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ORIGINAL RESEARCH

Relapse Predictors of Idiopathic Retroperitoneal Fibrosis: A Long-Term Cohort Study

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Objective: This study aims to identify predictive factors for the relapse of idiopathic retroperitoneal fibrosis (IRF) and provide instructions for the optimization of the maintenance therapy.

Methods: All patients with a clinical diagnosis of IRF were enrolled and followed up every 3–6 months. Their clinical characteristics, laboratory data and treatment strategies were recorded at each visit.

Results: 96 IRF patients (77 males and 19 females) with a median age of 55 years (interquartile range [IQR], 50–61) were enrolled. The median follow-up time was 2.50 (IQR, 1.75–4.13) years. During the follow-up, 21 patients experienced at least one relapse, with cumulative relapse rates of 10.6%, 32.3%, and 62.4% at 2.5, 5, and 7.5 years, respectively. Initial hydronephrosis was an independent predictor of relapse (Hazard ratio [HR], 5.35; p=0.001). Discontinuation of maintenance therapy (HR, 3.41; 95% CI, 1.4–8.314; p=0.007) was closely associated with relapse. Use (HR, 0.12; p<0.001) and dose (HR, 0.73; p=0.01) of glucocorticoids (GC) in maintenance period were protective factors against relapse. Among patients with hydronephrosis, those who discontinued GC had a higher relapse rate (p=0.009). GC monotherapy or combined immunosuppressants (IM) therapy were more effective in preventing relapse than IM alone (p<0.001).

Conclusion: Our study reveals that initial hydronephrosis and GC withdrawal during maintenance therapy are significant predictors of IRF relapse. Long-term, low-dose GC therapy is benefit for maintaining remission and preventing relapse, especially in patients with initial hydronephrosis.

Keywords: retroperitoneal fibrosis, recurrence, risk factors, glucocorticoids/therapeutic use, cohort studies

Introduction

Idiopathic retroperitoneal fibrosis (IRF) is a rare and chronic inflammatory disorder manifesting as the development of fibrous tissue in the retroperitoneal space, which can encase and obstruct adjacent structures such as the ureters and great vessels.[1,2] IRF follows remission and deterioration/relapse clinical courses, with an overall 17–48% chance of relapse.[3–7]

To date, the risk factors associated with relapse in IRF remain controversial, with several retrospective cohort analyses yielding conflicting results.[5,7–9] Raffiotta et al identified baseline antinuclear antibody positivity and male sex as being associated with relapse, while initial treatment with GC appeared to prevent relapse, with increased effectiveness at higher doses.[5] Zhao et al found that lower baseline erythrocyte sedimentation rate (ESR) levels and long-term use of

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GC were protective.[8] Smoking habit, acute kidney injury (AKI) at diagnosis, antinuclear antibody (ANA) positivity and lumbar pain were found associated with relapse by Moriconi et al.[9] Conversely, Zampeli et al reported no associations between relapse and initial clinical/imaging findings or any treatment used, but noted that patients with high immunoglobulin (Ig) G4 levels had a higher rate of relapse.[7] Additionally, Morin et al found that persistent FDG uptake on follow-up PET/CT was independently associated with an increased risk of relapse, highlighting the value of metabolic imaging in identifying patients with ongoing subclinical disease activity.[10]

Despite these insights into relapse predictors, a standardized maintenance therapy to prevent recurrence has yet to be established. GC are the cornerstone in the treatment of IRF due to their potent anti-inflammatory effects, but long-term use leads to significant adverse effects.[11–14] Evidence from the only randomized controlled trial to date further demonstrated that prednisone was markedly more effective than tamoxifen in preventing relapse during both the treatment and extended follow-up phases.[15] However, the substantial toxicity associated with prolonged GC exposure highlights the unmet need for better maintenance strategies that can both prevent relapse and minimize adverse effects, or for identifying subgroups of patients who may safely discontinue GC with a low risk of relapse.

The primary aim of this study is to predict relapse factors of IRF based on a long-term ambispective observational cohort with both retrospective and prospective data collection. Moreover, we seek to optimize the maintenance therapy for IRF patients based on clinical evidence, to ensure treatment efficacy and meanwhile facilitate GC tapering.

Method

Study Design and Participants

In this ambispective observational cohort study, patients aged 18–75 with a diagnosis of IRF were included in this study from January 2013 to December 2024 at the Peking Union Medical College Hospital (PUMCH). This ambispective cohort included retrospectively identified patients diagnosed before January 17, 2020 and prospectively enrolled patients diagnosed thereafter. The clinical diagnosis criteria of IRF was established based on the following diagnostic criteria: (1) imaging findings of soft tissue density mass surrounding the abdominal aorta or iliac arteries and (2) histopathological findings which showed fibrous tissue with chronic inflammatory infiltrate comprised of lymphocytes and plasma cells.[16] Patients who fulfilled (1) but without histopathological examination were perceived as possible IRF. Exclusion criteria were as follows: 1) Patients with secondary causes of retroperitoneal fibrosis, such as malignancies, active tuberculosis and drug reaction; 2) Patients combined with other definite rheumatic and autoimmune diseases such as rheumatoid arthritis, IgG4 related disease (IgG4-RD), ankylosing spondylitis, etc; 3) Patients who had incomplete baseline information (clinical characteristics, imaging studies, and treatment) at the time of initial diagnosis. Since IRF is a rare disease, sample size calculation was not performed, and all patients meeting the criteria were enrolled. Participants were followed up every 3 months during the first two years, and then every 6 months thereafter at the Rheumatology and Immunology department of PUMCH. This observational cohort study was registered on ClinicalTrials.gov (NCT04312854) and approved by the Ethics Committee of Peking Union Medical College Hospital (Approval No. ZS-2292). The study was conducted in accordance with the ethical standards of the institutional research committee and with the principles of the Declaration of Helsinki. All participants provided written informed consent for the scientific use of their clinical data at the time of enrollment.

Examination and Data Collection

At the initial consultation, baseline information including demographic features, medical history (symptoms, comorbid conditions, smoking, and treatment), immunologic profiles (antinuclear antibody [ANA], rheumatoid factors [RF] and antineutrophil cytoplasmic antibody [ANCA]), and assessment of neoplastic markers (including carbohydrate antigens 19–9 and 125 and carcinoembryonic antigen) were collected. Symptoms, adverse events and medications were recorded at each follow-up visit. Results of laboratory tests were also recorded at baseline and each follow-up visit, including blood cell count, serum creatinine (Cr), ESR, high-sensitivity C-reactive protein (hsCRP), IgG, IgG4, IgA, IgM, IgE, complement component 3 (C3), and complement component 4 (C4) and urine analysis. In addition, imaging examinations—including abdominal computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography—were performed at

baseline and at six-month intervals. Follow-up imaging was conducted predominantly with abdominal CT (>90%), whereas MRI or ultrasonography were used only in selected situations, such as contrast contraindications, renal impairment and the need to avoid radiation exposure. All imaging findings were independently evaluated by a rheumatologist and a radiologist, and any discrepancies were resolved by consensus or with the involvement of a third reviewer.

Treatment

Clinical treatment for IRF patients includes two stages: the remission induction period and the maintenance period. In the first period, patients receive medium-to-high-dose GC with or without IM. The standard induction dose of oral prednisone is 0.6–1.0 mg/kg per day in the first month and gradually tapers by 5 mg per 1 or 2 weeks to the maintenance dose after patients achieve disease remission.[1] The maintenance period is defined as the stage when GC are administered at a dose of ≤10 mg per day. In this study, options for maintenance therapy included GC, IM, or tamoxifen monotherapy, as well as combinations of these drugs in dual or triple regimens. Traditional IM included cyclophosphamide (CYC, mycophenolate mofetil (MMF), methotrexate (MTX), azathioprine (AZA), leflunomide (LEF), tripterygium wilfordii, and hydroxychloroquine (HCQ). Additionally, the Janus kinase inhibitor (JAKi), tofacitinib, was utilized for maintenance therapy in some cases. GC tapering and discontinuation were undertaken only after patients had achieved clinical stability, with the goal of minimizing the potential adverse effects associated with long-term GC exposure. This study focused on the minimum maintenance treatment regimen during the process of gradual dose reduction, which was sustained for a minimum duration of 6 months to control for the potential confounding effects of treatment administered prior to the dose reduction.

Definitions

The primary endpoint of this study was clinical relapse. The following were defined as relapse: (1) the presence of imaging evidence, including enlarged retroperitoneal mass or thickening of the encasement around ureters that could possibly lead to hydronephrosis or (2) the reappearance of both abnormally elevated serum inflammatory markers (ESR or hsCRP) and clinical symptoms such as abdominal pain in patients when without imaging evidence. In addition, the exclusion of possible infections was carefully considered. Secondary endpoints included drug-related adverse events and clinical manifestations of relapse.

Statistical Analysis

Statistical analyses were performed to identify predictors of relapse and assess treatment efficacy. Continuous variables with the non-normal distribution were presented as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney *U*-test. Categorical variables were shown as frequencies and percentages and compared using the Chi-square test or Fisher's exact test as appropriate. Because relapse and non-relapse groups were outcome-defined rather than predefined exposure groups, follow-up duration was not used as a comparative baseline characteristic. Instead, Cox proportional hazards models accounted for differences in observation time, and Kaplan–Meier curves were used to estimate cumulative relapse incidence.

To assess the association between maintenance treatment strategies and relapse risk, logistic regression models were used to compare the odds of relapse among patients receiving GC monotherapy, IM monotherapy, and combined GC + IM therapy. Odds ratios (ORs) with 95% confidence intervals (CIs) and corresponding p-values were calculated to estimate the relative relapse risk. In addition, patients who discontinued all maintenance therapy were compared separately to each monotherapy group. All models were evaluated for statistical significance using a two-sided p-value threshold of <0.05.

The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the predictive value of maintenance GC dose on relapse. The area under the curve (AUC) was calculated to assess the model's discriminative ability. The optimal cutoff point was determined based on the Youden index.

The Cox proportional hazards regression model was utilized to identify factors associated with the time to relapse. The univariable Cox regression analysis was first performed to identify potential predictors. Integration of practical clinical implications, variables with a p value <0.1 in the univariable analysis were included in the multivariable Cox

regression model to adjust for confounding factors. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported.

All statistical analyses were performed using R 4.3.3 or GraphPad prism.

Results

Demographic and Clinical Characteristics at Baseline

From January 2013 to December 2024, a total of 131 patients with IRF primarily visited the Rheumatology and Immunology department in PUMCH, from whom 35 patients were excluded. To be specific, 30 patients were excluded because their follow-up period was less than one year or they had not started maintenance therapy and 5 patients were excluded due to loss to follow-up (Figure 1).

IRF was diagnosed in the remaining 96 patients. Demographic and clinical characteristics on admission are shown in Table 1. The median age of participants was 55 (IQR, 50–61) years, including 77 males and 19 females. Among the 96 patients, 74 (77%) patients presented with initial symptoms of abdominal pain or back pain, while 10 (10%) asymptomatic patients were found to have imaging abnormalities during routine physical examinations. Regarding urinary system involvement, hydronephrosis was observed in 52 (54%) patients, with 27 patients affected unilaterally and 25 bilaterally. 47 (49%) patients had a history of D-J tube drainage, and 4 (4%) had undergone ureterolysis. Additionally, 14 (15%) and 36 (38%) patients had a history of coronary heart disease and smoking respectively. The median follow-up time was 2.50 (IQR, 1.75–4.13) years.

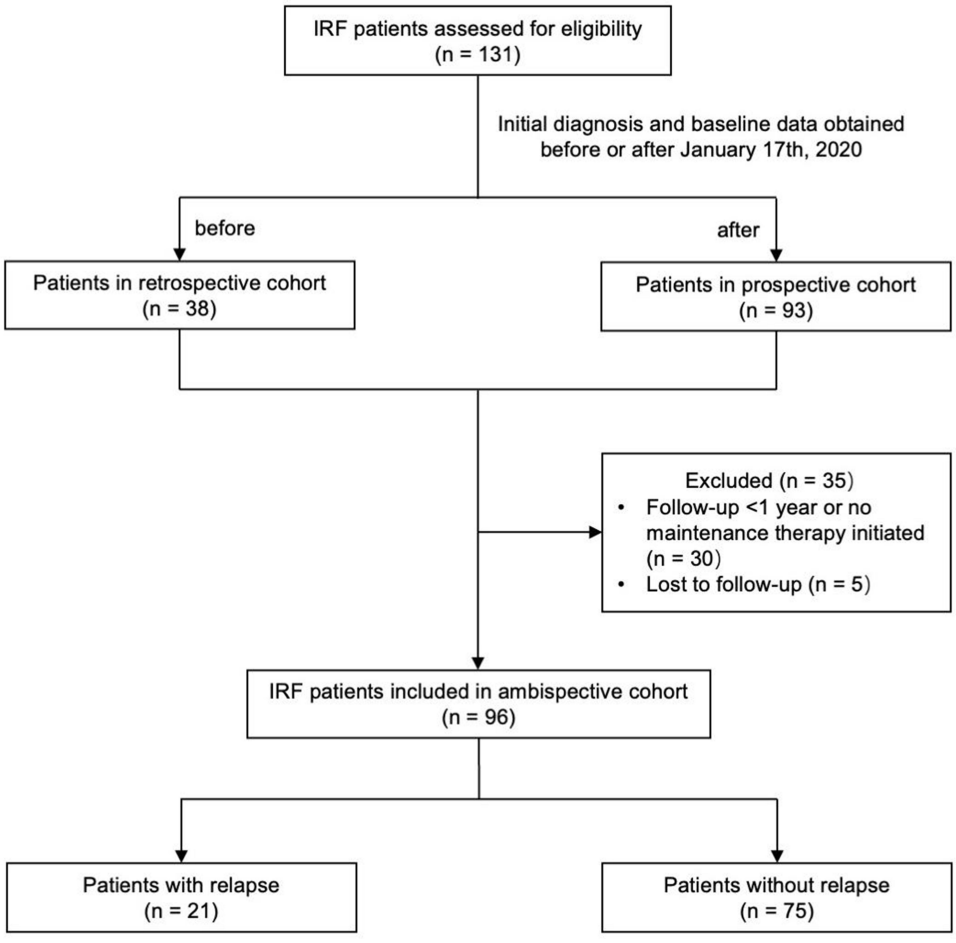

Figure 1 Flow diagram of patient enrollment and follow-up. From January 2013 to December 2024, 131 patients with IRF were assessed, of whom 35 were excluded (30 with follow-up <1 year or no maintenance therapy initiated, and 5 lost to follow-up).
Abbreviation: IRF, idiopathic retroperitoneal fibrosis.

Table 1 Demographic and Clinical Characteristics of Patient with IRF at Baseline

Parameter	IRF Patients (N=96)
Male	77 (80%)
Age at diagnosis (year)	55 [50–61]
Clinical manifestations	
Back/abdominal pain	74 (77%)
Hematuria	7 (7%)
Leg edema	9 (9%)
Fever	7 (7%)
Fatigue	11 (11%)
Weight loss	5 (5%)
Asymptomatic	10 (10%)
Involvement of urinary system	
Hydronephrosis	52 (54%)
Unilateral	27 (28%)
Bilateral	25 (26%)
History of D-J tube drainage	47 (49%)
History of ureterolysis	4 (4%)
Retroperitoneal lymph node	9 (9%)
Laboratory examinations	
WBC, $\times 10^9$/L	7.61 [6.24–9.69]
ESR, mm/h	34 [18–64]
hsCRP, mg/L	8.30 [1.78–27.24]
ANA positive	27 (44%)
IgG4, mg/L	525 [248–921]
Serum creatinine, μmol/L	114 [86–282]
Comorbid conditions	
Hypertension	26 (27%)
Dyslipidemia	24 (44%)
Coronary heart disease	14 (15%)
Diabetes	10 (10%)
Gout	8 (8%)
Thyroid dysfunction	2 (2%)
History of Tuberculosis	4 (4%)
Smoking history	36 (38%)
Duration of follow-up (year)	2.50 [1.75–4.13]
Duration of disease (year)	3.03 [1.93–4.82]

Notes: Continuous variables are presented as median with interquartile range [IQR], and categorical variables are presented as number (percentage). Abnormal laboratory thresholds were defined as follows: ESR ≥20 mm/h, hsCRP ≥8 mg/L, ANA titers >1:320, and serum IgG4 ≥1400 mg/L. All variables were available for all patients except dyslipidemia, which was defined as meeting any one of the following criteria: total cholesterol ≥6.19 mmol/L, triglycerides ≥2.27 mmol/L, low-density lipoprotein cholesterol ≥4.14 mmol/L, or high-density lipoprotein cholesterol ≤1.04 mmol/L, with data unavailable for 41 patients.

Abbreviations: WBC, white blood cell; ESR, erythrocyte sedimentation rate; hsCRP, hypersensitive C-reactive protein; ANA, antinuclear antibody; IgG4, immunoglobulin G4; D-J, double-J.

Relapse of IRF During Follow-Up

During the follow-up, relapse occurred in 21 patients. The median time interval from diagnosis to the first relapse was 3.03 (IQR, 1.93–4.82) years. Among them, 18 patients relapsed once while 2 patients had two relapses and 1 patient had four relapses. As of the last follow-up, all patients were alive. The Kaplan-Meier curve in Figure 2a shows cumulative relapse rates of 10.6%, 32.3%, and 62.4% at 2.5, 5, and 7.5 years, respectively. At relapse, patients primarily presented

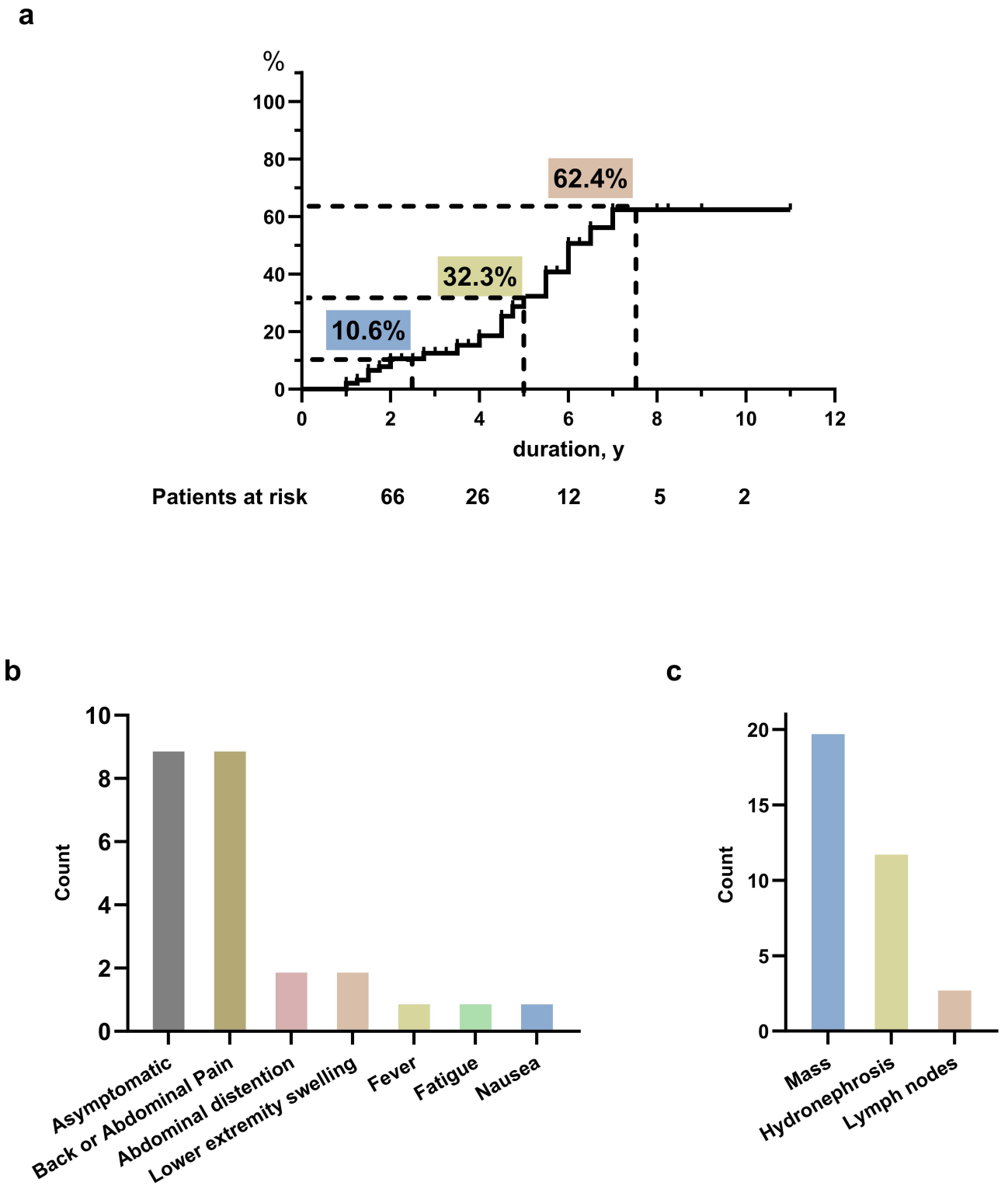

Figure 2 The relapse of IRF patients in this study. (**a**) Cumulative relapse rate in the IRF patients (Kaplan–Meier method). (**b**) Symptoms at the time of relapse in 21 patients. (**c**) Imaging features of the 21 patients at relapse.

with back or abdominal pain (43%) or were asymptomatic (43%). A few patients exhibited symptoms such as abdominal distention, lower extremity swelling, fever, fatigue, and nausea (Figure 2b). Moreover, imaging results indicated that the vast majority (95%) of patients had the enlargement or reappearance of retroperitoneal masses (Figure 2c). Additionally,

imaging revealed hydronephrosis in 12 (57%) patients and multiple small retroperitoneal lymph nodes in 2 patients (Figure 2c). The clinical presentations and outcomes of 21 patients at the first relapse are detailed in Table S1.

Baseline Clinical Features Between Patients with and without Relapse

The comparison of baseline clinical characteristics between patients with and without relapse was reported in Table S2. The observed follow-up duration was comparable between patients who experienced relapse (1.5–5.75 years) and those who did not (1.75–3.5 years), with no significant difference. No predisposition to relapse was identified with respect to gender, age or symptoms. However, patients with relapse had a higher proportion of hydronephrosis (p=0.006) at initial treatment compared to patients without relapse (Figure 3a). Nevertheless, it was not associated with whether the involvement was unilateral (p=0.09) or bilateral (p=0.15).

For laboratory indicators, CRP (p=0.29) and Cr (p=0.29) levels trended higher in the relapse group (Figure 3b and c), suggesting that patients with initial inflammation and renal dysfunction may be more prone to relapse, though not statistically significant. Other indicators, such as ANA positivity and IgG4 levels (Figure 3d), showed no difference between patients with and without relapse.

Treatment Between Patients with and without Relapse

The comparison of initial therapies for inducing remission between patients with and without relapse was shown in Table S3 and Figure S1a. Except for the 5 patients who used tocilizumab, the initial treatment for the other 91 patients consisted of medium-to-high-dose GC, with or without IM or tamoxifen. As shown in Figure S1b, patients without relapse received higher doses of GC compared to patients with relapse (p=0.04), suggesting that a higher dose of initial GC might be valuable for long-term prevention of relapse. There was no significant difference of IRF relapse among the different initial treatment groups (Figure S1c).

A range of maintenance therapies was used, and a comparison between patients with and without relapse was presented in Table S3 and Figure 4a. Among patients with relapse, 48% discontinued their medication, which was significantly higher compared to those who did not experience relapse (48% vs 3%, p<0.001). The maintenance doses of GC were lower in patients with relapse (p<0.001, Figure 4b). The ROC curve was used to detect the optimal cut-off value for predicting relapse in the GC monotherapy maintenance (AUC=0.82, p<0.001, Figure S2). The optimal cut-off of GC dosage for predicting IRF relapse was determined using the Youden's index, which was 0.625 mg per day (sensitivity, 81.82%; specificity, 86.49%). By comparing 4 maintenance therapies containing GC, we found that there was no significant difference in GC doses (Figure 4c). Additionally, the GC + IM dual therapy demonstrated a better effect in preventing relapse compared to the IM monotherapy (Odds ratio [OR], 102.0; 95% confidence interval [CI], 11.16–2583; p<0.001), but there was no significant difference when compared to GC monotherapy (OR, 6.8; 95% CI, 0.59–155.6; p=0.13), suggesting a high risk of relapse caused by GC withdrawal.

No serious adverse events occurred in all patients during the follow-up period. However, some patients experienced adverse events associated with IM, including transient elevation of liver enzymes (2 cases), leukopenia (2 cases), and rashes (1 case), leading to a subsequent change to alternative IM therapies.

Predictors of Relapse

The univariable cox proportional hazards regression revealed that hydronephrosis occurrence (Hazard ratio [HR], 5.35; 95% CI, 1.93–14.83; p=0.001) and hsCRP levels (HR per mg/L hsCRP, 1.02; 95% CI, 1.00–1.03; p=0.06) during the initial onset were associated with relapse (Table S4). In maintenance period, discontinuation of therapy (HR, 3.41; 95% CI, 1.4–8.314; p=0.007) was closely associated with relapse. Use (HR, 0.10; 95% CI, 0.03–0.30; p<0.001) and dose (HR per mg GC per day, 0.70; 95% CI, 0.55–0.89; p=0.004) of GC were also related to a lower rate of relapse.

Based on clinical significance and the results of univariate analysis above, two multivariate regression models were established (Table 2). Three variables selected in Model A were hydronephrosis, hsCRP and use of GC for maintenance. In Model B, the variable "use of GC for maintenance" was replaced by the "GC maintenance dose". Hydronephrosis was associated with relapse in both two models (Model A: HR, 3.94; 95% CI, 1.35–11.55; p=0.012. Model B: HR, 4.39; 95%

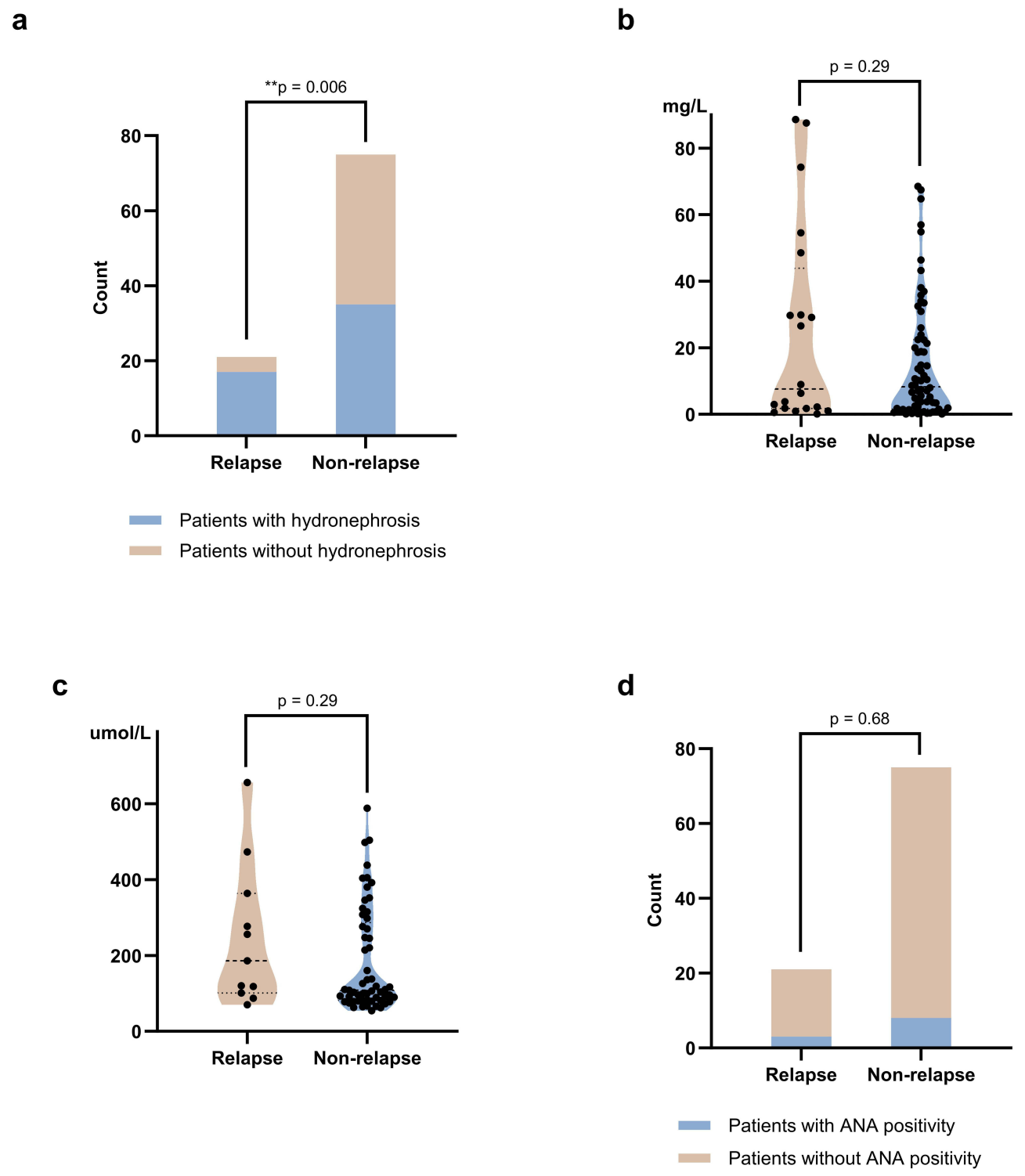

Figure 3 Comparison of baseline clinical characteristics between patients with and without relapse. (**a**) Comparison of the presence of hydronephrosis (Chi-square test). (**b**) Comparison of hsCRP levels (Wilcoxon rank-sum test). (**c**) Comparison of serum creatinine levels (Wilcoxon rank-sum test). (**d**) Comparison of ANA positivity (Chi-square test). Symbol: **indicates $p < 0.01$.

CI, 1.50–12.88; p=0.007), while use of GC for maintenance (HR, 0.12; 95% CI, 0.04–0.37; p<0.001) and the GC maintenance dose (HR, 0.73; 95% CI, 0.58–0.93; p=0.01) were protective factors against relapse in respective models. Figure 5a–c depicted cumulative relapse rate curves, showing significant differences between groups divided by the

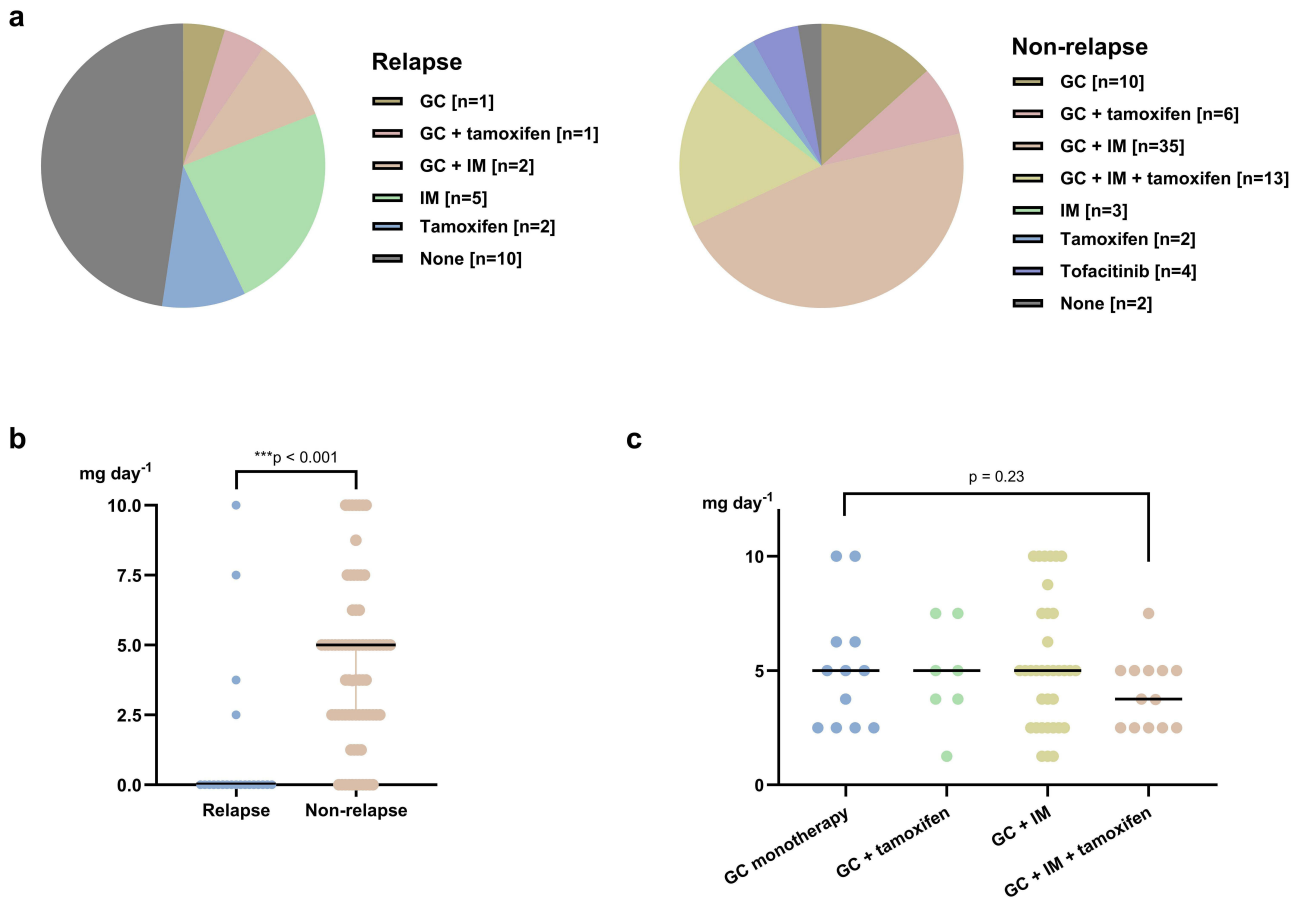

Figure 4 Comparison of maintenance therapies between patients with and without relapse. (**a**) Distribution of maintenance therapies in patients with and without relapse. (**b**) Comparison of GC maintenance doses between patients with and without relapse (Wilcoxon rank-sum test). (**c**) Comparison of GC maintenance doses among patients receiving GC monotherapy, GC + tamoxifen, GC + immunosuppressants (IM), and GC + tamoxifen + IM (Kruskal–Wallis test). Symbol: ***indicates $p < 0.001$.

presence of hydronephrosis and the use of GC in maintenance therapy. Notably, among patients with hydronephrosis, those on maintenance GC therapy had a lower risk of relapse (p=0.009). Therefore, maintenance GC therapy was recommended for patients with initial hydronephrosis.

Table 2 Predictors of Relapse in IRF via Multivariable Regression Analysis

	HR (95% CI)	p value
Model A		
Hydronephrosis	3.94 (1.35–11.55)	0.012
hsCRP, mg/L	1.00 (0.98–1.01)	0.42
Use of GC for maintenance	0.12 (0.04–0.37)	<0.001
Model B		
Hydronephrosis	4.39 (1.50–12.88)	0.007
hsCRP, mg/L	1.00 (0.98–1.02)	0.84
GC maintenance dose, mg/day	0.73 (0.58–0.93)	0.01

Notes: "GC maintenance dose" refers to the daily oral prednisone-equivalent dose used during maintenance therapy (mg/day).
Abbreviations: HR, hazard ratio; CI, confidence interval; GC, glucocorticoid; hsCRP, hypersensitive C-reactive protein (mg/L).

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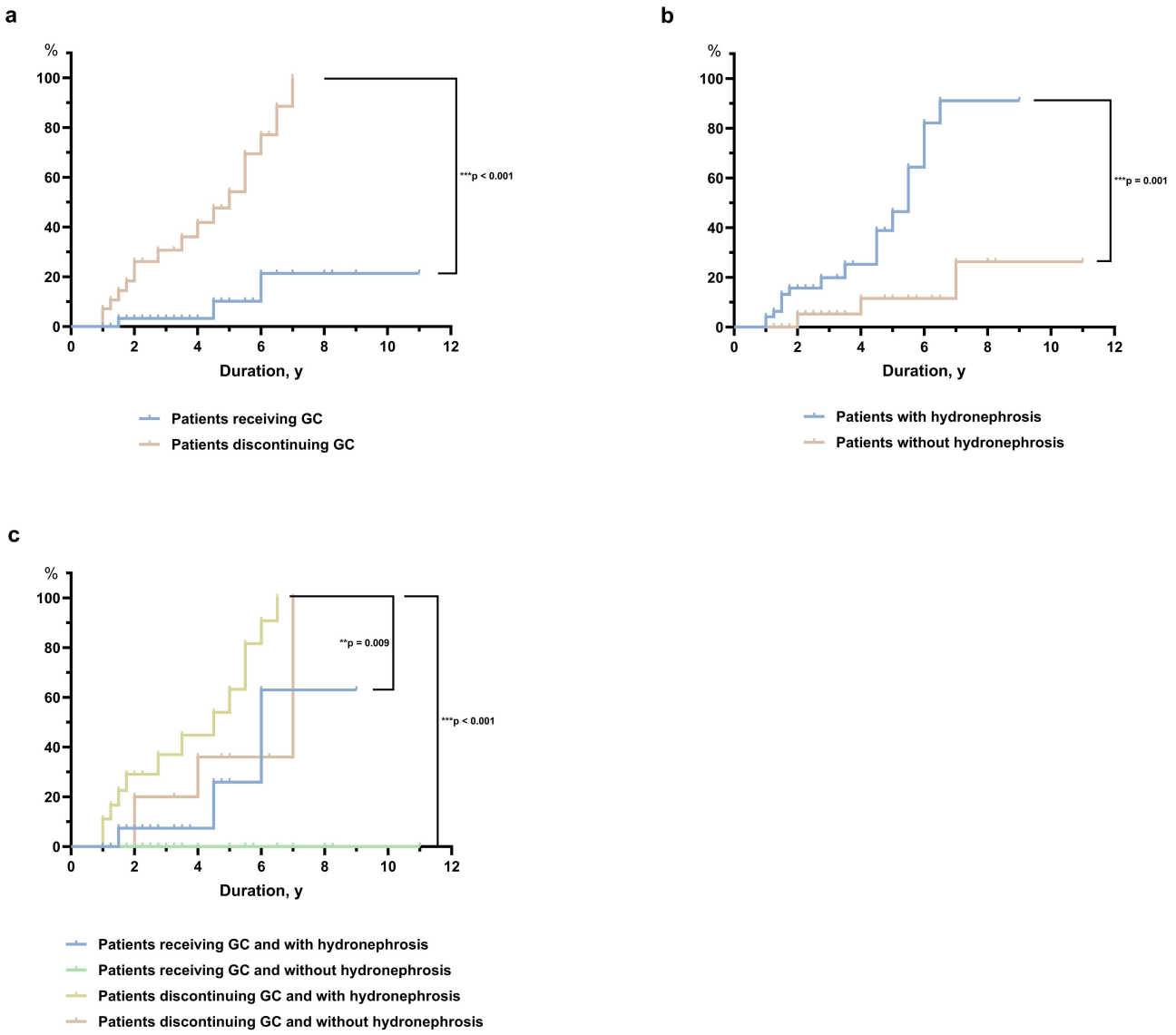

Figure 5 Cumulative relapse rate curves in subgroups. (**a**) Comparison of cumulative relapse rates between patients receiving GC and those discontinuing GC therapy (Log rank test). (**b**) Comparison of cumulative relapse rates between patients with and without hydronephrosis (Log rank test). (**c**) Stratified analysis combining GC exposure (receiving vs discontinuing) and hydronephrosis status (Log rank test). Symbols: **indicates $p < 0.01$; ***indicates $p < 0.001$.

Discussion

In this study, we evaluated the clinical characteristics, treatment strategies, and outcomes of 96 IRF patients, and further investigated potential predictive factors for IRF relapse. Previous studies on relapse risk factors have yielded inconsistent results, and there is no standardized international guideline for IRF treatment. It is therefore worthwhile to establish a clinical cohort with long-term follow-up to identify optimal treatment strategies and risk factors for relapse.

GCs play a central role throughout the treatment course of IRF.[17] Consistent with findings by Raffiotta et al,[5] our study confirmed that higher initial doses of GC in the remission induction period were associated with lower relapse rates. With regard to the long-term maintenance therapy, we found that continued use of GCs significantly reduced relapse rates. In particular, both GC monotherapy and GC + IM therapy showed greater efficacy in preventing relapse compared to IM monotherapy. This finding aligns with Zhao's research, which identified long-term GC therapy as a protective factor against disease relapse.[8] Moreover, our study examined the association between the minimum GC dose and relapse, finding that lower dose of GC in maintenance therapy was a risk factor for relapse. However, the prolonged use of GCs is known to carry substantial adverse effects, including elevated risks of cardiovascular events and metabolic complications, which severely

impact patients' health.[18,19] To date, limited evidence has been available regarding the minimal effective dose of GCs for relapse prevention. A GC maintenance dose of ≤0.625 mg/day as a threshold strongly associated to relapse was revealed by our ROC curve. Notably, none of the patients who received combination therapy with GC, IM and tamoxifen experienced a relapse during the study period. It was reported in a retrospective cohort that long-term and low-dose GC combined with IM might prevent the relapse of IRF.[20] In addition, Vianello et al suggested that methotrexate could serve as a useful and safe adjunct treatment, particularly for patients who are intolerant of or unresponsive to GC monotherapy.[21] Although no major GC-related adverse events were documented in this cohort, adverse events were not systematically collected and the absence of observed toxicity should be interpreted with caution. The findings of this study do not imply that prolonged GC therapy is free of risk, but likely reflect strict specialist monitoring, early tapering strategies, and reduced cumulative exposure in real-world practice. Taken together, the use of long-term, low-dose GC therapy to maintain remission is considered benefit for IRF patients, preferably in combination with IM or tamoxifen, to reduce GC exposure while sustaining disease control.

The role of hydronephrosis as a predictive factor for IRF relapse has been debated in the literature.[5,8] Our study identified hydronephrosis at the initial onset as a key risk factor for relapse. Hydronephrosis can lead to renal insufficiency and potential long-term effects, underscoring the need for timely interventions such as drainage. Our finding also implies that these high-risk patients may warrant closer monitoring for early signs of relapse and should be carefully considered for long-term, low-dose GC maintenance therapy. Similarly, baseline inflammatory markers like ESR and CRP have shown mixed results as predictors of relapse. A previous research identified elevated ESR as a risk factor for relapse,[8] but this conclusion was not supported by our study. Additionally, the univariate Cox regression analysis in our study indicated that elevated CRP might have a predictive value (p=0.06), but this was not significant in the multivariate model. This suggests that the severity of initial inflammation may not impact long-term relapse. Furthermore, consistent with most research on IRF relapse risk factors, it was found that various immunological indicators could not act as potential relapse predictors in this study, although Raffiotta and Moriconi's finding suggested an association of ANA positivity with a higher relapse risk.[5,9] Given the wide spectrum and titers of ANA, further detailed and accurate research is required to address this discrepancy. Elevated IgG4 levels have been identified as a risk factor for IRF relapse in previous studies.[7] However, in this study, patients with elevated IgG4 did not exhibit a higher relapse rate, and their IgG4 levels were not associated with relapse.

In addition to medical therapy, surgical management plays a crucial role in IRF patients with obstructive uropathy. Ureterolysis, performed through either an open or laparoscopic approach, achieves high success rates (>90%) with low complication rates, and laparoscopic surgery offers faster recovery when feasible.[22] Early decompression with ureteral stenting or nephrostomy remains essential, particularly because preoperative renal dysfunction has been linked to poorer long-term renal outcomes after surgical release.[23] Nevertheless, surgery primarily addresses mechanical obstruction and does not control underlying inflammatory activity; up to one-third of patients may still require immunosuppressive therapy during follow-up.[24] Accordingly, surgical intervention provides the most direct and effective relief of obstruction, whereas medical therapy remains essential for controlling the underlying inflammatory activity, underscoring the need for an integrated multidisciplinary approach.

This study has several limitations, including its single-center design and the relatively small sample size. Larger multi-center studies are needed to validate these findings. Additionally, given the heterogeneity of the treatment for IRF, research probing into alternative therapies and the long-term side effects of GC therapy is warranted to optimize IRF management.

In conclusion, hydronephrosis at the initial onset was identified as a significant predictor of IRF relapse. Using GC during maintenance period was found to be effective in preventing relapse and its effectiveness increased with the dosage. The study highlights that patients with initial hydronephrosis constitute a high-risk group for relapse. Accordingly, they should be followed more closely and maintained on ongoing GC therapy. It also suggests that combining GC with other IM and tamoxifen could support more effective GC tapering.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author Yunyun Fei and Wen Zhang, upon reasonable request.

Author Contributions

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

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Disclosure

The authors declare no competing interests.

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