Secondary analysis of Huangkui capsule in the treatment of IgAN

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Research Article

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Abstract

**Background:** IgA nephropathy is the most common primary glomerular disease and an important cause of chronic kidney disease. Previous clinical studies have confirmed that Huangkui capsule could reduce urine protein of IgA nephropathy by 100 mg/d losartan potassium. However, the effect of Huangkui capsule on IgA nephropathy is not clear.

**Methods:** Based on two multicenter, large sample phase IV clinical trials (NCT 02231125; NCT 02231138), eligible IgA nephropathy patients were screened and the related data were extracted for secondary analysis. Patients were grouped according to the baseline urinary protein, glomerular filtration rate, or pathologic characteristics using IgA nephropathy Oxford classification and the curative effect was analyzed. Taking the decrease of urine protein ≥30% after Huangkui capsule 6-month treatment as the effective standard, multiple regression analysis was used to analyze the influencing factors of Huangkui capsule in reducing urinary protein in IgA nephropathy patients.

**Results:** 503 patients with IgA nephropathy were enrolled. The efficacy of Huangkui capsule in reducing urinary protein in patients with baseline 24h urinary protein ≥1.0 g/d or glomerular filtration rate ≥60 ml/min reach the effective standard. 24h baseline urinary protein, body mass index, serum albumin, and serum creatinine were the independent influencing factors of Huangkui capsule in reducing urinary protein, but there was no significant correlation with the baseline pathological characteristics. After 6 months of Huangkui capsule treatment, the decrease rate of urine protein increased by 7.9% for every 100mg increase of 24h urinary protein and 6.7% for every 1g/L increase of ALB, while decreased by 1.1% and 7% respectively, for every 1μmmol/L increase of serum creatinine and 1kg/m² increase of body mass index.

**Conclusion:** The effect of Huangkui capsule is influenced by basic urinary protein, body mass index, serum albumin, and serum creatinine in IgA nephropathy patients. Huangkui capsule can effectively reduce urinary protein in patients with baseline urinary protein ≥1.0 g/d or glomerular filtration rate ≥60 ml/min.

**Introduction**

IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world, with 20%~40% of IgAN patients developing renal failure within 10~20 years after diagnosis[1]. Proteinuria was an important risk factor for IgAN progression. The results of a 30-year retrospective follow-up cohort of 1012 IgAN patients showed that the risk of progression to end-stage renal disease increased by 1.69 times (95% CI: 1.53 something 1.86) for each 1.0g/d increase in urine protein[2]. As shown in a meta-analysis of 1037 IgAN patients in 12 randomized trials, treatment effects on proteinuria accurately predicted treatment effects on the total glomerular filtration rate (eGFR) slope at 3 years and on the chronic slope starting 3 months after randomization; an observed treatment effect of approximately 30% reduction in
proteinuria would confer probabilities of at least 90% for nonzero treatment benefits on the total and chronic slopes of eGFR[3].

At present, renin-angiotensin system inhibitors (RASI) and steroids are the main drugs to reduce IgAN proteinuria. The results of 21 randomized controlled trials (RCT) of 1882 IgAN patients with proteinuria more than 1g/d showed that RASI combined with steroids may be the best treatment option, which can not only reduce proteinuria but also maintain long-term renal protection[4]. Meta-analysis of 24 randomized controlled trials in 2,000 IgAN patients showed that steroids significantly delayed the progression of renal deterioration (RR = 0.28, 95% CI = 0.13-0.51, SUCRA = 48.7%) and did not increase severe adverse events[5]. However, the small sample clinical trials selected in this study are difficult to reflect the incidence of adverse events caused by steroids. In the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgAN (STOP-IgAN) trial, compared with the supportive treatment, although steroids significantly increased the rate of clinical complete remission, there was no significant difference in the proportion of patients with eGFR ≥15 ml/min and the annual rate of eGFR reduction, and more patients developed severe infections, impaired glucose tolerance, and weight gain in the first year of treatment[6]. During a 7.4-year median follow-up in patients with the STOP-IgAN test, steroids or/and immunosuppressants had no significant benefit in the incidence of end-stage renal disease and the rates of eGFR loss over 40% and annual eGFR loss[7]. In the TESTING study, with an average of 2.1 years of follow-up, although steroids reduced the risk ratio of renal failure, death eGFR reduction by more than 40% (Hazard, 0.37 [95% CI, 0.17-0.85]), compared with placebo, the incidence of infection (risk difference, 8.1% [95% CI, 3.5%-13.9%]) and severe adverse events (risk difference, 11.5% [95% CI, 4.8%-18.2%]) increased significantly, and the study was terminated early[8]. Therefore, the toxicity of corticosteroids may outweigh the benefits in IgAN patients with obesity, diabetes, and potential infection, as well as cirrhosis, active peptic ulcer, osteoporosis, or clinically important mental illness[1]. 

Meta-analysis of 10 randomized controlled trials of 635 IgAN patients showed that alone use of ACEI (angiotensin-converting enzyme inhibitors) (MD=-0.75, 95% CI: -1.28-0.21) or ARB (angiotension II receptor blockers) (MD=-0.56, 95%CI: -0.82-0.30) or a combination of ACEI and ARB (MD=-0.63, 95%CI: -0.87-0.38) significantly reduced the levels of proteinuria in patients with IgAN. However, whether using ACEI or ARB alone or in combination with ACEI and ARB, there was no significant effect on serum creatinine (Scr), 24-creatinine clearance, and glomerular filtration rate in patients with IgAN[9]. However, a meta-analysis of 8 randomized controlled trials (33,454 patients) and 2 observational studies (148,144 patients treated with RAS blockers) showed that early deterioration of renal function caused by RASI increased the risk of all-cause death, whether in randomized studies (RR 1.22,95% CI: 1.04-1.42) or observational studies (OR 1.70,95% CI: 1.43-2.01) [10]. A meta-analysis of 1 prospective cohort and 13 retrospective cohort of 17,876 COVID-19 (coronavirus disease 2019) patients showed that ACEI (OR 2.32,95% CI: 1.16-4.65,I2 = 88.2%) and ARB (OR 2.45,95% CI: 1.35-4.44,I2 = 86.36%) significantly increased the risk of AKI[11]. In addition, RASI is not suitable for IgAN patients with low basal blood pressure or hypotension.

Huangkui capsule is the extract preparation of the effective components of Abelmoschus Manihot. The main pharmacological active ingredients are seven kinds of flavonoids, including rutin, hyperin, luteolin, isoquercetin, myricetin, quercetin, and quercetin-3-O-Robinson glycoside, which are used to treat kidney
diseases[12, 13]. Multiple clinical trials confirmed that Huangkui capsule has the effect of reducing urinary protein[14-17]. In our previous work, a multicenter, randomized, double-blind, double-dummy, placebo-controlled trial of 1470 IgAN patients confirmed that Huangkui capsule had no inferior effect on proteinuria than losartan potassium 100mg/d[15], and has no effect on renal function. The safety of Huangkui capsule was confirmed by a multicenter, prospective, open, single-arm trial of 2054 patients with chronic kidney disease[16]. However, in the clinical trial of Huangkui capsule in the treatment of IgAN, we found that the efficacy of Huangkui capsule in reducing proteinuria in IgAN patients is heterogeneous, and the clinicopathologic characteristics of Huangkui capsule for IgAN are not clear.

In this study, based on the individual data of IgAN patients in two multicenter, large-sample Phase IV clinical trials[15, 16], we analyzed the influence of baseline clinicopathologic characteristics of patients on the efficacy of Huangkui capsule, further clarifying the indications of Huangkui capsule in the treatment of IgAN, and guide clinical practice.

**Methods**

**Objectives:** To reveal the influencing factors of Huangkui capsule reducing urinary protein in patients with IgAN, and identify the best population for Huangkui capsule, to provide guidance for clinical rational application of Huangkui capsule in the treatment of IgAN.

**Design:** Based on the above two multicenter, large-sample clinical trials, relevant data were extracted for secondary analysis. According to 24h urinary protein < 1.0g/d, ≥1.0 and < 2.0g/d or ≥2.0g/d at baseline, eGFR ≥90ml/min, eGFR ≥60 and < 90ml/min or eGFR < 60ml/min at baseline, and 7 pathological characteristics of IgAN Oxford classification or active and inactive lesion groups, respectively, the curative effect of Huangkui capsule on reducing urinary protein was analyzed; Taking the decreasing rate of urine protein ≥30% or <30% after 6 months of Huangkui capsule treatment as the dependent variable, multiple regression analysis was used to analyze the independent influencing factors of Huangkui capsule reducing urinary protein.

**Inclusion criteria and exclusion criteria:**

The inclusion criteria are: In 2 clinical studies: age range from 18 to 70 years old; IgAN was diagnosed by pathology; Huangkui capsule was used as intervention measure; at least the experimental data of 24-hour urinary protein and SCr at baseline, 3-month and 6-month.

The exclusion criteria are: Other kidney diseases except IgAN; Cases treated with hormone immunosuppressant, ACEI/ARB, Tripterygium wilfordii or compound Chinese medicine; The patients without baseline, 3-month, 6-month 24h urinary protein and SCr test data.

**Statistical methods:** Categorical variables are expressed in percentage count and compared by chi-square test or Fisher Precision Test. If the data of continuous variables conform to the normal distribution, they are expressed as mean ± standard deviation and compared by T-Test (or Mann-Whitney U test) (two
independent samples) or analysis of variance (multiple independent samples). If the variable is not continuous, then a nonparametric test will be performed to compare baseline and posttreatment differences between groups. Univariate and multivariate logistic regression analysis was used to screen independent risk factors over the range of 6-month urinary protein exchange rate. In univariate analysis, the independent variables with P < 0.2 in univariate analysis were screened and included in multiple regression. The multicollinearity test was used to test the significant correlation among the factors. The Hosmer-Lemeshow test was used to explain the goodness of fit in multivariate logic models. The odds ratio and 95% confidence interval (CI) were calculated. All results were analyzed by SPSS statistics 26. P<0.05 was statistically significant.

Outcomes

Participants: A total of 845 patients with IgAN were enrolled in the two studies. First of all, 242 patients with ACEI/ARB, glucocorticoid, and immunosuppressants, 82 patients treated with Tripterygium wilfordii and compound Chinese medicine were excluded, and 18 patients without 24h urinary protein data for 6 months were excluded. Finally, a total of 503 patients with IgAN who met the criteria were included in this analysis (Figure1).

Efficacy Measurement

In this study, after 6 months of Huangkui capsule treatment, the overall urinary protein decline rate of IgAN patients was 32%. Therefore, referring to the relevant literature[3], this study takes the change rate of urinary protein of Huangkui capsule for 6 months as the evaluation index of curative effect, the decrease rate of urine protein ≥30% as an effective treatment, and the decrease rate of urinary protein < 30% as ineffective.

Baseline characteristics

1. Table 1 summarizes the characteristics of different baseline 24h urinary protein groups (< 1.0 g/d, ≥1.0 and < 2.0 g/d, ≥2.0 g/d). At baseline, compared with the group with urinary protein< 1.0 g/d, the proportion of patients with urinary protein ≥1.0 and < 2.0 g/d and with cellular or fibrocytic crescents (C)≥1 in Oxford classification of renal histopathology were significantly increased, and urinary protein ≥2.0 g/d group, systolic blood pressure, SCr, and urine protein were significantly increased, while serum albumin(ALB) and eGFR were significantly decreased; Compared with the group with urinary protein ≥1.0 g/d and <2.0 g/d, the ALB and urinary protein in the group with urinary protein ≥2.0 g/d were significantly decreased, and the proportion of patients with C ≥1.0 g/d was significantly decreased; There was no significant difference in other clinical and pathological indexes. At 3 months and 6 months after treatment, urine protein of < 1.0 g/d group did not reach the effective standard (the decrease rate of urine protein ≥30%), however, the urinary protein in the group with urinary protein ≥1.0 and < 2.0 g/d decreased increasingly, and the decrease rate of urinary protein was significantly higher than that of the group with urinary protein < 1.0 g/d, and the decrease rate of urinary protein ≥2.0g/d group was
significantly higher than that of protein $\geq 1.0$ and $< 2.0$ g/d group; There was no significant difference in eGFR among the three groups after treatment with Huangkui capsule.

Table 1. Baseline data and efficacy comparison of different baseline urinary protein groups
<table>
<thead>
<tr>
<th>Variables</th>
<th>urinary protein &lt;1.0g/d</th>
<th>urinary protein ≥1.0 and&lt;2.0g/d</th>
<th>urinary protein ≥2.0g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>number,n</td>
<td>231</td>
<td>175</td>
<td>97</td>
</tr>
<tr>
<td>age, year</td>
<td>36.0[29.0,46.0]</td>
<td>37.0[29.5,46.0]</td>
<td>37.0[29.0,48.0]</td>
</tr>
<tr>
<td>man,n(%)</td>
<td>95(41.1)</td>
<td>86(49.1)</td>
<td>54(55.7)</td>
</tr>
<tr>
<td>Baseline data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>systolic pressure,mmHg</td>
<td>122.0[114.,130.0]</td>
<td>123.0[118.0,130.0]</td>
<td>125.0[119.0,134.0]*</td>
</tr>
<tr>
<td>diastolic pressure,mmHg</td>
<td>80.0[72.0,82.0]</td>
<td>80.0[75.0,85.0]</td>
<td>80.0[74.0,85.0]</td>
</tr>
<tr>
<td>hemoglobin,g/l</td>
<td>138.0[125.5,149.0]</td>
<td>139.0[126.3,153.0]</td>
<td>135.0[122.0,150.0]</td>
</tr>
<tr>
<td>ALB,g/l</td>
<td>42.8[40.1,45.5]</td>
<td>42.7[39.5,45.5]</td>
<td>41.0[37.3,44.8]**#</td>
</tr>
<tr>
<td>SCr,μmmol/L</td>
<td>77.0[63.0,91.9]</td>
<td>81.0[65.0,95.9]</td>
<td>85.4[71.0,104.0]**</td>
</tr>
<tr>
<td>eGFR,ml/min/1.73m2</td>
<td>91.7[71.7,114.0]</td>
<td>86.2[65.9,110.4]</td>
<td>74.6[60.1,105.6]**</td>
</tr>
<tr>
<td>urinary protein,g/d</td>
<td>0.64[0.53,0.79]</td>
<td>1.40[1.12,1.68]**</td>
<td>2.53[2.20,2.93]**##</td>
</tr>
<tr>
<td>Oxford score of renal pathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 proportion, %</td>
<td>110(47.6)</td>
<td>86(49.1)</td>
<td>44(45.3)</td>
</tr>
<tr>
<td>E≥1 proportion, %</td>
<td>44(19.0)</td>
<td>37(21.1)</td>
<td>13(13.4)</td>
</tr>
<tr>
<td>I≥1 proportion, %</td>
<td>121(52.2)</td>
<td>99(56.4)</td>
<td>47(47.4)</td>
</tr>
<tr>
<td>S≥1 proportion, %</td>
<td>74(32.0)</td>
<td>66(37.7)</td>
<td>23(23.7)</td>
</tr>
<tr>
<td>T≥1 proportion, %</td>
<td>62(26.7)</td>
<td>59(33.6)</td>
<td>26(26.7)</td>
</tr>
<tr>
<td>C≥1 proportion, %</td>
<td>51(22.0)</td>
<td>63(36.0)**</td>
<td>26(26.8)#</td>
</tr>
<tr>
<td>A≥1 proportion, %</td>
<td>89(38.4)</td>
<td>71(40.5)</td>
<td>33(29.8)</td>
</tr>
<tr>
<td>clinical efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-month urine protein change value,g/d</td>
<td>-0.1 [-0.4,0.3]</td>
<td>-0.5 [-1.1,0.2]**</td>
<td>-1.7 [-2.3,-0. 5]**##</td>
</tr>
<tr>
<td>3-month change rate of urinary protein, %</td>
<td>-14.1[-60.8,47.2]</td>
<td>-39.0 [-82.0,11.8]**</td>
<td>-68.2 [-90.0,-15.3]**##</td>
</tr>
<tr>
<td>6-month urine protein change value,g/d</td>
<td>-0.1 [-0.4,0.3]</td>
<td>-0.6 [-1.1,0.1]**</td>
<td>-1.7 [-2.3,-0.6]**##</td>
</tr>
<tr>
<td>6-month change rate of urinary protein, %</td>
<td>-12.9 [-64.3,48.7]</td>
<td>-69.3[-92.1,</td>
<td></td>
</tr>
<tr>
<td>protein, %</td>
<td>-45.2 [-84.1,6.7]**</td>
<td>-18.0** [**]##</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>3-month eGFR change value, (ml/min/1.73m²)</td>
<td>0.0[-5.7,5.9]</td>
<td>-1.6[-7.8,4.9]</td>
<td>-2.2[-7.9,4.7]</td>
</tr>
<tr>
<td>3-month change rate of eGFR, %</td>
<td>0.0[-7.2,6.8]</td>
<td>-1.4[-9.8,7.8]</td>
<td>-2.6[-12.8,5.7]</td>
</tr>
<tr>
<td>6-month eGFR change value, (ml/min/1.73m²)</td>
<td>0.6[-6.3,7.1]</td>
<td>-0.7[-6.9,7.0]</td>
<td>-1.9[-6.8,5.2]</td>
</tr>
<tr>
<td>6-month change rate of eGFR, %</td>
<td>1.0[-8.0,8.1]</td>
<td>-0.8[-8.3,8.5]</td>
<td>-1.7[-14.1,8.1]</td>
</tr>
</tbody>
</table>

Note: Compared with urinary protein < 1.0g/d group, *: P<0.05; **: P<0.01; Compared with urinary protein ≥1.0 and <2.0g/d group, #: P<0.05; ##: P<0.01.

2. Table 2 summarizes the characteristics of different baseline renal function groups (eGFR ≥90 ml/min, eGFR ≥60 and <90 ml/min, eGFR <60 ml/min). At baseline, compared with eGFR ≥90 ml/min group, age, systolic and diastolic blood pressure, SCr, and renal tubular atrophy or renal interstitial fibrosis ≥1 in eGFR ≥60 and <90 ml/min groups and eGFR <60 ml/min groups were significantly increased and eGFR was significantly decreased; Hemoglobin and ALB were significantly increased in eGFR ≥60 and <90 ml/min group, and urinary protein was significantly increased in eGFR <60 ml/min group; Compared with eGFR ≥60 and <90 ml/min group, the age and SCr in eGFR <60 ml/min group increased significantly, while hemoglobin, ALB and eGFR decreased significantly. At 3 months after treatment with Huangkui capsule, the urinary protein in eGFR ≥90 ml/min group decreased significantly, however, the urine protein of eGFR ≥60 and <90 ml/min group and eGFR <60 ml/min group did not reach the effective standard, but there was no significant difference among the three groups. At 6 months after treatment, urine protein of eGFR ≥90 ml/min group and eGFR ≥60 and <90 ml/min group decreased significantly, and urine protein of eGFR <60 ml/min group did not reach the effective standard, and significantly lower than eGFR ≥90 ml/min group. Compared with eGFR ≥90 ml/min group, eGFR ≥60 and <90 ml/min group and eGFR <60 ml/min group showed slight improvement at 3 and 6 months after treatment, the eGFR change rate in eGFR ≥60 and <90 ml/min group and eGFR <60 ml/min was slightly improved, although there was statistical significance.

**Table 2. Baseline date and efficacy comparison of different baseline eGFR groups**
### Variables

<table>
<thead>
<tr>
<th></th>
<th>eGFR≥90ml/min</th>
<th>eGFR≥60and&lt;90ml/min</th>
<th>eGFR&lt;60ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>number,n</strong></td>
<td>235</td>
<td>176</td>
<td>92</td>
</tr>
<tr>
<td><strong>age,year</strong></td>
<td>34.0[28.0,43.5]</td>
<td>37.0[30.0,46.0] *</td>
<td>43.0[35.0,52.0] **##</td>
</tr>
<tr>
<td><strong>man,n(%)</strong></td>
<td>73(31.1)</td>
<td>106(60.2)</td>
<td>56(60.9)</td>
</tr>
</tbody>
</table>

### Baseline data

<table>
<thead>
<tr>
<th></th>
<th>eGFR≥90ml/min</th>
<th>eGFR≥60and&lt;90ml/min</th>
<th>eGFR&lt;60ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>systolic pressure,mmHg</strong></td>
<td>120.0[112.0,130.0]</td>
<td>126.0[120.0,131.2] **</td>
<td>130.0[120.0,135.0] **</td>
</tr>
<tr>
<td><strong>diastolic pressure,mmHg</strong></td>
<td>78.0[70.0,80.0]</td>
<td>80.0[75.0,86.0] **</td>
<td>80.0[78.0,85.2] **</td>
</tr>
<tr>
<td><strong>hemoglobin,g/l</strong></td>
<td>134.0[125.0,147.0]</td>
<td>144.0[128.0,156.2] **</td>
<td>135.0[117.0,145.0] ##</td>
</tr>
<tr>
<td><strong>ALB,g/l</strong></td>
<td>42.2[39.0,45.5]</td>
<td>43.4[40.0,45.7] *</td>
<td>41.6[39.3,44.7] #</td>
</tr>
<tr>
<td><strong>SCr,μmmol/L</strong></td>
<td>63.0[55.2,70.2]</td>
<td>88.2[83.0,94.0] **</td>
<td>124.8[119.0,146.8] **##</td>
</tr>
<tr>
<td><strong>eGFR, ml/min/1.73m2</strong></td>
<td>113.3[104.1,124.1]</td>
<td>74.4[67.9,80.6] **</td>
<td>47.8[38.6,54.1] **##</td>
</tr>
<tr>
<td><strong>urinary protein,g/d</strong></td>
<td>1.00[0.63,1.55]</td>
<td>1.13[0.66,1.85]</td>
<td>1.31[0.77,2.01] **</td>
</tr>
</tbody>
</table>

### Oxford score of renal pathology

<table>
<thead>
<tr>
<th></th>
<th>eGFR≥90ml/min</th>
<th>eGFR≥60and&lt;90ml/min</th>
<th>eGFR&lt;60ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M1 proportion, %</strong></td>
<td>111(47.2)</td>
<td>89(50.5)</td>
<td>40(43.4)</td>
</tr>
<tr>
<td><strong>E≥1 proportion, %</strong></td>
<td>50(21.2)</td>
<td>32(18.1)</td>
<td>12(13.0)</td>
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<tr>
<td><strong>I≥1 proportion, %</strong></td>
<td>123(52.2)</td>
<td>103(58.4)</td>
<td>41(44.4)</td>
</tr>
<tr>
<td><strong>S≥1 proportion, %</strong></td>
<td>73(31.0)</td>
<td>66(37.5)</td>
<td>24(26.0)</td>
</tr>
<tr>
<td><strong>T≥1 proportion, %</strong></td>
<td>54(23.7)</td>
<td>62(35.1) **</td>
<td>31(33.6) *</td>
</tr>
<tr>
<td><strong>C≥1 proportion, %</strong></td>
<td>64(27.2)</td>
<td>54(30.6)</td>
<td>22(23.9)</td>
</tr>
<tr>
<td><strong>A≥1 proportion, %</strong></td>
<td>85(36.0)</td>
<td>76(43.1)</td>
<td>32(34.6)</td>
</tr>
</tbody>
</table>

### Clinical efficacy

<table>
<thead>
<tr>
<th></th>
<th>eGFR≥90ml/min</th>
<th>eGFR≥60and&lt;90ml/min</th>
<th>eGFR&lt;60ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-month urine protein change value,g/d</strong></td>
<td>-0.3 [-0.9,0.2]</td>
<td>-0.3 [-0.9,0.2] **</td>
<td>-0.3[-0.9,0.2] **##</td>
</tr>
<tr>
<td><strong>3-month change rate of urinary protein, %</strong></td>
<td>-38.5 [-79.2,23.4]</td>
<td>-31.5[-77.4,18.1]</td>
<td>-21.3[-60.3,29.9]</td>
</tr>
<tr>
<td><strong>6-month urine protein change value,g/d</strong></td>
<td>-0.3[-0.9,0.1]</td>
<td>-0.4 [-1.0,0.1] **</td>
<td>-0.3[0.9,0.4] **##</td>
</tr>
<tr>
<td><strong>6-month change rate of urinary protein, %</strong></td>
<td>-0.4[-0.8,0.2]</td>
<td>-0.4[-0.8,0.2]</td>
<td>-0.2[-0.7,0.5] *</td>
</tr>
</tbody>
</table>
### Table 3. Influence of seven pathological features of baseline renal pathology Oxford classification on the urinary protein reduction rate after 6 months of Huangkui capsule treatment

<table>
<thead>
<tr>
<th></th>
<th>3-month change value, ml/min/1.73 m²</th>
<th>6-month change value, ml/min/1.73 m²</th>
<th>3-month change rate of eGFR, %</th>
<th>6-month change rate of eGFR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-month eGFR change</strong></td>
<td>-3.0[-11.2,1.7]</td>
<td>-1.5[-9.6,3.2]</td>
<td>-2.4[-10.3,1.5]</td>
<td>-1.4[-8.4,3.1]</td>
</tr>
<tr>
<td><strong>value, ml/min/1.73 m²</strong></td>
<td>1.3[-6.6,8.6]</td>
<td>2.2[-6.1,17.1]</td>
<td>1.7[-9.5,12.4]**</td>
<td>2.8[-8.9,22.9]**</td>
</tr>
<tr>
<td></td>
<td>1.4[-3.3,7.3]</td>
<td>0.9[-3.9,9.4]</td>
<td>3.1[-8.0,17.6]**</td>
<td>0.0[-9.1,21.9]**</td>
</tr>
</tbody>
</table>

Note: Compared with eGFR ≥ 90 ml/min group, *: P<0.05; **: P<0.01; Compared with eGFR ≥ 60 and < 90 ml/min group, #: P<0.05; ###: P<0.01.


Among 503 patients, 368 with an Oxford classification score were included in the analysis. The results showed that mesangial cell proliferation (M), interstitial inflammatory cell infiltration (I), endothelial cell proliferation (E), cellular or fibrocystic crescentic (C), segmental sclerosis or adhesion (S), renal tubular atrophy or renal interstitial fibrosis (T) and arteriopathy (A) inbaseline renal tissue were not significantly correlated with the change rate of urinary protein after 6 months after Huangkui capsule treatment (Table 3). Active lesions (M, I, E, or C score any 1 ≥ 1) and inactive lesions (S, T, or A score any 1 ≤ 0) were divided into groups, of which 335 were active lesions, 285 cases of active lesions. There was no significant difference in the curative effect of Huangkui capsules between active and inactive lesions (Table 4). The patients were divided into groups according to the degree of pathological changes in renal tissue, among them, there were 19 patients with neither active and inactive lesions (all of the 7 pathological characteristics scores were 0), 52 patients with simple active disease (M, I, E, or C score of any 1 ≥ 1, and S, T, or A score of any 1 = 0), 13 patients with simple inactive lesions (S, T, or A score ≥ 1, M, I, E, or C score = 0), and 284 patients had both active and inactive lesions. There was no significant difference in the curative effect of Huangkui capsule with four different pathological types; there was no significant difference in the curative effect of Huangkui capsule with patients with active, inactive lesions or both active and inactive lesions (Table 5).

Table 3. Influence of seven pathological features of baseline renal pathology Oxford classification on the urinary protein reduction rate after 6 months of Huangkui capsule treatment
<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
<th>n</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td>0</td>
<td>128</td>
<td>0.851</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>240</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>83</td>
<td>0.192</td>
<td>0.493</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>221</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>122</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>275</td>
<td>0.117</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>218</td>
<td>0.751</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>134</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>1</td>
<td>159</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>207</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>0</td>
<td>214</td>
<td>0.482</td>
<td>0.658</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>134</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>157</td>
<td>0.532</td>
<td>0.183</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>160</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: P1: P for ‘with or without’ comparisons for each pathological feature; P2: P for comparisons of different severity of each pathological feature.

**Table 4. Comparison of curative effect of Huangkui Capsules in active and inactive renal lesions**
### Table 5. Comparison of curative effect of Huangkui Capsules on different degree of pathological changes in renal tissue

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>P5</th>
<th>P6</th>
</tr>
</thead>
<tbody>
<tr>
<td>neither active nor inactive lesion</td>
<td>19</td>
<td>0.146</td>
<td></td>
</tr>
<tr>
<td>only active lesion</td>
<td>52</td>
<td>0.471</td>
<td></td>
</tr>
<tr>
<td>only inactive lesion</td>
<td>13</td>
<td>0.134</td>
<td></td>
</tr>
<tr>
<td>both active and inactive lesions</td>
<td>284</td>
<td>0.139</td>
<td></td>
</tr>
</tbody>
</table>

Note: P5: P for 4 lesion comparisons; P6: P for compared to neither active nor inactive lesions.

#### Univariate and multivariate logistic regression analyses

According to the cut-off value of 30% urine protein reduction rate after 6 months treatment of Huangkui capsule, the patients were divided into two groups: the decrease rate of urine protein < 30% and ≥ 30%. Compared with the urinary protein reduction rate < 30% group, 24h baseline urinary protein and ALB in the group with urinary protein reduction rate ≥ 30% were significantly increased, body mass index (BMI) and
SCr were significantly decreased, and was no significant difference in other clinical and pathological indexes (Table 6). Among them, 24h urine protein, eGFR, BMI, SCr, and ALB were p < 0.2. However, due to the collinearity between SCr and eGFR, thus, 24h urine protein, BMI, SCr, and ALB were included in the multiple regression analysis as independent variables (Table 6). Figure 2 shows the results of multivariate analysis, 24h urine protein, BMI, SCr, and ALB are independent risk factors for Huangkui capsule to reduce urine protein. The decrease rate of urine protein increased by 7.9% for every 100 mg increase of 24h urine protein (OR 1.079, 95% CI: 1.051, 1.108); The decrease rate of urine protein increased by 6.6% for every 1G/L increase of ALB (OR 1.066, 95% CI: 1.025, 1.108); And urinary protein reduction rate decreased by 1.1% for every 1μmmol/L increase of SCr (OR 0.989, 95% CI: 0.983, 0.995); The urinary protein reduction rate decreased by 7% for every 1 kg/m² increase of BMI (OR 0.930, 95% CI: 0.879, 0.984).

Table 6. Comparison of baseline data between “ineffective” and “effective” groups in reducing urinary protein after Huangkui Capsule treatment for 6 months
### Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>6-month change rate of urinary protein&lt;30%</th>
<th>6-month change rate of urinary protein≥30%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>number,n</td>
<td>243</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>age,year</td>
<td>37.0[29.0,46.0]</td>
<td>37.0[30.0,46.0]</td>
<td>0.693</td>
</tr>
<tr>
<td>man,n(%)</td>
<td>109.0(44.8%)</td>
<td>126(48.4%)</td>
<td>0.418</td>
</tr>
<tr>
<td>BMI,kg/m2</td>
<td>23.8 [21.6,25.8]</td>
<td>22.9[21.0,25.1]</td>
<td>0.011</td>
</tr>
</tbody>
</table>

### Baseline data

<table>
<thead>
<tr>
<th>Variables</th>
<th>6-month change rate of urinary protein&lt;30%</th>
<th>6-month change rate of urinary protein≥30%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>systolic pressure,mmHg</td>
<td>124.0[118.0,130.0]</td>
<td>122.0[114.0,130.0]</td>
<td>0.262</td>
</tr>
<tr>
<td>diastolic pressure,mmHg</td>
<td>80.0[74.0,85.0]</td>
<td>80.0[74.0,85.0]</td>
<td>0.780</td>
</tr>
<tr>
<td>hemoglobin,g/l</td>
<td>138.0[126.0,151.0]</td>
<td>136.0[125.0,150.0]</td>
<td>0.539</td>
</tr>
<tr>
<td>ALB,g/l</td>
<td>41.8[39.3,44.6]</td>
<td>43.3[39.6,46.0]</td>
<td>0.012</td>
</tr>
<tr>
<td>SCr,μmol/L</td>
<td>82.0[67.4,97.5]</td>
<td>76.9[61.9,95.3]</td>
<td>0.028</td>
</tr>
<tr>
<td>eGFR,ml/min/1.73m2</td>
<td>82.9[66.1,110.0]</td>
<td>89.2[66.1,113.7]</td>
<td>0.068</td>
</tr>
<tr>
<td>urinary protein,g/d</td>
<td>0.9[0.6,1.5]</td>
<td>1.3[0.8,2.0]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Oxford score of renal pathology

<table>
<thead>
<tr>
<th>Variables</th>
<th>6-month change rate of urinary protein&lt;30%</th>
<th>6-month change rate of urinary protein≥30%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1 proportion,%</td>
<td>111(45.4%)</td>
<td>129(49.8%)</td>
<td>0.977</td>
</tr>
<tr>
<td>E≥1 proportion,%</td>
<td>40(16.3%)</td>
<td>54(20.8%)</td>
<td>0.341</td>
</tr>
<tr>
<td>I≥1 proportion,%</td>
<td>130(53.1%)</td>
<td>138(52.8%)</td>
<td>0.241</td>
</tr>
<tr>
<td>S≥1 proportion,%</td>
<td>81(33.1%)</td>
<td>82(31.6%)</td>
<td>0.496</td>
</tr>
<tr>
<td>T≥1 proportion,%</td>
<td>67(27.4%)</td>
<td>80(30.8%)</td>
<td>0.820</td>
</tr>
<tr>
<td>C≥1 proportion,%</td>
<td>68(27.8%)</td>
<td>72(27.7%)</td>
<td>0.949</td>
</tr>
<tr>
<td>A≥1 proportion,%</td>
<td>96(39.2%)</td>
<td>97(37.3%)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

## Discussion

In the multicenter randomized controlled trial on the efficacy and safety of Huangkui capsule in the treatment of IgAN, patients with urine protein 0.5 ~ 3.0 g and eGFR ≥45ml/min/1.73 m² were selected[15]. To investigate the effect of moderate and severe renal dysfunction on the effect of Huangkui capsule on reducing urinary protein, we conducted a multicenter, single-arm study on the efficacy and safety of Huangkui capsule in the treatment of chronic kidney disease[16], IgAN patients who met the inclusion and exclusion criteria were selected and supplemented. According to the meta-
analysis results that reducing IgAN urinary protein ≥30% can significantly improve the decrease of eGFR[3], we take the urine protein ≥30% after treatment of Huangkui capsule for 6 months as the effective standard, and analyze the influence of patients’ baseline clinical pathological characteristics on the efficacy of Huangkui capsule. The results showed that Huangkui capsule effectively reduced urinary protein of IgAN patients with basal urinary protein ≥1.0 g/d or eGFR ≥60 ml/min, baseline urinary albumin BMI, ALB and SCr affected the therapeutic effect of Huangkui capsule, but renal pathological characteristics of Oxford classification had no significant influence on the treatment effect of Huangkui capsule.

The data from experiments with animal models and cell cultures as described above have implicated that the possible mechanisms of Huangkui capsule treatment in kidney diseases may include reducing inflammation, improving immune response, anti-oxidative stress, and protecting renal tubular epithelial cells, inhibiting renal fibrosis, regulating autophagy and mitochondrial dynamics[12, 13]. However, there was no significant difference in the ratio of M1, E, I, S, T, or A ≥1 among the different baseline urinary proteins in this study, but the decreased rate of urine protein in patients with < 1.0 g/d did not reach the effective standard (the decrease rate of urine protein ≥30%), which may be related to the lower degree of inflammation, oxidative stress and immunologic imbalance in patients with urinary protein < 1.0 g/d.

Similar results can be seen in steroid treatment of IgAN. In the VALIGA study, compared with RAS blockers alone, RAS blockers combined with steroids significantly reduced urinary protein in IgA patients with IgAN urinary protein ≥1 g/d and delayed the progression of renal function; however, there was no significant difference in IgAN patients with urinary protein < 1 g/d[18]. Interestingly, the proportion of renal tissue C ≥1 in patients with urinary protein ≥1.0 g/d increased, especially in patients with urinary protein ≥1.0 and < 2.0 g/d, but Huangkui capsule had the significant effect on reducing urinary protein in these patients. Compared with patients with urine protein ≥1.0 and < 2.0 g/d, the ratio of renal tissue C ≥1 in patients with urine protein ≥2.0 g/d was significantly decreased, but the efficacy of Huangkui capsule was significantly increased. It is suggested that Huangkui capsule may have a therapeutic effect on the proteinuria caused by the crescentic lesions, but it is affected by the degree of crescentic lesions.

The risk factors for progression in IgAN included deteriorated renal function, higher amount of urinary protein excretion, hypertension, male, older, hematuria, higher uric acid, lower ALB, dyslipidemia, obesity, higher serum IgA or IgA/C3, anemia and cellular and microcellular crescent in renal tissue, endothelial hypercellularity, mesangial hypercellularity, tuft necrosis, global sclerosis, segmental sclerosis, fibrous crescent, glomerular tuft adhesion to Bowman’s capsule, mesangial matrix increase, interstitial fibrosis and tubular atrophy[19]. Although there was no significant change in eGFR after Huangkui capsule treatment in two clinical trials[15, 16], Huangkui capsule can effectively reduce urinary protein, which may delay the progress of IgAN. Although steroid therapy for six months in the STOP-IgAN trial did not improve the long-term prognosis of renal function in IgAN patients[7], unlike steroids, Huangkui capsule can be used for a long time, so it may have the effect of improving the long-term prognosis of renal function. And this study found that eGFR < 90 ml/min/1.73 m² patients, although the degree of mild, eGFR was statistically improved after the treatment of Huangkui capsule. However,
whether Huangkui capsule can improve the long-term prognosis of renal function needs further long-term trial verification. On the other hand, this study found that for patients with baseline eGFR < 60 ml/min/1.73 m², the decreased rate of urinary protein after Huangkui capsule treatment did not reach the effective standard. Similar results were also found in steroid therapy. In 2012, KDIGO clinical practice recommended that steroid therapy be limited to patients with urinary protein > 1 g and eGFR > 50 ml/min/1.73 m² [20]. In the STOP IgAN trial, steroids combined with immunosuppressive agents reduced urinary protein in patients with eGFR 30- 59 ml/min/1.73 m². However, considering that Huangkui capsule is a kind of plant medicine, its effect on reducing immune inflammation was lower than that of steroid combined immunosuppressants; So Huangkui capsule had no significant effect on reducing urinary protein in patients with baseline eGFR < 60 ml/min/1.73 m². It should be noted that patients with baseline eGFR < 60 ml/min/1.73 m² had a higher 24h urinary protein level of 1.31[0.77,2.01], which was significantly higher than that of patients with baseline eGFR ≥ 60 ml/min/1.73 m². Multivariate analysis showed that the decrease rate of urine protein increased by 7.9% (OR 1.079,95% CI: 1.051,1.108) for every 100 mg increase of urine protein; And when the SCr increased by 1 μmmol/L, the decrease rate of urinary protein declined by 1.1% (OR 0.989,95% CI: 0.983,0.995). It is suggested that the effect of kidney function impairment on reducing urinary protein in IgAN patients is higher than that of increasing urinary protein.

The composition of Huangkui capsule is complex, and 128 components have been identified [13]. The effective components of many kinds of Huangkui capsules are small molecular components, which need to combine with serum proteins for transport and be absorbed by cells. The results showed that the decrease rate of urine protein in IgAN patients treated with Huangkui capsules increased by 6.6% for every 1g/L increase of ALB. The reason may be that ALB is involved in the transport of the effective components and/or uptake by cells.

Many clinical trials have confirmed that overweight/obesity is a risk factor for increased proteinuria and progression of renal function in patients with IgAN [21-23]. Moreover, in patients with BMI ≥ 23.1 kg/m², the remission rate of urinary protein after steroid treatment for 5 years didn't significantly decrease [22]. In a retrospective study, compared with patients with BMI <25 kg/m², urinary protein excretion rate was significantly increased in patients with BMI ≥ 25 kg/m², but ACEI or ARB had no significant effect on reducing urinary protein [24]. In this study, we found that the BMI of patients with a decrease rate of urinary protein ≥ 30 after Huangkui capsule treatment was significantly lower than that of patients with a urinary protein decrease rate < 30%. Multivariate analysis showed that the decrease rate of urinary protein in IgA patients treated with Huangkui capsules decreased by 7% for every 1 kg/m² increase in BMI, suggesting that the effect of Huangkui capsules is also affected by weight/obesity.

Oxford classification of IgAN is the most commonly used pathologic diagnosis method for IgAN [25, 26]. However, the VILIGA study of 1,147 IgAN patients in 13 countries found that glucocorticoid / immunosuppressive therapy reduced the ability of Oxford classification to predict IgAN progression [27]. Another retrospective study also confirmed that the use of the Oxford Classification did not aid decision-making in the region of the use of immunosuppression [28]. The study
found that not only the seven characteristic pathological changes of Oxford classification, but also the acute lesion and chronic lesions and other different combinations based on Oxford classification could not predict the efficacy of Huangkui capsule in reducing urinary protein of IgAN. We speculate that the reason may be that Huangkui capsule has the functions of reducing inflammation, improving immune response, anti-oxidative stress, protecting renal tubular epithelial cells, inhibiting renal fibrosis, regulating autophagy and mitochondrial dynamics. However, the pathophysiological changes that can be improved by Huangkui capsule occur in the early stages of renal pathology changes or the process of disease progression. Therefore, the biomarkers of immune, inflammatory, and cell biological behavior in renal tissue may predict the efficacy of Huangkui capsule, but it needs to be confirmed by future research.

In summary, this study was based on a meta-analysis of patient data from two phase IV trials of Huangkui capsules and found that for IgAN patients with baseline urinary protein ≥1.0 g/d or eGFR ≥60 ml/min, Huangkui capsule has the effect of reducing urinary protein. Moreover, baseline urine protein, BMI, ALB, and SCr were independent risk factors for the efficacy of Huangkui capsule, which provided clinical evidence and reference for the rational use of Huangkui capsule in the treatment of IgAN. However, this study is a secondary analysis of large-scale clinical trial data, and the conclusions need to be verified by future clinical trials.

**Conclusion**

Huangkui capsule can effectively reduce proteinuria of IgAN patients with basic urinary protein ≥1.0 g/d or eGFR ≥60 ml/min, and the effect of patients on urinary protein ≥2.0 g/d is better. The more basic urinary protein and ALB level of IgAN, the better the effect of Huangkui capsule. The higher the basal SCr level and the higher BMI, the lower the curative effect of Huangkui capsule. Oxford classification of IgAN has no predicted effect of Huangkui capsule.

**Abbreviations**

SCr serum creatinine CKD chronic kidney disease IgAN IgA nephropathy ALB serum albumin RASI renin-angiotensin system inhibitors BMI body mass index eGFR glomerular filtration rate; ACEI angiotensin-converting enzyme inhibitors ARB angiotension II receptor blockers COVID-19 coronavirus disease 2019 M mesangial cell proliferation E endothelial cell proliferation I interstitial inflammatory cell infiltration S segmental sclerosis or adhesion T renal tubular atrophy or renal interstitial fibrosis C cellular or fibrocystic crescentic A arteriopathy STOP-IgAN the Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy.

**Declarations**

**Ethics approval and consent to participate:** The two clinical studies involved in this paper were reviewed and approved by the Medical Ethics Committee of the General Hospital of the People's Liberation Army of China (approval number: No. S2014-039-01, No. S2014-039-02), and all procedures of this clinical study
were fully in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

**Consent for publication:** Non-applicable.

**Availability of data and materials:** The datasets used in this study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

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**Author Contributions:** The study was conceived and designed by XF S, ZH X. The data were analyzed by ZH X, XF S, CL. The first draft of the manuscript was prepared by ZH X, YX Z and BH. The data was collected and interpreted by ZH X, XF S. All other authors provided the data and revised the manuscript critically for important intellectual content. The authors read and approved the final version of the manuscript.

**Acknowledgements:** Non-applicable.

**References**


Figures

![Figure 1]
Flowchart demonstrating the process of patients selection

![Flowchart](image)

**Figure 2**

Independent risk factors affecting the efficacy of Huangkui Capsule

**Note** Independent risk factors affecting the efficacy of Huangkui Capsule included baseline BMI, SCr, ALB and 24h urinary protein. The figures show the odds ratio (OR) and 95% confidence intervals (95%CI).