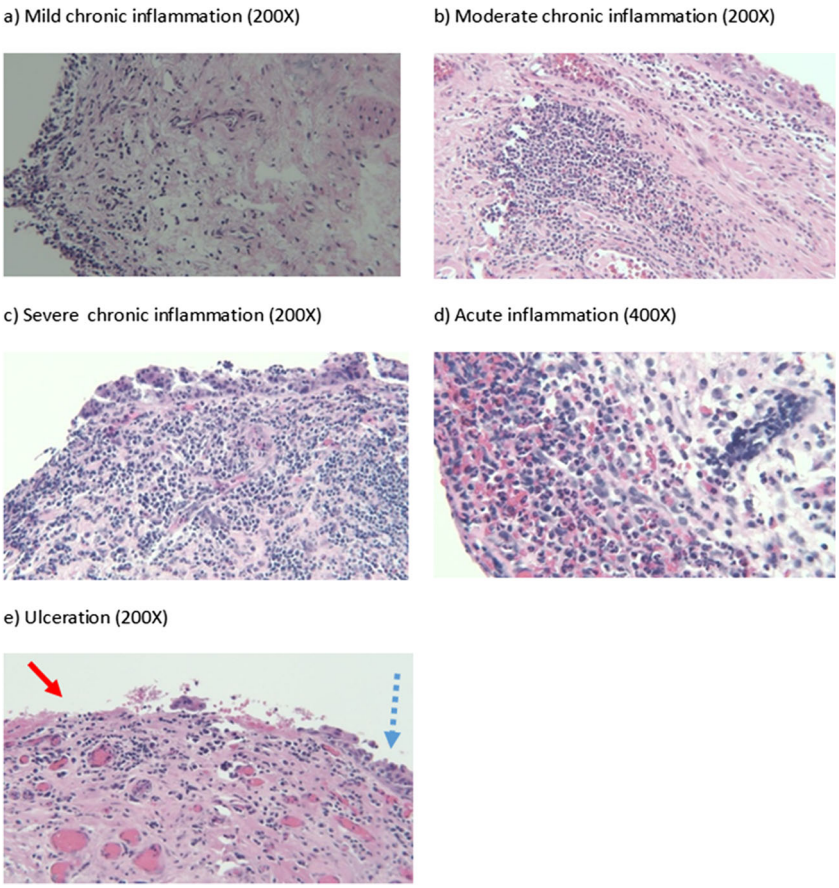

Fig. 1 Bladder biopsy tissue was collected from IC/BPS patients during hydrodistention under anesthesia and stained with H&E. Representative images that highlight some of the definitions set forth in scoring criteria are presented here. Panels **a–c** illustrate examples of *mild*, *moderate*, and *severe* chronic inflammation. Panel **d** (at 400×) illustrates the multi-lobulated nuclei of the **neutrophils** which are present in *acute* inflammation compared with the **plasma cells** and **lymphocytes** seen with *chronic* inflammation (panel **a–c**). Panel **e** represents erosion seen on microscopy as an absence of the superficial layer of cells (solid red arrow) compared with the transitional cells seen on the right side of the image (blue dotted arrow)

significantly lower scores compared with those with *any* level of chronic inflammation (data not shown). Similarly, there was a significant association between the ICSI scores and the level of chronic inflammation ($p = 0.0052$) as well as the presence of erosion on microscopy ($p = 0.0490$). Subjects with 'no chronic inflammation' had significantly lower ICSI scores than those with 'mild chronic inflammation,' and those with 'mild chronic inflammation' had significantly lower ICSI scores than those with 'moderate' or 'severe chronic inflammation' (data not shown). No significant association was found between ICPI or ICSI scores and the level of acute inflammation ($p = 0.6821$, $p = 0.3882$, respectively). With regards to the PUF questionnaire, there was no significant difference between the low BC and the comparator group ($p = 0.2183$; Table 4), nor were there any associations between the PUF scores and the levels of acute or chronic inflammation or of erosion on microscopy ($p = 0.1234$, $p = 0.0510$, $p = 0.1872$, respectively).

Discussion

In patients with IC/BPS, histopathological findings from bladder biopsies as noted by a single pathologist revealed that patients with low anesthetic bladder capacity have a significantly higher incidence of severe acute inflammation and chronic inflammation and are more likely to have erosion (as seen on microscopy). Mast cell counts did not differ significantly between the groups. In addition, low BC patients had significantly more severe problems and symptoms based on

Table 1 Demographic data by bladder capacity (BC) group

	Low anesthetic BC($N = 34$)	Bladder capacity > 400 ml ($N = 39$)	p value
Age (years)	57.65 ± 11.34	41.72 ± 14.31	* < 0.0001
Female	32 (94.12%)	39 (100.00%)	0.1246
Hunner's lesion on cystoscopy	16 (47.06%)	2 (5.13%)	* < 0.0001

Normally distributed data are represented as 'mean ± SD' and were compared with the Student's t-test. Categorical data are represented as '*n* (%)' and were compared using the chi-square test

Table 2 Histopathology findings by bladder capacity group

	Low anesthetic BC ($N = 34$)	Bladder capacity > 400 ml ($N = 39$)	p value
Acute inflammation			*0.0299
None	25 (73.53%)	38 (97.44%)	
Mild	6 (17.65%)	1 (2.56%)	
Moderate	2 (5.88%)	0 (0.00%)	
Severe	1 (2.94%)	0 (0.00%)	
Chronic inflammation			*0.0139
None	0 (0.00%)	2 (5.13%)	
Mild	13 (38.24%)	27 (69.23%)	
Moderate	16 (47.06%)	7 (17.95%)	
Severe	5 (14.71%)	3 (7.69%)	
Erosion on microscopy	10 (29.41%)	3 (7.69%)	*0.0155

Categorical data are represented as '*n* (%)' and were compared using the chi-square test or Fisher's exact test where appropriate

the ICPI and ICSI questionnaire scores. These findings provide additional support for the emerging concept that the IC/BPS population is made up of distinct sub-populations and that low anesthetic bladder capacity may be a rational categorical marker for a bladder-centric disease phenotype.

Our group has previously shown that IC/BPS patients with bladder capacity < 400 ml have a different bladder biopsy gene expression profile characterized by a downregulation of urothelial adhesion molecules and an upregulation of inflammatory markers as well as having a higher prevalence of Hunner's lesion and more bladder-centric symptomatology when compared with those with a BC > 400 ml (who were more likely to have systemic chronic pain disorders) [1, 8]. Mazeaud et al. have subsequently compared the voiding diaries of these two sub-populations and found that patients with low BC have more severe symptoms, such as higher frequency, nocturia, and an earlier onset of painful urgency of urination [12]. Results from Mazeaud et al., a study that was performed by a different group using a different study population, provide reproducibility of our original findings and further strengthen the evidence for distinct sub-populations within IC/BPS based on anesthetic bladder capacity.

Another hallmark of IC/BPS, the Hunner's lesion, is a distinctive inflammatory lesion with characteristic central fragility

Table 3 Mast cell histology findings by bladder capacity group

	Low anesthetic BC ($N = 34$)	Bladder capacity >400 ml ($N = 39$)	p value
Type of mast cell stain			*0.0011
c-kit (CK)	6 (17.65%)	24 (61.54%)	
Mast cell tryptase (MCT)	22 (64.71%)	14 (35.90%)	
Toluidine blue (TB)	2 (5.88%)	0 (0.00%)	
MCT stain (epithelial/lamina propria)	35.58 ± 12.52	31.58 ± 12.54	0.3715
MCT stain (detrusor)	14.89 ± 9.60	13.43 ± 7.70	0.7406
MCT stain (total)	40.73 ± 15.94	39.42 ± 18.95	0.8371
CK stain (epithelial/lamina propria)	26.67 ± 10.39	34.14 ± 11.40	0.1623
CK stain (detrusor)	10	10.31 ± 4.01	Insufficient data
CK stain (total)	28.33 ± 7.61	38.48 ± 13.59	*0.0296
TB stain (epithelial/lamina propria)	16.33 ± 11.93	No data	Insufficient data
TB stain (detrusor)	9.00 ± 2.83	No data	Insufficient data
TB stain (total)	22.33 ± 7.51	No data	Insufficient data
Total mast cell count by epithelial/lamina propria (all stains)	33.35 ± 15.10	28.97 ± 15.67	0.2286
Total mast cell count by detrusor (all stains)	4.76 ± 8.65	5.85 ± 6.99	0.5627
Total mast cell count (all stains and all locations)	38.12 ± 17.70	34.82 ± 18.80	0.4431

Normally distributed data are represented as mean ± SD and were compared with Student's t-test. Skewed data are represented as median (25th percentile, 75th percentile) and were compared using the Wilcoxon signed-rank test. Categorical data are represented as '*n* (%)' and were compared using the chi-square test or Fisher's exact test where appropriate

Table 4 IC/BPS questionnaires by bladder capacity group

	Low anesthetic BC bladder capacity	Bladder capacity > 400 ml	*p* value
ICPI Questionnaire	15 (13, 16)	13 (10, 15)	*0.0154
ICSI Questionnaire	16 (14, 18.25)	13 (10, 16)	*0.0005
PUF Questionnaire	25 (22, 29.25)	23.50 (18.50, 27.25)	0.2183

Ordinal data are represented by median (25th percentile, 75th percentile) and were compared using the Mann-Whitney U test

and mucosal and submucosal denudation with fibrin deposition [11]. HL is the most characteristic lesion of IC/BPS despite not being pathognomonic. Interestingly, it has been estimated that no more than ~10% of all patients with a clinical diagnosis of IC/BPS have Hunner's lesion on cystoscopy, yet in this study 47% (16/34) of patients with *low BC* had HL compared with only 5% (2/39) of the comparator group. As noted previously, when a comparison of mucosal gene expression analysis was performed on IC/BPS patients (both low and non-low BC) and controls, those with low BC/HL- clustered together with the low BC/HL+ group [8], providing further evidence that low bladder capacity, *with or without* Hunner's lesions, may be a valid marker for the bladder-centric IC/BPS phenotype.

During our initial review of the original 82 histology reports (generated by 25 different pathologists), it became clear that a more standardized method for reporting pathology findings for IC/BPS specimens would be needed if meaningful comparisons between patient findings were the goal. Since there are no universal definitions for 'mild,' 'moderate,' or 'severe' inflammation in IC/BPS bladder biopsies, a more objective scoring method was generated for this blinded review. This grading scale was designed prior to review of any slides. Any grading system is subject to bias by a pathologist, which is why it was critical that the pathologist be blinded to the patient information.

Mast cell counts were also considered in this study. The significance of mast cell counts as a marker for IC/BPS continues to be debated, and one important confounder is the lack of a single universally used histology stain that is regarded as the most reliable for the identification of mast cells [13–15]. Many studies have found a significant increase in mast cell counts associated with IC/BPS [16–22]. Even within the group that argues that mast cell counts are a marker of IC/BPS, there is disagreement as to the relevant location of the mastocytosis. While some have suggested urothelial mastocystosis, most support the detrusor muscle as the location most correlated with IC/BPS [16, 18–20, 23]. Liu et al. found that patients with IC/BPS have increased mast cell counts compared with controls, but subjects with overactive bladder syndrome have similarly elevated counts. The study concluded that elevated mast cell counts may be indicative of inflammation and may not be specific to IC/BPS [24]. Others have found no difference in mast cell counts between those with IC/BPS and those without [25–27].

Regarding mast cell count results, the current study is limited by the heterogeneity in mast cell stains used when the original slides were prepared. In addition, the modest number of samples processed using any one of the three mast cell stains does not supply the statistical power necessary for the formation of any meaningful conclusions regarding their ability to discriminate IC/BPS phenotypes.

All of the histology slides were reviewed and graded by a single pathologist (GEP), which is a key feature of the design of this study, but it is also a limitation. We attempted to minimize bias by creating an objective set of scoring criteria to be used for grading histology slides and also by blinding the pathologist to all other clinical data. Another potential limitation of this study was the retrospective nature by which the questionnaire scores were obtained. Upon review of the EMR for this cohort, 97% of the ICPI, the ICSI, and the PUF questionnaire scores were identified for the BC > 400 ml group. For the low BC group, while 88% of the ICPI and the ICSI scores were identified, only 53% of the PUF questionnaire scores had been entered. This may help to explain why the ICPI and the ICSI findings of this study concur with a previous study that examined a larger more complete cohort, whereas the PUF scores do not [1]. It is interesting to note that the presence of erosion or the severity of chronic inflammation was significantly associated with the ICPI and ICSI scores compared with acute inflammation, which was not. One additional limitation of this study is that the majority of patients in this study are women, so the results may not be generalizable to males with IC/BPS. The low BC group was also significantly older than the non-low BC group. This may suggest that bladder capacity decreases with time and low BC is merely a progression of the disease. However, from patients who have undergone several HOD procedures over several years, we have found that bladder capacity does not generally decrease significantly for the IC/BPS population as a whole. It may, however, decrease and progress only in the 'bladder-centric' phenotype. The significant difference in age in this study may also only be significant because of the relatively

small sample size, and the difference may not persist with larger samples. Many patients in our cohort, who have had symptoms for >10 years, have a non-low bladder capacity.

Strengths of this study include the prospective enrollment of subjects into the database and having had all of HOD procedures and biopsy collections performed in a standardized manner by the same clinician (RJE). In addition, this study benefits from having an appropriate comparator group comprised of IC/BPS patients who underwent the same procedures by the same surgeon and who were identified in a consecutive manner to decrease selection bias. The use of validated questionnaires to assess IC/BPS symptoms allowed for the observation that those with low BC not only have more severe microscopic inflammation and erosion but also have more severe symptoms and problems. Lastly, the blinded review of all slides by a single pathologist with a standardized grading method provided an appropriate backdrop with which comparisons between the groups could be made.

Conclusions

IC/BPS patients with low anesthetic bladder capacity have histological evidence of significantly more acute and chronic inflammation, as well as erosion, compared with patients with a non-low bladder capacity. These findings, together with the additional patient demographic and questionnaire data, provide further support for distinct IC/BPS subtypes and nominate *low anesthetic bladder capacity* as an important marker for a bladder-centric disease state. In the future, treatments could be directed toward the appropriate IC/BPS phenotype and may lead to improvement in therapeutic efficay rates in this difficult-to-treat population. Thus, identification of a marker of these sub-types is of critical importance.

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Compliance with ethical standards

Conflicts of interest None

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