Effect of focal and diffuse hypervascularization as cystoscopic findings on predicting intravesical therapy response in patients with bladder pain syndrome

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ABSTRACT

Objective: To define the relationship between cystoscopic findings, including novel findings such as the hypervascularization, of bladder pain syndrome/interstitial cystitis (BPS/IC) and the response to intravesical therapy.

Material and methods: We retrospectively evaluated cystoscopy findings in patients who had a preliminary diagnosis of BPS/IC. All patients received early intravesical combined therapy (ICT), ie, within 2 hours after hydrodistention. Additionally, ICT was continued according to our protocol. Cystoscopic findings were classified as glomerulations, hypervascularization, and Hunner's lesion (HL). The therapy responses were evaluated at 1st, 3rd, 6th, and 12th months using the visual analog scale (VAS), O'Leary/Sant interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI) scores.

Results: Out of 61 patients, HL was diagnosed during cystoscopy in six (9.8%) patients, glomerulations in 35 (57.4%) patients, and hypervascularization in 15 (24.6%) patients. No pathological findings were defined in five (8.2%) patients. In the glomerulation and hypervascularization group, the median VAS, ICSI, and ICPI scores were lower than those in the preoperative period in the follow-up. In patients with HL, the median VAS scores were lower in the entire follow-up compared to the preoperative period, with an increase at 1st year compared to 6th month, and ICSI scores were lower than preoperative period in the entire follow-up, with an increase at 3rd month and 1st year. ICPI scores were also lower during the follow-up, with an increase observed in the 1st year.

Conclusion: The presence of hypervascularization should be defined since it might show different characteristics that may affect the ICT response. Patients with glomerulations might be good candidates for early combined intravesical therapy.

Keywords: Bladder pain syndrome; chondroitin sulfate; glomerulations; hyaluronic acid; hypervascularization; interstitial cystitis.

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Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is one of the most challenging disorders in urology clinical practice and affects both sexes. It is characterized by persistent or recurrent chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as an urgent need to void or increased urinary frequency.[1] Differential diagnosis is especially important for the diagnosis of BPS/IC, and many clinical situations, such as carcinoma in situ of the bladder, cystitis with various etiologies, prostate-related diseases, etc., must be first excluded.[2]

Although cystoscopy has been widely used in the diagnosis of BPS/IC, there is no consensus on its diagnostic role. The European Society

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for the Study of Interstitial Cystitis (ESSIC) guidelines recommend cystoscopy for phenotyping, and the American Urological Association recommends cystoscopy only for complex presentations. Defining different phenotypes of BPS/IC plays an important role in the management and prognosis of disease because of diverse symptoms and different levels of pain. ESSIC recommends the classification of types of BPS on the basis of the combination of cystoscopy with hydrodistention and bladder biopsy. Cystoscopy findings were defined as normal, glomerulations (including only grade 2 or 3 glomerulations), and Hunner's lesions (HLs). According to ESSIC, this classification was constructed to create homogeneous groups to better analyze the disease.[2,3]

There are various studies classifying BPS/IC as classic and nonulcer disease according to the presence of HLs. Peeker and Fall[4] showed that patients with classic BPS/IC have smaller bladder capacity, and there was no difference between the two groups in terms of symptom severity. Thus, they emphasized that cystoscopic subtyping is mandatory, and that two different subtypes should be evaluated individually. Doiron et al.[5] compared the severity of symptoms according to whether the patients had HL. They found that patients with HL had higher rates of pain, frequency, and nocturia. Glomerulation and submucosal hemorrhage during bladder filling are auxiliary factors when subdifferentiating BPS/IC. Glomerulations are not specific to BPS/IC and can be found in healthy populations. However, only a few studies have investigated the relationship between glomerulations and symptom severity, and no significant difference has been revealed.[6,7]

BPS/IC patients exhibit a wide range of symptom severities and variations and different degrees of treatment responses. A limited number of studies have evaluated symptom severity and treatment responses according to the different phenotypes of BPS/IC, which revealed controversial results. In this study, we aimed to analyze different subtypes of BPS/IC according to cystoscopic findings and their relationship with intravesical therapy response.

Main Points

- To predict intravesical combined therapy response, cystoscopic classification should be used.
- Hypervascularization as a cystoscopic finding shows different characteristics in the manner of intravesical-combined therapy response.
- Glomerulations might be good candidates for early combined intravesical therapy.

Material and Methods

Clinical data were obtained retrospectively from a prospectively populated database of a single referral center. All procedures in this study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments. Ethical committee approval was received from Istanbul Medeniyet University Ethics Committee (No. 2019/0124). Verbal informed consent was obtained from all participants who participated in this study. Between January 2017 and December 2019, patients with chronic pelvic pain, pressure, or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as the persistent urge to void or frequency, were diagnosed with BPS/IC according to ESSIC criteria.[2] Detailed history, physical examination, urine analysis, urine culture, uroflowmetry, postvoid residual urine volume, prostate-specific antigen value in male patients older than 50 years, and urinary ultrasound were performed routinely. After excluding other-related disorders, patients who had a diagnosis of BPS/IC were planned for cystoscopy and hydrodistention. Demographic characteristics, previous treatments related to BPS/IC, previous interventions and surgeries, 3-day bladder diary, and concomitant incontinence were noted. Patients who had previous treatments for BPS/IC and also treatment naïve patients were included in our study (Table 1).

A total of 83 patients were evaluated for BPS/IC. Ten patients missing follow-up data, three patients who did not tolerate intravesical treatment, and nine patients who did not accept the cystoscopy and hydrodistention procedure were excluded from the study. Sixty-one patients underwent cystoscopic examination and hydrodistention with a sterile urine culture.

Cystoscopy was performed by the same urologist (BE) in our institution under general anesthesia, and all patients started early 50 mL intravesical combined therapy (ICT) (2% sodium chondroitin sulfate + 1.6% sodium hyaluronic acid; iAluril®; IBSA, Lugano, Sweden) within 2 hours after surgery. The National Institute of Diabetes and Digestive and Kidney Diseases recommends that cystoscopy and HD be performed under anesthesia at a pressure of 80-100 cm H_2O, lasting 1-2 minutes, and up to two cycles. Emptying should be started after waiting for 3 minutes with the bladder fully distended. During filling and emptying, which can be repeated one more time, endoscopic assessment is performed. Cystoscopic findings were noted as glomerulations, hypervascularization with or without glomerulation, and HL (Figures 1-4). The presence of HLs or glomerulations that are diffuse in at least three quadrants with

Table 1. Demographic and Clinical Characteristics of Total Cohort and Groups

		Minimum-maximum	Median	Ave. ± SD
Total				
Age (years)		13.0-74.0	53.0	51.0 ± 14.0
Sex	Female			58 (95.1%)
	Male			3 (4.9%)
Previous treatments	None			34 (55.7%)
	Anticholinergics			13 (21.3%)
	Intravesical treatment			8 (13.1%)
	Pregabalin			6 (9.8%)
	Pentosan polysulfate			6 (9.8%)
	Ozone therapy			2 (3.3%)
	Botox			1 (1.6%)
Height (cm)		145.0-185.0	160.0	161.7 ± 7.2
Weight (kg)		45.0-95.0	71.0	71.9 ± 12.2
BMI (kg/m^2)		18.1-39.1	27.3	27.6 ± 4.9
Number of micturitions (day)		4.0-38.0	10.5	12.4 ± 6.8
Number of micturitions (night)		0.0-10.0	3.0	4.1 ± 2.9
Number of urgency		0.0-20.0	1.0	5.7 ± 6.9
No Cystoscopic Findings				
Age (years)		44.0-64.0	61.0	57.2 ± 8.1
Sex	Female			5 (100.0%)
	Male			0 (0.0%)
Previous treatments	None			1 (20.0%)
	Anticholinergics			1 (20.0%)
	Intravesical treatment			2 (40.0%)
	Pregabalin			0 (0.0%)
	Pentosan polysulfate			2 (40.0%)
	Ozone therapy			0 (0.0%)
	Botox			0 (0.0%)
Height (cm)		155.0-170.0	158.0	160.2 ± 6.1
Weight (kg)		61.0-94.0	71.0	74.0 ± 13.1
BMI (kg/m^2)		24.4-39.1	27.1	28.9 ± 5.8
Number of micturitions (day)		7.0-20.0	12.0	12.8 ± 5.9
Number of micturitions (night)		2.0-10.0	6.5	6.3 ± 4.3
Number of urgency		0.0-0.0	0.0	0.0 ± 0.0
Glomerulations				
Age (years)		13.0-74.0	51.0	47.9 ± 16.0
Sex	Female			32 (91.4%)
	Male			3 (8.6%)
Previous treatments	None			21 (60.0%)
	Anticholinergics			6 (17.1%)
	Intravesical treatment			2 (5.7%)
	Pregabalin			2 (5.7%)
	Pentosan polysulfate			4 (11.4%)
	Ozone therapy			1 (2.9%)
	Botox			0 (0.0%)

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Table 1. Demographic and Clinical Characteristics of Total Cohort and Groups (Continued)

		Minimum-maximum	Median	Ave. ± SD
Height (cm)		145.0-185.0	162.0	162.9 ± 8.4
Weight (kg)		45.0-95.0	70.0	69.6 ± 13.8
BMI (kg/m^2)		18.1-37.1	26.0	26.3 ± 5.2
Number of micturitions (day)		4.0-38.0	10.0	12.2 ± 7.8
Number of micturitions (night)		0.0-10.0	2.0	3.4 ± 2.9
Number of urgency		0.0-20.0	0.5	5.1 ± 7.1
		Hypervascularization		
Age (years)		40.0-70.0	55.0	54.8 ± 9.6
Sex	Female Male			15 (100.0%) 0 (0.0%)
Previous treatments	None Anticholinergics Intravesical treatment Pregabalin Pentosan polysulfate Ozone therapy Botox			8 (53.3%) 4 (26.7%) 4 (26.7%) 4 (26.7%) 0 (0.0%) 1 (6.7%) 0 (0.0%)
Height (cm)		150.0-165.0	158.0	159.1 ± 4.3
Weight (kg)		60.0-95.0	74.0	75.7 ± 9.6
BMI (kg/m^2)		24.7-35.0	30.4	29.9 ± 3.4
Number of micturitions (day)		5.0-20.0	14.5	13.6 ± 5.7
Number of micturitions (night)		2.0-10.0	4.0	4.6 ± 2.4
Number of urgency		0.0-20.0	9.5	9.0 ± 6.6
		Hunner's Lesion		
Age (years)		33.0-65.0	57.5	54.3 ± 11.9
Sex	Female Male			6 (100.0%) 0 (0.0%)
Previous treatments	Nonee Anticholinergicse Intravesical treatmente Pregabaline Pentosan polysulfatee Ozone therapye Botox			4 (66.7%) 2 (33.3%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 1 (16.7%)
Height (cm)		153.0-170.0	165.0	162.8 ± 6.2
Weight (kg)		70.0-77.0	74.0	73.7 ± 2.5
BMI (kg/m^2)		24.2-32.9	27.2	27.9 ± 2.9
Number of micturitions (day)		6.0-16.0	10.0	11.0 ± 4.0
Number of micturitions (night)		2.0-8.0	6.0	5.2 ± 2.3
Number of urgency		0.0-15.0	0.0	3.8 ± 7.5

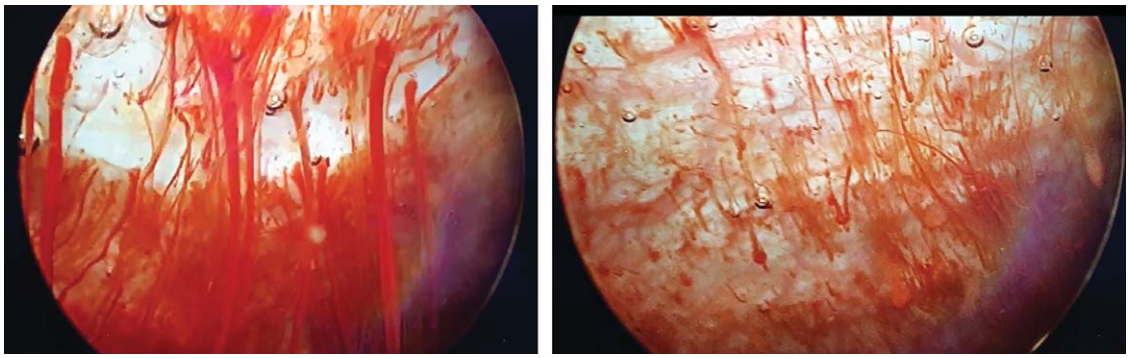


Figure 1. Diffuse global mucosal bleeding after hydrodistention that was defined as glomerulation.

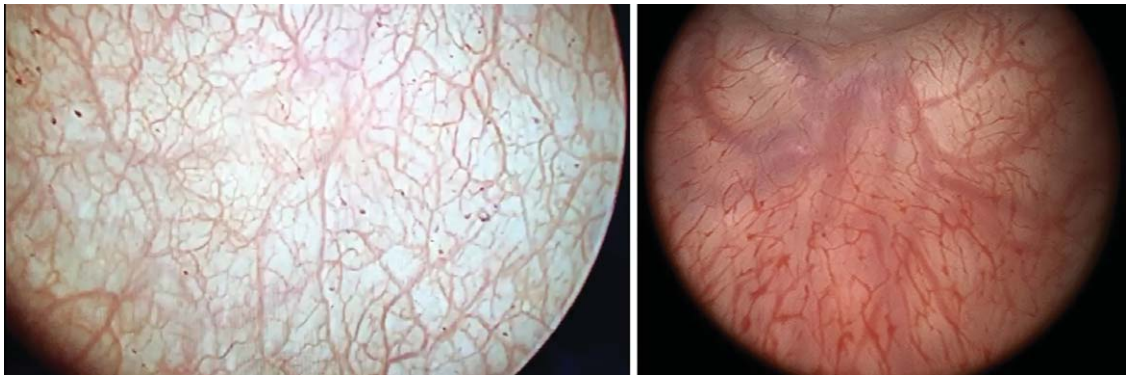


Figure 2. Increased vascularization in more than two walls of the bladder that was defined as diffuse hypervascularization.

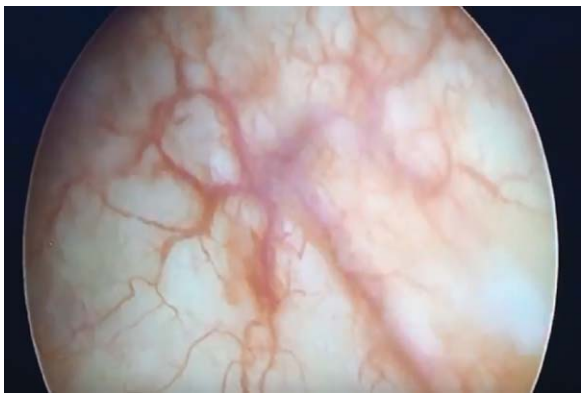


Figure 3. Increased vascularization in one or two walls of the bladder that was defined as focal hypervascularization.

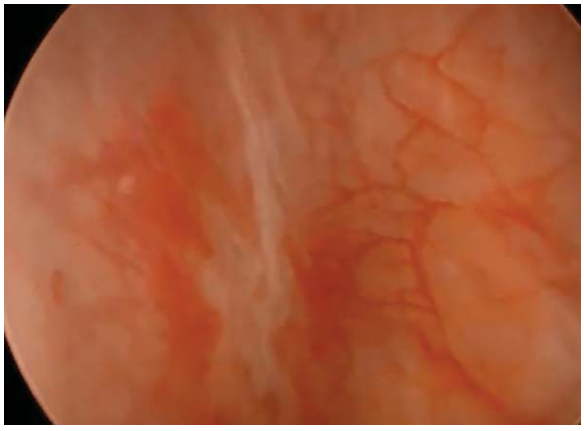


Figure 4. Reddened mucosal area with small vessels radiating toward a central scar that was defined as Hunner's lesion.

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10 glomerulations per quadrant was considered positive findings in favor of IC/BPS. HLs fulguration was not applied. There are patients who do not have normal cystoscopic findings and do not fit with glomerulations or HLs. Bladder tissues that have an abnormal or excessive formation of blood vessels are defined as increased vascularization. It was defined as diffuse vascularization if increased vascularization was observed in more than two walls of the bladder, and as focal vascularization if increased vascularization was observed in one or two walls of the bladder. It is also important differing hypervascularization from carcinoma in situ which has flat, reddish mucosal lesions, that clearly differs from "Hypervascularization" phenotype because in hypervascularization, there is no mucosal pathology. In the present study, we examined the type, severity, and consistency of vascularization as a new predictive factor in treatment response to ICT.

Additionally, ICT was continued weekly for 8 weeks, two times in the following month, and then monthly for 7 months (17 times in total). The therapy responses were evaluated face to face using visual analog scale (VAS), O'Leary/Sant interstitial cystitis symptom index (ICSI), and interstitial cystitis problem index (ICPI) scores.[8] The relationship between cystoscopic findings and early started ICT response was evaluated at the 1st, 3rd, 6th, and 12th months, before the intravesical therapies.

Statistical Analysis

Average, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov–Smirnov test, assuming normality at $P > .05$. The Wilcoxon test was used to analyze dependent quantitative data. $P \leq .05$ was considered to be significant. Statistical Package for the Social Sciences (SPSS) version 26 (IBM SPSS Corp.; Armonk, NY, USA) was used for the analysis.

Results

Among 61 patients, 58 were female (95.1%) and three were male (4.9%). The mean age was 51 years, with a range between 13 and 74 years (mean 51 $\pm$ 14 years). The previous treatment history and demographic features of the patients are summarized in Table 1.

The entire cohort was divided into four groups according to the cystoscopic findings. Patient demographics, cystoscopic findings, and treatment responses were analyzed. Five (8.2%) patients had no pathological findings on cystoscopy. Glomerulations were diagnosed in 35 (57.4%) patients, hypervascularization in 15 (24.6%) patients, and HLs in six (9.8%) patients.

Median VAS, ICSI, and ICPI scores were significantly decreased in the glomerulation group in the 1st month compared to baseline (median 90 vs. 30 for VAS scores, $P = .001$; median 17 vs. 8 for ICSI scores, $P = .001$; median 16 vs. 8 for ICPI scores, $P = .001$), and these scores were significantly lower than the preprocedural period in the 3rd and 6th months, as well as in the final assessment (Table 2).

In the hypervascularization group, VAS, ICSI, and ICPI scores were significantly lower at the 1st, 3rd, 6th, and 12th months than at the first evaluation ($P < .005$). Additionally, all scores maintained the decrease as a straight curve in the follow-up (Tables 2 and 3). In the hypervascularization group, it was also observed that in the 1st month of treatment, those patients had higher VAS and ICPI scores than those in the glomerulation group (50 vs. 30, $P = .03$; 12 vs. 8, $P = .053$) (Table 4).

In patients with HL, VAS scores decreased in the 1st month, and these scores were lower at the 3rd and 6th months but slightly increased at the last follow-up. Similarly, ICSI scores decreased in the 1st month; however, ICSI scores were found to be increased at the 3rd month and last follow-up. ICPI scores decreased in the 1st month; however, at the last follow-up, ICPI scores increased to the initial values (Table 5). No cystoscopic findings group and the HLs' group had a limited number of patients, so we did not perform any statistical analysis of the groups (Table 3).

Bladder capacity was also measured after hydrodistention was performed under general anesthesia. Patients with HLs had the smallest bladder capacity, but no significant difference was noted among all the groups (median 400 mL for the HLs group vs. 675 mL for the hypervascularization group and 650 mL for the glomerulation group, $P = .166$) (Table 6).

Discussion

For patients with BPS/IC, after lifestyle and behavioral changes are made, intravesical therapy is the second-line treatment option and is the treatment of choice worldwide.[3] There are various intravesical treatment regimens applied by clinicians, and we prefer to start intravesical treatment early as possible after hydrodistention, as it can be applied to low-grade noninvasive bladder cancer. Similarly, we intended to increase its efficacy by providing optimal penetration of intravesical therapy into disrupted and exposed bladder tissue after hydrodistension. In daily practice, some patients respond to intravesical treatments, while others do not respond and need further treatments such as neuromodulation and even cystoplasty, regarded as the last treatment choice.[3] There is no consensus to predict which patients will not respond to treatment. Therefore,

Table 2. Intravesical Treatment Responses in "Glomerulations" Group and "Hypervascularization" Group

	Minimum-maximum	Median	Ave. ± SD	*P**	*P***
		Glomerulations			
		VAS			
Before cystoscopy	30.0-100.0	90.0	79.1 ± 23.3		
1st month	0.0-90.0	30.0	30.8 ± 27.4	***.000***†	
3rd month	0.0-100.0	20.0	32.6 ± 36.3	***.000***†	.254†
6th month	0.0-100.0	80.0	60.9 ± 38.4	***.047***†	.222†
1st year	0.0-100.0	45.0	42.1 ± 35.9	***.000***†	***.043***†
		ICSI			
Before cystoscopy	7.0-20.0	17.0	16.1 ± 3.8		
1st month	2.0-18.0	8.0	8.5 ± 4.2	***.000***†	
3rd month	1.0-20.0	9.0	9.7 ± 6.0	***.001***†	.581†
6th month	1.0-20.0	12.0	10.5 ± 7.0	***.001***†	.342†
1st year	0.0-20.0	6.0	9.1 ± 6.7	***.000***†	.509†
		ICPI			
Before cystoscopy	7.0-20.0	16.0	14.0 ± 3.0		
1st month	2.0-15.0	8.0	7.1 ± 3.5	***.000***†	
3rd month	0.0-16.0	8.0	8.0 ± 5.1	***.000***†	.861†
6th month	0.0-16.0	9.0	8.9 ± 6.0	***.000***†	.383†
1st year	0.0-16.0	7.0	7.9 ± 5.6	***.000***†	.430†
		Hypervascularization			
		VAS			
Before cystoscopy	30.0-100.0	100.0	87.3 ± 23.1		
1st month	20.0-100.0	50.0	59.2 ± 22.3	***.011***†	
3rd month	0.0-100.0	50.0	44.0 ± 34.1	***.012***†	***.041***†
6th month	10.0-100.0	50.0	58.6 ± 38.0	***.039***†	.891†
1st year	0.0-100.0	40.0	49.1 ± 35.3	***.011***†	.461†
		ICSI			
Before cystoscopy	3.0-20.0	18.0	16.8 ± 4.8		
1st month	4.0-20.0	13.0	12.1 ± 5.7	***.008***†	
3rd month	0.0-20.0	10.5	10.6 ± 6.7	***.018***†	.285†
6th month	6.0-20.0	10.0	11.3 ± 5.1	***.027***†	.593†
1st year	4.0-20.0	12.0	12.2 ± 5.5	***.016***†	.598†
		ICPI			
Before cystoscopy	4.0-16.0	16.0	13.3 ± 3.9		
1st month	2.0-16.0	12.0	10.5 ± 4.8	***.012***†	
3rd month	0.0-18.0	8.0	9.6 ± 5.8	***.044***†	.854†
6th month	1.0-16.0	7.0	8.3 ± 4.9	***.048***†	.194†
1st year	1.0-16.0	10.0	10.2 ± 4.5	***.024***†	.345†

Abbreviations: ICPI, O'Leary/Sant interstitial cystitis problem index; ICSI, O'Leary/Sant interstitial cystitis symptom index; VAS, visual analog scale.

*Compared to "Before cystoscopy."

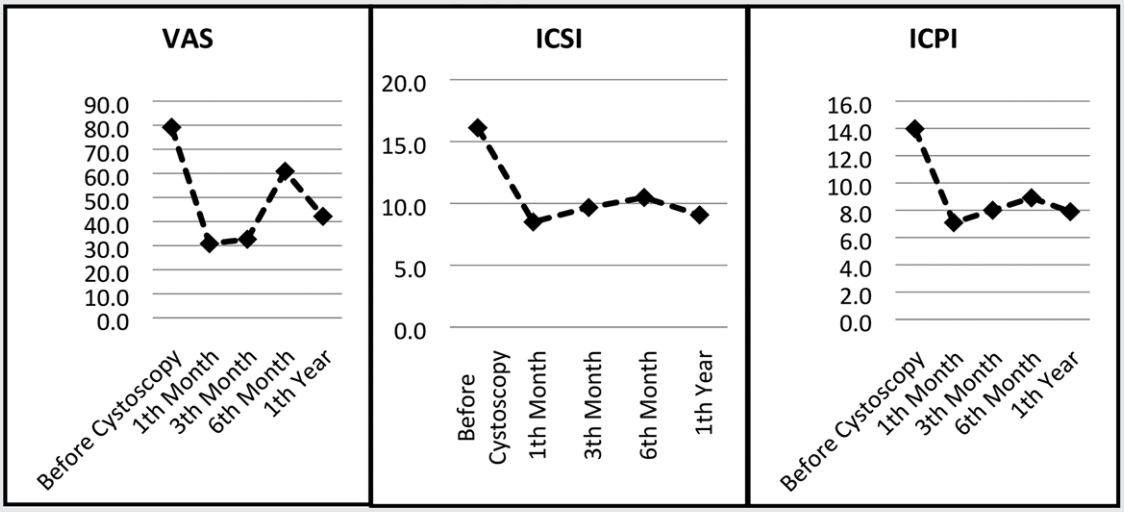
**Compared to former evaluation.

†Wilcoxon test.

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Table 3. Treatment Responses According to Cystoscopic Findings

Glomerulations



Hypervascularization

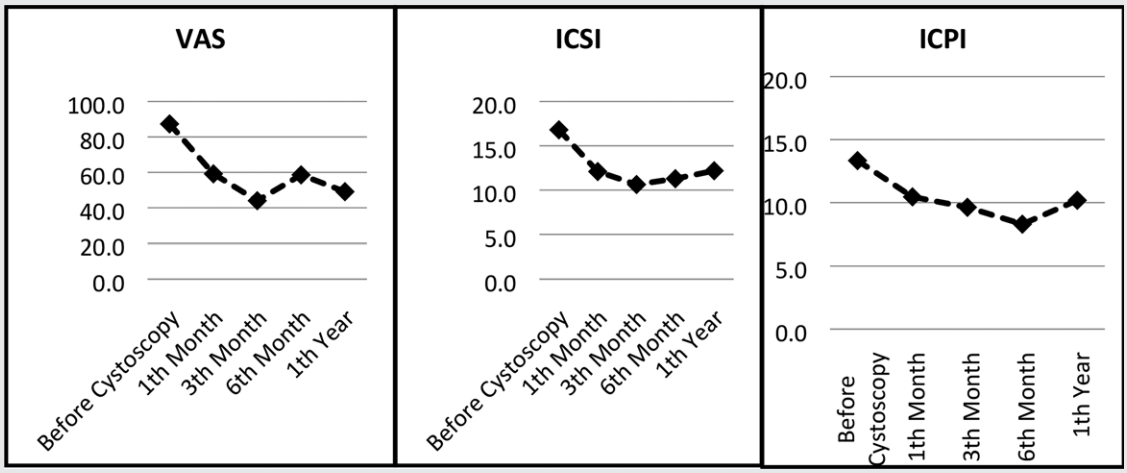
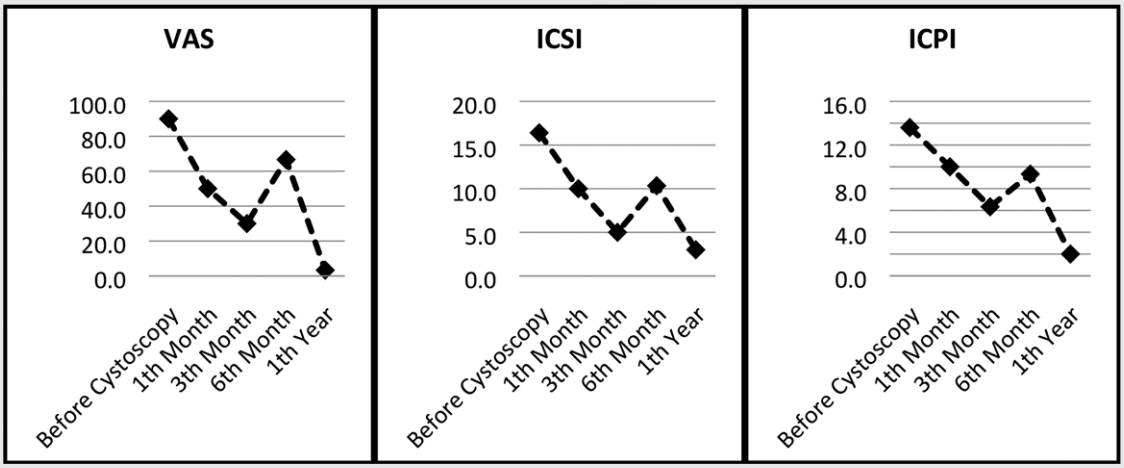
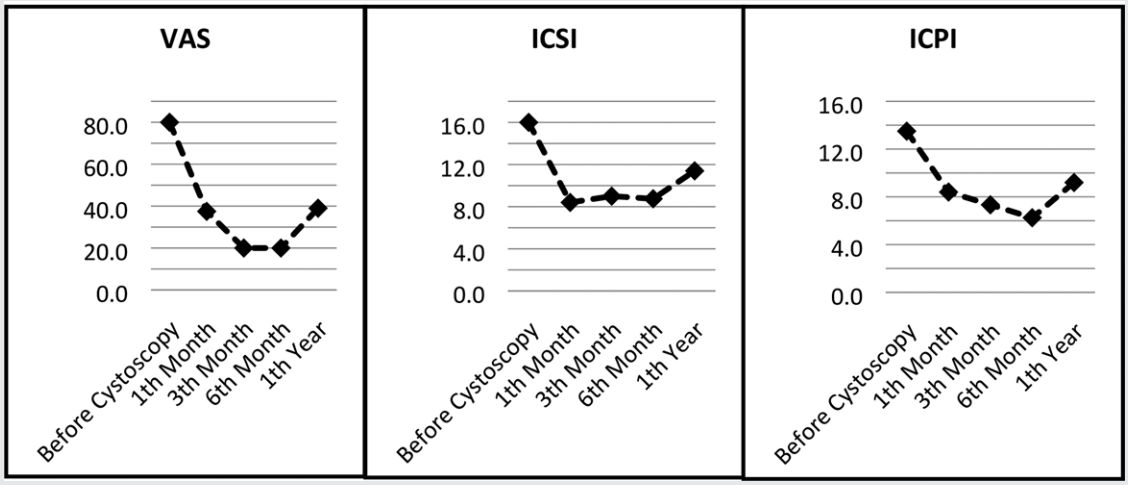


Table 3. Treatment Responses According to Cystoscopic Findings (Continued)

No cystoscopic findings



Hunner's lesion



Abbreviations: ICPI, O'Leary/Sant interstitial cystitis problem index; ICSI, O'Leary/Sant interstitial cystitis symptom index; VAS, visual analog scale.

we aimed to investigate the role of cystoscopic findings in predicting the response to intravesical treatment. The phenotyping of patients by cystoscopy might have great implications when dealing with BPS/IC. During the intravesical treatment, we observed that some patients had higher pain and symptom scores than others (Table 5). Some of those patients had diverse cystoscopic findings that differed from those previously defined, such as glomerulations or HLs as defined by ESSIC, which only show focal or diffuse increased vascularity on the bladder tissue.[2] We created this new definition because we thought that cystoscopic definitions in BPS were insufficient, and we observed that this increased vascularization manifested with different symptoms (Figures 1-4). Therefore, we considered patients with evidence of hypervascularization only as a separate group and evaluated their responses to intravesical therapy. This is the first study that defines increased vascularization as a cystoscopic finding and links those cystoscopic phenotypes to intravesical therapy response.

When we evaluated the responses, the hypervascularization group had significantly higher VAS and ICPI scores than the glomerulation group in the first month during the treatment. While the pain score in the glomerulation group decreased to one-third, the score in the hypervascularization group

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decreased by half in the first month. Kiuchi et al.[9] evaluated the relationship between increased vascular endothelial growth factor (VEGF) expression and pain severity in BPS/IC. They emphasized that in BPS/IC, when they examined cold-cup biopsies, they found immunohistochemically increased VEGF expression, microvessel density, and immature microvessels. Furthermore, they combined increased VEGF expression with pain severity and found that the increased VEGF expression was significantly higher in patients with severe pain than in patients with mild pain. However, they associated increased vascularity with glomerulation; in our study, there was a separate group of patients with only hypervascularization and without glomerulation.

Peng et al.[10] investigated the VEGF, Bcl-2-associated X protein (Bax), and phospho-p38 (p-p38), and immunohistochemistry staining for apoptotic and mast cell activity in BPS/IC patients treated with 100-U onabotulinum toxin A. They found that increased VEGF was associated with reduced bladder capacity and bladder inflammation, which decreased after repeated injections and hydrodistention. VAS pain scores have also decreased after repeated treatment. Furuta et al.[11] studied bladder biopsies of BPS/IC female patients. In their study, it was stated that bladder angiogenesis, which was shown by the expression of CD31 and VEGF immunohistochemically, was correlated with pain severity and urinary frequency in BPS/IC.

Table 4. Comparison of VAS, ICSI, and ICPI between "Glomerulations" and "Hypervascularization" Groups

	Glomerulations vs. hypervascularization	
	Median	***P***
VAS		
Before cystoscopy	90.0 vs. 100.0	.145*
1th month	30.0 vs. 50.0	**.03***
3th month	20.0 vs. 50.0	.403*
6th month	80.0 vs. 50.0	.98*
1th year	45.0 vs. 40.0	.529*
ICSI		
Before cystoscopy	17.0 vs. 18.0	.289*
1st month	8.0 vs. 13.0	.133*
3rd month	9.0 vs. 10.5	.683*
6th month	12.0 vs. 10.0	.749*
1st year	6.0 vs. 12.0	.125*
ICPI		
Before cystoscopy	16.0 vs. 16.0	.793*
1st month	8.0 vs. 12.0	**.053***
3rd month	8.0 vs. 8.0	.461*
6th month	9.0 vs. 7.0	.730*
1st year	7.0 vs. 10.0	.239*

Abbreviations: ICPI, O'Leary/Sant interstitial cystitis problem index; ICSI, O'Leary/Sant interstitial cystitis symptom index; VAS, visual analog scale.

*Mann–Whitney U test.

As intravesical treatment, we preferred a combination of chondroitin sulfate and hyaluronic acid. In every subgroup, we observed significant improvements in VAS and ICSI and ICPI during the entire follow-up. There are various studies that show significant improvements with combination therapies. Sherif et al.[12] applied combination therapy for 16 weeks and noticed significant symptom relief, and its progressive improvement lasted 3 months after the treatment. Cervigni et al.[13] compared the efficacy and safety of intravesical combination therapy versus dimethyl sulfoxide (DMSO) in BPS/IC patients in their randomized multicenter study. They found that combination therapy is as effective as DMSO, which is the only FDA-approved intravesical treatment. Additionally, combination therapy had fewer adverse events than DMSO treatment.

BPS/IC is a highly heterogeneous disease with different symptom levels and complex pathophysiology. Phenotyping is recommended by ESSIC guidelines to better identify and understand the disease.[2] Hunner lesions and glomerulations are the most commonly used subtypes identified by cystoscopy and hydrodistention. The biggest problem with glomerulations is that they are not specifically related to BPS/IC. Waxman et al.[14] investigated 19 patients without any symptoms related to BPS/IC, and eight of them had glomerulations. Glomerulations can also be seen in patients with bladder stones, chronic inflammation, and benign prostatic hyperplasia. Currently, only HLs have been phenotypically characterized, which has some implications for diagnosis, symptom severity, and treatment responses in some studies. Logadottir et al.[15] analyzed 210 Hunner and 183 non-Hunner BPS/IC patients and found that Hunner patients were older and had smaller bladder capacity than non-Hunner patients. Lamale et al.[16] formed a cystoscopic severity score that consists of maximal capacity under hydrodistension, presence or absence of terminal hematuria, and mucosal lesions, including glomerulations, flame hemorrhages, and Hunner's ulcers. They found that the severity score is associated with pain, smaller bladder capacity, and lower bladder frequency. Boudry et al.[17] also found that patients with HLs have lower bladder capacities, increased frequency, nocturia, and greater relief of symptoms upon voiding.

Our study differs from those studies by investigating the clinical response during the long-term follow-up of intravesical

Table 5. Intravesical Treatment Response in Total Cohort and Groups

	Minimum-maximum	Median	Ave. ± SD
Total			
VAS			
Before cystoscopy	30.0-100.0	100.0	82.1 ± 23.4
1st month	0.0-100.0	45.0	40.5 ± 31.7
3rd month	0.0-100.0	30.0	34.6 ± 33.7
6th month	0.0-100.0	60.0	56.5 ± 37.8
1th year	0.0-100.0	40.0	41.0 ± 34.7
ICSI			
Before cystoscopy	3.0-20.0	18.0	16.3 ± 4.2
1st month	2.0-20.0	8.5	9.6 ± 4.6
3rd month	0.0-20.0	9.0	9.4 ± 5.8
6th month	0.0-20.0	10.0	10.4 ± 6.6
1th year	0.0-20.0	10.0	9.7 ± 6.4
ICPI			
Before cystoscopy	4.0-20.0	16.0	13.7 ± 3.2
1st month	2.0-16.0	8.0	8.4 ± 4.1
3rd month	0.0-18.0	8.0	8.2 ± 5.0
6th month	0.0-16.0	8.0	8.5 ± 5.6
1th year	0.0-16.0	8.0	8.2 ± 5.3
No Cystoscopic Findings			
VAS			
Before cystoscopy	70.0-100.0	100.0	90.0 ± 14.1
1st month	0.0-100.0	50.0	50.0 ± 52.3
3rd month	0.0-50.0	40.0	30.0 ± 26.5
6th month	30.0-100.0	70.0	66.7 ± 35.1
1th year	0.0-10.0	0.0	3.3 ± 5.8
ICSI			
Before cystoscopy	7.0-20.0	20.0	16.4 ± 5.7
1st month	3.0-14.0	11.5	10.0 ± 5.0
3rd month	2.0-7.0	6.0	5.0 ± 2.6
6th month	2.0-17.0	12.0	10.3 ± 7.6
1th year	0.0-5.0	4.0	3.0 ± 2.6
ICPI			
Before cystoscopy	6.0-16.0	15.0	13.6 ± 4.3
1st month	3.0-14.0	11.5	10.0 ± 5.0
3rd month	2.0-12.0	5.0	6.3 ± 5.1
6th month	2.0-13.0	13.0	9.3 ± 6.4
1th year	0.0-6.0	0.0	2.0 ± 3.5

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Table 5. Intravesical Treatment Response in Total Cohort and Groups (Continued)

	Minimum-maximum	Median	Ave. ± SD
Hunner's Lesion			
VAS			
Before cystoscopy	30.0-100.0	100.0	80.0 ± 31.6
1st month	0.0-100.0	32.5	37.5 ± 39.0
3rd month	0.0-50.0	10.0	20.0 ± 26.5
6th month	0.0-50.0	15.0	20.0 ± 24.5
1th year	0.0-75.0	40.0	39.0 ± 27.5
ICSI			
Before cystoscopy	9.0-20.0	16.5	16.0 ± 4.2
1st month	6.0-11.0	8.0	8.4 ± 2.1
3rd month	5.0-12.0	10.0	9.0 ± 3.6
6th month	0.0-20.0	7.5	8.8 ± 8.3
1th year	4.0-20.0	11.0	11.4 ± 5.7
ICPI			
Before cystoscopy	10.0-16.0	13.5	13.5 ± 2.5
1st month	5.0-11.0	8.0	8.4 ± 2.3
3rd month	5.0-10.0	7.0	7.3 ± 2.5
6th month	0.0-14.0	5.5	6.3 ± 5.9
1th year	2.0-14.0	11.0	9.2 ± 4.5

Abbreviations: ICPI, O'Leary/Sant interstitial cystitis problem index; ICSI, O'Leary/Sant interstitial cystitis symptom index; VAS, visual analog scale.

Table 6. Cystometric Capacities of Groups During Hydrodistention

	Total			*P*
	Minimum-maximum	Median	Ave. ± SD	
No cystoscopic findings (mL)	300-600	500	490.0 ± 124.5	
Glomerulations (mL)	200-1,000	650	619.4 ± 209.9	
Hypervascularization (mL)	230-1,050	675	672.9 ± 229.2	
Hunner's lesion (mL)	300-740	400	478.0 ± 204.7	0.166*

*Kruskal–Wallis test.

treatment and combining that response with clinical phenotypes. In our study, we also investigated whether HLs-positive patients had decreased bladder capacities during hydrodistention compared with other subtypes; however, the difference was not statistically significant ($P = .166$). We observed statistically significant decreases in VAS, ICSI, and ICPI scores in all clinical phenotypes during the entire follow-up. Within the hypervascularization group, it was observed that, especially in the first month of treatment, there were higher pain scores (1st month: 50 vs. 30, $P = .03$) and ICPI scores (1st month: 12 vs. 8, $P = .053$) than in the glomerulation group. In patients with HL, unlike other subgroups, the response to the treatment curve was observed to increase again at the last follow-up. Due to the low number of patients in HL group, no statistical analyses were performed, but additional studies will be conducted in the future with more patients.

This is the first study investigating the role of cystoscopic findings, such as glomerulations, hypervascularization, and HL, in intravesical treatment response. Furthermore, we have defined a new cystoscopic finding that has potentially different characteristics than other subtypes. The limited number of patients, especially within

subgroups when divided, is the first limitation of our study. The second limitation of our study is that it is not a placebo-controlled study. While evaluating intravesical therapy responses, all patients received a standard treatment. In previous studies, hydrodistension showed temporary effect on pain relief, and it has been shown that hydrodistension has greater benefit with combination therapies.[18] Therefore, we did not randomize patients as with and without intravesical treatment. The lack of biopsy is another limitation, and combining different clinical phenotypes with immunohistochemical expression might be a good option for future studies. Although we have chosen BPS/IC patients with a great care and evaluated them elaborately, lack of urodynamic evaluation may be considered as an another limitation.

To conclude, a more complex phenotyping is important to better stratify BPS/IC patients. Hypervascularization is an overlooked cystoscopic finding, and its presence should be defined since those patients have different symptoms. Our results showed that patients with glomerulations can better respond to intravesical combined drug instillations. However, larger series with controlled and randomized groups are needed to obtain definitive conclusions.

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Informed Consent: Verbal informed consent was obtained from all participants who participated in this study.

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