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Article

# Quality of Life and Treatment Modalities in Patients with Interstitial Cystitis: A Patients Perspective

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**Abstract:** Background: Quality of life (QoL) in IC/BPS patients is an evidence gap in guidelines, because studies are limited and outdated. Therefore, guidelines might not reflect the current situation accurately, and no possible improvements in QoL of these patients. Secondly, guidelines suggest multimodal approach in therapy, however unknown is how the efficacy of these therapies are perceived by the patient themselves. The aim of this study is to investigate the perception of IC/BPS patients on their QoL and to determine which treatments they received and how they evaluate the efficacy of these various (alternative) therapies. Methods: Quantitative retrospective database study in IC/BPS patients, compiled of existing patient survey data (n=217) from July 2021. Results: The QoL of patients is affected significantly by IC/BPS. This is evident from the substantial self-reported impact by patients, the various affected domains on EQ-5D 5L. The QoL was not negatively affected by delayed diagnosis, but there were differences between female and males. Secondly, there was the wide array of (alternative) treatments utilized, although some have doubtful results and high dropout rates. Conclusion: QoL is considerably impaired in IC/BPS patients. Coagulation therapy and intravesical GAG therapy were most appreciated treatments. The diverse responses and adherence to various treatments warrant a personalized approach (phenotype-oriented therapy). To achieve improvement in the QoL, it is important to incorporate the patient's perspective in treatment guidelines.

**Keywords:** interstitial cystitis; bladder pain syndrome; quality of life; therapies; lifestyle

## 1. Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by ESSIC as a rare chronic inflammatory disease of the bladder, with complaints of pain, urgency and/or frequency [1]. In 1995, Bade et al. conducted a study amongst urologists in the Netherlands and calculated the prevalence of IC/BPS to be around 8 to 16 per 100,000 female patients, with a female-to-male ratio of 10:1 [2]. This finding aligns well with international literature [3]. Weidenaar et al. extrapolated those numbers to approximately 1,860 IC/BPS patients in the Netherlands in 2022, but it is likely there are many undiagnosed patients due to diagnostic delay and misdiagnosis [4]. The disease is uncommon, but it does impact a number of patients in the Netherlands.

Although there are studies that report on QoL in IC/BPS [5–16], in current guidelines quality of life (QoL) is only sparsely mentioned. The European Association of Urology (EAU) and the Dutch association of urology do not currently elaborate on QoL [17,18]. The American Urology Association briefly discusses QoL and the adverse impact that IC/BPS has on patients [19]. However, these statements rely on literature dating back 15-20 years and do not incorporate improvements in healthcare approaches [5,7,9–16,20,21]. Evidence based guidelines do not necessarily align with the

patient's perspective. Rare diseases often have few recommendations that have a grade level of evidence. This shows the importance of performing studies that incorporates a patient perspective.

When treating IC/BPS, EAU recommends to adopt 'multimodal approaches that encompass behavioral, physical and psychological techniques alongside the oral or invasive treatments'[22]. While research has shed light on the efficacy and potential contributions of various therapies, it remains unclear how these therapies, including alternative approaches and behavioral modifications, are currently being utilized and perceived by patients in clinical practice.

Another gap in knowledge pertains to the presentation of male IC/BPS patients. IC/BPS is a rare disease predominantly found in women, which has led to a research focus also primarily on women. There is limited understanding of potential differences in symptoms, QoL or treatment efficacy between men and women.

The primary aim of this study is to evaluate how BPS/IC patients perceive their QoL in different domains and to investigate how patients rate efficacy of different therapies offered to them in order to obtain better insight of the patients' view on real life clinical practice. Additionally, secondary objectives of this study are to scrutinize data concerning demographics, symptomatology, therapies, sex differences and lifestyle adjustments related to IC/BPS.

## 2. Materials and Methods

### 2.1. Methodology and Ethical statements

A quantitative database study was conducted to assess the effect of IC/BPS on patients' QoL. The database used in this study was provided by the Dutch IC/BPS patient association (ICP) and consisted of survey data previously gathered by the ICP. Our institute approved this database under registration number: 115067. No ethical consent from the Ethical Review Board (Centrale Commissie Mensgebonden Onderzoek Oost Nederland) was needed because of the non-invasive and non-burdensome nature of this study (registration number 2023-16852).

### 2.2. Study design

The database comprised responses to 147 questions related to symptoms and QoL, voluntarily completed by individuals affected by IC/BPS and associated with the ICP. These data were anonymously collected by the ICP in July 2021, with 217 participants responding. The database encompassed a diverse group, including those diagnosed with IC/BPS, former IC/BPS patients and partners. For the analysis, only adult patients who had received the IC/BPS diagnosis at the time of the questionnaire were included. Former patients and partner, as well as IC/BPS patients who had undergone cystectomy were excluded from this analysis.

The main outcome measures of this study were: the influence of IC/BPS on their daily lives, the current experience of the disease and the EQ-5D 5L questionnaire. Secondary study outcomes were: 1) patient characteristics, such as: age, sex, subtype IC/BPS, presence of Hunner lesions (HL), 2) symptomatology, 3) given (alternative) treatments and their perceived efficacy by patients themselves and 4) applied lifestyle adjustments and their efficacy. These study outcomes measures were collected from a database, which included the answers from a survey filled in by patients themselves. The survey consisted of four parts: 1) The demographic section: participants were asked about their sex and age category. 2) The diagnosis and symptom section: this section included questions concerning type of symptoms, severity of symptoms, diagnosis, diagnosis-delay, cystoscopy findings, urinary tract infections related questions, presence of concurrent chronic diseases and the O'Leary Sant Interstitial Cystitis Symptom Index and Problem Index (ICSI/PI). 3) The quality-of-life section: Initially, participants were inquired about the magnitude of the influence IC/BPS has on their daily lives, their current experience of the disease, and any potential sleep-related challenges. The section ended with the administration of the EQ-5D 5L validated questionnaire, designed to assess their QoL.

4) The treatment section: this section covered many different (alternative) treatment options for IC/BPS that are used by patients within the Netherlands. Participants were asked to answer per

treatment: if they had undergone the treatment, efficacy on symptoms, presence of complications and (dis)continuation with the treatment. The treatment options included: medication, bladder instillations, neuromodulation, transurethral Hunner lesion (HL) resection, intravesical botulin injections, hydrodistension, pelvic floor physical therapy (PFPT) and specialized care in a pain center. Participants were also asked if they had considered undergoing bladder removal and the reasons behind their consideration. Additionally, the same questions used for standard therapy were also applied for alternative therapies, such as: cannabis oil, smoking cannabis, acupuncture, orthomolecular therapy, osteopathy, manual therapy and food supplements. Finally, a section of ten questions collected data concerning life style adjustments, such as: diet, meditation, exercise, stress management and sleep health.

### 2.3. Statistical analysis

Data analysis was performed using SPSS v27 (Statistical Package for the Social Sciences, Chicago, IL, USA). Data are reported as number (%) with 95%-confidence interval, median (interquartile range) or mean (standard deviation). For questions with possible multiple answers, the percentages illustrate the percent of cases. Where comparisons were made, the independent sample T-test was used for normally distributed data and the Mann-Whitney U test for not normal distributed data. Correlations were assessed with 1) cross tabs, interpreting the linear by linear association or Chi-square and 2) linear regression analysis for continue variables. For all tests significance was set at 5%.

## 3. Results

### 3.1. Demographics

In the analysis 193 participants were included, the demographic data is summarized in Table 1A. The majority of patients were female (89%). The age distribution showed that 33% were between 41-60 years old, while 54% were between 61-80 years old. In almost all patients diagnosis was made by a urologist with cystoscopy. In 46% of the patients HL were identified. Half of the patients were affected by concurrent urinary tract infections and symptoms of irritable bowel syndrome. Auto-immune associations, such as allergies, rheumatoid arthritis and fibromyalgia were seen in 22-38% of the cases.

**Table 1. Demographic overview and symptoms** This table presents data on sex, age, IC/BPS subtypes and comorbidities. Along with information on main symptoms, symptom scores and the burden and/or prioritization of in treatments.

All patients (n=193)		
A. Demographics	N (%)	[95%-CI]
Sex		
Female	166 (89)	[84-93]
Male	20 (11)	[7-16]
Age		
19-40 years	16 (9)	[5-14]
41-60 years	62 (33)	[26-40]
>60 years	109 (58)	[51-65]
Subtype IC/BPS <sup>†</sup>		
Type 1 (normal bladder wall)	6 (3)	[1-7]
Type 2 (glomerulations)	81 (44)	[37-52]
Type 3 (Hunner's lesions)	84 (46)	[38-53]
Unknown	13 (7)	[4-12]
Comorbidities		
Bacterial cystitides	104 (54)	[47-61]
Irritable bowel syndrome	56 (45)	[36-54]

Allergy or sensitivity	47 (38)	[29-47]		
Rheumatoid Arthritis	28 (22)	[15-31]		
Fibromyalgia	28 (22)	[15-31]		
Migraines	27 (22)	[15-30]		
<b>B. Symptoms</b>	<b>N (%)</b>	<b>[95%-CI]</b>	<b>N (%)</b>	<b>[95%-CI]</b>
Main symptoms <sup>2</sup>			First priority in	
Pain	177 (92)	[87-95]	therapy	[53-68]
Frequency	151 (78)	[72-84]	107 (60)	[18-32]
Sleep difficulties	147 (76)	[70-82]	37 (25)	[12-25]
Urgency	140 (73)	[66-79]	26 (18)	[9-21]
			20 (14)	
	<b>Mean ± SD</b>	<b>range</b>		
<b>O'Leary Sant Questionnaire</b>				
<i>IC-symptom index</i>				
Total score	12,9 ± 4,6	0-20		
Urgency	3,24 ± 1,6	0-5		
Frequency	3,37 ± 1,6	0-5		
Nocturia	3,24 ± 1,5	0-5		
Bladder pain	3,02 ± 1,4	0-5		
<i>IC-problem index</i>				
Total score	8,9 ± 3,7	0-16		
Urgency	1,30 ± 1,3	0-4		
Frequency	2,40 ± 1,2	0-4		
Nocturia	2,44 ± 1,4	0-4		
Bladder pain	2,72 ± 1,2	0-4		
Do you experience any problems with sleep?				
0 (no problem) – 5 (big problem)	2,40 ± 1,5	0-5		

<sup>1</sup>Based on the ESSIC classification of types of bladder pain syndrome; <sup>2</sup>Percent of cases.

### 3.2. Symptoms

Data showed that there was considerable diagnostic delay of >6 years 30% of patients. It also shows that this diagnostic delay is decreasing over time, thereby implying that there is an improvement in recognizing and diagnosing the syndrome by clinicians. The most frequently reported symptom was pain (92%) and was the top priority in treatment for over 60% of the patients. Frequency and urgency were commonly reported symptoms, but for urgency, up to 76% of the patients reported either no problem or only a minor issue. Nearly all patients experienced nocturia, with 50% needing to urinate four or more times during the night. Moreover, although 76% of the patients reported experiencing sleep difficulties, and over half of the study population experienced moderate to big sleep problems, the priority for addressing these symptoms in treatment was lower compared to other symptoms. The presence of pain leads to significant more sleep problems ( $p=0,007$ ). A summary of the experienced symptoms and burden are shown in Table 1B. There was no significant difference in reported symptoms between patients with (HL+) and without HL (HL-).

### 3.3. Quality of Life

Data concerning QoL is shown in Table 2. About half of the patients in our cohort experienced symptoms at least two years before diagnosis. For a considerable number of patients, this diagnostic delay extended beyond ten years. A prolonged diagnostic delay led to a statistically significant increase in the experienced pain ( $p=0,015$ ), difficulties related to pain ( $p=0,038$ ) and difficulties concerning urinary frequency ( $p=0,049$ ).

More than 80% of the patients reported a moderate to severe impact of IC/BPS on their daily lives. Among HL+ patients this impact was significantly greater compared to those without HL, with respective means of 4,75 versus 4,34 (range 1-6,  $p=0,019$ ), but this difference is clinically very small. The majority of the patients (72%) experienced at that time point either that the disease is fading to the background or it is acceptable in terms of living with the condition, while a smaller portion struggled or even felt overwhelmed by the disease. This did not correlate with how long someone suffered from IC/BPS.

Furthermore, the patients' QoL was impacted across various domains, as assessed by the EQ-5D 5L questionnaire, divided in 'any problems' and 'no problems'. The domains most notably affected were pain (93%) and usual activities (75%). Over half of the patients reported having feelings of anxiety and/or depression. Lastly, concerning self-care, the least affected domain, nearly all patients stated having no problems in this area.

Moreover, there was a significant correlation between the experience of the disease and the impact on the domain pain (R square = 0,55;  $p<0,001$ ), with patients who scored worse on this domain also experience their disease as more severe. This correlation was also found for the anxiety domain (R square = 0,018;  $p=0,006$ ). Twenty seven percent of the participants said they had considered bladder removal, with the three most occurring reasons being unbearable pain (41%), low QoL (29%) and no other treatment options (14%).

**Table 2. Impact of symptoms of IC/BPS upon quality of life** This table presents the perceived burden on quality of life by IC/BPS, moreover the results from the validated questionnaire EQ-5D 5L.

	All patients (n=193)	
	N (%)	[95%-CI]
Symptoms before diagnosis		
0 – 2 year	88 (46)	[38-53]
3 – 5 year	45 (23)	[18-30]
6 – 10 year	17 (9)	[5-14]
11 – 20 year	23 (12)	[8-17]
>20 year	17 (9)	[5-14]
Unknown	3 (2)	[0-4]
	<b>mean/median</b>	<b>SD/IQR</b>
What is the influence of IC/BPS on your life? 0 (very small) – 5 (very big)	3,54	1,18
How do you experience your IC/BPS at this moment? 0 (no complaints) – 4 (overwhelmed)	2,13	0,98
<b>EQ-5D-5L</b>	<b>N (%)</b>	<b>95%-CI</b>
<i>Mobility</i>		
No problems	88 (46)	[39-53]
Any problems	104 (54)	[47-61]
<i>Self-care</i>		
No problems	170 (88)	[83-92]
Any problems	23 (12)	[8-17]
<i>Usual activities</i>		
No problems	48 (25)	[19-32]
Any problems	145 (75)	[68-81]
<i>Pain</i>		
No problems	14 (7)	[4-12]
Any problems	178 (93)	[88-96]
<i>Anxiety</i>		
No problems	91 (47)	[40-55]
Any problems	102 (53)	[46-60]

EQ VAS scale (0-100)	
Mean $\pm$ SD	55,9 $\pm$ 25,3

### 3.4. Treatments

#### 3.4.1. Standard treatments

All patients received treatment from a urologist, while a gynecologist was involved in the treatment in 50% of the cases. Pain specialists were only engaged in the care of 17% of the patients. A similar percentage had been referred for counseling from a psychologist /psychiatrist for their IC/BPS complains. Patients who experienced more feelings of anxiety sought counseling from a psychologist/psychiatrist more often ( $p=0,014$ ).

Concerning treatment, in Table 3 the summary of all reported treatments is shown. A wide range of therapies is available, and the most commonly offered ones include bladder instillations (undefined which ones) (81%), pelvic floor physical therapy (PFPT) (77%), medication (75%), such as paracetamol (67%), tricyclic antidepressant (23%) and nonsteroidal anti-inflammatory drug (NSAIDs) (21%), neuromodulation (39%) like percutaneous tibial nerve stimulation (PTNS) (47%), transcutaneous electrical nerve stimulation (TENS) (39%) or sacral nerve stimulation (SNS) (15%) and lasty, transurethral HL coagulation (30%). 60% of the HL+ patients underwent transurethral coagulation of the HL. There was no difference in the use of bladder instillations between HL+ and HL- patients.

When examining the efficacy of these therapies on symptoms as reported by patients themselves, transurethral HL coagulation and bladder instillations (undefined) yielded the best results. For pain, the treatments showed improvements in respectively 76% and 65% of the patients. Treatment in a pain therapy center did also improve pain symptoms in more than half of the patients. For urgency and frequency, the success rate was lower. Transurethral coagulation of HL was the only treatment that demonstrated notable improvement in sleep difficulties, with approximately one-third of the patients experiencing positive outcomes.

Intravesical botulin A injections were given in 20% of the patients, looking at that subgroup, those patients reported significantly more urinary frequency (90% vs 75%,  $p=0,041$ ) and urgency (85% vs 79%,  $p=0,045$ ). There was a slight correlation observed in these patients between the desire to treat urgency and the use of intravesical botulin A injections ( $p=0,058$ ).

Unfortunately, numerous patients did not experience any beneficial effect from various treatments. For PFPT, neuromodulation (especially PTNS and TENS) and hydrodistension over half of the patients reported no positive impact. A noticeable number of patients discontinued these treatments, with the majority (84%) of those having received PFPT reported that they had stopped. For transurethral HL resection and bladder instillations these numbers were evidently better. This demonstrates that treatment response varies between patients.

Regarding medication (Table 3C), more than two-third of the patients reported the use of paracetamol, which had a positive effect on symptoms in half of the cases. Other drugs, such as tricyclic antidepressant (like amitriptyline), NSAIDs and tramadol were used in fewer patients, and they also had a less impact on alleviating symptoms. Oxycodone was rarely used and had minimal effect on symptoms. Half of the patients reported use of prophylactic antibiotics in the past years for urinary tract infections.

**Table 3. Reported therapies received and perceived efficacy** This table presents data regarding the reported (alternative) therapies and the effect on symptoms and adherence to the treatment.

	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]
<b>A. Therapies</b>	<b>Received treatment</b>		<b>No effect</b>		<b>Pain</b>		<b>Urgency</b>		<b>Frequency</b>		<b>Sleep</b>		<b>Stopped treatment</b>	
Bladder instillation	153 (81)	[74-86]	46 (30)	[23-28]	100 (65)	[57-72]	61 (40)	[32-48]	55 (36)	[28-44]	24 (16)	[10-22]	86 (56)	[48-64]
Pelvic Floor Physical Therapy	146 (77)	[70-83]	84 (58)	[50-66]	38 (26)	[19-34]	29 (20)	[14-28]	29 (20)	[14-28]	7 (5)	[2-10]	124 (84)	[78-90]
Neuromodulation	75 (39)	[32-46]	42 (57)	[45-68]	24 (32)	[22-44]	16 (22)	[13-33]	12 (16)	[9-27]	4 (5)	[1-13]	48 (67)	[55-77]
Laser/coagulation	58 (30)	[24-37]	12 (21)	[11-33]	44 (76)	[63-86]	33 (57)	[43-70]	32 (55)	[41-68]	21 (36)	[24-50]	22 (42)	[28-56]
Hydrodistension	58 (30)	[24-37]	33 (56)	[42-69]	18 (31)	[19-44]	19 (32)	[21-46]	17 (29)	[18-42]	10 (17)	[8-29]	-	-
Intravesical botulin Therapy in Pain center	40 (21)	[15-27]	19 (48)	[32-64]	14 (35)	[21-52]	10 (25)	[13-41]	11 (28)	[15-44]	4 (10)	[3-24]	25 (63)	[46-77]
	31 (16)	[11-22]	12 (39)	[22-58]	18 (58)	[39-76]	4 (13)	[4-30]	3 (10)	[2-26]	3 (10)	[2-26]	19 (63)	[44-80]
<b>B. Alternative therapies</b>	<b>Received treatment</b>		<b>No effect</b>		<b>Effect on pain</b>		<b>Effect on urgency</b>		<b>Effect on frequency</b>		<b>Effect on sleep</b>		<b>Stopped treatment</b>	
Food supplements <sup>2</sup>	73 (38)	[31-46]	14 (19)	[11-30]	-	-	-	-	-	-	-	-	33 (46)	[34-58]
Acupuncture	59 (31)	[25-38]	36 (60)	[47-72]	22 (37)	[25-50]	8 (13)	[6-25]	8 (13)	[6-25]	5 (8)	[3-18]	50 (85)	[73-93]
Cannabis oil	54 (28)	[22-35]	28 (52)	[38-66]	18 (33)	[21-47]	4 (7)	[2-18]	4 (7)	[2-14]	17 (31)	[19-46]	38 (71)	[58-83]
Osteopathy	44 (23)	[17-30]	29 (64)	[49-78]	14 (31)	[18-47]	7 (16)	[7-30]	7 (16)	[7-30]	6 (13)	[5-27]	31 (72)	[56-85]
Orthomolecular therapy	28 (15)	[10-21]	13 (46)	[28-66]	13 (46)	[28-66]	4 (14)	[4-33]	5 (18)	[6-37]	5 (18)	[6-37]	12 (50)	[29-71]
Manual therapy	11 (6)	[3-10]	7 (58)	[28-85]	5 (42)	[15-72]	2 (17)	[2-48]	0 (0)	[0-3]	1 (8)	[0-38]	7 (64)	[31-89]
Smoking Cannabis	10 (5)	[3-10]	1 (9)	[0-41]	8 (72)	[39-94]	1 (9)	[0-41]	1 (9)	[0-41]	6 (55)	[23-83]	9 (69)	[39-91]
<b>C. Medication</b>	<b>Current use</b>		<b>Effect on symptoms<sup>1,3</sup></b>											
	N (%)	[95%-CI]	N (%)	[95%-CI]										
Paracetamol	96 (67)	[58-74]	65 (51)	[42-60]										

Amitriptyline	33 (23)	[16-31]	22 (17)	[11-25]
NSAIDs	30 (21)	[15-28]	33 (26)	[19-35]
Tramadol	26 (18)	[12-25]	11 (9)	[4-15]
Gabapentin/Pregabalin	14 (10)	[15-16]	10 (8)	[4-14]
Pentosan Polysulfate	14 (10)	[5-16]	28 (22)	[15-30]
Oxycodone	11 (8)	[4-13]	14 (11)	[6-18]

Percentages are in percent of cases. <sup>1</sup>This includes all patients, also earlier use. <sup>2</sup>This includes: Cystoprotek® (3), Prelief® (7), probiotics (45), Tumeric (22) and others (36). <sup>3</sup>Effect on symptoms, answered yes or no.

### 3.4.2. Alternative treatments

In addition to standard care, numerous patients (73%) sought relief through alternative therapies (Table 3B). Among these, food supplements (such as Probiotics, Cystoprotek®, Prelief® and Turmeric) were the most commonly used. Combined, they had the highest success rate with beneficial effects reported in 81% of the patients using them. However, from the group that used food supplements, only probiotics were frequently used and considered effective in 36% of these patients while all the other supplements were used less frequently by patients. Other alternative therapies, such as acupuncture, cannabis oil and osteopathy were used as well. However, a large percentage of patients reported no positive impact on symptoms of these therapies, which led to a high number of patients who discontinued them.

### 3.4.3. Lifestyle adjustments

Adjustments in lifestyle were frequently adopted by patients (Table 4). 66% of the patients reported to have changed their diet. Moreover, the majority of the patients adapted their lifestyle on different levels as well, such as: stress management (62%), exercise (38%), meditation (24%) and/or sleep health (22%). The urologist played a primary role in providing dietary advice, while the patient association also contributed to informing the patients. In terms of other lifestyle adjustments, additional contribution of the internet and personal experiences played a role.

Among the various lifestyle modifications, dietary changes demonstrated the most positive impact on symptoms, particularly in relation to pain relief. A small percentage of patients (22%) reported no noticeable effect, and an even smaller portion stopped their dietary changes. The second most applied and beneficial lifestyle adjustment was stress management, with a similar ratio of patients reporting no effect or discontinuing this change. Exercise and meditation yielded slightly lower success rates overall, except for sleep problems. Sleep-related lifestyle changes had a significant positive impact on sleep problems, but had comparatively less effect on other symptoms.

**Table 4. Reported Lifestyle adjustments** This table presents the reported lifestyle adjustments and the adherence to it. Moreover, the effect on symptoms is shown.

	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]	N (%)	[95%-CI]
Lifestyle adjustments	Applied adjustments		No effect		Stopped			
Dietary	127 (66)	[59-72]	24 (22)	[15-32]	17 (16)	[10-24]		
Avoid stress	87 (62)	[53-70]	16 (20)	[12-30]	15 (18)	[10-28]		
Exercise	54 (38)	[30-46]	15 (31)	[18-45]	4 (8)	[2-19]		
Meditation	34 (24)	[17-32]	9 (28)	[14-47]	3 (9)	[2-24]		
Sleep	31 (22)	[6-30]	10 (33)	[17-53]	4 (13)	[4-31]		
	Effect on pain		Effect on urgency		Effect on frequency		Effect on sleep	
Dietary	78 (73)	[63-81]	34 (32)	[23-41]	28 (26)	[18-36]	18 (17)	[10-25]
Avoid stress	37 (46)	[35-58]	9 (11)	[5-20]	10 (13)	[6-22]	8 (10)	[4-19]
Exercise	15 (31)	[18-45]	6 (12)	[5-25]	4 (8)	[2-20]	9 (18)	[8-32]
Meditation	13 (41)	[24-59]	1 (3)	[0-2]	1 (3)	[0-2]	8 (25)	[11-43]
Sleep	3 (10)	[2-27]	0 (0)	[0-12]	2 (7)	[1-22]	15 (50)	[31-69]

Percentages are percent of cases.

### 3.5. Men versus Women

This study cohort included 20 male patients, which is a distinctive group for analysis of a rare disease occurring mostly in women. Male patients were slightly older, 85% was older than 60 years in comparison to 55% for women. There were no significant differences in type of IC/BPS, but HL subtype was slightly more reported (55% versus 45%). Looking at symptoms, male patients showed more lower urinary tract symptoms (LUTS), significant more frequency complains ( $p=0,013$ ) and a trend towards more urgency symptoms ( $p=0,065$ ).

Concerning QoL, the influence of IC/BPS on their life and their experience of the disease did not differ from the female population. However, male patients did score significantly higher on the self-rated health score (EQ VAS), mean  $66,2 \pm 19,9$  versus  $54,1 \pm 25,9$  ( $p=0,045$ ) and had significantly fewer problems with anxiety (25%) in comparison to women (57%) ( $p=0,007$ ).

For treatments, there was only a significant difference for transurethral HL coagulation. Zooming in on the HL subgroup, male patients ( $n=11$ ) had undergone significant more transurethral HL coagulation in comparison to female HL+ patients ( $n=70$ ),  $p=0,027$ . The beneficial effect of this therapy on urinary frequency was better in the male population (80% reported a positive effect versus 47% in women,  $p=0,058$ ). Bladder instillations were also used slightly more often in men, 90% versus 79%, but this was not significant. Male patients made fewer use of alternative therapies, 40% versus 73% ( $p=0,023$ ). Lifestyle adjustments were applied in similar amounts, 75% versus 77%.

**Table 5. Differences between male and female participants** This table summarizes the most important findings between male and female participants, including; demographics, symptoms, quality of life and treatments.

A. Demographics	Male (n=20)		Female (n=166)		p-values
	N (%)	[95%-CI]	N (%)	[95%-CI]	
Age					
19-40 years	1 (5)	[1-25]	15 (9)	[5-14]	p=0,082
41-60 years	2 (10)	[1-32]	60 (36)	[29-44]	
>60 years	17 (85)	[62-97]	91 (55)	[47-63]	
Subtype IC/BPS <sup>1</sup>					
Type 1 (normal bladder wall)	2 (10)	[2-32]	3 (2)	[0-5]	p=0,770
Type 2 (glomerulations)	6 (30)	[12-54]	72 (46)	[38-54]	
Type 3 (Hunner's lesions)	11 (55)	[32-77]	71 (45)	[37-53]	
<b>B. Symptoms</b>					
Main symptoms <sup>2</sup>					
Pain	17 (85)	[62-97]	153 (94)	[87-96]	p=0,281
Frequency	20 (100)	[83-100]	126 (77)	[69-82]	<u>p=0,013</u>
Sleep difficulties	15 (75)	[51-91]	127 (78)	[69-83]	p=0,881
Urgency	18 (90)	[68-99]	117 (72)	[63-77]	p=0,065
<b>C. Quality of Life</b>					
What is the influence of IC/BPS on your life?					
0 (very small) – 5 (very big)	4,55	1,91	4,53	1,18	p=0,927
How do you experience your IC/BPS at this moment?					
0 (no complaints) – 4 (overwhelmed)	3,21	0,92	3,11	0,99	p= 0,927
EQ-5D 5L	N (%)	[95%-CI]	N (%)	[95%-CI]	p-values
<i>Mobility</i>					
No problems	9 (47)	[24-71]	73 (44)	[36-52]	p=0,778
Any problems	10 (53)	[29-76]	93 (56)	[48-64]	
<i>Self-care</i>					
No problems	18 (90)	[68-99]	146 (88)	[82-92]	p=0,789
Any problems	2 (10)	[1-32]	20 (12)	[8-18]	
<i>Usual activities</i>					
No problems	6 (30)	[12-54]	39 (24)	[17-31]	p=0,521
Any problems	14 (70)	[46-88]	127 (76)	[69-83]	
<i>Pain</i>					
No problems	0(0)	[0-17]	14 (8)	[5-14]	p=0,177
Any problems	20 (100)	[83-100]	151 (92)	[86-95]	
<i>Anxiety</i>					
No problems	15 (75)	[51-91]	72 (43)	[36-51]	<u>p=0,007</u>
Any problems	5 (25)	[9-49]	94 (57)	[49-64]	
	Mean	SD	Mean	SD	p-values

EQ VAS scale (0-100)	66,15	19,87	54,05	25,85	p=0,045
<b>D. Therapies</b>	<b>N (%)</b>	<b>[95%-CI]</b>	<b>N (%)</b>	<b>[95%-CI]</b>	<b>p-values</b>
<i>Received therapies<sup>2</sup></i>					
Bladder instillations	17 (90)	[67-99]	129 (79)	[72-85]	p=0,268
Pelvic Floor Physical Therapy	15 (75)	[51-91]	126 (77)	[70-83]	p=0,817
Neuromodulation	11 (55)	[32-77]	60 (36)	[29-44]	p=0,101
Laser/coagulation	10 (50)	[27-73]	47 (29)	[22-36]	p=0,051
Hydrodistension	3 (15)	[3-38]	54 (33)	[26-41]	p=0,103
Intravesical botulin A	3 (15)	[3-38]	34 (21)	[15-27]	p=0,555
Therapy in pain center	1 (5)	[1-26]	29 (18)	[12-24]	p=0,167
<i>Alternative therapies</i>					
Yes	8 (40)	[19-64]	102 (68)	[59-75]	p=0,023
No	12 (60)	[36-81]	49 (32)	[25-41]	
<i>Lifestyle adjustments</i>					
Yes	15 (75)	[51-91]	125 (77)	[69-83]	p=0,867
No	5 (25)	[9-49]	38 (23)	[17-31]	

Percentages are in percent of cases; <sup>1</sup>Based on the ESSIC classification of types of bladder pain syndrome; <sup>2</sup>Counts of participants who reported to have received the treatment.

#### 4. Discussion

This study showed that the QoL is clearly affected by IC/BPS. This is evident from the substantial self-reported impact by patients, the various affected domains (with in particular pain, everyday activities and anxiety-related issues), as well as the delayed diagnosis. The latter being >6 years in 30% of participants. Pain was the dominant symptom and, together with anxiety affect subjective perception of disease severity. Interestingly, in our study, there were fewer reported issues and less emphasis on addressing urgency, a key symptom of IC/BPS. Another important finding was the occurrence of problems with sleep. Finally, the third major finding was the wide array of (alternative) treatments utilized, although with doubtful results and high dropout rates.

Regarding the primary question of this study, our findings are in line with the previous research which has shown that the IC/BPS population experiences lower health related QoL [5,8,10,13]. This study revealed that HL+ patients experience a significant greater impact on their lives compared to HL- patients. Even though, this difference was clinically very small and the symptom burden did not differ within our study. But still this small difference underlines that these patients could be regarded as a more severe subgroup [19]. For all patients, there was a more positive disease experience in their current situation than what might have been expected based on their symptoms, impact on QoL, among other factors. This could suggest that these patients have adopted certain coping mechanisms. Previous research has linked catastrophizing and dwelling on distress to poorer experiences of the disease and prolonged distress [9,23,24]. Conversely, seeking emotional or instrumental social support has been associated with better adjustment [25,26]. Therefore, since this study population is drawn from the patient association, this may explain the more optimistic disease experience.

The second objective of this study covered demographics and symptoms. The study population resembled the known IC/BPS population concerning sex- and age distribution [5,15]. Diagnostics delay, as highlighted in previous research, was also negatively correlated with pain in our own study [5]. Not surprisingly, together with anxiety, pain is associated with a more negative perspective on the disease. The process of pain sensitization have been well described for chronic pain patients [27]. Nickel et al. found comparable results, and reported that depression scores were significantly correlated with poorer QoL and increased pain [10]. Furthermore, mental health disorders are common in patients with urological pain syndromes [11]. Even though urgency was not reported a very dominant symptom in our survey. At least, not as what would have been expected. It is a key symptom of IC/BPS. The sensation of urinary urgency often differs in IC/BPS compared to patients suffering from overactive bladder (OAB) and relates more to pain and discomfort during bladder filling instead of sudden onset urgency with fear of incontinence that is more typical for OAB [28]. Our study also revealed a high prevalence of sleep disturbances. These results are consistent with

previous research [6,15]. As stated by Nickel et al, these disturbances can encompass more than just nocturia and potentially set up a vicious cycle, as poor sleep itself is linked to mood disturbances and diminished QoL [15,29–31]. Even though, we found that patients do not prioritize addressing sleep problems in their treatment, which might be because this topic receives insufficient attention in clinical consultations.

A third focus was patients perceived efficacy on the various treatments. Bladder instillations were received most often. In the Dutch clinical guideline, bladder instillations mostly concern glycosaminoglycan (GAG) instillations, with a shift from dimethyl sulfoxide to GAG instillations since 1995 [2,18]. European guidelines recommends intravesical GAG therapies with low level of evidence, but it is not mentioned in the AUA guideline since it is not FDA approved. The latter still mainly focuses on dimethyl sulfoxide [18,19,22]. Transurethral resection of HL is strongly recommended in all guidelines and is commonly received with good success rates in our study, indicating its suitability for HL+ patients. Availability and treatment approaches vary in the world, reflected in our study with no triamcinolone injections the low use of pentosan polysulfate, which only became available and reimbursed since 2020 within the Netherlands and no data on oral cyclosporine, which has only become available off label since 2023.

This study highlighted a striking number of patients who experienced no therapy benefit and discontinued treatments. This emphasizes the importance of personalized care and stratifying patients to determine the most suitable treatment for each individual. In case of PFPT, only 40% received biofeedback and 17% trigger point therapy. Among these subgroups, there was a slightly better response. Our study was not designed to specifically measure therapy efficacy but reflects the patient experience and their adherence to treatment. Also it did not evaluate whether treatments were combined, such as PFPT with pharmacological pain management, which could influence patient perceived efficacy. Therapies in the alternative field were explored often by patients, but yielded only minimal beneficial effects on symptoms.

Guidelines acknowledge the additional significance of behavioral modification therapies, which our study shows patients have successfully adopted. In particular, dietary adjustments and stress management, also recommended by guidelines, yielded the best results in our study. We observed that patients were able to adhere to lifestyle modifications when implemented. It is worth noting that our study did not measure whether the level of modifications remained in the long-term, but the observed effects seem substantial enough for patients to continue these changes to some degree.

Lastly, the analysis of the male subgroup of IC/BPS revealed a 1:9 male to female ratio in this dataset and an older age distribution compared to women, consistent with findings of Tincello et al. [5]. In our cohort, male patients presented with more LUTS complaints, which makes them a more challenging group to identify within an already rare disease. HL- male patients could be under or misdiagnosed because of potential prostate related disease that is prevalent in the reported age category. Male patients experienced their overall health better compared to women, and also reported significantly fewer issues with anxiety. Serious problems with mental health have been reported similar for male and female IC/BPS patients [11]. It could be speculated that male patients both received and preferred more thorough treatments options, as they underwent transurethral coagulation of HL significantly more often and sought relief in alternative therapies less frequently.

One potential limitation of this research lies in its retrospective nature, which could potentially increase the likelihood of recall bias. The survey was made accessible to individuals through the Dutch IC/BPS patient association. Nonetheless, since participation was voluntary, it may be susceptible to response bias. This may be reflected in the relatively high number of HL patients in this dataset. Questions were designed to limit survey bias, however, it is important to note that only a minor fraction of the questions (approximately 10%) was derived from validated questionnaires. Together these factors could potentially lead to an underrepresentation of IC/BPS patients experiencing mild symptoms.

## 5. Conclusions

This study reaffirms that the QoL of individuals with IC/BPS remained impaired. There is a reduction in diagnostic delay and some treatments like coagulation therapies and intravesical treatments are the most appreciated by patients. The diverse responses and sometimes poor efficacy and adherence to various treatments is an intriguing issue, which could possibly be addressed by a more personalized approach, often referred to as phenotype-oriented therapy, which potentially could yield better outcomes. Also taking into consideration that there are sex differences in BPS/IC symptom burden and treatment appreciation. The ongoing challenge is to underscore the importance of incorporating QoL and patient perspective on treatments in guidelines..

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