Review Article

Int Neurourol J 2023;27(Suppl 1):S13-20
https://doi.org/10.5213/inj.2346106.053
pISSN 2093-4777 · eISSN 2093-6931

INTERNATIONAL NEUROUROLOGY JOURNAL
INJ
OPEN ACCESS

Intravesical Bladder Treatment and Deep Learning Applications to Improve Irritative Voiding Symptoms Caused by Interstitial Cystitis: A Literature Review

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Our comprehension of interstitial cystitis/painful bladder syndrome (IC/PBS) has evolved over time. The term painful bladder syndrome, preferred by the International Continence Society, is characterized as "a syndrome marked by suprapubic pain during bladder filling, alongside increased daytime and nighttime frequency, in the absence of any proven urinary infection or other pathology." The diagnosis of IC/PBS primarily relies on symptoms of urgency/frequency and bladder/pelvic pain. The exact pathogenesis of IC/PBS remains a mystery, but it is postulated to be multifactorial. Theories range from bladder urothelial abnormalities, mast cell degranulation in the bladder, bladder inflammation, to altered bladder innervation. Therapeutic strategies encompass patient education, dietary and lifestyle modifications, medication, intravesical therapy, and surgical intervention. This article delves into the diagnosis, treatment, and prognosis prediction of IC/PBS, presenting the latest research findings, artificial intelligence technology applications in diagnosing major diseases in IC/PBS, and emerging treatment alternatives.

Keywords: Interstitial cystitis; Diagnosis; Treatment; Convolutional neural network; Deep learning

• **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

The terminology, definitions, and diagnostic criteria for interstitial cystitis (IC) have been subject to a great deal of confusion and evolution over the years. In spite of numerous attempts and studies, clear definitions remain elusive. The definition most prevalently used today is that of the International Continence Society (ICS). Painful bladder syndrome (PBS) is defined as suprapubic pain correlated with bladder filling, along with an increased frequency of urination during the day and night, without any confirmed urinary infection or other discernible pathology. IC is a clinical diagnosis that mainly rests on symptoms of urgency/frequency and pain in the bladder or pelvis. It is typified by the presence of certain bladder findings like glomerulations or Hunner ulcers, and histological evidence of submucosal inflammation and/or the presence of a certain number of mast cells [1]. The European Society for the Study of Interstitial Cystitis has recently proposed new terminology, diagnostic criteria, and classification to help alleviate the confusion surrounding these terms [2].

IC is a condition typified by suprapubic pain associated with bladder filling, with no discernible underlying causes such as

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Submitted: May 9, 2023 / **Accepted after revision:** May 17, 2023

urinary tract infection. It often includes symptoms of increased daytime and nighttime frequency of urination and urgency. Active research is being conducted on various treatment options for this condition [3]. Recently, artificial intelligence (AI) has been integrated into urological research and practice, leading to heightened accuracy in disease diagnosis and the development of predictive models to track responses to medical treatments [4-8]. This review paper aims to provide a comprehensive overview of crucial treatment options for IC in urology, emerging therapies, as well as a summary of diagnostic techniques, prognostic prediction, and prevention of IC using AI.

RECENT BLADDER INTRAVESICAL THERAPY

Several treatments have been trialed for IC/PBS, including behavioral therapy, pharmacotherapy, intravesical drug instillation therapy, and surgical intervention. Studies suggest that the duration of sustained pain relief from hydrodistension is approximately 4.4 months. The clinical course is highly variable and is marked by repeated cycles of improvement and exacerbation. Thus, the focus of treatment should be on symptom improvement rather than achieving a complete cure, and patient education is of paramount importance for long-term management [3,9]. Currently, there is no definitive cure for IC. The primary approach to treatment is symptomatic therapy. Common treatments encompass oral medications like pentosan-polysulfate sodium (PPS), amitriptyline, cimetidine, and hydroxyzine. These drugs act as mucosal protectants, covering the bladder lining, and intravesical therapy with substances like dimethyl sulfoxide (DMSO), heparin, and lidocaine serves as an initial treatment. PPS is a treatment option for IC. Structurally and chemically, it is akin to glycosaminoglycan (GAG), and it contributes to the regeneration and supplementation of the GAG layer of the bladder mucosa, thereby reducing the permeability of the bladder mucosa. PPS, which bears a structural resemblance to heparin, is a synthetic mucopolysaccharide. It shields the bladder mucosa from harmful substances in the urine by coating the mucous layer of the bladder. PPS is primarily administered orally, proving effective in treating IC symptoms such as bladder pain and urinary difficulties.

PPS, an oral treatment, is an U.S. Food and Drug Administration-approved medication for IC in both men and women. It works by restoring and protecting the GAG layer of the bladder wall. Parsons et al. [10] conducted a double-blind, placebo-controlled study involving 148 IC patients. They found that 32% of the treatment group showed improvement compared to 16% in the placebo group. The treatment group also reported a 38% reduction in pain, compared to an 18% reduction in the placebo group. In a more recent study by Nickel et al. [11] involving 380 patients, no significant difference was found in treatment response based on PPS dosage. However, a significant difference was observed based on treatment duration, leading the authors to conclude that duration of treatment is more important than dosage. PPS is a common method for treating IC. Its administration is convenient, and it avoids the risk of pain or infection associated with bladder instillation. Typically, PPS is taken at a dose of 100 mg 3 times a day, initially starting at 200 mg per day for the first few weeks and gradually increasing. The medication is usually taken for 3–6 months to evaluate its effectiveness. While generally safe, rare side effects of PPS can include liver damage, reduced platelets, blood clotting, gastrointestinal disorders, and hair loss. However, despite the use of GAG-replenishing agents like PPS, oral therapy has significant drawbacks. The drug must be absorbed by the digestive system and enter the circulatory system to reach the bladder, which can reduce the drug's efficacy and increase the risk of side effects. For instance, PPS must be taken for over 3 months for its effects on the GAG layer to be felt, and long-term oral administration of PPS can cause serious side effects.

Bladder instillation is a bladder-specific treatment that can maintain high drug concentrations within the bladder while reducing systemic side effects. Numerous treatments, such as DMSO, bacillus Calmette-Guérin, hyaluronic acid (HA), resiniferatoxin, heparin, chondroitin sulfate, and liposome injections, have been reported to alleviate IC symptoms by protecting the bladder mucosal layer. The therapeutic effects of these drugs are varied, including suppression of inflammatory responses in the bladder, coating of the bladder mucosa to prevent penetration of toxic substances in urine, and protection of the bladder from microdamage. Intravesical therapy involves direct administration of drugs into the inflamed bladder for IC treatment, which allows for high-dose drug delivery directly to the bladder with fewer systemic side effects compared to oral administration. Morales et al. [12] reported that 71% of 25 IC patients, who did not respond to conventional therapy, responded to weekly intravesical administration of HA for 4 weeks at the 12-week mark. Porru et al. [13] reported that 30% of 10 patients showed a response to HA treatment for 6 weeks. Riedl et al. [14] found that, among 126 patients treated with intravesical HA until their symptoms improved, 85% showed

symptom improvement, and 55% had their symptoms almost disappear, with no reported side effects.

Most physicians typically use a combination of various substances in an effort to maximize therapeutic effects, and numerous studies on such combination therapies are ongoing. For instance, Leppilahti et al. [15] reported that most patients experienced symptom improvement following weekly bladder instillations of HA for 4 weeks after diagnostic bladder distension. Ghoniem et al. [16] administered a combination therapy of DMSO, methylprednisolone, and heparin sulfate via bladder instillation over 6 weeks to 25 IC patients who did not respond to single-agent bladder instillation. They reported that 92% of patients experienced symptom relief for an average of 8.1 months. Whitmore [17] administered a cocktail therapy composed of gentamicin, heparin, bupivacaine, sodium bicarbonate, and hydrocortisone. Additionally, Davis et al. [18] reported that the group receiving both oral and bladder instillation of PPS had better treatment outcomes than the group that received oral administration alone.

IC, which is considered a rare disease, is believed to involve multiple causative factors. As such, a treatment method currently under study is a complex drug-based ultrasound-guided microbubble-mediated drug delivery system. This approach explores the possibility of additional and synergistic effects of different drugs. Recent publications have proposed the use of this ultrasound-mediated microbubble drug delivery system where microbubbles, loaded with therapeutic drugs, are injected into the bloodstream. These drugs are then locally secreted to target organs using ultrasound for targeted impact. This study explored the effects of this system on an animal model of orchiectomy and testosterone-induced BPH using rats [19]. The ultrasound-guided microbubble drug delivery system operates by injecting microbubbles loaded with therapeutic drugs into blood vessels. These drugs are then locally secreted to target organs, depending on the disease and the necessary drugs for treatment [19]. This method selectively enhances the permeability of therapeutic drugs in targeted organs or specific cells. This is achieved by using a specific output of ultrasound to move the microbubbles to the desired area. Various types of drugs can be loaded onto the microbubbles depending on the disease, and the use of ultrasound, which is harmless to the human body, is advantageous (Fig. 1). The bladder, located just behind the pelvic cavity, is easily accessible by ultrasound. It also has a high need for selective drug action. Therefore, the development of a new drug delivery system using ultrasound-guided microbubbles as a targeting tool for the bladder has a high potential to improve the

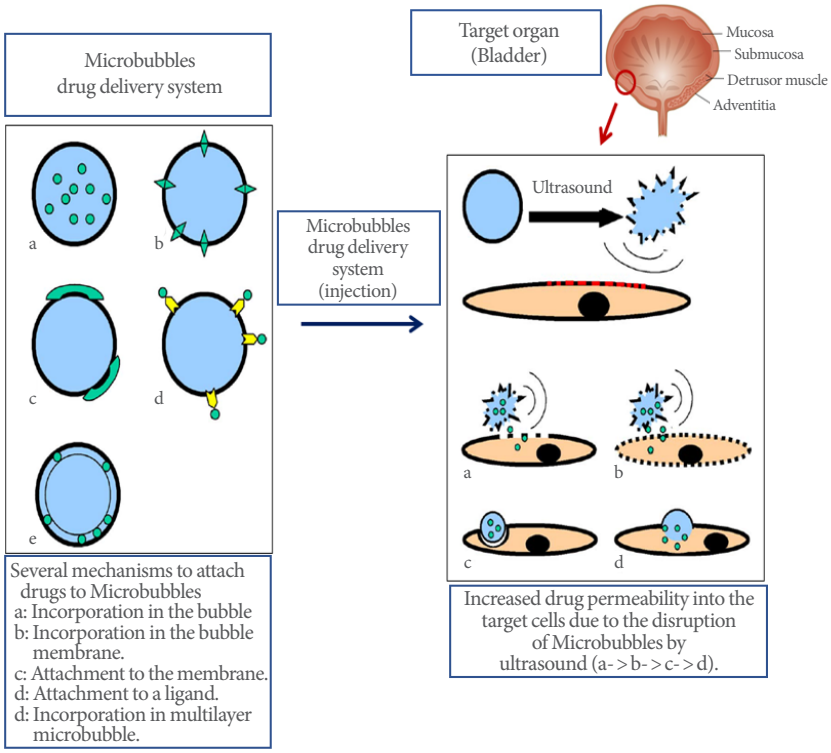

Fig. 1. Mechanism of action of microbubbles loaded with therapeutic drugs.

therapeutic efficacy of urinary dysfunction treatment. Cho et al. [19] developed an ultrasound-guided microbubble-mediated drug delivery system that selectively acts on the bladder and prostate, and its efficacy has been validated for representative urological diseases. Initially, to evaluate stability and delivery efficacy depending on ultrasound stimulation intensity, the researchers administered microbubbles to the bladder and vein of experimental animals and established the ultrasound stimulation protocol with the highest efficacy (Fig. 2). Subsequently, candidate drugs were loaded into liposome nanoparticles and included in microbubbles for efficacy analysis. Next, 2 candidate drugs were loaded into microbubbles and administered to an animal model of overactive bladder through 2 routes of administration: the bladder wall and abdominal cavity. This method was compared and analyzed with a control group that received general drug administration with ultrasound stimulation, using the protocol selected from the previous year's experimental process. Through this process, the researchers proved that thera-

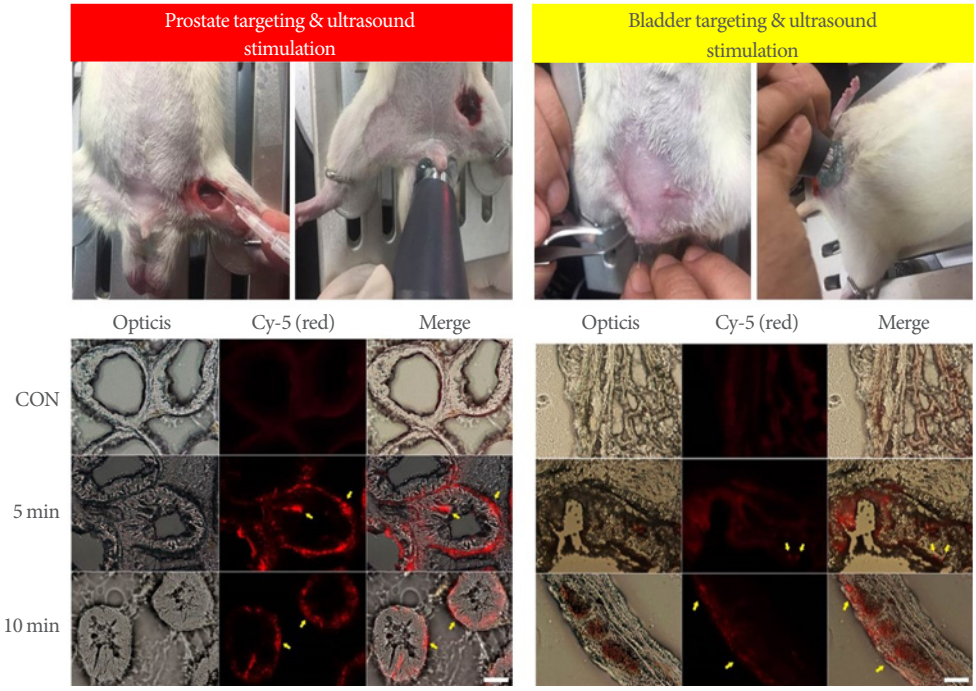

Fig. 2. Analysis of the ultrasound stimulation protocol for microbubbles.

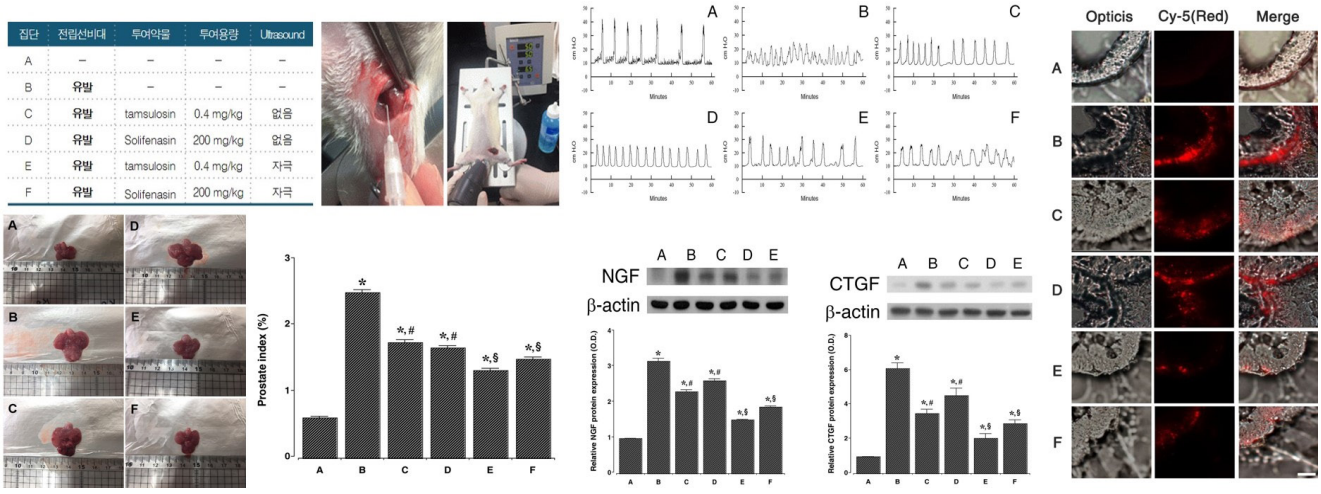

Fig. 3. Analysis of the therapeutic efficacy of candidate drugs loaded in microbubbles for the treatment of prostate hypertrophy.

peutic drugs loaded into microbubbles are distributed to the target site upon receiving ultrasound stimulation of a specific intensity, resulting in increased therapeutic efficacy (Fig. 3). To target urogenital organs other than the bladder, the researchers evaluated candidate drugs using a prostatic hypertrophy animal model using the same method, and showed significant therapeutic efficacy in the prostate (Fig. 3). These results suggest that the development of treatments for intractable diseases is viable through the selection of drugs loaded into microbubbles and the establishment of ultrasound protocols, especially for intractable diseases without specific treatment methods that only manage symptoms.

Therefore, the use of drug combination (PPS and HA) in an ultrasound-induced microbubble-mediated drug delivery system for bladder therapy can minimize side effects that may occur with oral therapy and present results for more efficient therapeutic effects. This, in turn, could improve the quality of life for patients and enable the expansion of treatment technology through securing original technology. Based on these studies, animal experiments are being prepared for the development of a treatment for IC.

APPLICATIONS OF ARTIFICIAL INTELLIGENCE

Machine learning (ML) is a collection of techniques that can automatically identify patterns in data, using these patterns to predict future data or aid decision-making in uncertain scenarios [20]. As a subfield of AI, ML relies on large datasets and involves minimal human intervention in the decision-making process. A specific type of ML, deep learning, utilizes artificial neural networks to emulate the layered human cognition system. Deep learning is attracting attention due to its ability to analyze vast healthcare data. Although artificial neural networks have existed since the 1950s, their application to real-world issues was hindered by the lack of computing power and sufficient training data. However, recent advancements in technology and algorithms have allowed deep learning approaches to deliver impressive results across various fields. ML algorithms have been employed to detect structural abnormalities and categorize them into disease classes, leading to the development of computer-aided diagnosis (CAD) systems. However, earlier CAD systems were found to produce more false positives than human readers, causing increased assessment time and additional biopsies. The advent of deep learning technology is expected to overcome these limitations, resulting in enhanced detection accuracy and increased productivity for human readers. Deep learning can also be utilized to extract valuable knowledge from large medical datasets, such as automatically identifying lesions, suggesting differential diagnoses, and composing preliminary radiology reports. In recent years, deep learning has gained momentum in medical domains, especially in diagnostic imaging [21-25]. AI research that employs deep learning models based on medical images or data is continuously progressing, showing many promising results in classification, detection, and segmentation (Fig. 4). These areas represent some of the most notable and representative approaches in AI research, with new

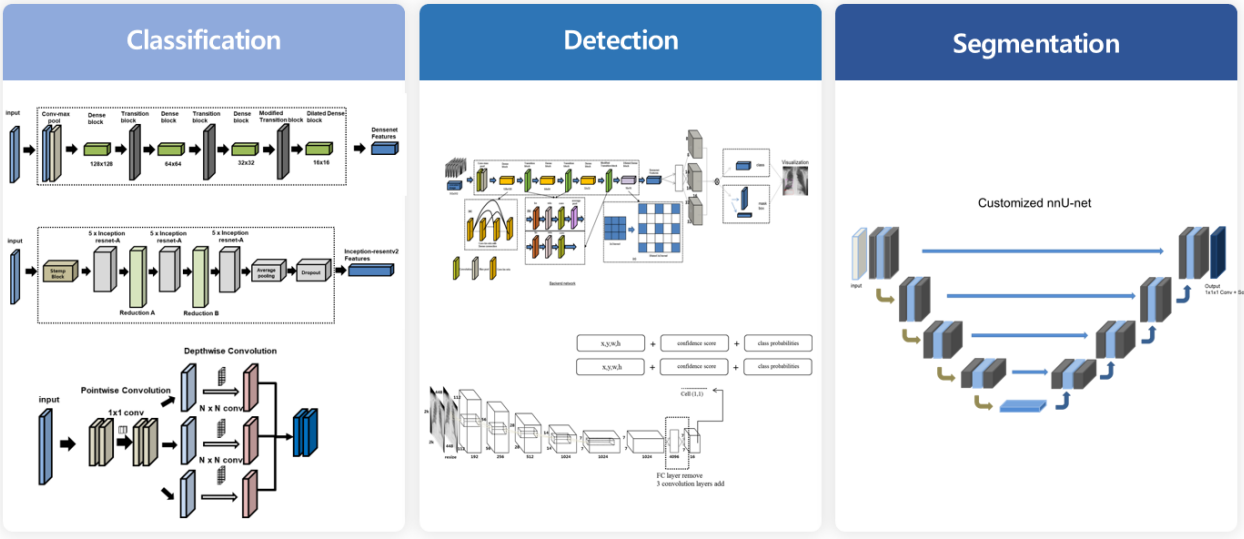

Fig. 4. Artificial intelligence; classification, detection, and segmentation.

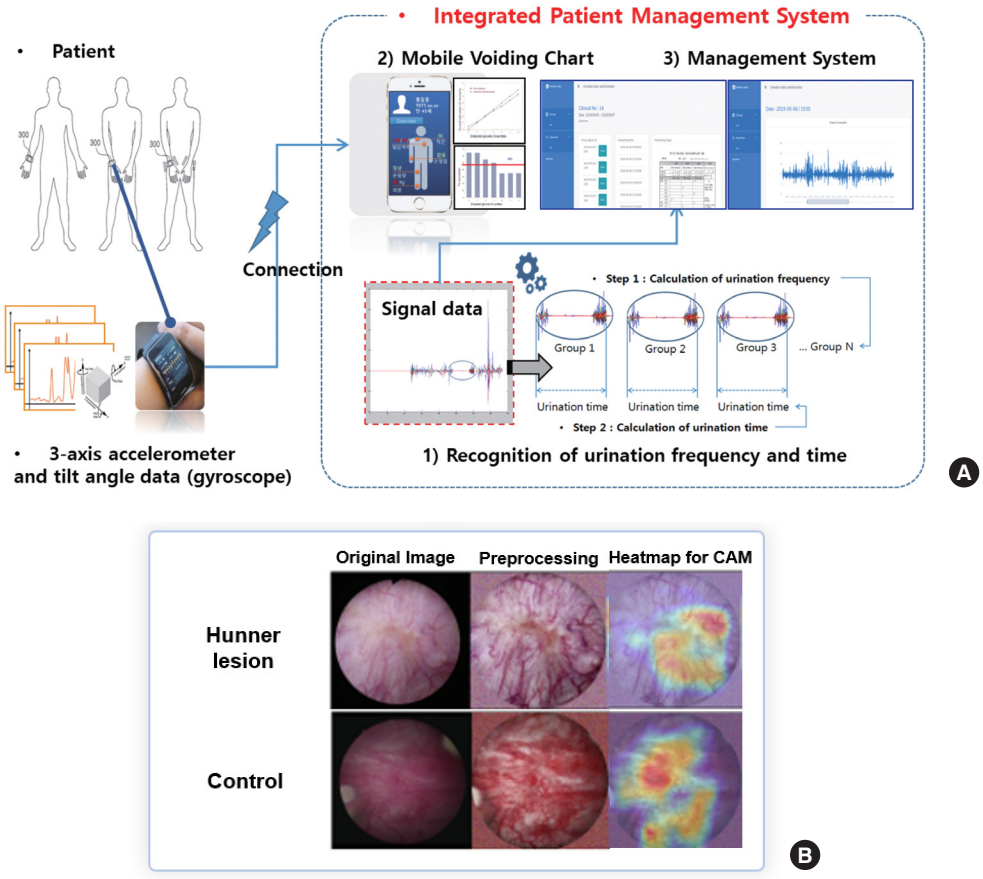

Fig. 5. (A) Mobile application for urination management monitoring system [30] and (B) a computer-aided diagnosis system based on deep learning to detect Hunner lesions. CAM, class activation map.

methods being constantly developed across all fields.

Several studies have indicated that deep learning algorithms have outperformed human capabilities in detecting various diseases, including bladder cancer [15-18,22,26-28]. The use of AI [29] enhances the accuracy of disease diagnosis and facilitates the creation of predictive models for monitoring the effectiveness of medical treatments (Fig. 5A) [30]. Iwaki et al. [8] developed a deep learning computer-aided diagnosis (CAD) system for detecting cystoscopic recognition of Hunner lesions (Fig. 5B). The accurate identification of Hunner lesions during cystoscopy is crucial for improving treatment outcomes in individuals with Hunner-type IC. However, this can be challenging due to the inconsistent appearance of Hunner lesions. To enhance the accuracy of cystoscopic recognition of Hunner lesions, Iwaki et al. [8] processed cystoscopic images captured from 2 different types of cystoscopes (Fig. 5B). They identified a region of interest (ROI) in each image and adjusted the color tone and brightness of the bladder mucosa within the ROI. They then employed a pretrained convolutional neural network (CNN) model known as InceptionResNetv2, which was originally trained on natural images from the ImageNet database (http://www.image-net.org) [31], to build CAD systems. To account for the limited volume of training images, they used a 5-fold cross-validation method to evaluate the CAD system. They randomly divided the training dataset into 5 subsets, retraining the CNN model with images from 4 subsets and validating the retrained models using images from the remaining subset.

PROPOSING TREATMENT BASED ON PROGNOSTIC PREDICTIONS

In urology, the application of AI for disease diagnosis and treatment recommendations, as well as for the creation of personalized diagnostic and treatment methods, is crucial in providing more precise and beneficial prognostic and treatment systems for patients, particularly for chronic conditions such as IC. The

utilization of AI or deep learning, along with the novel ultrasound-guided microbubbles drug delivery system [19], could be game-changing in the field of urology. Urine contains various irritants such as ions, minerals, waste, and bacteria, and the bladder urothelium is protected from these substances by the GAG layer. However, in patients with IC, the GAG layer is frequently damaged. The ultrasound-guided microbubbles drug delivery system can assist in restoring the GAG layer by directly delivering drugs with similar components into the bladder. This approach aims to develop personalized treatment strategies for the management and prevention of IC/PBS. It involves creating a deep learning model to predict a patient's prognosis and accordingly suggesting the best treatment strategy. Since IC/PBS can exhibit a range of symptoms and progressions, traditional treatment strategies may not always be effective. Therefore, personalized treatment strategies that take into account individual prognoses are essential. This method establishes a prediction model that analyzes a patient's prognosis to forecast the treatment effect based on various factors such as personal characteristics, medical history, and test results. Based on the prediction model, the ideal treatment strategy is suggested for the patient. This involves considering the expected treatment effect based on the prediction model's outcomes and proposing suitable drug or surgical treatment accordingly. By offering personalized treatment strategies, this method can optimize treatment effectiveness.

CONCLUSION

This article has detailed the primary technologies for the diagnosis, treatment, and prognosis prediction of IC/PBS, incorporating recent research findings on IC treatment and AI for diagnosing major diseases in IC/PBS. AI is a transformative technology that has reshaped society, impacting everything from smartphones to surgical robots. As AI continues to evolve, the potential applications in medical fields are endless. AI systems for prognosis prediction can be created to personalize patient treatment for chronic diseases like IC. Furthermore, attention must be paid to the ethical, regulatory, and legal issues that emerge from the use of patient clinical data in AI development. Lastly, the development of AI and personalized treatment strategies in urology can offer powerful tools for exploring, understanding, and applying complex medical information.

AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *SY*
· Formal analysis: *YC, SY*
· Methodology: *YC, SY*
· Writing - original draft: *YC*
· Writing - review & editing: *YC, SY*

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