

Crescentic IgA Nephropathy: Prognosis and Predictors of Outcomes

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Running title: Short-term outcomes in crescentic IgA nephropathy

ABSTRACT

Introduction: Crescentic IgA nephropathy is associated with poor outcomes; 50-90% progress to End Stage Kidney Disease (ESKD) in the short term. In the present study, we report the predictors of short-term outcomes in crescentic IgA nephropathy and tested the utility of a creatinine cutoff of 6.8 mg/dL (601.26umol/L) in predicting adverse outcomes.

Methods: All cases of crescentic IgA nephropathy admitted from January 2013 to December 2023 were included. Outcomes were defined at one year as either complete recovery (eGFR >60), partial recovery (eGFR 15–60), or Major Adverse Kidney events (MAKE). MAKE was defined as the presence of any one among the following at the end of one year: ESKD, dialysis independence with an eGFR <15 ml/min/1.73 m², death, or preemptive transplant.

Results: Forty-nine cases were identified over 11 years, and around 87% received immunosuppressive therapy. MAKE was reported in 72 % at the end of one year, with ESKD in 57.4%. Serum creatinine at the time of biopsy [OR 1.540, 95% CI 1.064, 2.229] and percentage of fibrocellular crescents [OR 1.098, 95% CI 1.006, 1.198] were predictive of MAKE at one year. A serum creatinine cut-off of 6.8 mg/dl (601.26umol/L) at admission had a sensitivity of 79 % (95% CI 62, 91) for MAKE and 96% (95% CI 81,100) for ESKD at one year.

Conclusions: Despite receiving immunosuppressive therapy, crescentic IgA nephropathy is associated with non-recovery in more than three-fourths of affected individuals. A serum creatinine of >6.8 mg/dl (601.26umol/L) at presentation portends a poor prognosis.

Keywords: Rapidly Progressive Glomerulonephritis, IgA deposits, Crescents, glomerular disease

INTRODUCTION

IgA nephropathy (IgAN) is characterized by mesangial IgA deposits, causing immune-mediated damage to the glomeruli. The clinical presentation is broad, ranging from asymptomatic urinary abnormalities to rapidly progressive kidney disease. The most common presentation reported is glomerular proteinuria and hematuria. Acute Kidney Injury (AKI) is uncommon in IgAN, with less than 5% prevalence, either resulting from acute tubular injury due to obstruction by casts or, even rarely, due to rapidly progressive glomerulonephritis (RPGN)¹. Non-circumferential crescents are common in IgAN; the reported prevalence is around 20–30% of patients with IgAN². A higher percentage of crescents is reported in individuals of Asian ethnicity. The presence of cellular or fibrocellular crescents is considered an adverse prognostic marker. An increasing number of crescents (>25%) portends an unfavorable prognosis for IgAN, even if immunosuppression is given. Recognising the prognostic significance, crescents have been added to the Oxford–MEST scoring system, with C2 having the maximum score, accounting for >25% of glomeruli showing crescents². IgAN presenting as RPGN is often associated with >50% crescents in glomeruli. Crescentic IgAN is considered an unusual presentation, with a poor treatment response and a higher progression rate to end-stage kidney disease (ESKD) or advanced chronic kidney disease (CKD). There is limited data on the management of crescentic IgAN; the current KDIGO recommendations suggest using a regimen similar to ANCA-associated vasculitis. There is a very little information on the long-term outcomes of crescentic IgAN, primarily due to the rarity of this clinical presentation. Whether the present IgA risk scoring algorithms are practical in prognosticating crescentic IgAN remains unknown. Most patients with crescentic IgAN progress to ESKD within a year of presentation. This raises a significant concern about the risks vs. benefits of intense immunosuppressive protocols employed in crescentic IgAN. To date, only a single internally validated prognostic model is available to predict the occurrence of ESKD at one year². According to the prognostic model proposed by Lv et al, in crescentic IgAN, the serum creatinine is predictive of the long-term prognosis rather than the percentage or nature of crescents. The prognosis remains poor when creatinine is >2.7 mg/dL (238.7 $\mu\text{mol/L}$), with practically no recovery at values >6.8 mg/dL (601.26 $\mu\text{mol/L}$). The data is derived and validated in patients of Chinese ethnicity and requires further external validation before wide application. These findings also call for reevaluating the treatment considerations in crescentic IgAN; exploring new management paradigms and avoiding prolonged immunosuppression in patients less likely to recover. In the present study, we attempt to identify the clinical and histopathological characteristics and outcomes of crescentic IgAN in an Asian Indian cohort and the utility of a serum creatinine cutoff of 6.8 mg/dL (601.26 $\mu\text{mol/L}$) for treatment futility.

MATERIALS AND METHODS

This is a record-based study from the rapidly progressive glomerulonephritis (RPGN) database maintained by the

Department of Nephrology. Since January 2013, all patients aged >14 years, presenting with RPGN, with a kidney biopsy showing > 50 percent crescents, were included in this register. Relevant clinical information at the time of biopsy, with follow-up data for up to one year, was entered into the register. All patients with crescentic IgAN enrolled from January 2013 to December 2023 were identified from the database. The detailed data on clinical presentation, laboratory parameters, histopathological data, treatment given, and clinical outcome were obtained from the hospital information system. Follow-up data was collected up to one year. Those with secondary IgAN and IgA vasculitis or with features of ANCA vasculitis were excluded. Two renal pathologists, blind to clinical data, retrieved and reviewed all biopsies. A semi-quantitative grading was used to grade tubular atrophy and interstitial fibrosis (1-25% - mild, 26-50% moderate, and >50 % severe). The institute's ethical committee approved the protocol.

Definitions of outcome:

Major Adverse Kidney events (MAKE) were defined as the presence of any one of the following at the end of one-year follow-up: End-stage kidney disease (ESKD), dialysis independence with an eGFR <15 ml/min/1.73 m², death, or preemptive transplant.

Partial recovery was defined as eGFR between 15-60 ml/min/1.73 m² at the end of one year of follow-up, with dialysis independence.

Complete recovery was defined as GFR >60 ml/min/1.73 m².

Statistical methods:

All continuous variables were expressed as mean with standard deviation or median with interquartile range, depending on the data distribution. Categorical variables were expressed as frequencies and percentages. The Chi-square test, Student's t-test, and Mann–Whitney U-test were used to compare the groups, depending on the nature of the data. A logistic regression analysis was used to assess the independent predictors of MAKE at one year. ROC curves were used to identify the usefulness of different criteria to predict MAKE and ESKD. Diagnostic accuracy of various criteria was expressed as sensitivity and specificity with 95% confidence intervals. The data were analysed using SPSS version 25 (IBM Corporation; Armonk, NY, USA).

RESULTS

A total of 49 patients with a follow-up of 1 year were included in the study. The prevalence of crescentic IgAN among those with a biopsy of IgAN was 11.4%. The affected individuals were young (mean age 27 (20–38)) and had a relatively short duration of symptoms. None had reported a history of gross hematuria in childhood or adolescence. The majority had severe kidney failure requiring dialysis at the time of presentation. None of the affected individuals had a previous history of documented IgAN. The clinical characteristics are given in Table 1.

Table 1. Baseline clinical and laboratory parameters of the study population.

Characteristics	Total (n = 49)
Age (Years) †	27 (20–38)
Male sex, n (%)	40 (81.6)
Presenting complaints, n (%)	
Microhaematuria	49 (100)
Hypertension	45 (91.8)
Oedema	44 (89.7)
Dyspnoea	16 (32.7)
UPCR >3.5g/g	12 (24.4)
Gross haematuria	7 (14.3)
Symptom duration (days) †	30 (17.5–60)
Urine output at presentation (ml/day) †	800 (550–1500)
Oliguria, n (%)	8 (16)
Urine protein creatinine ratio †	1.6 (0.9–3.5)
Serum creatinine at biopsy (mg/dl) †	8.5* (4.6–11.2)
Need for dialysis at presentation, n (%)	31 (61.3)
Total protein (g/dl) *	5.6 ± 0.8
Serum albumin (g/dl) *	2.8 ± 0.4

* Mean with SD; † median with interquartile range; # conversion factor × 88.42 µmol/L

Histopathological characteristics: The crescents were primarily cellular, followed by fibrocellular. Twelve patients (24%) had 100 per cent cellular crescents in glomeruli. Fibrous crescents were present only in eight (16%), and the proportions varied from 9–40%. Even though tubular atrophy and

interstitial fibrosis were reported in the majority, the degree of involvement was mild to moderate. Fibrinoid necrosis was seen in five patients (10%). The histopathological characteristics are given in Table 2.

Table 2. Histopathological characteristics.

Characteristics (n = 49)	Value
Number of glomeruli in the biopsy †	10 (8–16)
Number of sclerosed glomeruli †	2 (1–4.5)
No of viable glomeruli †	7 (5–12)
Percentage of crescents †	71 (60–100)
Percentage of cellular crescents †	64 (37–95)
Percentage of fibrocellular crescents †	33 (0–60)
Endocapillary proliferation n, (%)	28 (57)
Neutrophils in glomeruli n, (%)	20 (41)
Mesangial proliferation n, (%)	38 (78)
Interstitial inflammation, n %	
Mild (up to 25%)	23 (47)

Characteristics (n = 49)	Value
Moderate (25–50%)	23 (47)
Acute tubular necrosis n, (%)	
Mild (up to 25%)	19 (39)
Moderate (25–50%)	13 (27)
Interstitial fibrosis n, (%)	
Mild (up to 25%)	23 (47%)
Moderate (25–50%)	14 (29)
Tubular atrophy n, (%)	
Mild (up to 25%)	19 (39%)
Moderate (25–50%)	27 (57)

† Median with IQR.

Management and Long-term Outcomes

Immunosuppressive therapy was given to the majority; 37 (76%) patients were treated with corticosteroids and monthly intravenous cyclophosphamide, four patients (8%) received steroid monotherapy, one (2%) received steroid and Mycophenolate Mofetil (MMF) combination, and one received Rituximab. Plasma exchange was not given to any patients. Six patients (12%) did not receive any immunosuppression, as the treating physicians decided against immunosuppression due to the advanced lesions of fibro cellular crescents with significant tubular atrophy and interstitial fibrosis.

No follow-up data were available for two patients. Among the 47 patients with follow-up data, MAKE was reported in 34 patients (72 %) at the end of one-year follow-up, with ESKD in 27 patients (57.4%). There were two deaths, and both patients had ESKD. Of these 27 patients with ESKD, 25 had presented with dialysis-

requiring kidney failure at presentation; they did not recover kidney function, despite receiving immunosuppressive therapy. Among the 13 patients who did not have MAKE, 11 patients had CKD 3 & 4, and only 2 (4%) had complete recovery (Figure 1). Those who had MAKE at one year had more severe kidney failure at presentation, a higher number of fibrocellular crescents and interstitial fibrosis on kidney biopsy (Table 3). Out of eight patients with fibrous crescents, six patients were with MAKE, and two were with partial or complete recovery. The extent of mesangial, endocapillary proliferation or fibrinoid necrosis was not associated with MAKE. On a sensitivity analysis, ESKD (n = 27) vs non-ESKD (n = 20), the only parameters that differed were serum creatinine (9.6 mg/dl [IQR 8.5, 14] vs 4.4 mg/dl [IQR 3.0, 8.8], $p < 0.001$) and requirement for dialysis (92.6% in ESKD vs 7.4 % in non-ESKD; $P < 0.001$). Immunosuppression was given to 21 patients (78%) with ESKD and all non-ESKD patients. None of the other clinical/histological/biochemical parameters differed between the two groups.

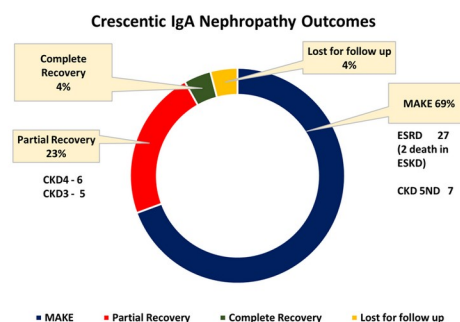


Figure 1.

Crescentic IgA Nephropathy — One-year outcomes.

Table 3. Clinical and biochemical parameters of those with MAKE and no MAKE.

Characteristics	MAKE (n = 34)	Partial + complete recovery (n = 13)	P value
Age	28.5 ± 10.2	34.4 ± 15.2	0.214

Characteristics	MAKE (n = 34)	Partial + complete recovery (n = 13)	P value
Males, n (%)	30 (88.2)	8 (61.5)	0.037
Need for dialysis at presentation, n (%)	26 (76.5)	5 (38.5)	0.014
Serum Creatinine (mg/dL) †	9.2* (6.8–11.6)	5* (2.6–9.3)	0.012
Albumin (g/dL) †	2.7 (2.5–3.2)	2.9 (2.8–3.1)	0.340
24 hr urine protein (g) †	1.8 (0.9–3.8)	1.5 (0.8–2.8)	0.468
Urine output (ml) †	850 (487–1462)	800 (600–2000)	0.528
Percentage of sclerosed glomeruli †	23 (0–34)	33 (6–42)	0.322
Percentage of crescents †	80 (60–100)	67 (52–100)	0.353
Percentage of cellular crescents †	52 (16–80)	77 (54–100)	0.032
Percentage of fibrocellular crescents †	47 (20–68)	0 (0–37)	0.012
Tubular atrophy †	30 (18–30)	30 (10–32)	0.400
Interstitial fibrosis †	17.5 (10–30)	10 (0–25)	0.034
Fibrinoid necrosis n, (%)	5 (15)	0	0.303
Immunosuppressive therapy, n (%)	28 (82)	13 (100)	<0.001
GC + Cyclophosphamide	27	8	
GC + MMF	0	1	
GC alone	0	4	
Rituximab	1	0	

GC — glucocorticoids; MMF — mycophenolate mofetil; # conversion factor $\times 88.42 \mu\text{mol/L}$.

To identify the independent clinical and histological predictors of MAKE, a logistic regression analysis was done incorporating the variables with a P value of <0.05 on univariate analysis (Male sex, percentage of cellular crescents, percentage of fibrocellular crescents, interstitial fibrosis, and serum creatinine). The variables independently associated with MAKE were serum creatinine at the time of biopsy [OR 1.540, 95% CI 1.064, 2.229] and percentage of fibrocellular crescents [OR 1.098, 95% CI 1.006, 1.198]. Using serum creatinine as a dependent variable, we calculated the probability of MAKE at one year using logistic regression. The curve showed a parabolic relationship, with serial

increments in creatinine leading to accelerated increases in the likelihood of MAKE (Figure 2). The ROC curves for serum creatinine to predict ESKD and MAKE were 0.842 (95% CI 0.720, 0.963) and 0.755 (95% CI 0.536, 0.975), respectively. We calculated the sensitivity and specificity of dialysis and a serum creatinine cut-off of 6.8 mg/dL (601.26 $\mu\text{mol/L}$) in predicting MAKE and ESKD at the end of one year (Table 4). Serum creatinine cut-off of 6.8 mg/dl (601.26 $\mu\text{mol/L}$) had a relatively better sensitivity and specificity in predicting ESKD and MAKE than the dialysis requirement at presentation.

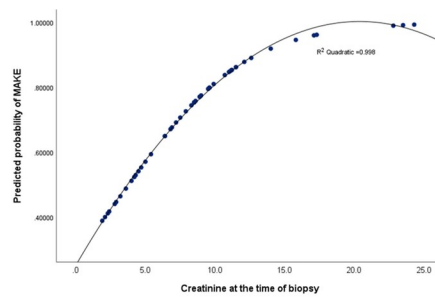


Figure 2.

Logistic regression curve showing predicted probability of MAKE at one year based on serum creatinine at presentation.

Table 4. Sensitivity of various cutoffs in predicting MAKE and ESKD.

Criteria	MAKE at 1 year		ESKD at one year	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Dialysis at presentation	77 (59, 89)	62 (32, 86)	93 (75, 99)	70 (46, 88)
Creatinine >6.8 mg/dl	79 (62, 91)	62 (32, 86)	96 (81, 100)	70 (46, 88)

DISCUSSION

Crescentic IgAN, characterised by >50% crescents, is a rare presentation that can occur as the first clinical manifestation of IgAN. Because of the rarity of the presentation, no definite evidence-based treatment guidelines exist for management. Generally, crescentic IgAN is considered to have a worse prognosis, with a renal survival of 50% at one year and 20% at 5 years⁴. The KDIGO 2021 clinical practice guidelines recommend aggressively treating crescentic IgAN and rapidly declining kidney function with glucocorticoids and immunosuppressants, like the regimens used in ANCA-associated vasculitis. However, the evidence supporting the utility of immunosuppressive medications in Crescentic IgAN comes from observational studies with relatively small numbers or mixed populations with crescentic IgAN and Henoch-Schonlein purpura^{6,7,8,9}.

In the present study, we found that Crescentic IgAN is associated with an inferior prognosis, with advanced kidney failure documented in more than 2/3rd of affected individuals. A complete recovery of kidney function was less likely; those who recovered eventually had varying degrees of moderate to severe CKD. Despite using aggressive immunosuppression, the ESKD rates we encountered were around 58%. These figures are considerably higher than the reported literature on crescentic IgAN outcomes. A large Chinese cohort of crescentic IgAN Nephropathy reported ESRD rates of 42% at one year, progressively increasing to 55% by 5 years, with cyclophosphamide-based regimens administered to around 40% individuals². The proportion of patients receiving cyclophosphamide-based regimens in our study was nearly 80%.

Tang et al. reported a kidney survival rate of 67% at a median follow-up of 5 months in patients with crescentic IgAN nephropathy⁷. We believe that the poor outcomes in the present study might be due to the severe kidney involvement at the initial clinical presentation. The kidney failure was severe, with a median creatinine of 8 mg/dl (707.36 μmol/L) (as against 4.3–4.7 mg/dl (380.2–415.6 μmol/L)^{2,7}), and two-thirds of the patients required dialysis. In the present study, of the 27 patients with ESKD at one year (including two deaths), 25 were dialysis dependent from admission itself.

Another potential contributor to poor outcomes might be the Asian Indian ethnicity. It is widely believed that IgAN in Asian Indians carries a poor prognosis. Despite the younger age of presentation, the disease tends to be more severe at initial presentation, with significant chronicity on biopsy. A recent study also corroborates this observation - 40% of patients with non-crescentic forms of IgAN exhibit rapid progression within a time frame of three years, characterised by one of the following outcomes: >50% decline in eGFR, CKD 5, kidney replacement therapy, or death¹⁰. The reasons for the increased severity remain largely unknown; this calls for extensive multicentre studies, looking into possible genetic, epigenetic, and ethnicity-specific factors contributing to rapid progression¹¹.

In univariate analysis, the total proportion of crescents was not a predictor of MAKE; however, more active lesions characterised by cellular crescents had overall better outcomes. Those with more fibrocellular crescents showed adverse outcomes. The proportion of fibrous crescents was too small to draw any meaningful conclusions. On multivariate analysis, the only prognostic factors deciding adverse outcomes were serum creatinine and

proportions of fibrocellular crescents. Even though a higher proportion of crescents is an unfavourable prognostic factor, once the proportion of crescents including cellular, fibrocellular and fibrous crescents exceeds 50%, serum creatinine appears to have the best predictive power in defining outcomes. A recent study also reported that more than 43.7% crescent proportion indicates a poor response to immunosuppression⁸. Lv et al proposed that a creatinine cut-off of 6.8 mg/dL (601.26 μmol/L) would identify ESKD at one year in 100% of cases in the discovery and validation cohorts. We also found that a creatinine cut-off of 6.8 mg/dL (601.26 μmol/L) had a 96% sensitivity in identifying ESKD. Those who present with serum creatinine of 6.8 mg/dl are unlikely to respond to immunosuppression with high-dose glucocorticoids and cyclophosphamide. This raises a pertinent question on adding plasma exchange to existing immunosuppressive protocols, like treating ANCA-associated vasculitis. The data on the utility of plasma exchange is limited in crescentic IgAN. Small case series have reported a 50% dialysis independence in crescentic IgAN, compared to no dialysis independence in historic controls¹². A systematic review has reported 60% progress to ESKD, despite receiving plasma exchange¹³. We did not give plasma exchange to any of the patients. The poor prognosis seen in the present study calls for more prospective trials on employing plasma exchange as an adjunctive therapy for crescentic IgAN.

This is the first study looking into the long-term outcomes of crescentic Ig nephropathy from the Indian subcontinent to the best of our understanding. The study's strength is the availability of data systematically collected from an existing database, maintained over 11 years. The limitations include the differing treatment options, which limit the individual treatment effects of each modality. In addition, six patients with adverse kidney outcomes were not given immunosuppression due to the significant underlying chronicity.

These conclusions may not be generalisable to non-Asians, patients with less than 50% crescents, and those in the earlier stages of the disease.

CONCLUSIONS

Despite receiving immunosuppressive therapy, crescentic IgAN is associated with progression to major adverse kidney endpoints in 72% and ESKD in 57.4%. A serum creatinine >6.8 mg/dl (601.26 μmol/L) is associated with a high chance of ESRD and MAKE at one year.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest

DISCLOSURE

Nil

ACKNOWLEDGEMENTS

None

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