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# IgA-Dominant Idiopathic Membranoproliferative Glomerulonephritis: Insights into Clinicopathological Characteristics and Kidney Outcomes in a Developing Country

Articoli originali

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**ABSTRACT**

**Background.** IgA-dominant idiopathic membranoproliferative glomerulonephritis (MPGN) is a rare and understudied renal condition that overlaps morphologically with atypical IgA nephropathy (IgAN) and infection-related glomerulonephritis (IRGN). Its unique presentation and limited literature necessitate a deeper examination of its clinical features and outcomes.

**Methods.** This retrospective study analyzed 10 biopsy-confirmed cases of IgA-dominant idiopathic MPGN diagnosed between 1999 and 2019 at the Sindh Institute of Urology and Transplantation (SIUT), Karachi. All patients were followed post-biopsy, and secondary causes, including infections and systemic illnesses, were excluded.

**Results.** Patients had a median age of 22 years (range: 15–30), with 60% being male. Common clinical manifestations included nephrotic-range proteinuria, hematuria, and renal insufficiency. Median estimated glomerular filtration rate (eGFR) at presentation was 29 mL/min/1.73 m². Complement levels were normal, and serological tests were negative. Hypertension was noted in 40% of cases, all of whom required kidney replacement therapy (KRT). Immunosuppressive therapy was administered to 60% of patients. At 3-year follow-up, 80% had progressed to end-stage kidney disease (ESKD), one patient died (10%), and two achieved partial remission (20%) but were subsequently lost to follow-up.

**Conclusion.** IgA-dominant idiopathic MPGN exhibits an aggressive course with poor renal outcomes compared to typical IgAN. The absence of identifiable secondary causes and high progression to ESKD highlight its severity and the urgent need for targeted research to better understand its pathogenesis and refine treatment approaches.

**KEYWORDS**: Immunoglobulin A (IgA), membranoproliferative glomerulonephritis (MPGN), IgA nephropathy (IgAN), end-stage kidney disease (ESKD), kidney replacement therapy (KRT).

## Key points

- IgA-dominant idiopathic MPGN is increasingly recognized as a rare and distinct kidney disorder with specific pathological and immunological characteristics, differentiating it from conventional IgA nephropathy.
- Despite its clinical relevance, this variant remains underexplored in the literature. This study aimed to delineate the clinicopathological features and treatment outcomes of this rare entity.
- Due to its unfavorable prognosis, deeper investigation is essential to clarify its mechanisms and develop effective therapies.

## Introduction

Membranoproliferative glomerulonephritis (MPGN), also referred to as mesangiocapillary glomerulonephritis (MCGN), represents a unique and intricate pattern of immune or non-immune mediated kidney injury. This condition mostly arises as a result of the deposition of immune complexes or complement fragments within the glomeruli, leading to inflammation and structural alterations. Immune-mediated MPGN can be further classified based on findings obtained through immunofluorescence (IF) microscopy, distinguishing between immune complex (IC)-mediated and complement (C)-mediated MPGN subtypes [1].

Among the IC-mediated variants lies a rare and complex entity known as Immunoglobulin A (IgA)-dominant MPGN. This condition accounts for a small proportion, estimated at only 0.2% to 0.3%, of the native kidney biopsy cases [2]. It is defined by its distinctive histological features observed under light microscopy (LM), characterized by a membranoproliferative pattern of injury coupled with dominant or codominant IgA staining detected on IF. Notably, this rare kidney pathology differs significantly from IgA nephropathy (IgAN) [3] as well as from IgA-dominant infection-related glomerulonephritis (IRGN) [4–6]. The unique morphological features of IgA-dominant MPGN include frequent subendothelial immune complex deposition, remodeling of the glomerular basement membrane in peripheral capillary loops, and the scarcity of exudative changes. Furthermore, cases exhibit infrequent subepithelial deposits and lack definitive correlation with infectious etiologies.

Despite the identification of IgA-dominant MPGN, there remains a paucity of detailed literature regarding its idiopathic variant, which poses significant challenges for clinicians and researchers alike. Existing documentation comprises isolated case reports describing this disease in diverse contexts, including pediatric patients [7, 8], children with cirrhosis and portal hypertension [9], individuals with alcoholic cirrhosis [10], patients suffering from cirrhosis prior to the identification of the hepatitis C virus (HCV) [11, 12], and adults experiencing urinary tract infections [13]. However, these reports are sporadic and leave considerable gaps in understanding the broader implications and mechanisms of this disease.

Kidney outcomes in patients diagnosed with idiopathic MPGN vary depending on numerous factors, including disease severity, the patient's response to therapeutic interventions, and associated underlying conditions [14]. While poor kidney outcomes have been documented among patients with infection-related IgA-dominant MPGN [4], the clinical trajectory and prognosis of IgA-dominant idiopathic MPGN remain largely unknown. Nonetheless, limited research highlights its tendency toward progressive kidney damage, with one particular study suggesting that the kidney survival rate in IgA-dominant idiopathic MPGN might be inferior to both IgAN and aggressive variants of IgAN [2].

Given the significant knowledge gap concerning IgA-dominant idiopathic MPGN, a focused study has been conducted to shed light on its clinicopathological characteristics. This investigation aimed to provide a comprehensive understanding of the disease's clinical presentations and long-term kidney outcomes. By deepening insights into this unique morphologic finding, the study aspires to address unanswered questions and enhance approaches to diagnosis and management.

## Materials and Methods

### *Ethics Statement*

This study received approval from the Institutional Review Board of the Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan (approval number: SIUT-ERC-2025/A-551). All research activities were conducted in strict adherence to the ethical principles outlined in the Declaration of Helsinki.

### *Study population*

This study retrospectively analyzed the medical records of patients aged 15 years and older who were referred to the Kidney Division of the SIUT, Karachi, Pakistan. These referrals spanned from January 1999 to December 2019, specifically for native kidney biopsies. Eligible patients were those with a histopathological diagnosis of idiopathic MPGN who had been monitored at the kidney clinic following their kidney biopsy. Patients who reached the study endpoint within 12 months were included regardless of follow-up duration, while others were followed for a minimum of 12 months. Among the reviewed cases, only 10 patients were identified with dominant or co-dominant IgA deposition on IF and an absence of exudative features.

The diagnosis of idiopathic MPGN was established clinically, adhering to the algorithm outlined in UpToDate 2024 [15], after rigorously excluding all secondary causes. These excluded causes encompassed infections, autoimmune diseases, plasma cell dyscrasias, lymphoproliferative disorders, and cryoglobulinemia. Special attention was given to excluding secondary causes in MPGN cases with C1q positivity on IF, using viral and autoimmune serology. Furthermore, patients presenting with Henoch-Schönlein purpura (HSP), hemolytic uremic syndrome (HUS), segmental or focal MPGN features, exudative characteristics, monoclonal Ig deposition diseases with κ and λ staining, or those previously treated with corticosteroids or other immunosuppressive agents were excluded from the study.

### *Data Collection*

Patient medical records were thoroughly examined, encompassing clinical, biochemical, serological, and histopathological findings both at the time of biopsy and during subsequent follow-ups. Clinical data included factors such as age, gender, biopsy indications, presence of hypertension, administered treatment protocols, the necessity for kidney replacement therapy (KRT), and follow-up details. Laboratory investigations recorded serum creatinine and albumin levels upon admission and at subsequent intervals, along with complement levels (C3 and C4) categorized as either normal or reduced. Additionally, a comprehensive urinalysis was conducted, including the urine protein-to-creatinine ratio (PCR) at baseline and during follow-ups, as well as 24-hour urinary protein measurements, where available. The estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) creatinine formula [16].

## Histopathology

The histopathological assessment comprised a detailed analysis of the total number of glomeruli, including those exhibiting sclerosis. It also evaluated the proportion of glomeruli displaying crescents categorized as cellular, fibrocellular, or fibrous, along with mesangial and endocapillary hypercellularity, which was noted as either diffuse or focal. Additional features such as capillary wall double contours and the extent of interstitial fibrosis and tubular atrophy (IFTA) were graded into four categories: none (0–5%), mild (6–25%), moderate (26–50%), or severe (>50%). Immunofluorescence (IF) results demonstrated positivity for IgA, IgG, IgM, C3, C1q, κ, and λ, with staining patterns and intensities rated on a scale ranging from 0 to 3+ (Figure 1). Pathological variables were scored using the 2016 revised Oxford Classification MEST-C criteria, [17] encompassing mesangial hypercellularity (M0/M1), endocapillary hypercellularity (E0/E1), segmental glomerulosclerosis (S0/S1), tubular atrophy/interstitial fibrosis (T0/T1/T2), and crescents (C).

All cases initially diagnosed as idiopathic MPGN through LM were reclassified using IF-based criteria as either IC-MPGN or C-MPGN. This reevaluation was conducted by two renal pathologists with significant experience, one with over 20 years and the other with 10 years, who performed independent analyses followed by collaborative review in cases of disagreement. Both pathologists were blinded to patient outcomes. IgA-dominant MPGN was characterized by IgA deposition at a level of ≥2+, accompanied by C3 and/or non-dominant IgG staining at ≥1+, with the IgG intensity lower or equal to IgA. Additional criteria included the presence of negligible (<+1) C1q staining and the absence of significant exudative features (such as glomerular neutrophilic infiltration) or extraglomerular deposits. Electron microscopy (EM) was not universally performed in all cases.

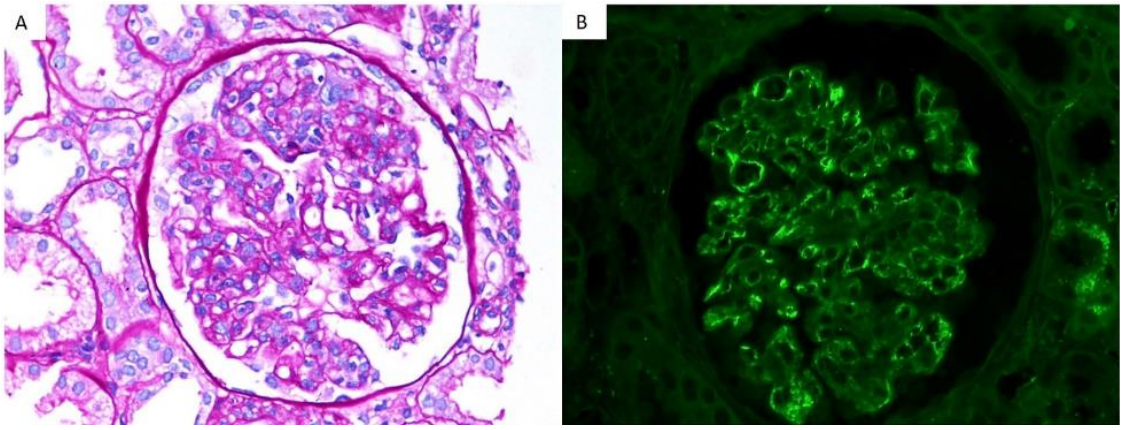


**Figure 1. Histopathological features of IgA-dominant membranoproliferative GN. A) Membranoproliferative pattern of injury with lobular accentuation, mesangial proliferation, endocapillary hypercellularity, and segmental duplication of the glomerular basement membranes (PAS stain, ×400). B) Granular staining for IgA (2+) in peripheral capillary loops and some mesangial regions by immunofluorescence (IF) (IgA by IF, ×400).**

## Outcomes

In the absence of established guidelines for determining remission in MPGN, we applied criteria typically used for proliferative lupus nephritis (LN) and classified patients into three distinct groups [18]:

- **Complete Remission (CR)**: characterized by a normal urinalysis, indicated by a dipstick result that is either negative or shows trace amounts of protein and blood, serum albumin levels >3.5 g/dl, along with an eGFR > 90 mL/min/1.73 m².

- **Partial Remission (PR)**: denoted by an abnormal urinalysis, which may reveal as microscopic hematuria or proteinuria ≥1, serum albumin levels < 3.5 g/dl, and the eGFR within the range of 60 to 90 mL/min/1.73 m².
- **No Remission (NR)**: defined as persistent proteinuria > 3 g/day or a progressive decline in kidney function.
- **Kidney Survival**: refers to the duration from the initial kidney biopsy to the earliest instance of initiating dialysis, undergoing a kidney transplant, or a reduction in eGFR to <15 mL/min/1.73 m², with no subsequent recovery to levels above 15 mL/min/1.73 m² during the follow-up period.
- **Kidney Flare**: describes a recurrence or exacerbation, evidenced by a dipstick result turning positive after previously being negative, or an increase in proteinuria identified either through dipstick analysis or elevated PCR levels in patients previously achieving CR or PR [19].

## Study endpoints

- The **primary endpoint** was defined as kidney survival without the onset of ESKD or death.
- The **secondary endpoint** focused on the proportion of patients achieving CR or PR during the follow-up period.

## Statistical Analysis

The statistical analysis was performed using version 25.0 of the Statistical Package for the Social Sciences (SPSS) software (IBM Corp, Armonk, NY, USA). Continuous variables were presented as either mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical data were reported as frequencies and percentages, while discrete variables were expressed in terms of proportions. Kaplan–Meier methodology was employed to construct the overall survival curve. A p-value below 0.05 was regarded as indicative of statistical significance.

## Results

Between 1999 and 2019, a total of 10 patients were diagnosed with biopsy-confirmed IgA-dominant MPGN.

*Patient Demographics and Clinical Characteristics at Presentation*

Table 1 summarizes the demographic, clinical, and serological attributes of individuals with IgA-dominant idiopathic MPGN. The median age at diagnosis was 22 years (range: 15–30 years), with the cohort comprising 6 males (60%) and 4 females (40%). Upon presentation, all patients exhibited edema alongside nephrotic-range proteinuria and/or nephrotic syndrome accompanied by microscopic hematuria. Hypertension was noted in 4 patients (40%), while none displayed macroscopic hematuria. Additionally, complement levels were found to be within normal ranges across all cases at the time of presentation. The median serum creatinine concentration was recorded at 3.2 mg/dl (range: 1.0–8.9 mg/dl), whereas the median eGFR was 29 ml/min/1.73 m² (range: 6.75–78.75 ml/min/1.73 m²). Furthermore, 4 patients (40%) required KRT upon admission.

| | n=10 |
|---|---|
| Age at biopsy (years), median (IQR) | 22 (15-30) |
| **Gender:**<br>Male, n (%)<br>Female, n (%) | <br>6 (60)<br>4 (40) |
| Weight (Kg), mean ± SD | 66.8 ± 9.1 |
| HTN, n (%) | 4 (40) |
| Presence of Edema, n (%) | 10 (100) |
| Evidence of recent infection, n (%) | 0 |
| Asymptomatic, n (%)<br>Urinary abnormality<br>Abnormal creatinine<br>Newly diagnosed HTN<br>Symptomatic<br>Nephrotic syndrome<br>Nephritic syndrome<br>Gross hematuria | <br>0<br>0<br>0<br><br>10 (100)<br>0<br>0 |
| Proteinuria (Dipstick), n (%)<br>Trace<br>+1<br>+2<br>+3<br>+4 | <br>0<br>0<br>0<br>9 (90)<br>1 (10) |
| Microscopic hematuria, n (%)<br>Trace<br>+1<br>+2<br>+3<br>+4 | <br>1 (10)<br>3 (30)<br>0<br>5 (50)<br>1 (10) |
| Serum Creatinine (mg/dl), median (IQR) | 3.2 (1.0-8.9) |
| eGFR (ml/min/1.73$^2$), median (IQR) | 29 (6.75-78.75) |
| Serum albumin (g/dl), median (IQR) | 2.8 (2.07- 3.15) |
| 24-hr Urinary protein (g/day), median (IQR) | 4.2 (3.7-9.2) |
| **Serum C3 levels, n (%)**<br>Low (< 80 mg/dL)<br>Normal (>80 mg/dL) | <br>0<br>10 (100) |
| **Serum C4 levels, n (%)**<br>Low (< 16 mg/dL)<br>Normal (>16 mg/dL) | <br>0<br>10 (100) |
| Required KRT (%) | 4 (40) |
| Median follow-up in months (IQR) | 12 (3.0- 27) |

**Table 1. Baseline Demographic and Clinical Characteristics of Patients IgA-dominant MPGN. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; SD: standard deviation; IQR: interquartile range; kg: kilogram; HTN: hypertension; eGFR: estimated glomerular filtration rate; KRT: kidney replacement therapy.**

## *Kidney Histopathological Characteristics*

The histopathological features of the kidneys in patients with IgA-dominant idiopathic MPGN are summarized in Table 2. The median number of glomeruli observed was 14 (range: 8.7–27.5). A diffuse and global MPGN pattern of injury was noted in all cases. Segmental glomerular sclerosis was evident in 2 out of 10 patients (20%), while the median percentage of globally sclerotic glomeruli was 3 (range: 1–6). Extracellular crescentic proliferation was a prominent feature, present in 9 patients (90%). Furthermore, tubular atrophy was noted in 7 patients (70%) as mild to moderate and in 1 patient (10%) as severe. All patients demonstrated a MEST-C score of 3 or higher. IgA emerged as the dominant immunoglobulin in all cases, with staining intensities of 2+ or above. In half of the biopsy samples (50%), IgG coexisted with a staining intensity of 1+ or trace levels. Nearly all cases exhibited positive C3 staining, with 60% showing intensities of 2+ or greater. C1q staining was either trace or absent, and both lambda and kappa light chains were detected in all cases.

| | n = 10 |
|---|---|
| **Total glomeruli,** median (IQR) | 14 (8.7-27.5) |
| **Globally sclerosed,** median (IQR) | 3 (1.0-6) |
| **Mesangiocapillary proliferation, n (%)** | |
| Focal | 0 |
| Diffuse | 10 (100) |
| **Segmental glomerular sclerosis, n (%)** | |
| S0 | 8 (80) |
| S1 | 2 (20) |
| **Tubular atrophy / interstitial fibrosis, n (%)** | |
| T0 | 2 (20) |
| T1 | 7 (70) |
| T2 | 1 (10) |
| **Cellular crescents, n (%)** | |
| C0 | 1 (10) |
| C1 | 5 (50) |
| C2 | 4 (40) |
| **MEST-C Score** | |
| 1 | 0 |
| 2 | 0 |
| 3 | 1 (10) |
| 4 | 5 (50) |
| 5 | 3 (30) |
| 6 | 1 (10) |
| **Immunofluorescence results** | |
| **Ig A, n (%)** | |
| Negative | 0 |
| Trace | 0 |
| +1 | 0 |
| +2 | 4 (40) |
| +3 | 6 (60) |
| **Ig G, n (%)** | |
| Negative | 5 (50) |
| Trace | 4 (40) |
| +1 | 1 (10) |
| +2 | 0 |
| +3 | 0 |
| **Ig M, n (%)** | |
| Negative | 3 (30) |
| Trace | 0 |
| +1 | 4 (40) |
| +2 | 3 (30) |
| +3 | 0 |
| **C3, n (%)** | |
| Negative | 0 |
| Trace | 3 (30) |
| +1 | 1 (10) |
| +2 | 3 (30) |
| +3 | 3 (30) |
| **C1q, n (%)** | |
| Negative | 6 (60) |
| Trace | 4 (40) |
| +1 | 0 |
| +2 | 0 |
| +3 | 0 |

**Table 2. Histopathological Characteristic in patients with IgA-dominant MPGN. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; SD: standard deviation; IQR: interquartile range; IF/TA: interstitial fibrosis/ tubular atrophy; MEST C Score: mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, tubular atrophy, and interstitial fibrosis, crescents.**

*Treatment and Outcomes*

Table 3 provides an overview of the therapeutic interventions and kidney outcomes in patients diagnosed with IgA-dominant MPGN. At a median follow-up or study endpoint post-kidney biopsy (range: 12–27 months), 6 out of 10 patients (60%) had undergone immunosuppressive therapy. Of these, three received steroid monotherapy at a dose of 1 mg/kg for a total of 6 months, while the remaining three were treated with combination therapy consisting of steroids (1 mg/kg for 6 months) and cyclophosphamide (CYC) at 1.5 mg/kg for 3 months. One of these patients was subsequently maintained on azathioprine (AZA) for an additional 6 months. One patient received antiproteinuric treatment alone, whereas three individuals did not receive any therapeutic intervention due to advanced disease progression. PR was achieved in 2 patients (20%) at 12 and 24 months, respectively; however, both patients were subsequently lost to follow-up. The remaining 8 patients (80%) exhibited progression to ESKD by 36 months, with one patient succumbing to sepsis. Kaplan-Meier survival analysis was employed, encompassing the interval from treatment initiation to either the conclusion of follow-up or mortality. At 36 months, renal survival among the cohort was nonexistent, as all surviving patients were reliant on dialysis (Figure 2).

| Case no: | Age (yrs) | Sex | 24-hr Urinary protein (g/day) on admission | eGFR (ml/min/1.73$^2$) at presentation | MEST-C Score | Treatment | Outcomes | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|
| 1 | 21 | M | 4.28 | 19 | 4 | Prednisolone, CYC, AZA | ESKD | 24 |
| 2 | 22 | M | 3.45 | 95 | 3 | Prednisolone | PR with proteinuria of 2.5g/day, lost to follow-up | 12 |
| 3 | 28 | F | 3.8 | 14 | 5 | Prednisolone, CYC | ESKD | 12 |
| 4 | 19 | M | 8.3 | 13 | 6 | No IS | ESKD, listed for transplant | 03 |
| 5 | 17 | M | 3.1 | 8 | 4 | No IS | ESKD, listed for transplant | 02 |
| 6 | 15 | F | 12.2 | 84 | 5 | Prednisolone, CYC | ESKD | 36 |
| 7 | 20 | M | 4.17 | 47 | 4 | Prednisolone | ESKD | 36 |
| 8 | 30 | F | 3.85 | 77 | 5 | ACE inhibitor | PR, lost to follow-up | 24 |
| 9 | 25 | M | N/A | 07 | 4 | No IS | ESKD-Mortality | 03 |
| 10 | 23 | F | 4.2 | 39 | 4 | Prednisolone | ESKD | 12 |

**Table 3. Clinical course of IgA-dominant MPGN patients. IgA: Immunoglobulin A; MPGN: membranoproliferative glomerulonephritis; M: male; F: female; eGFR: estimated glomerular filtration rate; MEST C Score: mesangial hypercellularity, endocapillary hypercellularity, segmental sclerosis, tubular atrophy, and interstitial fibrosis, crescents; PR: partial remission; CYC: cyclophosphamide; AZA: azathioprine; ESKD: end stage kidney disease: IS: immunosuppressive; ACE: angiotensin-converting enzyme inhibitor; N/A: not available.**

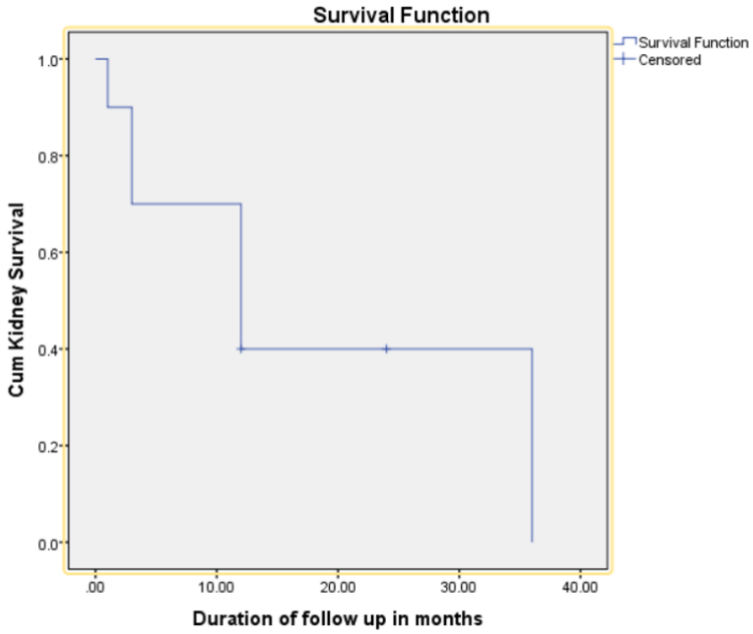


**Figure 2. Kaplan-Meier survival analysis of IgA-dominant membranoproliferative GN patients.**

## Discussion

This study presents an in-depth analysis of the clinical, biochemical, serological, and histopathological characteristics, alongside kidney and patient outcomes, in individuals diagnosed with idiopathic IgA-dominant glomerulonephritis displaying a membranoproliferative pattern of injury. This condition is characterized by a predominantly diffuse MPGN injury pattern observed under LM, devoid of exudative features. IF reveals IgA-dominant or co-dominant staining, with prominent deposits along the peripheral capillary walls and within the mesangium. Although the findings are based on a single-center study, this work holds significant importance, as it stands among the first to explore this distinctive clinicopathological entity in Asia and offers a representative glimpse into the Pakistani population.

A novel insight of this study lies in its observation that patients with this disease exhibit distinct pathological characteristics and a clinical progression that sets it apart from other conditions within its differential diagnosis spectrum, including IgAN [3], IgA-dominant IRGN [4–6], IgA-proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) [20], and LN. The clinical features bear similarities to IgAN, including male predominance, early age of onset, and normal serum complement levels. However, a key distinction from IgAN is the rapid deterioration of kidney function, in contrast to the 50% ESKD rate observed over 30 years in a large IgAN cohort [21]. Additionally, among the 244 IgAN cases reported by Haas M, none displayed MPGN-like histological features [3]. Instead, it closely resembles other forms of IC-MPGN. These findings suggest that IgA-dominant idiopathic MPGN may constitute either a unique clinicopathological entity or an aggressive variant of IgAN.

The long-term prognosis for kidney survival in patients diagnosed with IgA-dominant idiopathic MPGN remains inadequately defined, primarily due to the limited availability of data. Current knowledge is derived from a handful of case reports and a single cohort study, both of which exhibit variability in their associations and outcomes. Cases of IgA-dominant MPGN have been documented in the pediatric population, including isolated instances involving an infant [8] and two children [7].

These pediatric cases were largely asymptomatic and were identified incidentally through routine screening processes. Among them, only one child exhibited clinical symptoms, specifically a history of fever accompanied by gross hematuria, sterile cultures, and nephrotic-range proteinuria with preserved kidney function. These children responded well to immunosuppressive therapy, demonstrating favorable outcomes. In contrast, adult cases of this condition have been reported predominantly in association with underlying factors such as infections, systemic diseases, cirrhosis, vaccination, malignancy, or severe injuries like burns [10–13, 22–24]. Adults typically presented with advanced uremia and, in many instances, required KRT. Despite treatment, the kidney outcomes in this demographic have been generally poor. This divergence highlights the variability in disease presentation and outcomes between pediatric and adult patients. The findings of the current study underscore the overlapping clinical characteristics between children and adults. While the patients in this cohort were relatively young and presented with nephrotic-range proteinuria, a feature more akin to the pediatric population [7–8], the majority also exhibited moderate to severe kidney impairment. This level of kidney dysfunction necessitated KRT in many cases, mirroring the unfavorable outcomes observed in adult populations [2]. These observations align with the findings of Andeen et al. [2], the only existing study to detail poor outcomes in primary IgA-dominant MPGN, which included 15 adult patients.

The rarity of this condition poses significant challenges in fully comprehending its natural progression and treatment response. Anecdotal reports from nephrologists treating such cases suggest that patients often exhibit a positive response to intensified immunosuppressive therapies. Notably, a recent adult case demonstrated favorable outcomes with a combination of steroids and cyclosporine treatment [25], lending credence to the hypothesis of the disease's intrinsically aggressive nature. Furthermore, three individuals from the current study cohort presented with an eGFR below 15 mL/min/1.73 $m^2$ at diagnosis and did not receive immunosuppressive therapy because of advanced disease, highlighting the severity and aggressive clinical manifestation of this condition at the time of presentation.

## Strengths and limitations of the study

The study boasts several notable strengths. Foremost among these is its distinction as the pioneering research to examine adult cohorts of biopsy-confirmed IgA-dominant MPGN cases originating from a developing South Asian nation. Given the rarity of this condition and the scarcity of existing data, this study fills a significant knowledge gap, marking the first published dataset on patient outcomes related to this rare entity in Pakistan. Furthermore, the patients involved were diligently monitored up to the study's endpoint, enabling individualized assessments of treatment efficacy. Another notable contribution of this study is its presentation of data concerning ESKD and mortality rates, adding invaluable insights into the prognosis of this disease. However, the study is not without limitations. Firstly, as a retrospective investigation, certain missing data may have influenced the robustness of the final analysis. Moreover, the inherent constraints of a retrospective study design make it challenging to account comprehensively for all potential confounding variables. Secondly, the single-center nature of the research restricts the generalizability of the findings, as the results may not fully reflect the broader population of the country. Thirdly, EM studies were not conducted for all cases, which may have limited the depth of pathological insights. Lastly, the lack of standardization in treatment regimens introduces variability in patient outcomes, potentially obscuring clearer interpretations of therapeutic effectiveness.

## Conclusion

IgA-dominant idiopathic MPGN represents a unique clinicopathological condition, distinguished by its severe progression and significantly worse outcomes relative to IgAN or even its more aggressive subtypes. The unfavorable prognosis highlights an urgent need for in-depth investigations to unravel its underlying mechanisms and develop more effective treatment approaches to prevent the development of histological sclerotic lesions characteristic of MPGN.

## Acknowledgments

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## Data Availability

The datasets generated and/or analyzed during this study are available upon reasonable request from the corresponding author.

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