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Original contribution

# Renal outcomes in primary IgA nephropathy patients with segmental glomerular necrosis: a case–control study☆,☆☆

**Min Pan MD[a], Ji Zhang MD[b], Xiaohan You MD[b], Duo Li MD[b], Yinqiu Lv MD[b], Jianna Zhang MD[b], Xiaokai Ding MD[b], Zhanyuan Li MD[a], Feifei Xu MD[b], Chaosheng Chen MD[b,*]**

[a]*Department of Nephrology, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, PR China, 325000*
[b]*Department of Nephrology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, PR China, 325000*

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**Summary** The renal prognosis and treatment of primary IgA nephropathy (IgAN) patients with segmental glomerular necrosis (SGN) remain controversial. Patients with primary IgAN confirmed by renal biopsy were enrolled. Patients with SGN on renal biopsy were selected as the necrosis group, and a propensity score matching method was used to match a control group according to age, gender, weight, height and follow-up time. A total of 825 IgAN patients were enrolled in the present study. Seventy-three (8.8%) patients with SGN were selected as the necrosis group, and 292 patients without SGN were matched as the control group. Compared to the control group, a significantly increased serum fibrinogen level (3.97 g/L *vs* 3.54 g/L, $P = .002$) and proportion of patients with macroscopic hematuria (35.6% *vs* 14.7%, $P<.001$) was observed in the necrosis group. According to the new IgA pathological classification system, crescent formation was more pronounced in the necrosis group ($P = .001$). The average estimated glomerular filtration rate was obviously higher in the necrosis group and decreased more slowly during follow-up. However, the time-averaged urine protein-to-creatinine ratio remained low in the necrotic group, whereas it gradually increased in the control group. SGN suggests an active renal inflammatory state, but it was not an independent risk factor for a poor renal outcome in patients treated with immunosuppressive therapy. Furthermore, patients with SGN had a more stable renal function and low urinary protein excretion during follow-up, which may be attributable to aggressive immunotherapy.


## 1. Introduction

IgA nephropathy (IgAN) is the most common type of primary glomerulonephritis worldwide, and approximately 30%–40% of patients eventually develop end-stage renal

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* Corresponding author at: Nanbaixiang, Ouhai District, Wenzhou, Zhejiang, PR China, 325000
*E-mail address:* wzccs8@163.com (C. Chen).

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disease (ESRD) within 20–30 years of renal biopsy [1-3]. The typical light microscopy lesion of IgAN demonstrates focal or diffuse mesangial hypercellularity with expansion of the extracellular matrix [1]. Furthermore, a wide variety of glomerular lesions are present in patients with IgAN, ranging from minimal change to segmental necrotizing lesions with diffuse crescent formation [4,5]. IgAN is not always a benign disease. However, because of its variable of pathological changes, it is difficult to predict the prognosis of patients with IgAN based on renal pathology.

Recently, the new Oxford classification of IgAN (MEST-C scoring system) has been used to provide systematic pathological predictors of the prognosis in IgAN patients. Nevertheless, due to the limitations of the included cases, several pathological parameters, such as vascular lesions and segmental glomerular necrosis (SGN), have not been fully evaluated in primary IgAN [6,7].

SGN lesions are frequently found in Henoch-Schönlein purpura (HSP) or anti–neutrophil cytoplasmic antibody (ANCA)–associated vasculitis [8,9]. Furthermore, they are not rare in patients with primary IgAN, and approximately 6.1% to 10.3% of IgAN patients show segmental necrotizing lesions [10,11]. However, the relationship between SGN and the prognosis in IgAN remains unclear, and whether more aggressive immunosuppressive therapy in these patients is needed is still controversial [12]. The main objectives of this study were to investigate the clinical and pathological differences between IgAN patients with and without segmental necrotizing lesions and to examine the power of segmental necrotizing lesions to predict renal outcomes to indicate the aggressiveness of the immunosuppressive treatment.

## 2. Materials and methods

### 2.1. Subjects

Patients with a biopsy-based diagnosis of primary IgAN between March 2002 and April 2017 at The First or Second Affiliated Hospital of Wenzhou Medical University and who had been followed up for at least 3 months were enrolled in the study. The following patients were excluded from the study: (1) patients with secondary IgAN, such as that due to systemic lupus erythematosus, HSP, ANCA-associated vasculitides or hepatic diseases and (2) patients with severe combined diseases, such as chronic infectious disease, diabetic nephropathy, hypertensive nephropathy, or malignant tumors.

### 2.2. Renal biopsy

Kidney tissues were obtained from all patients during routine renal biopsies. All specimens were processed routinely for light and immunofluorescence microscopy by standard methods. The minimum sample length of kidney biopsies was 8 mm, and approximately 16 to 24 sections were examined per sample. SGN was defined as a segmental destructive lesion of the glomerular capillary loop, with fibrin deposition within and around the capillaries [10]. All renal biopsies were reviewed and scored by two renal pathologists (X.Y. and J.Z.) according to the Oxford Classification: M0 and M1 were defined as ≤ and >50% of glomeruli with mesangial cell proliferation, respectively; E0 and E1 were defined as the presence and absence of endocapillary hypercellularity, respectively; S0 and S1 were defined as the presence and absence of segmental sclerosis or tuft adhesions, respectively; T0, T1, and T2 were defined based on the degree of tubular atrophy or interstitial fibrosis (<25%, 25%–50%, and >50%, respectively), and C0, C1 and C2 were defined as the absence of cellular/fibrocellular crescents and the presence of cellular/fibrocellular crescents in at least one glomerulus or in >25% of glomeruli, respectively [6,7].

### 2.3. Collection of clinical variables

Demographic data (age and gender) and clinical features, including systolic and diastolic blood pressure (BP), body weight, and body height, as well as serum creatinine, and 24-h urine protein levels were collected at the time of renal biopsy and during follow-up. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease (CKD) Epidemiology Collaboration equation [13]. Use of medications including glucocorticoids and antihypertensive medications (angiotensin-converting enzyme inhibitor [ACEI] and an angiotensin receptor blocker [ARB]) was also recorded.

### 2.4. Statistical analysis

Numerical variables are presented as the means (standard deviations [SD]) or medians with interquartile ranges (IQRs), and categorical variables are presented as counts with percentages (%). Patients with no fibrinoid necrosis (control group) were matched with necrosis patients (necrosis group) according to age, sex, weight, height, serum creatinine on biopsy, and follow-up time using the *MatchIt* package at a 1:4 ratio [14]. The primary endpoint was a poor renal outcome, defined as a decrease of more than 50% in the eGFR from the baseline level or progression to ESRD during follow-up. Renal survival was defined as the absence of the primary endpoint during follow-up. Univariate and multivariate Cox proportional hazard modeling was performed using the *rms* package [15] to calculate hazard ratios (HRs) and p values of the correlation of clinical and histopathological parameters with poor renal outcomes. Parameters with p values of less than 0.1 in univariate Cox models were included in the multivariate Cox regression models. All reported *P* were two-tailed, and *P* less than .05