





# Idiopathic Retroperitoneal Fibrosis-Related Hydronephrosis: Evaluation of Comprehensive Management and Prediction of Inflammatory Markers for Stent-Free Outcomes

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**Objective:** This study investigated the efficacy of comprehensive management and predictable inflammatory markers for idiopathic retroperitoneal fibrosis (iRPF)-related hydronephrosis outcomes.

**Methods:** Patients with iRPF-related hydronephrosis underwent surgical (ureteral stent and/or nephrostomy tube placement) and medical (corticosteroid-based multiple immunosuppressants) management were classified according to stent-indwelling outcomes. Univariate analysis of clinical profiles was conducted to screen possible predictors of hydronephrosis remission.

**Results:** In a series of 38 patients, 52.6% achieved hydronephrosis remission and stent/tube removal (stent-free group). The median indwelling time in the stent-free group (12 months) was significantly lower than that in the treatment-failure group (37 months,  $p < 0.05$ ). Mean retroperitoneal mass diameters was significantly reduced (anteroposterior by 11.66 mm (95% CI 2.31–21.01), transverse by 15.41 mm (95% CI 3.37–27.46), suprainferior by 30.53 mm (95% CI 4.87–56.19);  $p < 0.05$ ) during the treatment course, in line with mean renal pelvis width (by 36.2%) and renal function parameters (serum creatinine by 16.9%, blood urea nitrogen by 12.9%). Renal function improved (36.9%) or remained stable (44.7%) in most patients, the mean estimated glomerular filtration rate increasing by 8.7% (from 55.4 mL/min/1.73 m<sup>2</sup> to 60.2 mL/min/1.73 m<sup>2</sup>). At the initial diagnosis, median serum immunoglobulin IgG and CRP levels were significantly higher in the stent-free group than in the treatment-failure group (IgG 17.55 g/L vs. 13.50 g/L, CRP 19.60 mg/L vs. 3.15 mg/L;  $p < 0.05$ ). Decline in serum IgG (−5.80 g/L vs. −2.30 g/L), CRP (−18.93 mg/L vs. −1.72 mg/L) and erythrocyte sedimentation rate (−22.00 mm/h vs. −1.50 mm/h) levels in the stent-free group surpassed those in the treatment-failure group ( $p < 0.05$ ).

**Conclusion:** Comprehensive management benefits iRPF patients with hydronephrosis by preserving renal function. The 24-month scale might guide stent/tube removal. Elevated inflammatory markers (IgG and CRP) at the initial iRPF diagnosis and IgG, CRP, and erythrocyte sedimentation rate (ESR) variations associated with hydronephrosis outcomes.

## Plain Language Summary:

- The 24-month scale might guide the decision of final removal.
- Elevated inflammatory markers (IgG and CRP) at initial iRPF diagnosis and IgG, CRP, and ESR decreasing during the treatment course could predict hydronephrosis remission and stent-free outcomes.
- Alternative treatments, such as immunosuppressants other than corticosteroids, rather than longer stent indwelling could be recommended for patients with minimal possibility of hydronephrosis remission.

**Keywords:** idiopathic retroperitoneal fibrosis, hydronephrosis, ureteral stent, immunosuppressant medications, stent-free outcome

## Introduction

Hydronephrosis is not unusual in idiopathic retroperitoneal fibrosis (iRPF), as hyperplastic fibrous tissue might surround or invade the ureter and other retroperitoneal organs.<sup>1</sup> Patients have received different treatments based on divergent comprehension of the disease for the goal of “hydronephrosis control.” From the rheumatologic point of view, given a confirmation of IgG<sub>4</sub>-related disease (IgG<sub>4</sub>RD) in a portion of iRPF patients, corticosteroids combined with other immunosuppressants are used to alleviate hydronephrosis through mass reduction.<sup>2</sup> However, it is more desirable for most urologists to relieve upper urinary obstruction and preserve renal function as soon as possible. In these cases, endoscopic drainage procedures (transurethral ureteral stent placement or nephrostomy) are preferred.<sup>3</sup>

It is a worthwhile pursuit to have medical and surgical therapeutic strategies “meet at the top of the hill.” Considering the morbidities, including infection, bleeding, pain, and lower urinary tract syndrome, long-term indwelling ureteral stents and nephrostomy tubes ultimately need to be removed. Additionally, retroperitoneal sclerosis might develop in a number of late-stage iRPF patients, even under standard medical therapeutic strategies. This can lead to stent-free failure and suggest that certain characteristics, such as baseline inflammatory markers and disease activity index and their response to medication, may determine hydronephrosis outcomes. This study evaluated the efficacy of immunosuppressive medications in combination with urological endoscopic therapy in the management of iRPF-related ureteral obstruction. Additionally, the determinants of ureteral obstruction relief and hydronephrosis remission were investigated.

## Methods

### Study Participants

Medical records of iRPF patients with hydronephrosis were retrospectively reviewed from January 2014 to December 2019 at Peking University People’s Hospital with the approval of the institutional board. iRPF was diagnosed using cross-sectional imaging (computed tomography and/or magnetic resonance imaging). Positron emission tomography–computed tomography has also been used for malignancy detection. Ureteral obstruction caused by a malignant-related mass or masses related to previous abdominal/pelvic surgery was excluded.

All patients enrolled in this study had to have received at least one urological procedure to place a ureteral stent (retrogradely) or nephrostomy tube (anterogradely). Subsequently, the stent/tube would be replaced regularly according to the condition of each patient. Surgical resection and ureterolysis would also be selected for a relative proportion of patients who had persistent hydronephrosis after the stent placement. Follow-up >12 months was achieved for all patients.

The primary endpoints in this study were hydronephrosis remission and/or stent free:

1. All ureteral stents and nephrostomy tubes were removed at the last follow-up;
2. There was neither hydronephrosis recurrence nor serum creatinine level deterioration after removal.

Removal of the stent or tube was attempted throughout the course of treatment when the resolution of hydronephrosis was observed. The patient was considered to have hydronephrosis remission if the dilated pelvicalyceal system was less than 0.5 cm under ultrasound or cross-sectional imaging. When hydronephrosis recurrence was observed shortly after stent or tube removal, re-stenting was performed consequently. Patients were classified into the stent-free group if they reached the endpoints. Patients who had not yet had their ureteral stents removed and those who developed unilateral or bilateral renal failure regardless of their stent-indwelling status were assigned to the treatment-failure group.

### Data Collection

The following data were collected for all enrolled participants.

1. Demographic and baseline clinical characteristics: gender, age at disease onset, results of pathological biopsy and IgG<sub>4</sub>RD diagnosis.

2. Surgical and medical management: tube/stent drainage duration, dosage and duration of corticosteroid and other immunosuppressants.
3. Kidney function monitoring: serum creatinine and blood urea nitrogen levels at first stent/tube placement and after final removal. Estimated glomerular filtration rate (eGFR) was also calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. eGFR variation <20% was considered stable renal function. An increase in eGFR >20% was considered improvement in renal function, and a decrease in eGFR >20% was considered worsening.<sup>4</sup>
4. Inflammatory markers: antinuclear antibody, serum erythrocyte sedimentation rate (ESR), CRP, Ig level (especially IgG<sub>4</sub>), and C3 and C4 levels at medication initiation and last follow-up.
5. Imaging features of retroperitoneal mass: diameters measured by cross-sectional images and imaging staging according to the Scheel reporting system.<sup>5</sup>

## Statistical Analysis

In the descriptive analysis, categorical variables are presented as numbers and percentages. Continuous variables are presented as means  $\pm$  SD or medians with interquartile range, unless otherwise stated. Univariate analysis, such as one-way ANOVA,  $\chi^2$  test, and/or Fisher's exact test, and the Mann-Whitney *U* test when variables were not normally distributed were conducted to screen possible predictive parameters for hydronephrosis remission. Those analyses were conducted using SPSS software (version 21.0, SPSS Inc., Chicago, IL, USA). Two-sided  $p < 0.05$  was considered statistically significant.

## Results

### Demographic and Clinical Characteristics and iRPF Management

Medical records of 38 iRPF-related hydronephrosis patients with a median follow-up of 29 (22–41) months were reviewed. The median age of onset in this series was 61 (53–66) years, and 68.4% of patients were male (Table 1). Twenty patients (52.6%) reached the predefined endpoints and were classified into the stent-free group. Four patients in the stent-free group and eight patients in the treatment-failure group had bilateral hydronephrosis. All patients had ureteral stent indwelling and 15.8% of patients underwent nephrostomy during the disease course. In addition to ureteral stents and/or nephrostomy tube placement, 30 patients (78.9%) underwent needle biopsy or laparoscopic resection of retroperitoneal masses at the time of hydronephrosis diagnosis. IgG<sub>4</sub>RDs were confirmed by serological indicators and pathological findings in 14 patients (36.8%).

Prednisone acetate was administered to all patients after the diagnosis of iRPF. The initial dose was 0.8 mg/kg (maximum dose is 60 mg/day). The dose was reduced by 5 mg per week after 2–4 weeks to 40 mg/day, then by 2.5 mg per week to 30 mg/day, by 2.5 mg every 2 weeks to 15 mg/day, and by 2.5 mg per month to 7.5–10 mg/day. Finally, prednisone was maintained or stopped as appropriate. In this case series, two patients were treated with prednisone as the only medical intervention, while 36 others received immunosuppressants in combination with prednisone. Among these, 20 were treated with more than one immunosuppressant agent aside from prednisone, including mycophenolate mofetil, cyclophosphamide, azathioprine, and tamoxifen (Table 1). A higher tendency for mycophenolate mofetil application was detected in the stent-free group (80% vs. 33.3% in treatment-failure group,  $p = 0.070$ ).

### Role of Comprehensive Management on Renal Function Preservation

As depicted in Table 1, the median stent-indwelling time in the stent-free group was 12 (2–36) months, which was significantly lower than that in the treatment-failure group (37 [10–76 months];  $p < 0.05$ ). Compared with the initial diagnosis point, mean retroperitoneal mass diameter in this series was significantly reduced when the stent was removed or at last follow-up (anteroposterior diameter reduced by 11.66 mm, 95% CI 2.31–21.01; transverse diameter reduced by 15.41 mm, 95% CI 3.37–27.46; suprainferior diameter reduced by 30.53 mm, 95% CI 4.87–56.19;  $p < 0.05$ ; Table 2 and Figure 1B). In addition, mean renal pelvis width decreased by 36.2% (from 22.83 mm to 14.57 mm, Table 2 and Figure 1A). Two cases of Scheel stage degradation (both from stage III to I) were found in the stent-free group.

**Table 1** Patient demographic and clinical features and iRPF management

	<b>Overall (n=38)</b>	<b>Stent-free group (n=20, 52.6%)</b>	<b>Treatment-failure group (n=18, 47.4%)</b>	<b>p</b>
<b>Onset age (years)</b>				
Median (interquartile range)	63 (53–66)	62.5 (48.75–67.25)	63.5 (59.5–71.5)	0.477
<b>Sex</b>				
Male	26 (68.4%)	14 (70%)	12 (66.7%)	1
Female	12 (31.6%)	6 (30%)	6 (33.3%)	
<b>Follow-up (months)</b>				
Median (interquartile range)	29 (22–41)	28.50 (20.25–46.50)	40 (28.5–96.0)	0.133
<b>Ureteral stent indwelling (months)</b>				
Median time (interquartile range)	24 (20.5–57.5)	12 (8–25)	37 (27–46)	0.004
<b>Retroperitoneal mass biopsy</b>				
Surgical resection	22 (57.9%)	8 (40%)	14 (77.8%)	0.211
Needle biopsy	8 (21.1%)	6 (30%)	2 (11.1%)	0.582
<b>IgG<sub>4</sub>-related disease diagnosis</b>	14 (36.8%)	10 (50%)	4 (22.2%)	0.350
<b>Stent-related symptoms</b>				
Back pain or LUTS		4 (20%)	6 (33.3%)	0.628
Urinary infection		12 (60%)	14 (77.8%)	0.628
Stent displacement		2 (10%)	4 (22.2%)	0.582
Stent-related calculi		12 (60%)	8 (44.4%)	0.656
Stent stenosis		2 (10%)	6 (33.33%)	0.303
<b>Glucocorticoid duration (months)</b>		23.80±7.98	22.44±12.61	0.780
<b>Immunosuppressant agents</b>				
Mycophenolate mofetil		14 (80%)	6 (33.3%)	0.070
Cyclophosphamide		14 (70%)	10 (55.6%)	0.650
Azathioprine		2 (10%)	2 (11.1%)	1
Tamoxifen		2 (10%)	2 (11.1%)	1

**Abbreviation:** LUTS, lower urinary tract symptoms.

After comprehensive management, including drainage of hydronephrosis and immunomodulatory medications with adequate dose and course, mean levels of serum creatinine and blood urea nitrogen decreased by 16.9% (from 169.22  $\mu\text{mol/L}$  to 140.57  $\mu\text{mol/L}$ ) and 12.9% (from 9.31 mmol/L to 8.12 mmol/L), and eGFR increased by 8.7% (from 55.40 mL/min/1.73 m<sup>2</sup> to 60.20 mL/min/1.73 m<sup>2</sup>). Renal function improved in 14 patients (36.8%), but worsened in 18.4% (seven patients). It is worth noting that renal function in the patients in the treatment-failure group was also improved to a certain extent (Table 2).

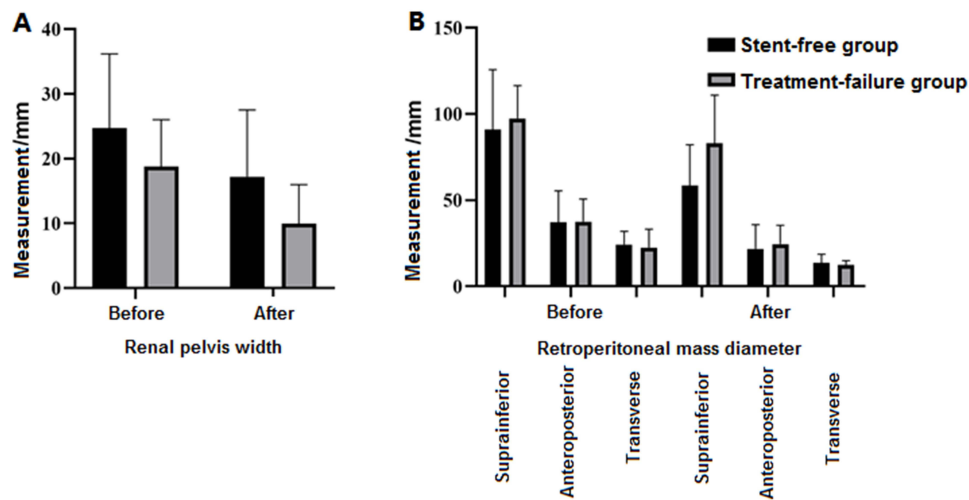
**Table 2** Patient renal function preservation under comprehensive management

	Overall (n=38)	Stent-free group (n=20, 52.6%)	Treatment-failure group (n=18, 47.4%)	p
<b>First stent/tube placement</b>				
SCr ( $\mu\text{mol/L}$ )	169.22 $\pm$ 31.78	118.38 $\pm$ 12.69	235.30 $\pm$ 67.39	0.120
BUN (mmol/L)	9.31 $\pm$ 1.13	8.77 $\pm$ 1.02	10.09 $\pm$ 2.15	0.560
eGFR (mL/min/1.73 m <sup>2</sup> )	55.40 $\pm$ 6.11	63.98 $\pm$ 26.18	43.00 $\pm$ 9.65	0.092
Renal pelvis width (mm)	24.74 $\pm$ 4.33	24.71 $\pm$ 4.34	18.76 $\pm$ 3.62	0.380
<b>Stent removal or last follow-up</b>				
SCr ( $\mu\text{mol/L}$ )	140.57 $\pm$ 29.44	101.46 $\pm$ 7.69	185.64 $\pm$ 59.32	0.189
BUN (mmol/L)	8.12 $\pm$ 1.18	7.06 $\pm$ 20.68	9.06 $\pm$ 2.26	0.391
eGFR (mL/min/1.73 m <sup>2</sup> )	60.20 $\pm$ 5.12	69.35 $\pm$ 5.64	51.38 $\pm$ 7.40	0.063
Renal pelvis width (mm)	17.20 $\pm$ 3.90	17.20 $\pm$ 3.90	9.98 $\pm$ 3.01	0.238
<b>Renal function variation</b>				
SCr ( $\mu\text{mol/L}$ )	-28.65 $\pm$ 28.51	-16.91 $\pm$ 12.15	-28.27 $\pm$ 61.12	0.845
BUN (mmol/L)	-1.20 $\pm$ 0.96	-2.26 $\pm$ 1.10	-0.11 $\pm$ 1.75	0.297
eGFR (mL/min/1.73 m <sup>2</sup> )	4.80 $\pm$ 4.36	5.37 $\pm$ 5.65	16.20 $\pm$ 10.34	0.348
<b>Renal function summary</b>				
Improved, n (%)	14 (36.9%)	8 (40%)	6 (33.3%)	0.797
Stable, n (%)	17 (44.7%)	9 (45%)	8 (44.4%)	
Worsened, n (%)	7 (18.4%)	3 (15%)	4 (22.2%)	
<b>Imaging features of retroperitoneal mass (mm)</b>				
<b>Anteroposterior diameter</b>				
Before	24.29 $\pm$ 2.88			0.022
After	12.63 $\pm$ 2.02			
<b>Transverse diameter</b>				
Before	37.23 $\pm$ 6.91			0.020
After	21.81 $\pm$ 5.28			
<b>Suprainferior diameter</b>				
Before	85.33 $\pm$ 13.98			0.028
After	54.80 $\pm$ 9.41			

**Abbreviations:** SCr, serum creatinine; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

## Prediction of Inflammatory Markers for Stent-Free Outcomes

Although confirmed IgG<sub>4</sub>RD patients were uniformly distributed, the median serum IgG and CRP levels at initial diagnosis were significantly higher in the stent-free group than the treatment-failure group (IgG 17.55 g/L vs. 13.50 g/L,  $p < 0.05$ ; CRP 19.60 mg/L vs. 3.15 mg/L,  $p < 0.05$ ; Table 3). The variation in those inflammatory parameters throughout the



**Figure 1** Variation in renal pelvis width and retroperitoneal mass diameter before and after the comprehensive management. (A) Pelvis width and (B) retroperitoneal mass diameter in the two groups displayed in chronological order (x-axis) against the measurement (y-axis).

treatment course also predicted patients’ stent-free outcomes. The median decline in both serum IgG and CRP in the stent-free group was significantly superior to the treatment-failure group (IgG  $-5.80$  g/L vs.  $-2.30$  g/L,  $p < 0.05$ ; CRP  $-18.93$  mg/L vs.  $-1.72$  mg/L,  $p < 0.05$ ; Table 3). Moreover, greater decline in serum ESR was identified in the stent-free group ( $-22.00$  mm/h vs.  $-1.50$  mm/h,  $p < 0.05$ ; Table 3), which suggested it as a predictor.

**Table 3** Patient inflammatory profile during comprehensive management

	Stent-free group (n=20, 52.6%)	Treatment-failure group (n=18, 47.4%)	p
<b>Before medication therapy</b>			
ANA-positive, n (%)	12 (60%)	2 (11.1%)	0.057
IgG (g/L)	17.55 (13.58–22.10)	13.50 (11.80–14.65)	0.013
IgG <sub>4</sub> (mg/dL)	158.50 (36.7–278.5)	46.80 (25.28–131.30)	0.122
C3 (g/L)	1.03±0.26	0.89±0.13	0.173
C4 (g/L)	0.24±0.08	0.24±0.05	0.961
CRP (mg/L)	19.60 (4.25–41.61)	3.15 (1.34–3.86)	0.040
ESR (mm/h)	28.0 (12.5–86.0)	17.0 (4.50–25.75)	0.139
<b>Variation during treatment course</b>			
IgG (g/L)	$-5.80$ ( $-10.45$ - $-4.00$ )	$-2.30$ ( $-5.60$ - $-1.30$ )	0.016
IgG <sub>4</sub> (mg/dL)	$-105.1$ ( $-347.0$ - $-24.30$ )	$-34.75$ ( $-59.03$ - $-23.98$ )	0.230
C3 (g/L)	$-0.45 \pm 0.19$	$-0.08 \pm 0.26$	0.772
C4 (g/L)	$-0 \pm 0.07$	$-0 \pm 0.11$	0.952
CRP (mg/L)	$-18.93$ ( $-29.33$ - $-4.09$ )	$-1.72$ ( $-2.68$ - $-0.11$ )	0.023
ESR (mm/h)	$-22.0$ ( $-74.50$ - $-9.0$ )	$-1.50$ ( $-13.25$ - $2.00$ )	0.018

**Abbreviations:** ANA, antinuclear antibody; ESR, serum erythrocyte sedimentation rate; C3, complement 3.

## Discussion

In spite of iRPF's low incidence of about 1.3/100,000, the advanced age of onset (around  $64.0 \pm 11.1$  years) makes patients more vulnerable to constitutional symptoms, such as abdominal pain (32.8–66.9%) and back pain (37.7–62%), as well as impairment in quality of life.<sup>6–8</sup> Kidney-function damage caused by hydronephrosis is one of the major long-term consequences of iRPF.<sup>9</sup> Previous studies on iRPF-related hydronephrosis have focused on medication therapy or surgical drainage in isolation.<sup>10–12</sup> Few studies have reported changes in renal function after multimodal treatment.

This study was designed to evaluate the efficacy of the comprehensive therapeutic model for renal function preservation and inflammation control. The treatment-failure group tended to have worse renal function at the time of first stent/tube placement than the stent-free group, which might be attributed to a delay in treatment initiation. With appropriate drainage, renal function remained stable or improved for the majority of patients in this series on corticosteroid-based therapy. However, nearly 20% of patients still experienced deterioration in renal function. A previous study reported similar results and suggested that the onset of acute kidney injury was associated with relapse of iRPF after remission and worse renal function outcomes.<sup>13</sup>

Always involving multiple organs, IgG<sub>4</sub>RD accounts for 30%–59% of iRPF.<sup>14</sup> To our knowledge, it is difficult to distinguish the clinical and imaging features and disease outcomes of IgG<sub>4</sub>-related RPF from iRPF.<sup>15</sup> The convergent management principles, along with difficulties in performing biopsy and pitfalls of histological diagnosis, not only adversely influenced the detection rate of IgG<sub>4</sub>RD in this study but also raise questions about the necessity of IgG<sub>4</sub>RD confirmation in the management of iRPF-related hydronephrosis.<sup>16</sup> Satisfactory reductions in retroperitoneal mass were observed in both groups in this study. Several inflammatory factors, particularly serum IgG levels, predicted hydronephrosis remission and stent-free prognosis. Furthermore, monitoring the variations in disease activity-related indicators, such as CRP and ESR, benefited decisions in surgical drainage interventions.

“Watchful waiting” is the common strategy in determining the optimal timing to remove ureteral stents and/or nephrostomy tubes. This passive mode might be attributed to an incomplete understanding of iRPF pathological features. In contrast to edema, congestion, and corticosteroid-sensitive inflammation in the early stage, iRPF is characterized by sclerosis and scattered calcification in the late stage.<sup>17</sup> The proliferating tissue surrounds the ureter and can even infiltrate the outer layer of the ureter.<sup>18,19</sup> Sclerosis and infiltrating inflammatory fibrosis are immunosuppressant-resistant and contribute to long-term implacable hydronephrosis.<sup>20</sup> The median time to ureteral obstruction alleviation was 9.3 (2.5–15) months, and most patients reached the stent-removal endpoint within 24 months.<sup>11</sup> In the current study, the median indwelling time in treatment-failure group was significantly longer than 24 months, especially considering that >70% of patients in this group underwent surgical resection of the mass. It is more appropriate to discontinue ureteral stent and/or nephrostomy tube indwelling to avoid further catheter-related complications, which have been broadly reported in both treatment-failure and stent-free groups. Alternative treatments to longer stent indwelling for patients with minimal possibility of hydronephrosis remission would be recommended. Application of immunosuppressants other than corticosteroids (e.g. mycophenolate mofetil) seems to shed light upon such a condition. Additionally, more aggressive treatment options, such as resection of retroperitoneal mass (as shown in Table 1) and ureterolysis, were also attempted in some of our patients. Ureterolysis with a laparoscopic or even robot-assisted approach has been considered an ultimate treatment for iRPF-related hydronephrosis, with the promise of improving the quality of life of patients.<sup>21</sup>

The limitations of this study were the retrospective design and incomplete data collection. These might have led to an underestimation of the strength of the evidence. The methods used to monitor renal function in this study were indirect and inadequate. It remained unclear whether conventional factors in iRPF development, such as exposure to asbestos and tobacco, were also associated with iRPF-related hydronephrosis remission.<sup>22</sup> They were not included in the current study. With expansion in sample size and updated pathological techniques, the significance of IgG<sub>4</sub>RD in iRPF-related hydronephrosis will be further determined and more detailed multivariate analysis conducted to detect independent factors.

## Conclusion

Middle-aged and elderly male patients constituted the iRPF population with hydronephrosis. Under the current comprehensive management model, integrating corticosteroid-based multiple immunosuppressant medication and surgical endoscopic drainage, the vast majority of patients achieved stable or improved long-term renal function and regression of the retroperitoneal mass. The 24-month scale might be applied to guide stent/tube indwelling and the decision on final removal. Beyond the reduction in retroperitoneal mass size, elevated inflammatory markers, such as IgG and CRP at initial iRPF diagnosis, combined with IgG, CRP, and ESR decreases during the treatment course, should be given sufficient consideration in predicting patients' hydronephrosis remission and stent-free outcomes.

## Data Sharing Statement

The datasets generated and/or analyzed during the current study are not publicly available due to limitations of ethics approval involving patient data and anonymity, but are available from the corresponding author on reasonable request.

## Ethics Approval and Consent to Participate

This study complied with the Declaration of Helsinki. This study was conducted with the approval of the Peking University People's Hospital Ethical Review Board (2021PHB342-001). The researchers confirm that all methods were performed in accordance with the relevant guidelines and regulations. Since patients authorized further scientific use as part of their informed consent to the surgical procedures, study-specific informed consent was waived.

## Acknowledgments

Zixiong Huang has been supported by Peking University People's Hospital Research and Development Funds (RDY2021-20 and RDJP2023-20). This work is partially supported by the Michigan Medicine and Peking University Health Science Center Joint Institute (JI) for Translational and Clinical Research. Deep gratitude to the crew members at the Department of Rheumatology and Immunology for their support.

## Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis, interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval to the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report there are no competing interests to declare.

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