

Clinical Characteristics and Renal Outcomes in Patients with IgM Nephropathy: A Retrospective Single-Center Study

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Background: Defining immunoglobulin M (IgM) nephropathy as a discrete clinical disorder remains controversial, with limited documentation in Saudi Arabian patients.

Aim: This study analyzes the clinical and pathological features, as well as the prognosis, of IgM nephropathy in the Saudi population.

Methods: This study is conducted as a retrospective descriptive study at the nephrology unit of King Saud University Medical City in Riyadh. The study included individuals with biopsy-proven IgM nephropathy from 2016 to 2024. Stringent diagnostic criteria were employed, focusing on immunofluorescence positivity (IgM 1+ to 3+). Clinical data were collected from a kidney biopsy registry from the pathology department at King Saud University, and renal pathology was evaluated by a single expert renal pathologist for various features, including mesangial cell proliferation and glomerulosclerosis.

Results: We analyzed a total of 15 patients with IgM nephropathy (n = 15), with a median age at diagnosis of 4 years (IQR: 2–8) and a male predominance (80%). Patients were categorized into early childhood onset (<4 years, 46.7%) and late childhood onset (≥4 years, 53.3%). Common manifestations included nephrotic syndrome (93.3%) and generalized body swelling (66.7%), with lower limb edema reported in all patients (100%). Nephrotic-range proteinuria was present in 93.3%, with preserved renal function (median eGFR: 158 mL/min/1.73m²). Biopsy results for nine patients revealed mesangial proliferation in 66.7%. The overall relapse rate was 93.3%, with early-onset patients exhibiting higher rates of steroid resistance and more frequent relapses.

Conclusion: This study enhances the understanding of IgM nephropathy in Saudi Arabia, indicating that early onset may be associated with a more aggressive disease course and higher relapse rates, highlighting the need for early identification of high-risk patients. Additionally, the use of rituximab in refractory cases may present a promising option for further evaluation.

Keywords: IgM nephropathy, proteinuria, kidney biopsy, renal outcomes

Introduction

The first description of the Immunoglobulin M Nephropathy (IgMN) as a separate disease entity was in 1978 by Cohen and Bhasin,^{1,2} who described the kidney biopsy findings in patients presenting with heavy proteinuria, in both reports, diffuse mesangial cellularity observed on light microscopy (LM) and predominant mesangial IgM deposition on immunofluorescence (IF). Since then, many reports have described similar pathological findings in patients presenting with nephrotic syndrome or asymptomatic proteinuria.^{3–5} The IgM nephropathy is characterized by a variable degree of mesangial expansion and hypercellularity on light microscopy, diffuse IgM deposition on immunofluorescence and mesangial electron-dense deposits on electron microscopy, along with a variable degree of foot process effacement.⁶

Currently, there is no consensus on the diagnostic criteria for IgM nephropathy. It remains uncertain whether it is a distinct disease or if it falls along a spectrum that includes minimal change disease and focal segmental glomerulosclerosis, suggesting a possible connection between these conditions.⁶ The frequency of IgMN has increased since its initial discovery. Early reports indicated an incidence of 2–6.1%,^{1,2} while a more recent report showed an incidence of 18.5% in children with idiopathic nephrotic syndrome.⁷ The clinical presentation is widely variable. While the disease is mainly described in children, it is not uncommon to be diagnosed in adults. In children the main presenting feature is idiopathic nephrotic syndrome, although asymptomatic proteinuria and/or hematuria have also been frequently reported in the literature.⁴ The prognosis of the disease is also variable. The reported incidence of progression to End Stage Kidney Disease (ESKD) ranges between 4% and 23% in the literature.^{4,8,9} Hypertension, the degree of proteinuria and fibrosis in the kidney biopsy are proposed predictors for the development of ESKD.^{4,10} There are currently no established guidelines for the treatment of IgMN. However, children with idiopathic nephrotic syndrome has generally been managed similarly to other forms of nephrotic syndrome, with steroids being the mainstay of treatment. The rate of steroid resistance varies significantly across different studies, ranging from 0% to 52%.¹¹ To our knowledge, there is only one study describing patients with IgMN in Saudi Arabia, highlighting a dearth of national data on this condition.⁹

This study aims to analyze the clinical and pathological features, as well as the prognosis, of patients diagnosed with IgMN in the Saudi population.

Methods

Study Design

The study was designed as a retrospective descriptive study conducted at the nephrology unit at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia.

Study Population

The study included individuals diagnosed with biopsy-proven IgM nephropathy from 2016 to 2024 (n=15), based on stringent immunofluorescence criteria (IgM positivity 1+ to 3+). Due to the unknown prevalence of IgM nephropathy in Saudi Arabia, convenience-based sampling was used from March 2024 to March 2025, screening a total of 30 patients. Inclusion criteria were biopsy-confirmed IgM nephropathy patients, while exclusion criteria eliminated those with systemic diseases (eg, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus) and patients with active viral infections.

Key Definitions

The key definitions for this study, including clinical outcomes and therapeutic responses, have been enlisted in [Table 1](#). Specific forms of IgM nephropathy, such as focal segmental glomerulosclerosis-like IgM nephropathy, minimal change disease-like IgM nephropathy, and mesangial proliferative glomerulonephritis-like IgM nephropathy, were classified based on light microscopy and immunofluorescence kidney biopsy findings.

Data Collection

Data abstraction was between March 2024 and March 2025. Clinical data were collected using a kidney biopsy registry, which included demographic and clinical details such as age, gender, smoking habits, co-morbid conditions, and laboratory findings. Blood biochemistry data included albumin, creatinine, ESR, BUN, high-sensitivity C-reactive protein, total protein, cholesterol, ferritin, C3, C4, IgA, HbA1c, hemoglobin, and immunoglobulin levels. eGFR was calculated using the CKD-EPI equation for subjects aged over 18 years, while the Schwartz formula was used for pediatric patients under 18. Proteinuria was assessed using UPCr assays. All biopsies were reviewed by a single pathologist who is an expert in renal pathology, with over 20 years of experience. This ensured a consistent and thorough evaluation of the histopathological findings. Renal pathology findings were evaluated for mesangial cell proliferation, matrix expansion, tubular necrosis, crescent formation, glomerulosclerosis, and arterial changes. Data were quantified

Table 1 The Key Clinical Definitions

Clinical Definitions	
Nephrotic Syndrome (NS)	Proteinuria > 3.5 g/day in adults or Protein-creatinine ratio (PCR) > 2 g/g (or 200 mg/mmol) or > 3+ protein in urine dipstick in Children. Hypoalbuminemia (serum albumin < 30 g/l) Edema
Nephrotic range proteinuria	Proteinuria > 3.5 g/day in adults or Protein-creatinine ratio (PCR) > 2 g/g (or 200 mg/mmol) or > 3+ protein in urine dipstick in Children without hypoalbuminemia or edema
Complete Remission (CR)	Normalization of serum albumin (> 30 g/l) Reduction of proteinuria <0.3 g/d in adults or protein-creatinine ratio (PCR) < 200 mg/g (or < 20 mg/mmol) or negative or trace urine dipstick
Partial Remission (PR)	Reduction of proteinuria < 3.5 g/day but > 0.3 g/day in adult, or protein-creatinine ratio < 2g/g but > 200 mg/g (or <200 mg/mmol but >20) in children
Relapse	Recurrence of nephrotic range proteinuria after achieved remission
Clinical Responses to Steroid Therapy	
Steroid Sensitive Nephrotic Syndrome (SSNS)	Patients who achieved complete remission after at least 4 weeks of prednisolone at standard doses in children and at least 8 weeks in adults
Steroid Resistant Nephrotic Syndrome (SRNS)	Patients who achieved no remission after at least 4 weeks of treatment with prednisolone at standard doses in children and at least 8 weeks in adults
Steroid Dependent Nephrotic Syndrome (SDNS)	Patients who achieved complete remission during the treatment but relapsed when the dose was reduced or within 2 weeks of stopping the steroid

and categorized using a standardized grading system. Validation of IF grading (1+ to 3+) was done, and tonsil tissue utilized as a positive control.

Ethical Approval

Ethical approval was sought from the institutional review board, and the study adhered to the Declaration of Helsinki. Participant confidentiality was maintained in all stages, with ethical approval's number E-24-8590 dated on March 04, 2024.

Statistical Analysis

The Shapiro–Wilk test was applied to assess the distribution of continuous data, indicating a non-normal distribution. Therefore, it was presented as the median with the interquartile range (IQR) and compared using the Mann–Whitney *U*-test. Categorical variables were expressed as percentages and compared using Fisher's exact test. Survival analysis was performed using the Kaplan-Meier curve with the Log rank test. Statistical significance was determined at an alpha level of 0.05. Data analysis and visualizations were performed using Stata version 15.1 and GraphPad Prism version 10.0.

Results

A total of 15 patients (n=15) with biopsy-proven IgM nephropathy were analyzed in this study. The demographic characteristics are summarized in Table 2, which has been reformatted into sub-tables for clarity. The median age at diagnosis was 4 years (IQR: 2–8), with a mean age of 5.0 ± 3.2 years. The cohort exhibited a notable male predominance (80%, n=12). Patients were categorized into early childhood onset (<4 years, 46.7%, n=7) and late childhood onset (≥ 4 years, 53.3%, n=8) groups for comparative analysis.

Table 2 Baseline Characteristics of Patients with IgM Nephropathy are Divided Based on the Age of Onset

	Total	Age of Onset		p-value
		Early Childhood (<4 Years)	Late Childhood (≥4 Years)	
	15	7 (46.7%)	8 (53.3%)	
Age of diagnosis, year	4 (2–8)	2 (2–3)	6.5 (4.5–11)	<0.01
Current age, year	18 (12–25)	12 (10–24)	21 (14.5–25.5)	0.16
Gender, male	12 (80%)	5 (71.4%)	7 (87.5%)	0.57
Smoking	2 (13.3%)	0 (0%)	2 (25%)	0.47
Presenting symptom(s)				
Asymptomatic hematuria	2 (13.3%)	0 (0%)	2 (25%)	0.47
Asymptomatic proteinuria	6 (40%)	2 (28.6%)	4 (50%)	0.61
Nephrotic syndrome	14 (93.3%)	7 (100%)	7 (87.5%)	1.00
RPGN	(0%)	(0%)	(0%)	
AKI	2 (13.3%)	0 (0%)	2 (25%)	0.47
Nephrotic range proteinuria	14 (93.3%)	7 (100%)	7 (87.5%)	1.00
Generalized body swelling	10 (66.7%)	5 (71.4%)	5 (62.5%)	1.00
Lower limbs edema	15 (100%)	7 (100%)	8 (100%)	
Proceeded by URTI	3 (20%)	1 (14.3%)	2 (25%)	1.00
Frank hematuria	1 (6.7%)	0 (0%)	1 (12.5%)	1.00
Medications at time of biopsy				
NSAID	(0%)	(0%)	(0%)	
Anti-HTN	2 (13.3%)	1 (14.3%)	1 (12.5%)	1.00
Immunosuppression	9 (60%)	5 (71.4%)	4 (50%)	0.61
Anti-rheumatoid	1 (6.7%)	1 (14.3%)	0 (0%)	0.47
None	4 (26.7%)	1 (14.3%)	3 (37.5%)	0.57
Others	5 (33.3%)	2 (28.6%)	3 (37.5%)	1.00
Labs at baseline				
Urine RBCs (/hpf)				
0–2	5 (33.3%)	2 (28.6%)	3 (37.5%)	1.00
3–10	4 (26.7%)	2 (28.6%)	2 (25%)	
>14	3 (20%)	1 (14.3%)	2 (25%)	
Not done	3 (20%)	2 (28.6%)	1 (12.5%)	
Urine WBCs (/hpf)				
0–2	4 (26.7%)	1 (14.3%)	3 (37.5%)	0.75
3–10	3 (20%)	2 (28.6%)	1 (12.5%)	
>14	5 (33.3%)	2 (28.6%)	3 (37.5%)	
Not done	3 (20%)	2 (28.6%)	1 (12.5%)	

(Continued)

Table 2 (Continued).

	Total	Age of Onset		p-value
		Early Childhood (<4 Years)	Late Childhood (≥4 Years)	
Urine protein*				
Nil	1 (6.7%)	0 (0%)	1 (12.5%)	0.54
+	2 (13.3%)	0 (0%)	2 (25%)	
++	3 (20%)	2 (28.6%)	1 (12.5%)	
+++	5 (33.3%)	2 (28.6%)	3 (37.5%)	
++++	4 (26.7%)	3 (42.9%)	1 (12.5%)	
ACR (n=6)	295.1 (35.2–2642.2)	478.1 (35.2–2642.2)	112.1 (3.4–15,134.3)	0.83
PCR (n=5)	14.2 (0.5–25.2)	14.2 (0.5–75.1)	12.8 (0.3–25.2)	0.56
Serum creatinine (μmol/L)	39 (19–50)	30 (18–44)	44 (35–88)	0.12
Estimated GFR	161.2 (114–255)	162.9 (134–279)	138.2 (181.4–176.7)	0.20
BUN (mmol/L)	4 (2.8–6.4)	3.8 (2.7–6.2)	4.5 (2.9–7.3)	0.35
Serum albumin (gm/L)	16 (10–31.2)	15 (9–18)	26 (12.5–35.6)	0.13
Total protein (g/l)	47 (38–62)	44 (35–49)	48.5 (42.5–70)	0.15
WBC (x10⁹/L)	9.3 (6.6–13.8)	11.7 (10.6–15.2)	7.3 (5.8–9.2)	0.03
Hb (gm/L)	130 (116–158)	130 (121–159)	136.5 (110.5–149)	0.42
Platelets (x10⁹/L)	339 (256–414)	347 (257–533)	305 (234–388)	0.30
Sodium (mmol/L)	138 (134–139)	138 (134–139)	138.5 (128.5–140.5)	0.60
Potassium (mmol/L)	4.2 (4.1–4.6)	4.3 (3.8–4.6)	4.2 (4.1–4.7)	0.95
dsDNA (n=7)	6.6 (3.8–11.9)	4.4 (1.3–6.6)	9.3 (5.3–97.4)	0.16
C3 (n=12)	1.3 (1.0–1.7)	1.5 (1.2–1.8)	1.2 (1.0–1.4)	0.20
C4 (n=11)	0.3 (0.3–0.3)	0.3 (0.3–0.4)	0.3 (0.3–0.3)	0.47
PR3 (n=4)	1.0 (0.7–1.2)	1.1 (0.9–1.4)	0.8 (0.5–1.1)	0.44
MPO (n=4)	0.8 (0.7–0.9)	0.9 (0.7–1.0)	0.7 (0.7–0.8)	0.44
ASO (n=4)	15.1 (13.6–18.3)	13.6 (13.6–13.6)	18.3 (16.5–20)	0.10
Total cholesterol (n=11) (mmol/L)	7.9 (6.5–12.2)	9.1 (7.9–12.2)	6.6 (4.5–10.7)	0.20
LDL (n=10) (mmol/L)	5.3 (4.4–8.8)	7.3 (5.2–8.9)	4.6 (2.8–8.7)	0.29
HDL (n=10) (mmol/L)	1.6 (1.3–2.0)	2.1 (1.6–2.5)	1.5 (1.1–1.6)	0.14
TG (n=10) (mmol/L)	1.5 (0.9–3.2)	3.2 (2.4–3.8)	1.1 (0.8–1.3)	0.02

Notes: *+ indicates 0.2–0.5 grams of urine protein/ 24 hours, ++ indicates 0.5–1.5 grams of urine protein/ 24 hours, +++ indicates 2.0–5.0 grams of urine protein/ 24 hours, ++++ indicates > 5.0 grams of urine protein/ 24 hours. Values in bold are statistically significant.

The most prevalent initial clinical manifestations included nephrotic syndrome (93.3%) and lower limb edema (100%), followed by generalized body swelling in 66.7% of cases. Notably, 20% of cases were preceded by upper respiratory tract infection, and no patients presented with rapidly progressive glomerulonephritis (RPGN). Asymptomatic proteinuria was observed in 40% of patients, with a higher prevalence in the late-onset group (50% vs 28.6%).

Relapse was defined as the recurrence of nephrotic-range proteinuria after achieving remission. Laboratory parameters at baseline revealed significant differences between early and late childhood onset groups. Patients with early-onset disease had significantly higher white blood cell counts (11.7 vs $7.3 \times 10^9/L$, $p=0.03$) and triglyceride levels (3.2 vs 1.1 mmol/L, $p=0.02$). Nephrotic-range proteinuria was observed in 93.3% of patients, with similar rates between early and late onset groups (100% vs 87.5%, $p=NS$). Baseline renal function was preserved in most patients, with a median estimated GFR of 158 mL/min/1.73m² (IQR: 145–215).

Renal biopsy findings are summarized in Table 3, with detailed immunological findings presented in Table 4. Biopsy reports were available for 14 patients (93%), while 60% had complete reports. The implications of missing data may limit the comprehensiveness of our findings. Mesangial proliferation was the predominant finding in 64.3% of biopsies, with markedly higher prevalence in the early-onset group (85.7% vs 42.9%, $p=0.27$). Immunofluorescence studies demonstrated moderate (++) IgM staining in 85.7% of patients and strong (+++) staining in 14.3% of patients. Staining methods included both qualitative and semi-quantitative assessments. Podocyte effacement patterns were

Table 3 Kidney Biopsy Findings of Patients with IgM Nephropathy

	Total	Age of Onset		p-value
		Early Childhood (<4 Years)	Late Childhood (≥4 Years)	
	15	7 (46.7%)	8 (53.3%)	
Renal Biopsy				
Yes	14 (93.3%)	7 (100%)	7 (87.5%)	1.00
No	1 (6.7%)	0 (0%)	1 (12.5%)	
Biopsy findings (n=14)	14	7	7	
Mesangial Expansion	5 (35.7%)	1 (14.3%)	4 (57.1%)	0.27
Mesangial Proliferation	9 (64.3%)	6 (85.7%)	3 (42.9%)	0.27
Segmental Sclerosis	1 (7.1%)	1 (14.3%)	0/7	1.00
Global Sclerosis	6 (42.9%)	3 (42.9%)	3 (42.9%)	1.00
IFTA				
<10%	10 (71.4%)	5 (71.4%)	5 (71.4%)	1.00
10–25%	4 (28.6%)	2 (28.6%)	2 (28.6%)	
IgM Staining**				
++	12 (85.7%)	6 (85.7%)	6 (85.7%)	1.00
+++	2 (14.3%)	1 (14.3%)	1 (14.3%)	
IgG Staining	1 (7.1%)	1 (14.3%)	0/7	1.00
IgA Staining	2 (14.3%)	1 (14.3%)	1 (14.3%)	1.00
C1q	0/14	0/7	0/7	
Albumin Staining	0/14	0/7	0/7	
Kappa Staining	6 (42.9%)	2 (28.6%)	4 (57.1%)	0.59
Lambda Staining	3 (21.4%)	1 (14.3%)	2 (28.6%)	1.00
Podocyte Effacement				

(Continued)

Table 3 (Continued).

	Total	Age of Onset		p-value
		Early Childhood (<4 Years)	Late Childhood (≥4 Years)	
None	2 (14.3%)	0/7	2 (28.6%)	0.59
Diffuse	5 (35.7%)	3 (42.9%)	2 (28.6%)	
Partial	7 (50%)	4 (57.1%)	3 (42.9%)	
Mesangial Dense Deposits	10 (71.4%)	5 (71.4%)	5 (71.4%)	1.00
Other Deposits	7 (50%)	3 (42.9%)	4 (57.1%)	1.00
Medications after biopsy (n=15)	15	7	8	
RAAS Blockade	4 (26.7%)	3 (42.9%)	1 (12.5%)	0.28
Statins	5 (33.3%)	2 (28.6%)	3 (37.5%)	1.00
SGLT2 Inhibitors	0/15	0/7	0/8	
Pulse Steroids	1 (6.7%)	1 (14.3%)	0/8	0.47
Oral Steroids	13 (86.7%)	7 (100%)	6 (75%)	0.47
Calcineurin Inhibitors	4 (26.7%)	3 (42.9%)	1 (12.5%)	0.28
Mycophenolate Mofetil	2 (13.3%)	2 (28.6%)	0/8	0.20
Rituximab	4 (26.7%)	3 (42.9%)	1 (12.5%)	0.28

Notes: **Score for the intensity of staining on IF study: ++ (moderate); +++ (severe).

graded, with partial effacement being the most common (50%), followed by diffuse effacement (35.7%) and no effacement (14.3%).

Therapeutic interventions detailed in Table 3 show oral steroids as the primary therapeutic approach in 86.7% of patients, with higher utilization in the early-onset group (100% vs 75%, $p=0.47$). Second-line therapies included calcineurin inhibitors (26.7%), rituximab (26.7%), RAAS blockade (26.7%), and mycophenolate mofetil (13.3%). Notably, immunosuppressive agents were used more frequently in the early-onset group, particularly mycophenolate mofetil (28.6% vs 0%) and calcineurin inhibitors (42.9% vs 12.5%, $p=0.28$), suggesting a more aggressive treatment approach was needed for younger patients.

Immunological serological analysis (Table 4) showed variable patterns across patients. Four patients (26.7%) had positive ANA titers (1:40 to 1:320), while all tested patients had negative anti-dsDNA antibodies despite some elevated levels (range 1.14–183.2). Complement levels (C3, C4) were normal in all tested patients, supporting the primary nature of IgM nephropathy in this cohort rather than secondary to lupus or other autoimmune conditions.

Treatment outcomes are presented in Tables 5 and 6, showing an overall relapse rate of 93.3%, with patients experiencing a median of 3 relapses (IQR: 2–5) during the follow-up period. The treatment response categories included steroid-resistant (33.3%), steroid-dependent (26.7%), and steroid-sensitive (13.3%), with the early-onset group showing markedly higher rates of steroid resistance (57.1% vs 12.5%). Significantly, patients with early-onset disease experienced more frequent relapses than the late-onset group (median 5 vs 2, $p=0.01$), with a median time to first relapse of 6.1 years (IQR: 0.8–13.3) across the entire cohort.

The overall relapse rate was remarkably high at 93.3%, with patients experiencing a median of 3 relapses (IQR: 2–5) during a median follow-up period of 9.4 years (IQR: 7.5–21.3). Patients with early-onset disease experienced more frequent relapses than the late-onset group (median 5 vs 2, $p=0.01$), suggesting a more aggressive disease course in younger patients. The median time to first relapse was 6.1 years (IQR: 0.8–13.3), with no significant difference between early and late onset groups (3.3 vs 8.8 years, $p=NS$).

Table 4 Immunological Serology of the Patients

Patient Serial No.	Date of Biopsy	Immunological Serology												
		ANA	DsDNA	C ₃	C ₄	IgA	IgG	IgM	PR ₃	MPO	ASO	SPEP	UPEP	Bence Jones Protein
1	9-Jan-2024	1:320 (+)	183.2 (-)	0.99 normal	0.32 normal	4.7 ↑	3.08 ↓	1.04 normal	0.53 (-)	0.67 (-)	20 (-)	N/A	Negative(-)	Negative(-)
2	18-Jan-2018	(-)	3.83 (-)	1.38 normal	0.33 normal	1.48 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	19-Apr-2018	(-)	1.25 (-)	1.30 normal	0.19 normal	N/A	N/A	N/A	1.36 (-)	1.02 (-)	13.6 (-)	N/A	N/A	N/A
4	30-Apr-2018	(-)	4.85 (-)	0.78 ↓	0.08 ↓	N/A	N/A	N/A	0.92 (-)	0.72 (-)	N/A	N/A	N/A	N/A
5	25-Jan-2024	(-)	1.14 (-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
6	1-Nov-2016	1:80 (+)	8.34 (-)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
7	30-Nov-2023	1:80 (+)	6.18 (-)	1.16 normal	0.28 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
8	13-Dec-2020	N/A	N/A	N/A	N/A	1.00 normal	5.37 ↓	0.72 normal	N/A	N/A	N/A	N/A	N/A	N/A
9	15-Oct-2017	(-)	6.61 (-)	1.26 normal	0.35 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
10	6-Apr-2017	(-)	6.79 (-)	1.62 normal	0.29 normal	2.57 normal	5.87 ↓	2.76 normal	N/A	N/A	N/A	N/A	N/A	N/A
11	14-Jul-2016	1:40 (-)	7.91 (-)	1.16 normal	0.27 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
12	6-Jun-2016	(-)	11.85 (-)	0.62 ↓	0.19 normal	1.82 normal	9.47 normal	1.38 normal	1.09 (-)	0.78 (-)	N/A	N/A	N/A	N/A
13	3-May-2016	(-)	7.81 (-)	1.06 normal	0.29 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
14	13-Mar-2016	1:40 (-)	13.86 (-)	1.43 normal	0.24 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
15	30-Aug-2021	1:80 (+)	24.14 (-)	1.46 normal	0.44 normal	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: ANA, Anti-nuclear Antibody; DsDNA, Double Standard DNA; C₃, Complement 3; C₄, Complement 4a; IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; PR₃, Anti-proteinase Antibody; MPO, Myeloperoxidase Antibody; ASO, Antistreptolysin O titer; SPEP, Serum Protein Electrophoresis; UPEP, Urine Protein Electrophoresis; N/A, Not Available.

Table 5 Outcomes of Patients with IgM Nephropathy

	Total	Age of Onset		p-value
		Early Childhood (<4 Years)	Late Childhood (≥4 years)	
	15			
Follow-up duration, years	9.4 (7.5–21.3)	9.4 (8.0–21.8)	9.0 (4.1–19.9)	0.30
Any relapse	14 (93.3%)	7 (100%)	7 (87.5%)	1.00
Number of relapses	3 (2–5)	5 (3–6)	2 (1–3)	0.01
Annualized relapse rates	0.42 (0.19–0.61)	0.37 (0.23–0.37)	0.49 (0.16–1.04)	0.68
Time to first relapse, years	6.1 (0.8–13.3)	3.3 (0.6–13.3)	8.8 (0.8–14.5)	0.75
Labs at last visit				
ACR (n=7)	6.2 (3.4–65.4)	65.4 (4.9–1315.2)	4.8 (2.4–9.3)	0.16
PCR (n=8)	4.1 (0.2–12.0)	6.6 (1.6–9.0)	0.2 (0.2–52.4)	0.46
Serum creatinine (μmol/L)	60 (44–92)	53 (42–109)	76 (51–89.5)	0.73
Estimated GFR	95.6 (65.5–126.4)	103 (57.7–126.4)	74.5 (66–121.8)	1.00
BUN (mmol/L)	4.3 (3.5–5.1)	4.7 (3.5–5.6)	4.1 (2.4–4.5)	0.20
Serum albumin (gm/L)	43.4 (42.5–44.9)	43.5 (42.5–44.9)	43.4 (41.9–45.2)	0.86
Total protein (g/l)	67.6 (65.5–69.8)	66.3 (65.2–67.6)	69.6 (67.4–71.4)	0.049
WBC (x10 ⁹ /L)	7.8 (6.2–9.3)	7.0 (5.8–8.3)	8.4 (7.3–9.3)	0.25
Hb (gm/L)	140 (123–153)	135 (116–144)	148 (132.5–158.5)	0.16
Platelets (x10 ⁹ /L)	291 (259–355)	301 (263–340)	277 (257–361)	0.77
Sodium (mmol/L)	140.1 (139.2–141)	139.7 (138.4–141.3)	140.8 (139.9–141)	0.42
Potassium (mmol/L)	4.4 (4.2–4.9)	4.2 (4.1–5.1)	4.5 (4.3–4.8)	0.73
Total cholesterol (n=10) (mmol/L)	4.4 (3.7–5.0)	4.4 (4.0–5.0)	4.3 (3.7–5.0)	0.83
LDL (n=10) (mmol/L)	2.5 (2.1–3.0)	2.4 (2.2–3.0)	2.6 (2.1–3.0)	0.75
HDL (n=10) (mmol/L)	1.3 (1.1–1.5)	1.5 (1.2–1.5)	1.2 (1.1–1.4)	0.52
TG (n=10) (mmol/L)	1.0 (0.8–1.1)	1.1 (1.0–1.3)	0.8 (0.6–1.1)	0.24
Patient's category				
Steroid sensitive	2 (13.3%)	0 (0%)	2 (25%)	0.41
Non-relapsing	1 (6.7%)	0 (0%)	1 (12.5%)	
Infrequent relapsing	1 (6.7%)	0 (0%)	1 (12.5%)	
Frequent relapsing	2 (13.3%)	1 (14.3%)	1 (12.5%)	
Steroid dependent	4 (26.7%)	2 (28.6%)	2 (25%)	
Steroid resistant	5 (33.3%)	4 (57.1%)	1 (12.5%)	

Notes: Values in bold are statistically significant.

Table 6 Treatment Course of Patients with IgM Nephropathy

Patient Serial No.	First Treatment After Biopsy	Outcome After the Initial Treatment	Any Relapse & What is the Treatment & Outcome	Any Other Relapse & What is the Treatment & Outcome	Outcome of Last Follow-Up
1	Oral steroid only	CR	Yes → oral steroid + Ritux → CR	No	CR
2	Oral steroid + CNI	SRNS → Ritux	Yes → Pulse steroid + CNI lost follow up	Lost follow up	Lost follow up
3	Pulse steroid + oral steroid + Ritux for previous SRNS before biopsy	CR	Yes → oral steroid → CR	Yes → oral steroid → CR	CR
4	Oral steroid + CNI + Ritux for SRNS	CR	Yes → oral steroid → SDNS → Ritux → CR	No	CR
5	Oral steroid + MMF	CR	No	No	CR
6	Oral steroid	CR	Yes → oral steroid + Ritux → CR	No	CR
7	Oral steroid	CR	No	No	CR
8	Oral steroid + Ritux for SDNS	CR	Yes → oral steroid + MMF → CR	No	CR
9	Oral steroid + CNI for SRNS	CR	Yes → oral steroid + CNI → CR	Yes → oral steroid + Ritux → CR	CR
10	Oral steroid + CNI for SDNS	PR	Yes → oral steroid + CNI + Ritux → CR then CNI replaced by AZA	No	CR
11	Oral steroid + CNI for SRNS → PR then Ritux → PR	PR	Yes → oral steroid + pulse steroid + CNI + MMF → lost f/u	Lost f/u then progressed to ESKD	ESKD → Transplant with no recurrence
12	No treatment given	CR	No	No	Lost follow up
13	Oral steroid + MMF for SRNS	PR	Yes → Ritux + oral steroid + CNI + AZA → PR	Yes → biopsy repeated → FSGS → steroid + CYC + AZA + PLEX → PR	PR
14	Oral steroid + CNI for SDNS	CR	Yes → oral steroid + CNI → CR	Yes → steroid + CNI → PR Yes → steroid + CNI → CR Then Ritux for non-compliance + MMF → CR	Lost follow up, but CR in last follow up
15	Oral steroid + CNI	CR	No → but given Ritux for non-compliance → CR	No	Lost follow up

Abbreviations: CR, Complete remission; PR, Partial remission; GCs, Glucocorticoids; Ritux, Rituximab; CNI, Calcineurin inhibitors; MMF, Mycophenolate mofetil; CYC, Cyclophosphamide; AZA, Azathioprine; PLEX, plasma exchange; ESKD, End stage kidney disease; SDNS, Steroid Dependent Nephrotic Syndrome; SRNS, Steroid Resistant Nephrotic Syndrome.

Long-term follow-up laboratory data showed normalization of serum albumin (median 43.4 g/L) and improvement in lipid profiles in most patients. Total protein levels at last follow-up were significantly higher in the late-onset group (69.6 vs 66.3 g/L, $p=0.049$), while other biochemical parameters showed no significant differences between groups.

Kaplan-Meier analysis (Figure 1) illustrated the time to first relapse pattern between early and late disease onset groups, with late-onset disease showing a trend toward longer relapse-free intervals, though this did not reach statistical significance. Figure 2 depicts the rituximab treatment flow and outcomes, indicating that 4 patients received rituximab primarily for steroid-resistant or frequently relapsing disease. The predicted probability of relapses over time (Figure 3) demonstrated a progressive increase in relapse risk with longer disease duration, modeled using time-to-event analysis.

Subgroup analyses should be interpreted with caution due to the small sample size, which limits statistical power. Additionally, baseline steroid use may confound relapse rates, necessitating careful consideration in future studies.

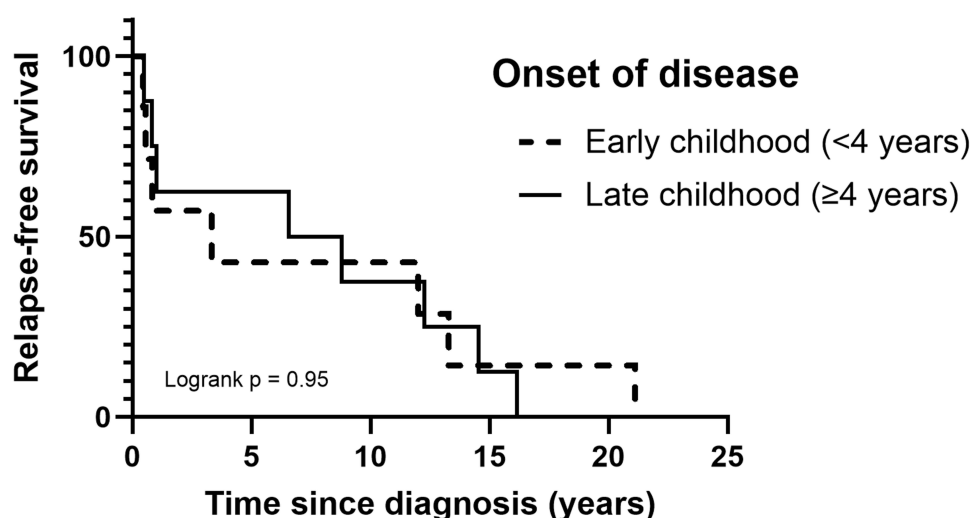


Figure 1 Kaplan-Meier curve showing the time to first relapse in patients with IgM nephropathy divided into early vs late disease onset.

Discussion

IgM nephropathy represents a distinct clinicopathological entity characterized by predominant mesangial IgM deposition and variable clinical presentations, including nephrotic and non-nephrotic proteinuria.¹² Our study aims to comprehensively investigate the clinical characteristics, histopathological features, treatment responses, and long-term outcomes of IgM nephropathy in a cohort of 15 Saudi patients. We also aim to stratify these findings by age of onset to reveal important prognostic implications. Our study provides comprehensive insights into the clinical characteristics, histopathological features, treatment responses, and long-term outcomes in a cohort of 15 Saudi patients, with stratification by age of onset revealing important prognostic implications.

The demographic profile of our cohort, with a median age of 4 years and male predominance (80%), aligns with existing literature indicating that IgM nephropathy primarily affects children and young adults, with males being more susceptible.^{4,13} The 4:1 male-to-female ratio observed in our study exceeds the typical 2:1 ratio reported in other populations,^{6,14} suggesting possible genetic or environmental factors unique to the Saudi population that may influence disease susceptibility.¹⁵

Our findings underscore the heterogeneity of clinical presentations in IgM nephropathy. Nephrotic syndrome was overwhelmingly common (93.3%), accompanied by universal lower limb edema (100%). However, the clinical course and treatment responses varied significantly between early and late-onset groups. Patients diagnosed before age 4 exhibited more frequent relapses and higher rates of steroid resistance compared to those diagnosed at or after age 4, indicating that early-onset disease may represent a more aggressive phenotype. This could necessitate more intensive immunosuppressive strategies from the outset. Furthermore, it is crucial to note that proteinuria classification plays a significant role in long-term renal function, where nephrotic proteinuria poses increased risks for chronic deterioration in renal health compared to non-nephrotic cases, which typically exhibit more stable renal function.

Patients with nephrotic syndrome excrete large amounts of protein in their urine, have swelling in various body parts due to fluid retention, have low levels of albumin in the blood, contribute to edema, and have increased cholesterol levels. They experience severe complications, including hypertension and a higher risk of thromboembolic events due to altered hemostatic parameters.^{4,16} The prognosis for patients with nephrotic syndrome can vary; some may respond well to corticosteroids, while others may have steroid-resistant disease.^{4,6} In contrast, non-nephrotic proteinuria is characterized by typically low levels of proteinuria (<3.5 g/d), without significant hypoalbuminemia, and maintains better renal function than those with nephrotic syndrome.¹⁷ Our cohort supports previous studies highlighting the need for differential treatment strategies between nephrotic and non-nephrotic presentations. Research indicates that a subset of patients with IgM nephropathy may present with non-nephrotic proteinuria without developing significant systemic complications.^{18,19} The latter group often has a more favorable prognosis compared to those with nephrotic syndrome. The clinical findings

13 PATIENTS RECEIVED RITUXIMAB DURING THE FOLLOW UP

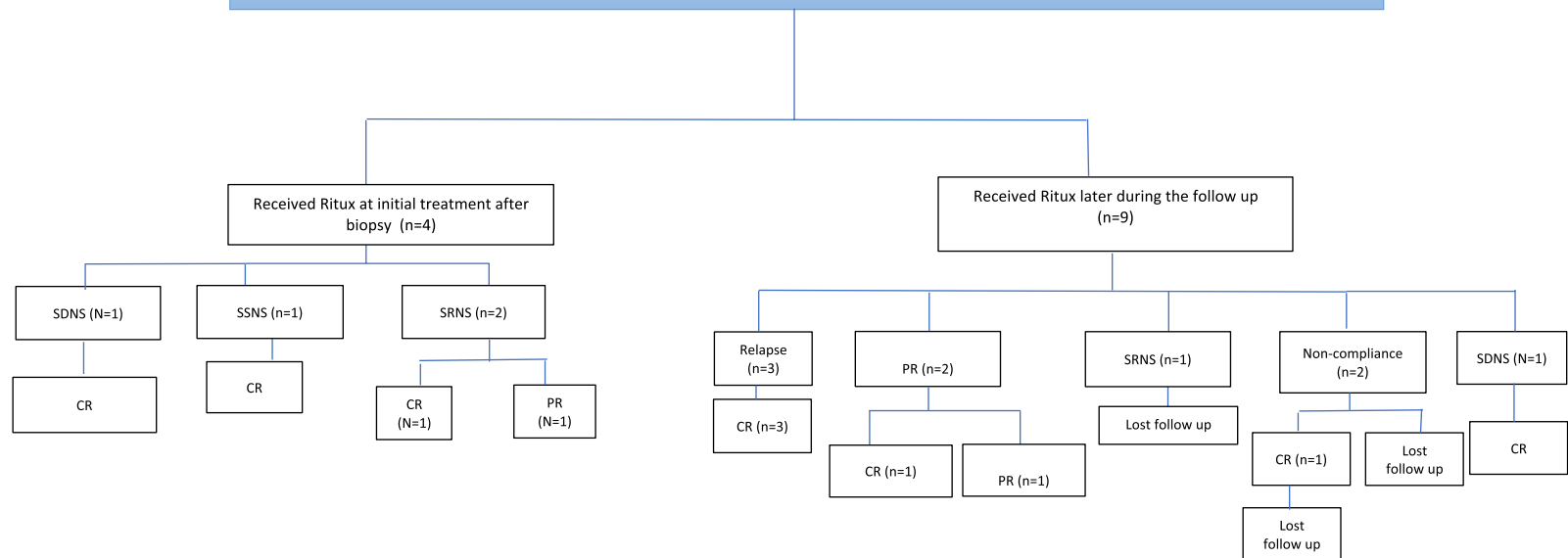


Figure 2 The flow diagram showing the rituximab treatment during the study.

Abbreviations: CR, Complete remission; PR, Partial remission; Ritux, Rituximab; SDNS, Steroid Dependent Nephrotic Syndrome; SRNS, Steroid Resistant Nephrotic Syndrome; SSND, Steroid Sensitive Nephrotic Syndrome.

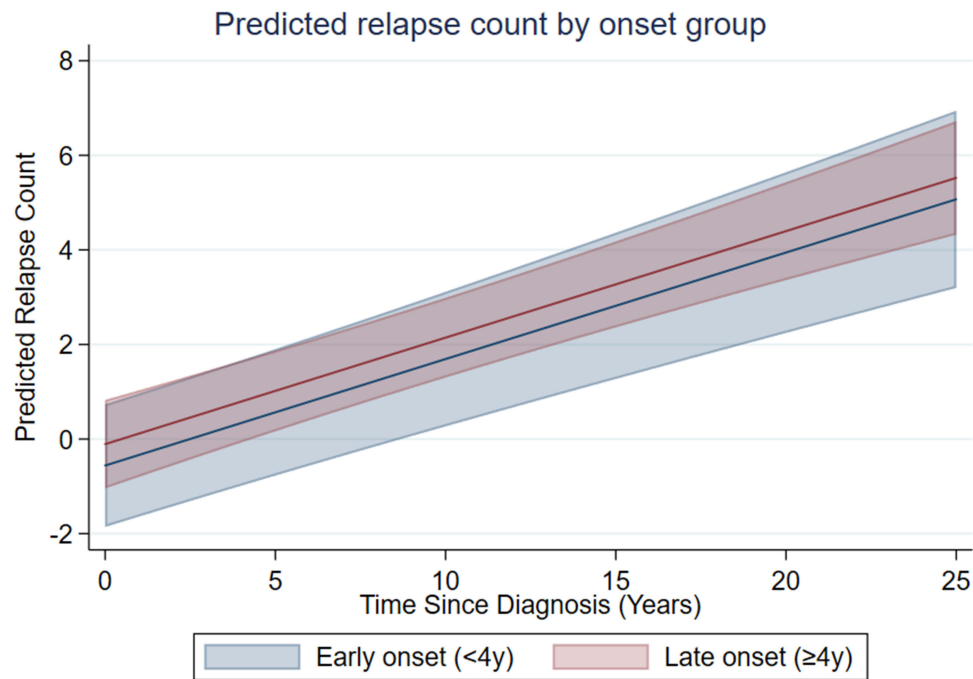


Figure 3 Predicted probability of relapses over time in patients with IgM nephropathy.

in our cohort matched the characteristics of the clinical presentation for these two groups. The differentiation between nephrotic and non-nephrotic proteinuria in IgM nephropathy is essential for guiding treatment strategies.¹⁶ The present study showed that nephrotic syndrome is linked to nephrotic range proteinuria and had a longer time to first relapse compared to non-nephrotic patients. Laboratory parameters at baseline, including urine RBCs and WBCs patterns, showed distinct distributions between nephrotic and non-nephrotic groups.

The histopathological findings in our cohort correspond with the classical descriptions of IgM nephropathy while revealing age-related differences. The prevalence of mesangial proliferation was twice as high in early-onset disease, providing a potential histological correlate for the clinical differences observed between these groups. The presence of global sclerosis in 44.4% of biopsies, despite the young age of our cohort, suggests a potentially progressive nature of the disease even in pediatric populations. This supports previous reports by Chae et al and Connor et al indicating that IgM nephropathy may follow a more aggressive course than previously recognized.

The most common histological finding in our biopsy, similar to the findings in Mokhtar et al's study,⁹ was glomerular mesangial proliferation (64.3%), while focal and segmental glomerulosclerosis was rare (7.1%). We also documented mild tubular atrophy with associated interstitial fibrosis in a few cases (28.6%). Diffused IgM deposition in the mesangium, with accompanying deposits of IgG and complement components, is a hallmark of IgM nephropathy.²⁰ This is typically observed as predominant staining for IgM, often accompanied by minor deposits of other immunoglobulins such as IgG and complement components.^{13,21} As for the immunofluorescence study, along with the strong diffuse mesangial IgM staining, we too had a few cases that exhibited mild mesangial staining with IgG (7.1%), IgA (14.3%), Kappa (42.09%), and Lambda (21.4%), which is similar to findings from the previous report in the Saudi population.⁹ Histological examination often reveals varying degrees of mesangial cell proliferation. This can range from minimal changes to more pronounced hypercellularity, which may be a precursor to more severe forms of glomerular damage.^{13,14}

The electron microscopy (EM) study demonstrated corresponding mesangial electron-dense immune deposits in most of our samples (71.4%), which confirms the earlier reports from Saudi Arabia.⁹ Other characteristic histopathological features found in our population were global sclerosis, mild interstitial fibrosis, and tubular atrophy. A significant proportion of patients may show features of global sclerosis, particularly upon repeat biopsy. In studies, up to 80% of patients undergoing subsequent biopsies were diagnosed with global sclerosis, which was also common in our cohort, indicating a potential transition from initial mesangial deposition to more advanced glomerular scarring.^{6,13}

Podocyte injury manifests as foot process effacement (FPE), a key pathological feature observed in renal biopsies. The varying podocyte effacement patterns observed in our study, with partial effacement predominating (55.6%), reflect the spectrum of podocyte injury in IgM nephropathy. Interestingly, the distribution of effacement patterns differed between age groups, with no instances of normal foot processes in the early-onset group compared to 33.3% in the late-onset group. This may explain the greater severity of proteinuria and relapse frequency in younger individuals, potentially influenced by factors such as genetic predisposition, developmental immaturity, and immune responses. This subtle difference highlights the need for larger studies to confirm this relationship. The degree of podocyte foot effacement observed in renal biopsies can correlate with clinical outcomes. Patients with extensive podocyte foot effacement may experience more severe proteinuria and a higher risk of progression to chronic kidney disease. However, some studies suggest that even significant podocyte foot effacement does not always equate to irreversible damage if the underlying cause is addressed effectively.^{22,23} Histopathological features were found to be linked with disease progression, particularly interstitial fibrosis and tubular atrophy (IFTA) severity.^{24,25}

Treatment responses in our cohort highlight the challenges in managing IgM nephropathy, particularly in early-onset disease. The overall steroid resistance rate of 33.3% and steroid dependence in 26.7% underscore the limitations of conventional steroid monotherapy. The markedly higher steroid resistance in early-onset disease (57.1% vs 12.5%) emphasizes the need for age-stratified treatment approaches and earlier consideration of steroid-sparing agents in younger patients. Analysis of second-line therapies reveals intriguing patterns. Calcineurin inhibitors, rituximab, and RAAS blockade were each utilized in 26.7% of patients, with higher usage of all three modalities in the early-onset group. This suggests that clinicians recognized the need for more aggressive therapy in younger patients, though we must reiterate that the limited sample size in our study negatively impacts our ability to draw definitive conclusions regarding the comparative efficacy of these interventions, particularly for rituximab's role in treatment. Furthermore, a significant limitation of our study is the lack of a control group, which limits the strength of our findings. Additionally, the lack of repeat biopsies in most patients represents another weakness that should be addressed in future investigations.

The role of rituximab in managing refractory IgM nephropathy deserves special consideration. Rituximab is a monoclonal antibody that targets CD20 on B cells and has emerged as a promising treatment option. Studies indicate that rituximab can lead to complete remission in some patients, particularly when used in combination with other agents like mycophenolate mofetil. In pediatric cases, combination therapy resulted in sustained remission for up to 30 months.^{26,27} In our cohort, rituximab was employed in patients with steroid-resistant or frequently relapsing disease. While our limited sample size precludes definitive efficacy assessments, recent case reports have demonstrated complete proteinuria remission and kidney function stabilization with rituximab in patients who failed other immunosuppressive agents. Betjes et al reported complete resolution of symptoms after two doses of rituximab in an adult patient with IgM nephropathy unresponsive to conventional therapy.²⁷ Similarly, Faroque et al described successful treatment of steroid-resistant IgM nephropathy with rituximab.²⁸ Our experience aligns with these reports, suggesting that rituximab may offer a valuable therapeutic option for refractory IgM nephropathy, particularly in early-onset disease with higher relapse rates. Given the high relapse rate of 93.3% observed in our cohort, this underscores the urgent need for more aggressive treatment strategies and closer patient monitoring to mitigate the risks of progression and complications. While further research is necessary to establish long-term efficacy and safety, current evidence supports rituximab's role in managing IgM nephropathy in adults.^{26,29}

Calcineurin inhibitors have also been reported to have a role in managing IgM nephropathy, particularly for patients resistant to other treatments.^{7,21} Recent evidence suggests that combining rituximab with mycophenolate mofetil may enhance treatment efficacy. This approach has demonstrated effectiveness in sustaining remission after initial treatment with rituximab.^{6,26} Analysis of rituximab in our cohort outcomes showed that treated patients experienced higher numbers of relapses but showed shorter times to first relapse, suggesting a potential role in managing more aggressive disease presentations.

The long-term outcomes in our cohort reveal a strikingly high relapse rate (93.3%) over a median follow-up of 9.4 years, underscoring the chronic, relapsing nature of IgM nephropathy. This high rate of relapse points to a critical need for proactive and aggressive therapeutic interventions, which may include both immunosuppressive therapies and ongoing surveillance to better manage this challenging disease. These findings indicate the importance of ongoing monitoring and tailored treatment plans for individuals with this condition. The significantly higher number of relapses in the early-onset group reinforces the concept of age-dependent disease phenotypes. Despite the frequent relapses, renal function remained relatively preserved in most patients (median eGFR 132 mL/min/1.73m²), with normalization of serum

albumin (median 43.4 g/L) and improvement in lipid profiles, suggesting that appropriate management can prevent progression to end-stage kidney disease in many cases.

The laboratory findings at last follow-up provide additional insights into the long-term disease course. The significantly higher total protein levels in the late-onset group (69.6 vs 66.3 g/L, $p=0.049$) suggest potentially better recovery of protein synthesis in these patients, though the clinical significance remains uncertain. The normalization of cholesterol levels (median 4.4 mmol/L) across both groups indicates effective management of the dyslipidemia associated with nephrotic syndrome. Overall, our study reaffirms the complexity of IgM nephropathy, highlighting the critical need for individualized treatment strategies based on age of onset and clinical presentation. The emphasis on pursuing future work through a prospective, multi-center cohort study design could provide more comprehensive insights and validation of the findings presented here, addressing some of the limitations we encountered.

Conclusions

This descriptive study from Saudi Arabia provides important insights into IgM nephropathy in Middle Eastern populations. Our findings suggest that age of onset is a critical prognostic indicator, with early-onset disease linked to a more aggressive clinical course and higher rates of relapse needing closer relapse monitoring. These results highlight the urgent need to develop treatment protocols for IgM nephropathy, particularly considering the potential role of rituximab in refractory cases, which warrants evaluation in prospective studies. Additionally, patients with nephrotic range proteinuria experience a longer time to first relapse, while mesangial proliferation, expansion, and global sclerosis are the predominant pathological findings. Implementing tailored treatment strategies based on these findings can enhance long-term outcomes for Saudi patients. Future studies should include diverse cohorts to further elucidate the clinical characteristics of IgM nephropathy and improve treatment protocols.

Data Sharing Statement

Data is available with the corresponding author upon reasonable request.

Abbreviations

CR, complete response; MMF, mycophenolate mofetil; CNI, calcineurin inhibitor; F/U, follow-up; PR, partial remission; SRNS, steroid-resistant nephrotic syndrome; Ritux, rituximab; SSNS, steroid-sensitive nephrotic syndrome; SDNS, Steroid steroid-dependent nephrotic Syndrome.

Ethics Approval: Consent to Participate

This retrospective study was approved by the Institutional Review Board at King Saud University (KSUMC), Riyadh, Saudi Arabia, under approval number E-24-8590, approved on March 04, 2024. Because this is a retrospective study, the KSUMC ethics committee/institutional review board waived the requirement for informed consent, and all identifying information was removed to protect patients' confidentiality. The study was conducted in accordance with the Helsinki Declaration and local institutional standards.

AI Declaration

The generative Ai tool (ChatGPT-4o mini) was used for proofreading, polishing grammar, transitions, and sentence structures. The authors take full responsibility for the accuracy of the information and reviewed and approved the edited text.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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