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Effectiveness and Safety of Spironolactone in the Treatment of IgA Nephropathy: A Retrospective Self-Controlled Study

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Keywords
IgA nephrology · Proteinuria · Spironolactone · Renal function

Abstract

Introduction: It is crucial to utilize combination therapy for immunoglobulin A nephropathy (IgAN) patients to reduce proteinuria and maintain stable kidney function. We demonstrate the safety and efficacy of low-dose spironolactone in the management of IgAN patients. ***Methods:*** Adult IgAN patients treated with spironolactone were evaluated. Patients were separated into two categories according to whether 24-h proteinuria was reduced by more than 20% after 2 months of spironolactone treatment compared to baseline levels. ***Results:*** Eighty-eight patients were analyzed and 24-h proteinuria decreased from 0.93 g to 0.70 g ($p < 0.001$) after 2 months of treatment with spironolactone, accompanied by a slight decrease in eGFR from 75.7 to 73.9 mL/min/1.73 m^2 ($p = 0.033$). Intriguingly, 47 patients in the effective mineralocorticoid receptor antagonist (MRA) group showed less endocapillary hypercellularity ($p = 0.040$). In the ineffective group, 18 patients discontinued MRA treatment because 24-h proteinuria increased from 0.83 g to 1.04 g, while the other 23 patients continued with spironolactone and proteinuria decreased to 0.57 g in the sixth month ($p = 0.001$). Furthermore, 12 patients with persistent high proteinuria during prednisone therapy were added with spironolactone. 24-proteinuria was dropped from 0.95 g to 0.73 g at the second month and to 0.50 g at the sixth month. ***Conclusions:*** In our study, we confirmed spironolactone's efficacy in reducing urine protein excretion in IgA nephropathy patients within 2 months of treatment. However, response varied among patients, with those showing endocapillary proliferation (E1) in renal biopsies having poor spironolactone responsiveness. Administering MRAs to patients with eGFR over 30 mL/min did not result in hyperkalemia, indicating the treatment's safety.

Introduction

Immunoglobulin A nephropathy (IgAN), a prevalent form of primary glomerular disease globally, stands as a major contributor to chronic kidney disease (CKD) and kidney failure. Large-scale epidemiological research in IgAN cohorts has pinpointed uncontrolled proteinuria as a standalone risk factor for disease progression in IgAN [1, 2]. A recent cohort study on IgAN discovered that, over a decade, patients with an average proteinuria level less than 0.44 g/g were 10% less likely to develop kidney failure compared to those with average proteinuria levels ranging from 0.44 to 0.88 g/g [3]. Therefore, consistently lowering proteinuria to minimal levels emerges as a vital

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therapeutic objective for IgAN patients to prevent or postpone the onset of end-stage renal disease.

IgAN often exhibits a protracted course with frequent relapses; even when proteinuria is efficiently managed for some time, most IgAN patients suffer relapses due to infections or unexplained reasons. Recent TESTING trial demonstrated that methylprednisolone markedly decreases urinary protein and the risk of kidney failure, although this effect becomes less noticeable after 3 years [4]. The serious side effects associated with steroids and immunosuppressants necessitate varying combinations of treatments at different disease stages. While employing a maximally tolerated renin-angiotensin system (RAS) blockade is advocated [5], RAS blocker treatment frequently fails to meet proteinuria treatment goals. Long-term use of angiotensin II type 1 receptor antagonists or ACE inhibitors has been shown to increase plasma aldosterone concentration, a phenomenon referred to as aldosterone breakthrough [6]. Aldosterone, the endogenous agonist of the mineralocorticoid receptor (MR), plays a role in CKDs such as CKD and diabetes due to MR overactivation. A meta-analysis revealed a 31% decrease in urinary protein or albumin excretion after treatment with a steroidal mineralocorticoid receptor antagonist (MRA) in patients with CKD [7]. Recent advances in nonsteroidal, selective MRAs have demonstrated a reduction in the urinary albumin-to-creatinine ratio in diabetic patients treated with an RAS blocker [8]. Research on the potential of MRA to reduce protein in IgAN is lacking. Although a small subset of IgAN patients were involved in CKD research, the specific effects on IgAN have not been thoroughly examined [7].

To investigate whether MRA could serve as a potential option within a combination of treatments for IgA, we conducted a retrospective cohort study involving 88 adult IgAN adult patients at a single Chinese center. Within our cohort, we explored the potential advantages and safety of MRA, encompassing patients with an initial eGFR of ≥30 mL/min per 1.73 m^2. Furthermore, we examined specific characteristics, such as the level of pretreatment proteinuria or pathological features, to determine which might produce a better response to MRA therapy.

Methods

Study Patients

This observational cohort study included adult IgA nephropathy patients treated with spironolactone at Huashan Hospital Fudan University in China from December 2010 to July 2020. All patients were diagnosed by renal biopsy and in stable condition during regular follow-up. Patients whose 24-h proteinuria was still ≥0.3 g when received adequate non-immunosuppressive and immunosuppressive therapy were prescribed spironolactone (20 mg qd po) and followed up to 6 months. Patients were excluded if they had recurrent hyperkalemia (>5.5 mmol/L) and pregnancy intention. Patients were divided into two groups based on whether 24-h proteinuria decreased by more than 20% (which was the mean change rate of proteinuria) after 2 months of treatment with spironolactone compared to the baseline when prescription of spironolactone.

Clinical and Biological Data

Demographic characteristics (age, gender), blood pressure, ACEI/ARBs, and immunosuppressants were recorded in the follow-up time. Clinical, biological, and histopathological data at biopsy, the onset of spironolactone treatment and 6 months follow-up were reviewed thoroughly and collected to evaluate the short-term and long-term effects of spironolactone. All laboratory tests were performed in Huashan Hospital, including urine routines, kidney function, electrolytes analysis when eGFR (calculated using the CKD-EPI equation) were <60 mL/min/1.73 m^2, and 24-h urinary protein quantification.

Histopathological Parameters

All patients in our cohort study were regularly followed up by IgA nephrology clinics. The clinical data and biochemical indicators of patients were recorded in detail during regular follow-up in outpatient clinic. We searched for patients receiving spironolactone in our center and their clinical data were recorded. All data were collected in a way that can be analyzed and crosschecked by two physicians. Diagnosis of IgAN and histologic evaluation of renal biopsy specimen findings were graded according to the Oxford classification.

Statistical Analysis

Statistical analysis of the data was performed using SPSS software, version 22.0. Continuous variables are expressed as the mean ± SD or the median and quartile range, and categorical variables are expressed as percentages. Comparisons between two groups were performed using an independent *t* test, Mann-Whitney U test for continuous variables, Pearson's, χ^2 test, or Fisher's exact test for categorical variables. A nonparametric test of two correlated samples and paired-samples *t* tests were used to compare the differences before and after the spironolactone prescription. All statistical tests were 2-sided, and differences were considered statistically significant with a p value of <0.05.

Results

Baseline Data

A total of 90 IgA nephropathy patients prescribed spironolactone were included in the study. However, 2 patients were excluded because they discontinued treatment in the first 2 months due to recurrent hyperkalemia and pregnancy intentions (Fig. 1). A total of 88 patients were then included in the final analysis. Of these, 53 patients were male, and the average GFR was

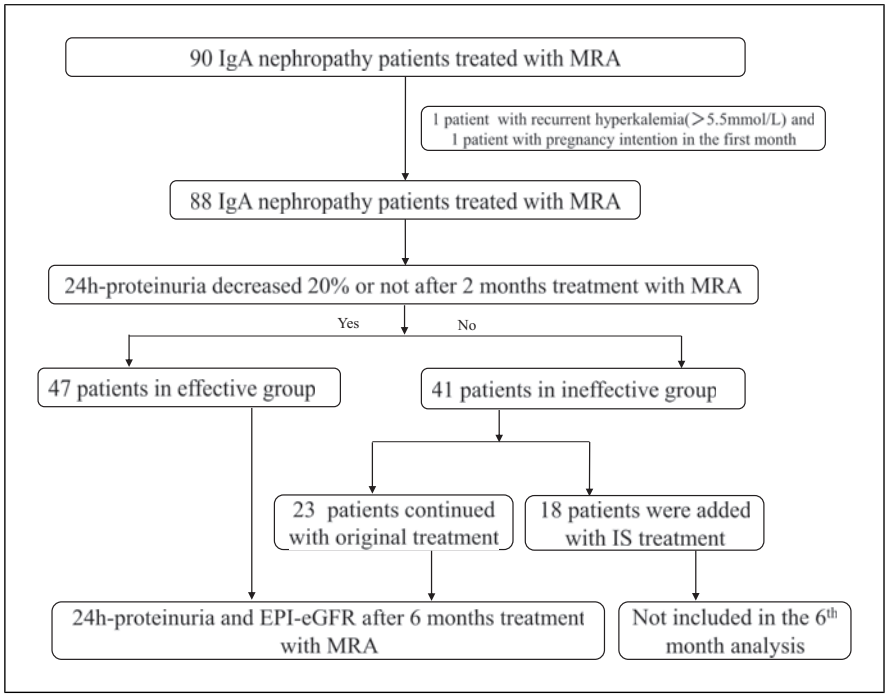

Fig. 1. Flow chart of the cohort study.

81.1 ± 28.4 mL/min/1.73 m^2 and the median of 24-h proteinuria was 1.50 (IQR 1.03–2.32) g at renal biopsy. When spironolactone was prescribed, the average eGFR was 75.7 ± 28.6 mL/min/1.73 m^2 and the median proteinuria was 0.93 g in our cohort. In the patient group, 33.0% had an eGFR that exceeded 90 mL/min/1.73 m^2, whereas 4.5% recorded an eGFR below 30 mL/min/1.73 m^2. Among these patients, 42 (47.7%) exhibited a 24-h proteinuria level higher than 1.0 g, while the remaining 46 patients (52.3%) showed a 24-h proteinuria level of less than 1.0 g (Table 1).

In our study, all patients were added to RAS inhibitors except for 2 patients due to low level of renal function (eGFR was 23.5 and 20.23 mL/min/1.73 m^2). The RAS inhibitors lasted for the whole research period and doses were adjusted with serum creatinine and blood pressure to the maximum tolerated dose. In our cohort, 1 patient was prescribed 20 mg olmesartan, 1 patient was prescribed 80 mg telmisartan, 9 patients were prescribed 150~300 mg irbesartan, 17 patients were prescribed 25~150 mg losartan, 58 patients were prescribed 40~240 mg (40 mg to 5 patients, 80 mg to 32 patients, 120 mg to 8 patients, 160 mg to 10 patients, 180 mg to 1 patient, and 240 mg to 2 patients) valsartan daily. Among the 88 patients, 26.1% (23/88) received prednisone or immunosuppressants, with 12 patients undergoing prednisone therapy also being prescribed spironolactone due to proteinuria levels averaging 0.95 (IQR 0.68–1.36) g/day after more than 3 months of prednisone treatment. Additionally, 14.8% (13/88) of patients received hydroxychloroquine as part of their foundational treatment.

Short-Term Effects

During the follow-up period, 1 patient experienced mild gynecomastia, and 2 patients were found to have hyperkalemia (up to 5.6 mmol/L) after 2 months of treatment with spironolactone. Their condition returned to normal following dietary education, and the original treatment regimen was continued. In the group of 88 patients, the median 24-h proteinuria was significantly reduced from 0.93 to 0.70 g ($p < 0.001$) after 2 months of applying spironolactone. This decrease was accompanied by a reduction in eGFR (from 75.7 ± 28.6–73.9 ± 29.8, $p = 0.033$) and diastolic BP (DBP) (from 80.0 ± 11.1–78.2 ± 9.8, $p = 0.041$). Although spironolactone showed a trend toward reducing systolic BP (SBP) ($p = 0.119$), it did not affect hematuria and serum potassium in the overall patient population (Fig. 2).

Preliminary analysis suggested that spironolactone could reduce IgAN proteinuria in a brief period of time. To further analyze the characteristics of patients with better response to spironolactone, we divided them into two groups, the effective and ineffective groups, depending on whether 24-h proteinuria decreased by more

Table 1. Clinical characteristics of total IgAN patients

	Total (n = 88)
At renal biopsy	
Age, years	34.8 (29.1, 43.2)
Gender (male)	53/88 (60.2%)
eGFR, mL/min/1.73 m^2	81.1±28.4
≥90 mL/min/1.73 m^2	36/88 (40.9%)
60~89 mL/min/1.73 m^2	30/88 (37.5%)
30~59 mL/min/1.73 m^2	19/88 (21.6%)
20~29 mL/min/1.73 m^2	3/88 (3.4%)
Serum creatinine, μmol/L	97.0 (77.0, 123.0)
Serum potassium, mmol/L	4.17±0.36
24-h proteinuria, g	1.50 (1.03, 2.32)
≥1.0 g	72/88 (81.8%)
<1.0 g	16/88 (18.2%)
Hematuria, /μL	72.7 (33.2, 214.1)
IgA, g/L	2.95 (2.39, 4.06)
IgM, g/L	0.92 (0.67, 1.28)
IgG, g/L	10.33±2.55
Renal pathology	
M1	33/86 (38.4%)
E1	19/86 (22.1%)
S1	76/87 (87.4%)
T1/2	36/87 (41.4%)
C1/2	38/85 (44.7%)
Fibrinoid necrosis	8/85 (9.4%)
λ-chain predominated	54/73 (74.0%)
Global glomerular sclerosis ratio, %	27.9 (16.7, 41.3)
At MRA prescription	
Age, years	36.2 (30.1, 45.1)
GC history	32/85 (37.6%)
SBP before spironolactone, mm Hg	124.0±15.0
DBP before spironolactone, mm Hg	80.0±11.1
eGFR, mL/min/1.73 m^2	75.7±28.6
≥90 mL/min/1.73 m^2	29/88 (33.0%)
60~89 mL/min/1.73 m^2	27/88 (30.7%)
30~59 mL/min/1.73 m^2	28/88 (31.8%)
20~29 mL/min/1.73 m^2	4/88 (4.5%)
Serum creatinine, μmol/L	101.5 (81.3, 140.0)
Serum potassium, mmol/L	4.40±0.49
24-h proteinuria, g	0.93 (0.62, 1.52)
≥1.0 g	42/88 (47.7%)
<1.0 g	46/88 (52.3%)
Hematuria, /μL	58.3 (23.6, 114.6)

than 20% after 2 months of spironolactone treatment compared to baseline. After 2 months of treatment with spironolactone, 47 patients joined the effective group, and the median of 24-h proteinuria decreased from 1.05 (IQR 0.68–1.56) g to 0.50 (IQR 0.33–0.83) g (p < 0.001). SBP was reduced from 125.7 ± 15.9–121.1 ± 14.7 mm Hg (p = 0.041), and a reduction in eGFR was also observed after spironolactone treatment (71.0 ± 26.3 vs. 66.8 ± 28 mL/min/1.73 m^2, p = 0.035) (Fig. 3).

In the case of 41 patients who responded less effectively to spironolactone, the median 24-h proteinuria increased from 0.83 g (IQR 0.55–1.31) to 1.04 g (IQR 0.67–1.66) (p = 0.003), with no differences observed in hematuria, eGFR, SBP, or DBP (Fig. 4). Further analysis revealed that 18 of these patients needed additional treatments, such as steroids or immunosuppressants, due to high proteinuria, which increased from 1.20 g/day (IQR 0.64–1.76) to 1.54 g/day (IQR 0.76–2.11) after 2 months of treatment. The remaining 23 patients in this group experienced a minimal decrease in proteinuria from 0.76 g/day (IQR 0.53–1.03) to 0.75 g/day (IQR 0.53–1.11) (Fig. 5c, d).

Between the two groups, there were no differences in eGFR, the severity of hematuria, 24-h proteinuria, age, gender, and serum immunoglobulin levels (IgA, IgM, and IgG) at the time of renal biopsy. Both SBP and DBP were well controlled and similar between the groups before spironolactone administration. However, the ineffective group had a higher proportion of glomerular endocapillary proliferation in renal biopsy findings (31.7% vs. 13.3%) (p = 0.040) (Table 2). Intriguingly, when treated with spironolactone, the effective group showed a trend toward a higher percentage of GCs history (45.5% vs. 29.3%, p = 0.124), more severe proteinuria (1.05 g [IQR 0.68–1.56] vs. 0.83 g [IQR 0.55–1.31], p = 0.085), and a trend of poorer renal function (eGFR 71.0 ± 26.3 vs. 81.0 ± 30.4, p = 0.102). This indicates that the IgAN patients in the effective group were in worse condition (Table 2).

Long-Term Effects

We examined the data after 6 months of treatment to investigate the long-term impact of spironolactone on IgAN patients. In the effective group, eGFR (66.8 ± 28.0 vs. 66.9 ± 25.0 mL/min/1.73 m^2, p = 0.480) and proteinuria (0.50 g [IQR 0.33–0.83] vs. 0.50 g [IQR 0.28–0.70] per day, p = 0.347) remained stable at the 6-month mark when compared to the measurements taken after 2 months of treatment (Fig. 5a, b).

Notably, in the ineffective group, 23 patients experienced only slight reductions in proteinuria, going from 0.76 g (IQR 0.53–1.03) to 0.75 g (IQR 0.53–1.11) after 2 months. However, the effect on proteinuria improved after 6 months of spironolactone use, decreasing to 0.57 g (IQR 0.31–0.76) (p = 0.001) (Fig. 5c, d), without changes in eGFR. Only one individual experienced mild gynecomastia, and there were no instances of recurrent hyperkalemia or other adverse reactions during the follow-up period.

Furthermore, 12 patients in our study had persistent high proteinuria during prednisone therapy and were

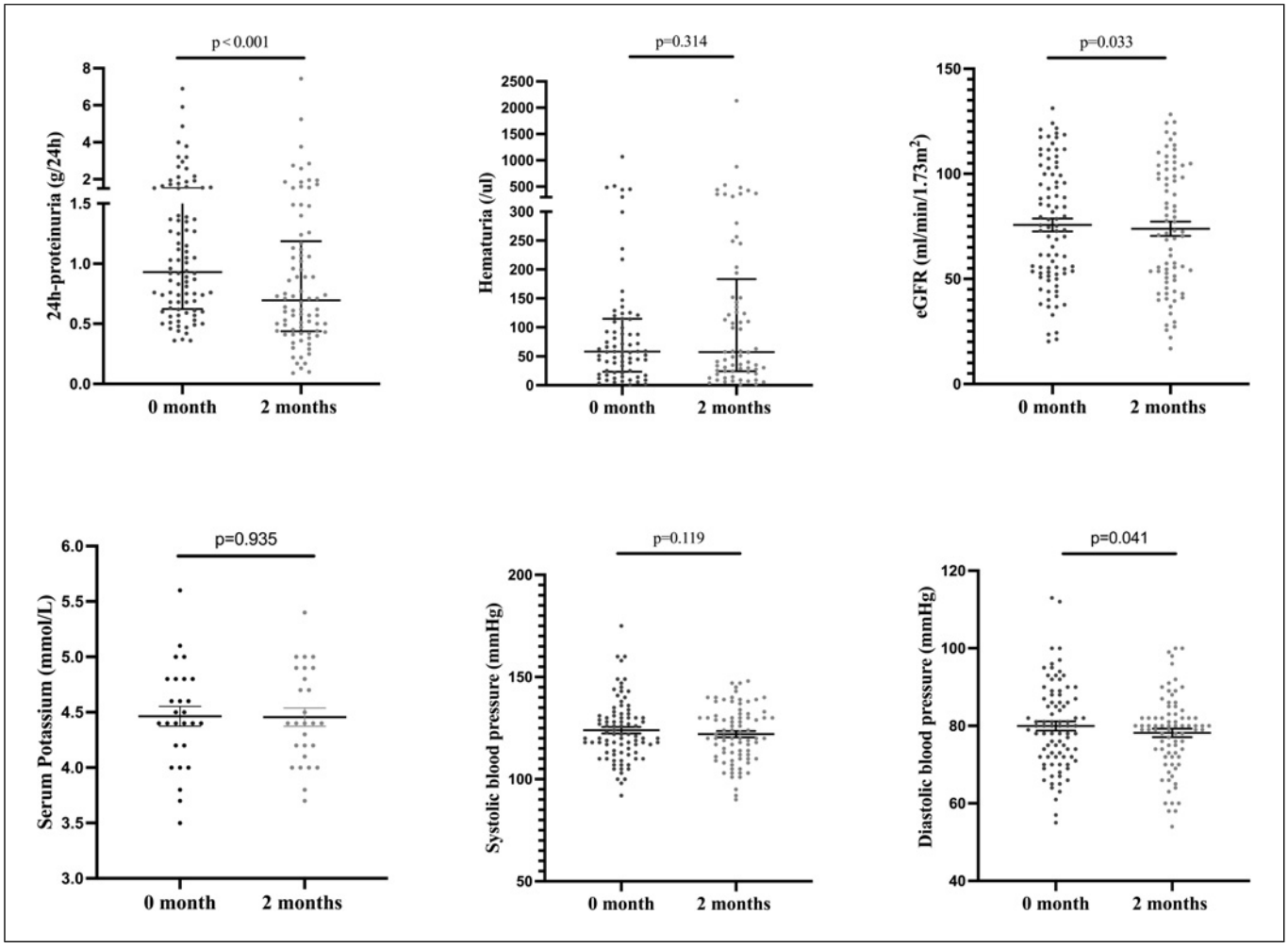

Fig. 2. Short-term effects of total IgAN patients treated with spironolactone.

then given spironolactone. After 2 months of combined treatment, proteinuria dropped from 0.95 g (0.68, 1.36) per day to 0.73 g (0.43, 1.01) per day, and it further declined to 0.50 g (0.31, 0.87) per day at the 6-month mark (p = 0.037) (Fig. 5e, f).

Discussion

This study aimed to assess the effectiveness of MRA in the treatment of proteinuria in patients with IgAN and to determine whether it was effective in all cases. The study examined a 6-month regimen of spironolactone in IgAN patients who were also receiving optimal RAAS inhibitor, steroid, or HCQ therapy and yet continued to have more than 0.3 g of proteinuria over a 24-h period. We found that a low dose of spironolactone (20 mg daily) successfully decreased proteinuria from 0.93 g (IQR 0.62–1.52) to 0.70 g (IQR 0.44–1.19) per day after 2 months of treatment in all IgAN patients. This reduction continued to 0.50 g (IQR 0.28–0.70) per day at the 6-month mark in the effective group. In those patients whose proteinuria was reduced by less than 20% following 2 months of therapy, the observed changes in renal pathology, specifically endocapillary proliferation, correlate with a poor response to treatment.

It is worth emphasizing that residual albuminuria has been identified as a potent predictor of negative renal outcomes in long-term studies involving patients with CKD [3]. Currently, the standard treatment for IgAN is intensive reduction of proteinuria through supportive care [5]. Despite receiving optimal supportive care, there is an urgent need for safe and effective treatments for

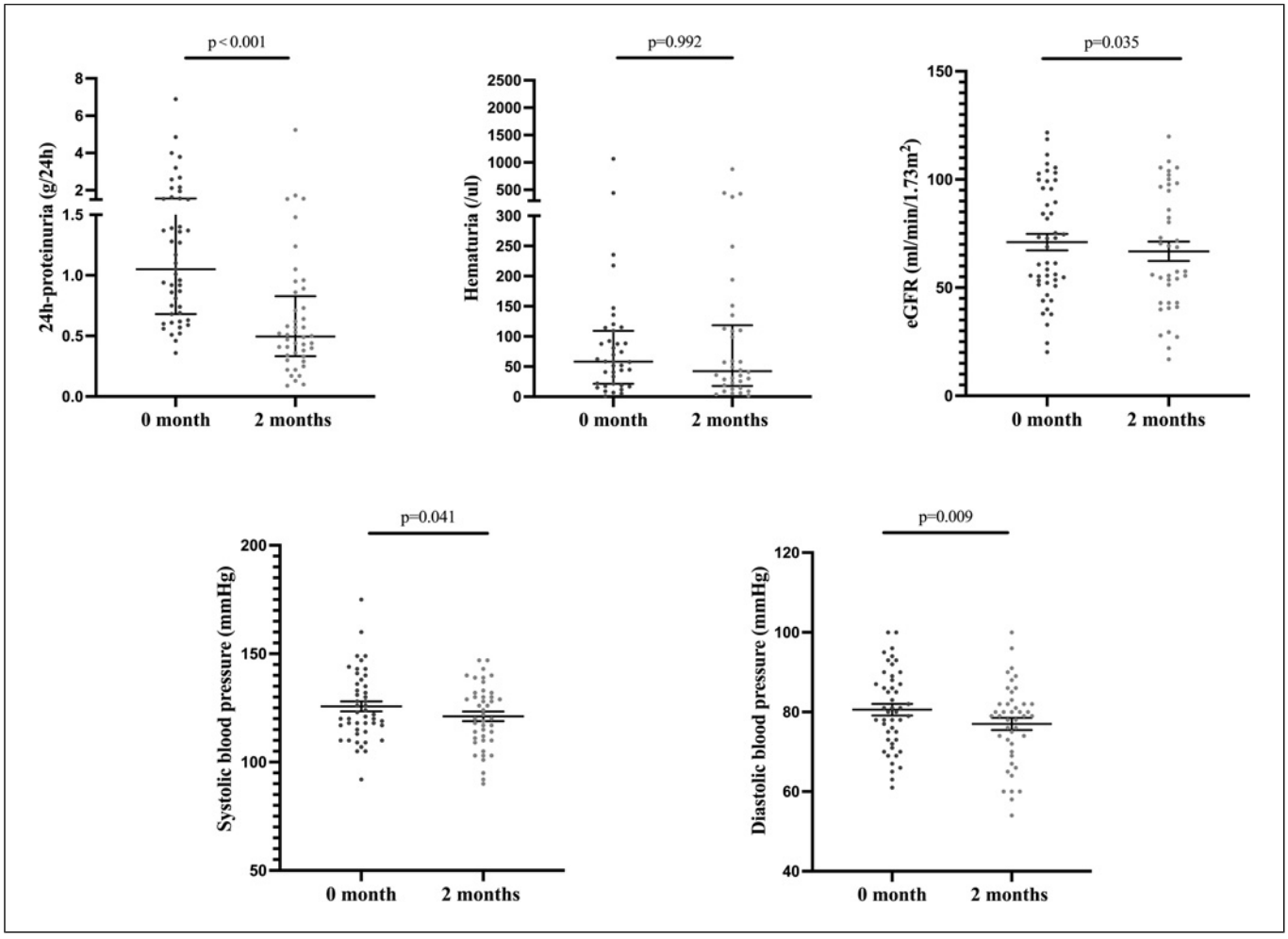

Fig. 3. Short-term effects of IgAN patients treated with spironolactone in the effective group.

high-risk patients. Spironolactone has been observed to provide a clinically meaningful benefit in reducing CKD proteinuria when used with RAS blockade at the maximum labeled dose and with well-controlled blood pressure. However, only 33 IgAN patients were included in these studies, and the effectiveness of spironolactone specifically for IgAN patients was not analyzed [9]. In our particular cohort, IgAN patients treated with spironolactone experienced a decrease in 24-h proteinuria from 1.05 g to 0.70 g after 2 months of treatment.

Interestingly, an early anti-proteinuria effect was observed from the 2-month treatment with spironolactone. Nevertheless, evidence-based data concerning using MRA for IgAN remain scarce. As a result, the findings from our cohort study indicate that spironolactone may serve as an effective therapeutic option for protecting the kidneys in IgAN patients.

In our study, we discovered that for patients who have been treated with steroids for nearly 5 months and still exhibit higher levels of proteinuria, the addition of spironolactone could significantly decrease their proteinuria levels. Within the current cohort, 12 patients continued to have proteinuria at a level of 0.95 (IQR 0.68–1.36) g/day even after undergoing prednisone therapy. Upon the addition of spironolactone, a reduction in proteinuria was observed at both 2 months (0.73 [IQR 0.43–1.01] g/day) and 6 months (0.50 [IQR 0.31–0.87] g/day). Corticosteroids typically function through mediation by the glucocorticoid receptor. However, glucocorticoid receptor is intimately associated with the MR, and some cross-reactivity between these receptors is evident [10]. At baseline levels, corticosteroids activate MR in most tissues, potentially exhibiting agonistic effects [11, 12].

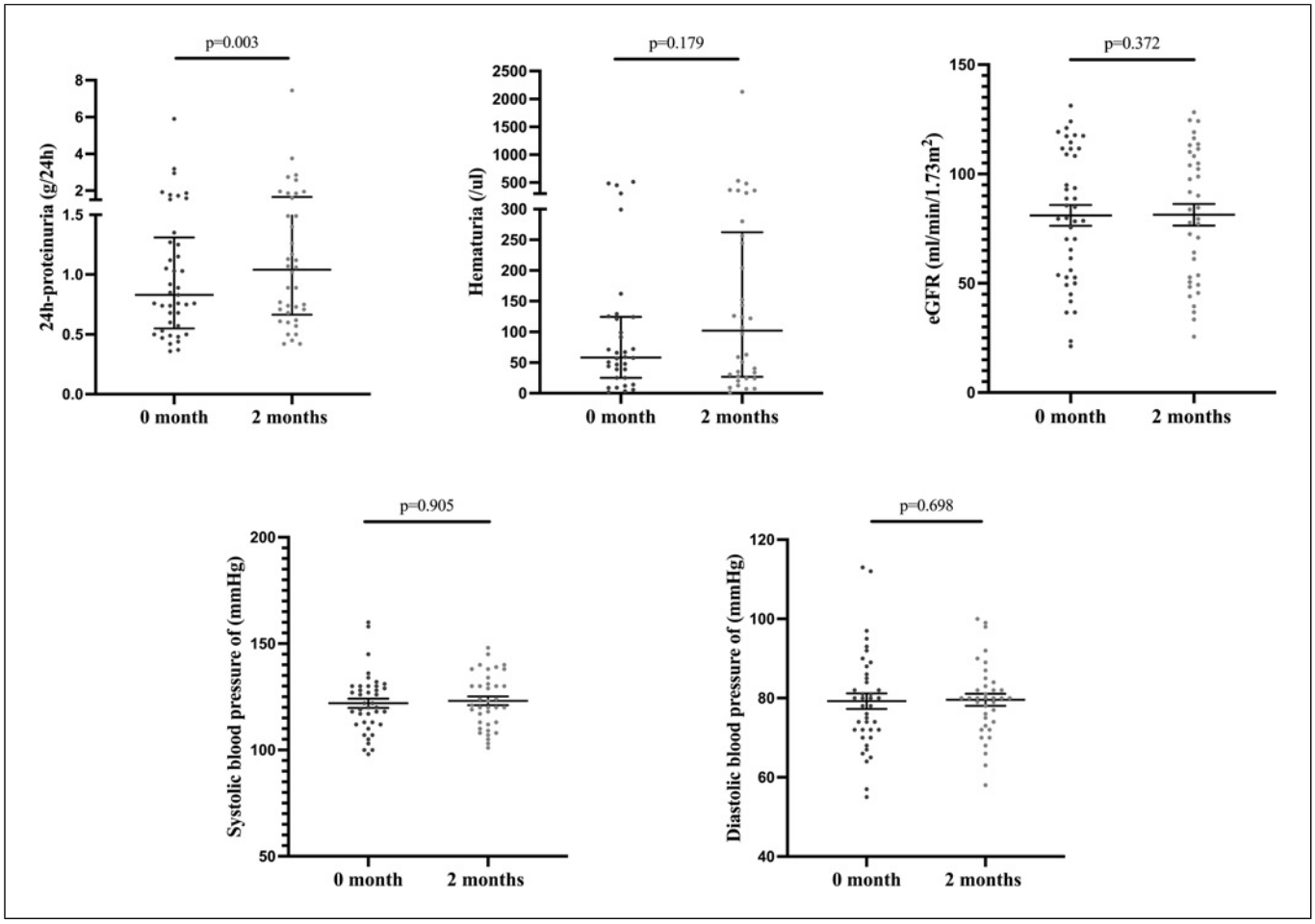

Fig. 4. Short-term effects of IgAN patients treated with spironolactone in the ineffective group.

Consequently, corticosteroid treatment may stimulate MR activation, leading to side effects similar to aldosterone breakthroughs. Therefore, we hypothesize that MR activation may be involved in the lack of remission in some IgAN patients treated with corticosteroids. For such individuals, the concurrent use of MRA may prove more beneficial, although additional studies are required to identify these patients beforehand.

This study noted an early decrease in proteinuria, accompanied by a slight alteration in blood pressure. Although both DBP and SBP were reduced by approximately 2 mm Hg at two or 6 months, this change was statistically significant only within the effective group. Before the introduction of spironolactone, all patients in this cohort maintained well-regulated blood pressure, with no discernible differences between the effective and ineffective groups. However, reduced blood pressure is favorable for controlling proteinuria and the delay of renal function impairment. Aldosterone, a steroid hormone, plays a role in the regulation of sodium reabsorption, water retention, and blood pressure management [13]. Spironolactone, a first-generation MR antagonist, exhibits antihypertensive properties.

Additionally, overactivation of MR boosts the expression of genes linked to inflammation and fibrosis [14]. The utilization of finerenone, a selective nonsteroidal MRA, led to a 31% reduction in the UACR among diabetes patients without causing a substantial decline in blood pressure [8, 15]. Therefore, we cannot determine whether the protective effect of low-dose spironolactone on proteinuria can be fully explained by its blood pressure-lowering effects.

MRAs induce natriuresis through their inhibitory action on epithelial sodium channels, sodium chloride co-transporters, and NaK-Cl co-transporters. Spironolactone

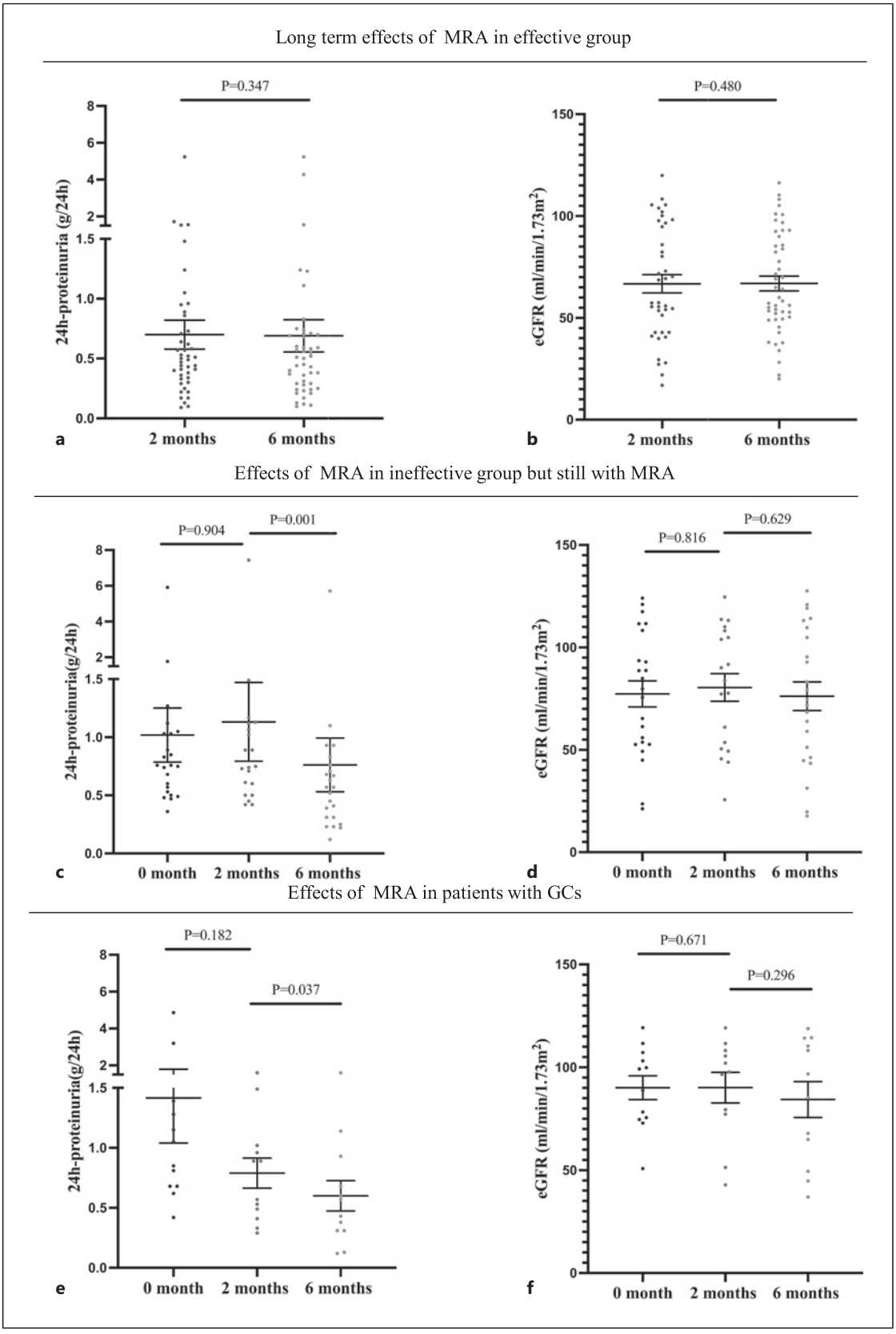

Fig. 5. a–f Long-term effects of patients with IgAN treated with spironolactone.

Table 2. Different clinical characteristics between the effective and ineffective groups

	Effective group (n = 47)	Ineffective group (n = 41)	p value
At renal biopsy			
Age, years	35.0 (30.0, 46.3)	33.6 (28.1, 39.8)	0.191
Gender (male)	29/47 (61.7%)	24/41 (58.5%)	0.762
eGFR, mL/min/1.73 m^2	76.7±26.0	86.2±30.5	0.121
≥90 mL/min/1.73 m^2	17/47 (36.2%)	19/41 (46.3%)	
60~89 mL/min/1.73 m^2	17/47 (36.2%)	13/41 (31.7%)	
30~59 mL/min/1.73 m^2	11/47 (23.4%)	8/41 (19.5%)	
20~29 mL/min/1.73 m^2	2/47 (4.3%)	1/41 (2.4%)	
Serum creatinine, μmol/L	98.0 (80.0, 131.0)	95.5 (61.3, 122.5)	0.307
24-h proteinuria, g	1.53 (0.98, 2.58)	1.35 (1.05, 1.82)	0.475
≥1.0 g	37/47 (78.7%)	35/41 (85.4%)	
<1.0 g	10/47 (21.3%)	6/41 (14.6%)	
Hematuria, /μL	65.6 (23.9, 169.4)	78.4 (41.0, 245.0)	0.320
IgA, g/L	3.11 (2.42, 4.46)	2.89 (2.38, 3.31)	0.272
IgM, g/L	0.98 (0.73, 1.28)	0.90 (0.66, 1.30)	0.646
IgG, g/L	10.59±2.41	10.01±2.71	0.347
Renal pathology			
M1	17/45 (37.8%)	16/41 (39.0%)	0.905
E1	6/45 (13.3%)	13/41 (31.7%)	**0.040**
S1	39/46 (84.8%)	37/41 (90.2%)	0.444
T1/2	19/46 (41.3%)	17/41 (41.5%)	0.988
C1/2	21/44 (47.7%)	17/41 (41.5%)	0.562
Fibrinoid necrosis	4/45 (8.9%)	4/40 (10.0%)	0.861
λ-chain predominated	28/38 (73.7%)	26/35 (74.3%)	0.953
Global glomerular sclerosis ratio, %	27.0 (16.7, 34.4)	32.1 (16.1, 50.0)	0.311
At MRA prescription			
Age, years	36.9 (31.0, 48.5)	36.09 (29.3, 40.4)	0.228
GC history	20/44 (45.5%)	12/41 (29.3%)	0.124
SBP before spironolactone, mm Hg	125.7±15.9	122.0±13.9	0.249
DBP before spironolactone, mm Hg	80.6±9.9	79.2±12.4	0.575
eGFR, mL/min/1.73 m^2	71.0±26.3	81.0±30.4	0.102
≥90 mL/min/1.73 m^2	13/47 (27.7%)	16/41 (39.0%)	
60~89 mL/min/1.73 m^2	14/47 (29.8%)	13/41 (31.7%)	
30~59 mL/min/1.73 m^2	18/47 (38.3%)	10/41 (24.4%)	
20~29 mL/min/1.73 m^2	2/47 (4.3%)	2/41 (4.9%)	
Serum creatinine, μmol/L	107.0 (83.0, 141.0)	96.0 (75.0, 131.5)	0.214
24-h proteinuria, g	1.05 (0.68, 1.56)	0.83 (0.55, 1.31)	0.085
≥1.0 g	25/47 (53.2%)	17/41 (41.5%)	
<1.0 g	22/47 (46.8%)	24/41 (58.5%)	
Hematuria, /μL	58.3 (21.6, 109.3)	58.3 (25.1, 124.3)	0.774

is a potassium-sparing diuretic which prevents our body from absorbing too much salt. The renin-angiotensin-aldosterone system is a key regulator of BP. Low dietary salt and blood volume stimulate the release of renin, which leads to a cascade of downstream effects including water and salt reabsorption and increased vascular tone mediated by angiotensin II, aldosterone and MR activation. However, when the renin-angiotensin-aldosterone system is dysregulated, such as in the case of primary aldosteronism, there is a loss of the negative feedback mechanism, leading to inappropriate MR activation promoting excess sodium and water reabsorption, hypertension and end-organ damage [16]. The participants in the EVALUATE trial were stratified based on their levels of sodium intake, and it was observed that the co-administration of RASSi with eplerenone can effectively decrease residual albuminuria in patients with hypertension and albuminuria who have a high sodium consumption. The eplerenone-treated patients in the highest tertile of sodium excretion, in

which patients consumed >13.5 g of salt per day, displayed a significantly greater reduction in albuminuria than the placebo-treated individuals in the same tertile (−22.5% vs. +21.8%, $p = 0.02$). In contrast, patients in the lowest (−10.2% vs. −0.84%, $p = 0.65$) or middle (−19.5% vs. +9.5%, $p = 0.22$) sodium tertile did not demonstrate an albuminuria-lowering effect of eplerenone. Similar SBP changes were observed [17]. Unfortunately, we did not maintain a record of patients' food intake to assess their salt consumption during the follow-up period while they were taking spironolactone. Our observational cohort study uncovered that within the initial 2 months of spironolactone treatment, patients exhibited a decrease in proteinuria, along with a modest reduction in both SBP and DBP (Fig. 3). Notably, the group that did not respond to spironolactone treatment did not show any significant decrease in blood pressure (Fig. 4). However, after 6 months of treatment, there was no discernible blood pressure difference between the group that responded effectively to the treatment and the group that did not (119.3 ± 15.0 vs. 119.8 ± 14.4, $p = 0.892$; 76.0 ± 10.4 vs. 75.9 ± 8.7, $p = 0.982$). This cohort of patients are long-term follow-up patients in our center, and under the guidance of the doctor following the KDIGO guidelines, the salt intake of our patients typically does not exceed 6 g per day. Thereafter, we believe that salt intake dose may be one of the reasons why patients in this study responded differently to spironolactone, but it is not the primary factor.

A slight decrease in eGFR was observed after 2 months on spironolactone. The eGFR decreased from 75.7 ± 28.6 to 73.9 ± 29.8 mL/min/1.73 m^2. However, eGFR remained stable until the end of 6 months of treatment. Spironolactone was reported to reduce eGFR in CKD patients in initial treatment [9] and had a significantly slower percent decline after follow-up for a year [8, 9, 15]. The mechanisms responsible for the initial acute reduction in eGFR remain unclear. This occurrence resembles the effects of RASS blockers and SGLT2 inhibitor medications but seems to be a temporary phenomenon [18–20].

We have validated that spironolactone has the ability to decrease urine protein excretion in patients with IgAN, and this effect is apparent even within the initial 2 months of treatment. However, the response was not consistent among all patients. To identify which patients might respond more favorably to spironolactone, we divided the cohort into two groups based on whether the reduction in proteinuria was greater than or less than 20%. We discovered that patients who exhibited endocapillary proliferation (E1) in their biopsies tended not to respond well to spironolactone. Endocapillary hypercellularity leads to constricting the glomerular capillary lumina due to a rise in endothelial cells and infiltrating inflammatory cells [21]. Endocapillary hypercellularity is one of the most significant pathological prognostic factors, representing active glomerular lesions [22]. In a research study involving 237 IgAN patients over an 82-month follow-up, endocapillary proliferation emerged as an independent factor predicting the loss of renal function in non-immunosuppressed patients but not in those receiving immunosuppressive treatment [23]. Therefore, glucocorticoids and immunosuppressants are more effective than MRA in treating endocapillary hypercellularity.

Regarding the safety analyses, the treatment was generally well accepted, except for 1 patient who stopped taking spironolactone due to hyperkalemia (potassium level of 6.0 mmol/L). Since the average eGFR for most of our patients was higher than 60 mL/min/1.73 $m^{2,}$ and the spironolactone dose was minimal, the occurrence of hyperkalemia in our study was notably lower compared to what has been reported in previous studies [17].

This study was conducted in a single center and was retrospective, lacking a placebo control. Therefore, there is a potential for bias in data assessment cannot be fully eliminated. The observation period for spironolactone treatment was only 6 months, making it uncertain whether a long-term reduction in ESKD endpoints can be achieved. Prospective studies on a larger scale are needed to address this issue. As this was a retrospective study, there is a lack of a unified clinical standard for the use of spironolactone in patients, which may result in inconsistent treatment effects and decrease the reliability of the study conclusions. Future prospective cohort studies investigating the use of MRAs in patients with IgA nephropathy, particularly the effects of third generation, warrant further exploration. Finally, only patients at high risk of hyperkalemia were monitored for blood potassium levels during follow-up in the IgAN clinic, and there was no comprehensive assessment on blood potassium.

Conclusion

The findings of this study suggest that MR antagonists can reduce proteinuria in patients with IgAN, complementing the effects of RAS blockers or even glucocorticoids. Nevertheless, to definitively prove the beneficial

effects of aldosterone antagonists on the progression of CKD, more extensive prospective randomized studies of longer duration are required.

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Statement of Ethics

The study was approved by the Ethics Committee of Huashan Hospital Fudan University, Approval No. 2023-605(X1). All of the patients provided written informed consent.

Conflict of Interest Statement

The authors have no conflicting interest to disclose.

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Author Contributions

The conception and design of the study were performed by Lingyun Lai and ChuanMing Hao. Data collection and analysis, as well as writing of the study, were performed by Da Shang, Yi Guan, and Shaojun Liu. All authors revised the manuscript and approved the final version.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but are available from the corresponding author Lai upon reasonable request.

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