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Clinical and Histopathological Predictors of Renal Survival in IgA Nephropathy Patients with Nephrotic Range Proteinuria: A Retrospective Survival Analysis

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Abstract

Background: IgA nephropathy (IgAN) presents with a wide spectrum of clinical features, most commonly hematuria accompanied by subnephrotic proteinuria. Nephrotic range proteinuria is rare, observed in approximately 6% of patients at diagnosis. Limited studies have examined the relationship between clinicopathological characteristics and renal prognosis in IgAN patients with nephrotic range proteinuria.

Methods: This retrospective, single-center case-control study included 114 patients diagnosed with IgAN via kidney biopsy at Şişli Hamidiye Etfal Training and Research Hospital from April 2004 to December 2016. Patients were divided into two groups: nephrotic (≥3.5 g/day) and subnephrotic (<3.5 g/day) proteinuria. Primary outcomes included a doubling of serum creatinine, while secondary outcomes measured the initiation of renal replacement therapy.

Results: Patients with nephrotic range proteinuria had significantly lower serum albumin levels (p=0.001), higher cholesterol levels (p=0.03), and increased fibrocellular crescent formation (p=0.01). Cox regression analysis identified baseline serum creatinine, uric acid, and albumin levels, along with histopathological findings such as glomerulosclerosis and crescent formation, as significant predictors of treatment response. The Kaplan-Meier analysis showed that patients with nephrotic range proteinuria had worse renal survival, with a significantly higher proportion reaching primary and secondary endpoints compared to the subnephrotic group.

Conclusion: Histopathological findings, particularly fibrocellular crescents, were more common in patients with nephrotic range proteinuria, and their presence was associated with poorer renal survival and lower treatment response rates. These patients require closer follow-up and may benefit from more aggressive therapeutic strategies.

Keywords: IgA nephropathy, proteinuria, nephrotic range, crescentic glomerulonephritis, renal survival, treatment outcome

INTRODUCTION

Immunoglobulin A nephropathy (IgAN), first described by Berger and Hinglais in 1968, is characterized by predominant glomerular mesangial deposition of IgA (1). While the "idiopathic" form of the disease is common, secondary forms associated with various diseases have also been described. Idiopathic IgAN remains the most frequent primary glomerulonephritis worldwide, accounting for up to 30-50% of cases in some Asian populations and around 20-30 % in Europe (2-4). In Turkey, IgAN is the most common primary glomerulonephritis, with a prevalence of 25.7 % (5).

Patients with IgAN present with a wide range of clinical manifestations, including episodic macroscopic hematuria (40-50%), asymptomatic hematuria with proteinuria (30-40%), and nephrotic range proteinuria and nephrotic syndrome about 6% of cases. Additionally, some patients present with acute kidney injury, particularly in older adults. The disease typically peaks in the second and third decades of life, with a male predominance. The long-term prognosis of IgAN varies, with up to 50% of patients progressing to end-stage renal disease (ESRD) within 20 years of diagnosis (6).

The pathogenesis of IgAN involves the accumulation of polymeric IgA1 molecules in the glomerular mesangium,

triggering mesangial cell proliferation and the release of extracellular matrix proteins and inflammatory mediators. Poorly galactosylated IgA1, particularly in its polymeric form, is thought to play a key role in disease progression. Genetic factors, as well as immune responses involving complement activation and cytokine release, further contribute to the development of glomerular damage (7). A recent report identified IgA autoantibodies targeting mesangial cells and specific autoantigens (β2-spectrin and CBX3) in both gddY mice and patients with IgA nephropathy (IgAN), redefining IgAN as a tissue-specific autoimmune disease potentially driven by commensal bacteria through molecular mimicry (8).

Histopathological findings in IgAN vary, ranging from mild mesangial proliferation to more severe forms such as crescentic glomerulonephritis. The presence of crescents, particularly fibrocellular crescents, has been associated with a more rapid progression to end-stage renal disease (ESRD). Treatment options for IgAN are primarily aimed at controlling proteinuria and blood pressure, with the use of renin-angiotensin system (RAS) inhibitors being the mainstay of therapy. In patients with persistent proteinuria despite optimal supportive care, corticosteroids and other immunosuppressive agents may be required (9). Moreover, new therapies are rapidly emerging that target various pathways, cells, and mediators involved in disease pathogenesis, including B cell priming in the gut mucosa, the cytokines APRIL and BAFF, plasma cells, complement activation, and the endothelin pathway.

Previous studies revealed the strong association between IgAN and proteinuria, as higher levels of proteinuria (≥1 g/day) are strongly associated with worse histological findings, including mesangial hypercellularity, segmental sclerosis, tubular atrophy, and the presence of crescents, which indicate more advanced kidney damage. Proteinuria is also one of the strongest clinical predictors of progression to kidney failure in patients with IgAN (10,11). The risk of kidney failure is particularly high in patients with baseline proteinuria levels ≥1.0 g/day, where even reductions in proteinuria to 0.3 to <0.5 g/day can not lower risk effectively. This demonstrates that patients starting with high proteinuria need more aggressive management to lower their risk of kidney failure, emphasizing the importance of achieving significant reductions in proteinuria (10,11).

This study aims to investigate the clinical and pathological features of IgAN patients presenting with nephrotic range proteinuria and to evaluate their response to treatment and long-term renal outcomes.

METHODS

Study Design and Population

This retrospective, single-center case-control study was conducted at the Şişli Hamidiye Etfal Training and Research Hospital, Nephrology Clinic. The study included 114 patients diagnosed with IgAN via kidney biopsy between April 2004 and December 2016. Patients were categorized into two groups based on proteinuria levels: nephrotic (≥3.5 g/day) and subnephrotic range (<3.5 g/day). A 1:3 matching case-control design was used, with patients matched by age, sex, and comorbidities (diabetes, hypertension).

Data Collection

Demographic, clinical, and laboratory data were extracted from patient records. Variables collected included age, gender, blood pressure, serum creatinine, serum albumin, uric acid, total cholesterol, 24-hour urinary protein excretion, and the presence of microscopic hematuria. Kidney biopsies were evaluated for glomerular sclerosis, crescent formation, mesangial hypercellularity, endocapillary proliferation, and tubulointerstitial damage. All kidney biopsies were examined by the same pathologist to ensure consistency in histological assessment.

Treatment Protocol

All patients received standard care, including dietary sodium restriction (2 g/day) and antihypertensive therapy aimed at achieving blood pressure targets of <130/80 mmHg for patients with proteinuria <1 g/day and <125/75 mmHg for those with ≥1 g/day. Patients with persistent proteinuria ≥1 g/day despite maximal RAS inhibition for six months were treated with corticosteroids, with some receiving intravenous pulse methylprednisolone followed by oral steroids. Patients unresponsive to corticosteroids received additional immunosuppressive therapy, such as mycophenolate mofetil.

In the treatment of IgAN, antihypertensive medications primarily included agents targeting the renin-angiotensin system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which are effective in reducing proteinuria and controlling blood pressure. Additional antihypertensive agents such as beta-blockers, calcium channel blockers, and diuretics were also utilized as adjunctive therapy when necessary. The antihypertensive therapy was administered with the aim of achieving a target blood pressure of <130/80 mmHg for patients with proteinuria <1 g/day, and <125/75 mmHg for those with proteinuria ≥1 g/day. The dosage and choice of antihypertensive medications were individualized based on each patient's clinical condition and disease progression. Therapy was optimized in accordance with current clinical guidelines, with regular follow-up ensuring appropriate dose adjustments to maintain optimal blood pressure control.

Outcome Measures

The primary outcome was a doubling of serum creatinine from baseline. The secondary outcome was

Table 1. Demographical and laboratory results of the participants

Parameter	Nephrotic Range Proteinuria Group (Mean ± SD)	Subnephrotic Range Proteinuria Group (Mean ± SD)
Age (years)	45 ± 15	44 ± 14
Male (%)	72%	67%
Follow-up (months)	35.7 ± 32.6	45.7 ± 38
Serum Creatinine (mg/dL)	1.8 ± 0.6	1.4 ± 0.5
Serum Albumin (g/dL)	3.0 ± 0.5	4.0 ± 0.4
Total Cholesterol (mg/dL)	250 ± 30	210 ± 25
Uric Acid (mg/dL)	7.0 ± 1.2	6.0 ± 1.0
Proteinuria (g/day)	4.0 ± 0.8	2.5 ± 0.7

the initiation of renal replacement therapy (dialysis or transplantation). Treatment response was classified as complete remission (proteinuria <0.3 g/day), partial remission (proteinuria <1 g/day or a 50% reduction), or non-response.

STATISTICAL ANALYSIS

The data were analyzed using IBM SPSS (Version 21.0, Armonk, NY: IBM Corp.). Continuous variables were expressed as mean ± standard deviation. Comparisons between groups were made using the independent t-test or Mann-Whitney U test for continuous variables and chi-square test for categorical variables. Kaplan-Meier survival analysis was used to estimate time to primary and secondary outcomes, and Cox regression analysis was performed to identify predictors of renal survival. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The study included 25 patients in the nephrotic range proteinuria group (Group 1) and 75 patients in the subnephrotic range proteinuria group (Group 2). The mean follow-up period was 35.7 ± 32.6 months in Group 1 and 45.71 ± 38 months in Group 2 (p=0.24). Serum albumin levels were significantly lower in Group 1 (p=0.001), while cholesterol levels were higher (p=0.03). The clinical and laboratory features of the participants are given in **Table 1.** The study was designed as a matched case control study, so for 25 nephrotic range proteinuria patients, 75 subnephrotic range proteinuria patients were selected. The selection was made in accordance with the demographic and clinical features of the group.

Table 2. Histopathological features of the study groups

Histopathological Feature	Nephrotic Range Proteinuria Group (%)	Subnephrotic Range Proteinuria Group (%)
Fibrocellular Crescents	46.2	14.2
Global	27.2	22.0
Tubulointerstitial Damage	40.0	33.3

Appropriate statistical methods, including sensitivity analyses, were applied to ensure that the missing data did not significantly impact the overall results.

Fibrocellular crescent formation was more prevalent in Group 1 (p=0.01), and the complete remission rate was significantly lower (p=0.004) compared to Group 2 (**Table 2**).

Renal Outcomes

Doubling serum creatinine occurred in 20% of patients in Group 1, compared to 4% in Group 2 (p=0.022). Kaplan-Meier analysis revealed that the time to primary outcome in Group 1 was significantly shorter with 87.3 months as opposed to Group 2, with 134.5 months (log-rank p<0.001) (**Figure 1**). The secondary outcome, renal replacement therapy or transplantation need was observed in 32% of patients in Group 1 and 5.3% in Group 2 (p=0.003) (**Figure 2 and Figure 3**).

Cox Regression Analysis

Cox regression analysis identified age (HR= 1.05 and p=0.002), baseline serum creatinine (HR= 1.65, p=0.005), uric acid (HR= 1.28, p=0.002), and albumin levels (HR= 0.88, p=0.001) as independent predictors of renal survival. Histopathological findings, including global glomerulosclerosis (HR= 1.45, p=0.003), crescent

Table 3. Cox regression analysis for renal survival

Variable	Hazard Ratio (HR)	95% Confidence Interval (CI)	P-value
Age (years)	1.05	1.02-1.07	0.002
Baseline Serum Creatinine (mg/dL)	1.65	1.17-2.44	0.005
Serum Albumin (g/dL)	0.88	0.72-1.09	0.001
Uric Acid (mg/dL)	1.28	1.03-1.55	0.002
Global Glomerulosclerosis (%)	1.45	1.02-2.06	0.003
Total Crescents (%)	4.6	1.16-13.0	0.004
Tubulointerstitial Damage (%)	1.7	1.00-2.63	0.01

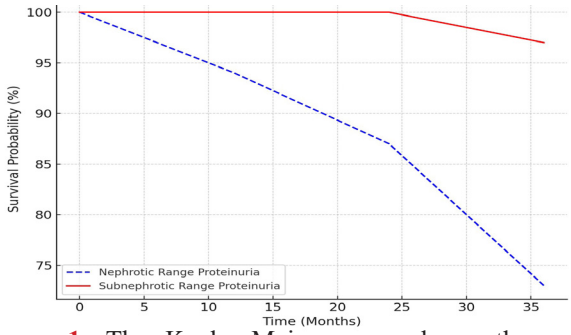

Figure 1. The Kaplan-Meier curve shows the survival probability for the primary outcome in patients with nephrotic and subnephrotic range proteinuria.

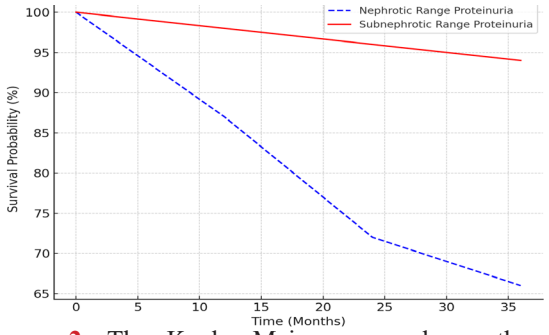

Figure 2. The Kaplan-Meier curve shows the survival probability for the secondary outcome in patients with nephrotic and subnephrotic range proteinuria.

formation (HR= 4.6, p=0.004), and tubulointerstitial damage (HR= 1.7, p=0.01), were also significant determinants (Table 3).

DISCUSSION

The present study aimed to investigate the clinical and pathological features of IgAN patients with nephrotic range proteinuria and assess their long-term renal outcomes. The key findings demonstrated that patients with nephrotic range proteinuria had significantly worse renal survival compared to those with subnephrotic proteinuria, as indicated by higher rates of serum creatinine doubling and progression to end-stage renal disease (ESRD). Histopathologically, fibrocellular crescent formation was more prevalent in patients with nephrotic range proteinuria, and this was associated with poorer treatment response and renal prognosis. Cox regression analysis identified baseline serum creatinine, uric acid levels, albumin, glomerulosclerosis, and crescent formation as significant predictors of renal survival. These results suggest that patients with nephrotic range proteinuria require closer monitoring and more aggressive therapeutic interventions to improve outcomes.

Immunoglobulin A (IgA) nephropathy is the most common glomerular disease worldwide, characterized by the deposition of polymeric IgA in the mesangium and sometimes the capillary mesangium (12). The proliferative and crescentic forms of IgAN are associated with nephrotic range proteinuria, accelerated hypertension, and faster progression to ESRD, although nephrotic range proteinuria is rare at presentation, occurring in approximately 6% of cases (13). Crescent formation varies in prevalence from 5-60%, with diffuse crescentic lesions (>50% involvement) observed in 1-4% of patients, making them rare but significant (14). While crescent formation was not highlighted as a predictor of renal survival in the Oxford classification or the VALIGA studies due to the low prevalence in those cohorts, several studies have since established that crescent formation negatively impacts prognosis. A meta-analysis by Xue Shao et al., reviewing 5285 IgAN patients, confirmed that those with crescents had

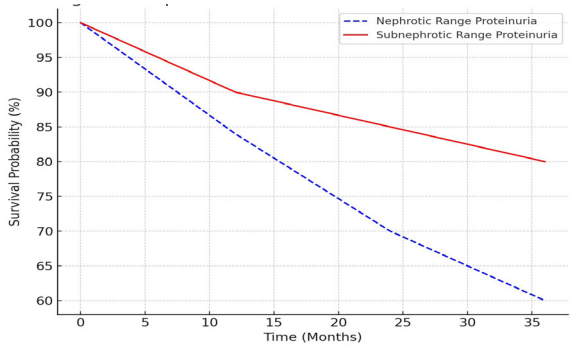

Figure 3. The Kaplan-Meier curve shows the renal survival probability in patients with nephrotic and subnephrotic range proteinuria.

lower GFR, higher proteinuria levels, and more frequent immunosuppressive therapy use, reinforcing crescent formation as a key prognostic factor in progression to renal failure (15).

Zhonghui Jia et al. further reported that, in a cohort of 63 IgAN patients with <50% crescent involvement, 14.2% had urinary protein levels above 3.5 grams, with crescents accounting for 5-47% of the lesions, most of which were cellular crescents (16). In our study, crescents were identified in 48% of patients with nephrotic range proteinuria, with a notable increase in fibrocellular crescents in this group, compared with subnephrotic proteinuria.

A study by Liang et al. involving 89 patients with IgAN, 19.1% of whom had nephrotic range proteinuria, reported a higher rate of crescent formation in those with nephrotic proteinuria. Of these, 91.8% had less than 25% crescent involvement (17). In this cohort, 13.3% patients experienced a 50% increase in serum creatinine or required dialysis after a median follow-up of 18 months, 28.6% of those with nephrotic proteinuria reaching these endpoints after a median follow-up of 11 months. Similarly, Silva et al. found that despite conventional treatment, 40% of IgAN patients with <50% crescent involvement had poor renal outcomes (18). In a retrospective study including 146 primary IgAN patients conducted by Walsh et al., the presence of any crescents (including fibrous crescents) was a significant independent predictor of doubling serum creatinine, ESRD, or death (19). Furthermore, a study by

Katafuchi et al. involving 702 patients demonstrated that crescents were associated with worse renal survival (20). In our study, 26% of patients with crescents progressed to ESRD, compared to 5.8% of those without crescents.

Proteinuria levels greater than 1 g/day are indicative of more severe IgAN, and uncontrolled proteinuria is a major risk factor for disease progression. The rate of progression is low when proteinuria is below 1 g/day but increases significantly when proteinuria exceeds 3-3.5 g/day. In a prospective cohort study of 332 patients, it was shown that the combined incidence of dialysis and death was significantly higher in patients with baseline proteinuria >1 g/day compared to those with lower levels (17% vs. 3% at 10 years, and 41% vs. 10% at 20 years). Patients who reduced their proteinuria to <1 g/day with treatment had lower rates of dialysis and death compared to those with persistent proteinuria above 1 g/day (21). However, a follow-up study of 542 patients by Reich et al. found that for patients with baseline proteinuria >3 g/day, the rate of renal function decline was 24 times faster, but there was no significant difference in progression to renal failure between those achieving partial remission (<1 g/day) and those starting with baseline proteinuria <1 g/day. In our study, doubling of serum creatinine and progression to ESRD were more frequent in patients with nephrotic range proteinuria. Even when partial remission was achieved, renal survival was worse in nephrotic group compared to subnephrotic group (22).

In a study by James Tumlin et al., even low levels of crescents were associated with poor outcomes and faster progression to ESRD. Notably, no correlation was found between nephrotic range proteinuria and treatment response or progression to ESRD in these patients (23). In our study, patients with nephrotic range proteinuria had significantly lower rates of complete remission and higher rates of treatment resistance. However, when assessing treatment response on renal survival, no significant difference was observed between the nephrotic and subnephrotic groups.

The use of corticosteroids and other immunosuppressive agents in the treatment of IgAN remains controversial. In patients with persistent proteinuria >1 g/day despite optimal supportive care, combining non-immunosuppressive therapy with immunosuppressive treatment is crucial (24). Some authors advocate for more aggressive treatment in patients with nephrotic proteinuria and/or rapidly progressive disease, especially if cellular crescents are present in more than 10% of glomeruli (25-26).

Higher serum uric acid levels, lower serum albumin and older age are associated with adverse outcomes (27-30). Similarly this study demonstrated that uric acid, and albumin have strong impact on IGAN-related outcomes.

In our study, although the treatment protocols for both groups were similar (with intravenous steroid use being more frequent in patients with nephrotic range proteinuria), the rate of treatment resistance was 9 times higher in the nephrotic group. We believe that the difference in crescent prevalence between the two groups may have contributed to the disparity in treatment response.

Limitations

This study has several limitations that need to be acknowledged. First, the retrospective design introduces inherent biases, such as reliance on medical records and the possibility of missing data, which could affect the accuracy of clinical and laboratory parameters. Moreover, being a single-center study, the findings may not be generalizable to other populations or healthcare settings, particularly those with different ethnic backgrounds or healthcare practices. Second, the sample size, especially in the nephrotic range proteinuria group, was relatively small. This limited the statistical power of certain analyses, such as subgroup comparisons and multivariate adjustments, which may have impacted the robustness of our conclusions. Third, the study did not account for genetic factors or differences in treatment regimens beyond corticosteroids and RAS blockers, which may have influenced disease progression and patient outcomes. The heterogeneity in immunosuppressive therapy could also have led to varying treatment responses that were not fully captured. Lastly, the follow-up period varied between patients, with some having relatively short observation times. This could have led to underestimation of long-term outcomes such as progression to ESRD, particularly for those who were followed for less than three years.

CONCLUSION

This study demonstrated the outcome differences between IgAN patients presenting with nephrotic and subnephrotic proteinuria and the possible factors interacting with this outcome. The patients with nephrotic range proteinuria had worse renal outcomes, including higher rates of treatment resistance and progression to ESRD, compared to those with subnephrotic proteinuria. Histopathological findings, particularly the presence of fibrocellular crescents, were significant predictors of poor renal survival and treatment outcomes.

Given these findings, it is clear that patients with nephrotic range proteinuria require closer monitoring and potentially more aggressive therapeutic approaches. Early identification of high-risk patients, including those with crescent formation, is critical for optimizing treatment and preventing long-term kidney damage. While the use of corticosteroids and immunosuppressive agents remains controversial, they may be necessary for patients with persistent proteinuria despite optimal supportive care.

Further research, particularly multicenter studies with larger cohorts and longer follow-up durations, is needed to better understand the optimal management strategies for these high-risk patients and to confirm the role of crescent formation as a prognostic marker in IgAN.

DECLARATIONS

Ethics approval and consent to participate: This study was produced from the graduation thesis of Feyza Bayraktar, MD., and was applied for approval by the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital. Written informed consent is not available since it is retrospective. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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

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Authors' contributions: Dr. Feyza Bayrakdar Çağlayan designed the study, collected the data, and performed the data analysis. Dr. Taner Baştürk supervised the study and contributed to the interpretation of results. Dr. Abdulkadir Ünsal provided overall guidance and critical revisions. All authors read and approved the final manuscript.

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