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Fibrillary Glomerulonephritis: Clinicopathological Characteristics and Outcome—Case Series From a Multicentre Australasian Cohort

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ABSTRACT

Aim: Fibrillary glomerulonephritis (FGN) is a rare deposition disease with unclear aetiology. There are limited case series of FGN described in the literature. Here, we describe the clinicopathological characteristics and outcomes of a series of 26 patients with FGN diagnosed at an Australian tertiary centre for renal diseases over a decade.

Method(s): The present study includes 26 patients with biopsy-proven FGN diagnosed between January 2011 and December 2021.

Results: The average age at presentation was 60 years, with a female predominance. The mean creatinine at presentation was 205 μmol/L. Most of the patients had significant proteinuria, with an average 24-h urine protein of 3.76 g. Associated conditions included four patients with autoimmune disease, one patient with malignancy, and two patients with Hepatitis C infection. Serum electrophoresis demonstrated monoclonality in three patients, although immunofluorescence did not reveal clonal restriction on the renal biopsy. Most patients had mesangial expansion, with an increase in mesangial cellularity and variable degrees of capillary wall thickening. An established membranoproliferative pattern was seen in 10 patients. The median follow-up period was 33 months. Three patients received therapy targeted at FGN. End-stage kidney disease developed in 10 patients, with 6 patients dying during the follow-up period, mostly due to additional cardiovascular disease or sepsis.

Conclusion: This case series of FGN demonstrates that a significant proportion of patients progress towards end-stage kidney disease. The mortality is significant although the cause of death is due to additional conditions rather than directly due to FGN.

1 | Background

Fibrillary glomerulonephritis (FGN) is a rare type of glomerular disease initially described in 1977 [1]. It was initially described as an amyloid-like deposit in the glomerulus, which did not stain with the typical amyloid stains. This was subsequently characterised by Duffy et al. who published a series of 8 patients presenting with proteinuria, haematuria, hypertension, and renal dysfunction with glomerular deposition of fibrils measuring 20 nm in width [2]. It is characterised by the glomerular

deposition of randomly oriented straight fibrils which lack a hollow centre at < 30 000 magnification, measure 12–24 nm in size, and demonstrate a positive stain for IgG [3, 4]. A highly sensitive and specific tissue marker named DNAJB9 has been identified as a marker for FGN, with 98% of cases demonstrating abundant DNAJB9 protein [5]. DNAJB9 is a member of the DNAJ family of proteins, which act as co-chaperones for the heat shock protein family members. The heat shock protein family members in the endoplasmic reticulum (ER) are involved in the folding-unfolding of proteins. Hence, increased expression of DNAJB9 may be an expression of ER stress [6]. A small proportion demonstrating a congophilic pattern has been described by Alexander et al. [7]. There is a slightly higher proportion of patients demonstrating a slightly smaller mean fibril size among congophilic FGN compared to congo-negative FGN, although the clinical outcomes are not different [3]. DNAJB9 is instrumental in accurately diagnosing FGN in those patients with congophilic FGN and distinguishing it from amyloidosis, as therapy is different in both conditions. The deposits are predominantly seen in the mesangium and basement membrane, with occasional extension into the subendothelial and subepithelial regions and capillary walls. These deposits present with different morphological patterns. There are five main morphological presentations of FGN including mesangial proliferative, membranoproliferative, diffuse proliferative, membranous and diffuse sclerotic [6]. These fibrils consist of immunoglobulin deposits due to their intense staining with IgG, C3, κ and λ with 5% of cases demonstrating selectivity for either κ or λ [6]. However, cases of immunoglobulin-negative FGN have been reported [8]. The pathophysiology of FGN is unclear, and the renal prognosis is poor. The prognosis depends on the morphological pattern, with the mesangioproliferative pattern doing better than other presentations and the membranoproliferative pattern or diffuse sclerosing pattern having a poor outcome. Cohen and Vilayur have previously described a case series from Australia where they described a poor renal prognosis for patients with this diagnosis unless they had minimal proteinuria at presentation [9]. An ANZDATA registry analysis revealed comparable patient survival in patients with FGN on dialysis and post-transplant in Australia [10]. Our review aims to update the data on fibrillary glomerulonephritis in Australasia from a wide demographic area and present a review of the clinicopathological features and outcomes of patients diagnosed with FGN from a single Australian tertiary referral centre over a decade. Our centre provides renal pathology services to Western Sydney, Greater western Sydney, and the Central coast of New South Wales (NSW), comprising nearly 10 hospitals spread over a wide region; hence, cases are drawn from a wide area and many centres in the state of NSW.

2 | Materials and Methods

Kidney pathology results from our database from 2011 to 2021 were retrospectively reviewed for a diagnosis of FGN. All renal biopsies underwent light microscopy, immunofluorescence, and immediate electron microscopy assessment by the lead pathologist and a second pathologist. Light microscopy included haematoxylin and eosin stain, Masson's trichrome and Periodic acid-Schiff stain. Immunofluorescence was performed on frozen section (IF-F) was processed for selectivity against light chains, IgG, IgA, IgM, C3 and C1q on all cases, and on pronase digested paraffin sections [11] in one case (IF-P) with monotypic deposits on IF-F. DNAJB9 histochemistry was performed using Abcam antibody (ab251877) at 1:100 dilution. Most biopsy specimens satisfied the following criteria: (1) glomerular deposition of randomly oriented straight fibrils on electron microscopy with mean fibril size ranging from 12 to 27 nm, (2) lacked hollow centres at magnification < 30,000, (3) positive staining for DNAJB9, (4) stained with anti-sera to IgG by immunofluorescence on frozen section. In the absence of DNAJB9 staining, electron microscopic appearance was considered confirmatory for the diagnosis of fibrillary glomerulonephritis.

Clinical history, investigation results and follow up data were obtained from clinical records. Proteinuria was classified as nephrotic range or sub-nephrotic. Proteinuria was quantified by 24 h urinary protein excretion greater than 3.5 g/day or protein to creatinine ratio with a ratio > 300 mg/mmol or albumin to creatinine ratio > 250 mg/mmol being considered nephrotic range proteinuria. Kidney dysfunction was defined by a creatinine > 110 mmol/L. Progression of kidney disease was recorded by the last available serum creatinine or estimated glomerular filtration rate (eGFR) and progression to end stage kidney disease (ESKD). Autoimmune disease was defined as a clinically diagnosed disorder involving at least one system with or without the presence of positive serology. The Institution review board and the Hospital Ethics Committee approved the study (2021PID01567) and it was conducted in accordance with the declaration of Helsinki.

3 | Results

A total of 27 cases of FGN were diagnosed among 6196 renal biopsies (0.44%) accessioned during the study period. One case was a post-transplant recurrence diagnosed 10 years prior and was excluded from the study, and the rest of the 26 cases were included for further analysis. Details are presented in Tables 1–4 and Figures 1–6.

3.1 | Clinical Features

More than half (15/26) of patients were female (Table 1). Ethnicity data were not available for all patients. However, from the available data, they were predominantly white (11/15). The mean age of diagnosis was 60 years (range 39–81). Coexistent conditions included Hepatitis C (2/26), diabetes mellitus type 2 (5/26), autoimmune disease (4/26), prostate cancer (1/26), cardiovascular and cerebrovascular disease (6/26). Among patients with autoimmune disorders, one patient had an undefined autoimmune disorder as further information was unavailable from clinical data, one patient had inflammatory bowel disease and reactive arthritis, one patient had rheumatoid arthritis, and one patient had seronegative arthritis. One of the six patients with cardiovascular disease also had myelodysplastic syndrome.

One patient had monoclonal gammopathy of uncertain significance (MGUS) with a kappa/lambda light chain ratio of 39, and bone marrow showed 2% plasma cells with monoclonal kappa restriction. This patient also had limited CMML (CMML-0) disease and received Bortezomib for the same

TABLE 1 | Baseline characteristics and medical conditions associated with patients presenting with fibrillary glomerulonephritis.

Clinical features	
Female:male ratio	15/11
Mean age in years (range)	60 (31–81)
Associated medical conditions	
Cardiovascular and/or cerebrovascular disease	6
Diabetes mellitus	5
Autoimmune disease	4
Malignancy	1
Hepatitis C infection	2
Mean serum creatinine, μmol/L (range)	205 (61–560)
Renal insufficiency, serum creatinine > 110 μmol/L	18
Mean 24 h urine protein, g/d (range)	3.76 (0.40–9.33)
Nephrotic range proteinuria (> 3.5 g/day or urine protein/creatinine ratio > 300 mg/mmol or urine albumin/creatinine ratio > 250 mg/mmol) (data unavailable for two patients)	10
Microscopic hematuria	19
Monoclonal protein on serum protein electrophoresis/immunofixation	3

TABLE 2 | Histopathological characteristics of patients with fibrillary glomerulonephritis.

Light microscopy	
Mean number of glomeruli sampled (range)	17 (3–39)
Globally sclerotic glomeruli, % (range)	34 (0–84)
Glomerular pattern of injury	
Mesangial expansion with/without variable hypercellularity, capillary wall thickening	16/26
Established MPGN with endocapillary hypercellularity	10/26
Location of fibrils	
Mesangial	26/26
Glomerular capillary wall	26/26
Tubular basement membrane	1/8 assessed
Interstitium	1/8 assessed
Vessels	0/15 assessed
Fibrils in urinary space	11/26 assessed

(Table 3). A second patient had biclonal gammopathy with IgM and IgG kappa paraproteinemia. Details of bone marrow studies were not available for this patient. A third patient had IgM lambda paraprotein measuring 1.5 g/L in the serum. However, no clonal population was demonstrated on bone marrow biopsy. Bone marrow studies were done in two other patients, revealing 2% polyclonal plasma cells in one patient and 6% polyclonal plasma cells in the second patient. Two patients had positive ANCA serology, with one patient demonstrating a single crescent and significant tubulointerstitial fibrosis and end-stage kidney disease and not considered as ANCA vasculitis by the treating team.

Proteinuria was noted in most patients with nephrotic range proteinuria in 10 patients and sub-nephrotic proteinuria in 15 patients. Urinary protein results were not available for one patient. Presentation with a nephritic picture manifested by haematuria was seen in 19 patients. Urine microscopy was unavailable for 3 patients. Kidney dysfunction at presentation was seen in 16 patients, with the average creatinine being 241 μmol/L in patients with kidney dysfunction. Nine patients presented with severe kidney dysfunction characterised by creatinine > 200 μmol/L.

3.2 | Kidney Pathology

Kidney biopsy revealed a predominant mesangial proliferative pattern or diffuse increase in mesangial matrix with patchy variable increase in mesangial cellularity (16/26) patients, all of whom showed variable degrees of capillary wall thickening (Table 2, Figure 1A–C). Among these patients, two cases additionally had nodular sclerosis due to underlying diabetic nephropathy. Established membranoproliferative pattern (MPGN) with varying degrees of endocapillary hypercellularity was noted in 10/26 patients (Figures 1D and 2A–C). Some patients had more than one pattern and were categorised under the more severe pattern. Diffuse sclerosing pattern where more than 60% of glomeruli showed global sclerosis was seen in 5/26 cases, with the viable glomeruli showing one of the above patterns, all of whom also showed severe interstitial fibrosis. Segmental sclerosis was seen in 16/26 patients with glomeruli showing any of the other patterns. Cellular crescents were seen in 4/26 patients (Figure 2A) and necrotizing lesions were seen in 2/26 patients, all of them showing established MPGN pattern of glomerulonephritis. None of the cases showed membranous pattern of glomerulonephritis reported in literature [12, 13]. Immunohistochemistry showed positive DNAJB9 in 25 patients (Figure 2D). DNAJB9 stain was unavailable in 2/26 patients. Tubular basement membrane staining was seen in eight cases. Additional peritubular capillary staining was seen in one case. No extraglomerular staining was seen in 16 cases.

Immunofluorescence revealed polyclonal fibrillary deposits in the renal biopsies in all patients. One of the patients with MGUS demonstrated kappa light chain restriction on the bone marrow biopsy as well as on the kidney biopsy, by both IF-F and IF-P (Figure 3A,B), but with polyclonal staining for IgG1 and IgG4 subclasses (Figure 3C–F). Interestingly, there was a congophilic fibrillary pattern in 7/26 patients. All these patients had positive

TABLE 3 | Clinical presentation, kidney pathology, course and outcome of patients with fibrillary glomerulonephritis.

		Proteinuria						Kidney biopsy					
	Age/sex	Protein/creatinine ratio (mg/mmol)	Albumin/creatinine ratio (mg/mmol)	24h urine (g/24h)	Nephrotic range proteinuria	Serum creatinine (μmol/L) at presentation	Haematuria	Light microscopy	Mean fibril size (nm) on electron microscopy	Follow-up period (months)	Clinical course, therapy, associated conditions	Dialysis	Mortality
1	42/M			7.83	Yes	90	Yes	Mesangial expansion, congophilic deposits; 13% global sclerosis, mild interstitial fibrosis, DNAJB9—N/A	17	12	Progressive kidney disease with creatinine 150 μmol/L at 12 months post diagnosis	No	No
2	46/M			2.3	No	310	Yes	Mesangioproliferative, capillary wall thickening, 78% global sclerosis, significant interstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	14.6	120	Positive HCV serology. Started dialysis 48 months after diagnosis	Yes	No
3	72/M			0.4	No	120	Yes	Mesangial expansion, capillary wall thickening, segmental sclerosis, 31% global sclerosis, moderate tubulointerstitial fibrosis, DNAJB9—N/A	15	96	Diagnosed with an undefined autoimmune disease. Treated with prednisolone 10 and 5 mg on alternate days. Creatinine stable at 120 μmol/L at last follow up	No	No
4	81/F			0.4	Yes	297	Yes	Established MPGN—mesangial expansion, patchy increase in cellularity. Single cellular crescent noted, congophilic deposits, no global sclerosis, severe interstitial fibrosis, DNAJB9—along occasional TBM	14.5	27	Progressive kidney dysfunction. Concomitant cardiac issues including atrial fibrillation and ischaemic heart disease. Died of non ST elevation myocardial infarction	No	Yes
5	58/F			0.94	No	100	Yes	Established chronic MPGN, associated diabetic changes (Kimmelstein Wilson lesion, capsular drop), congophilic deposits, segmental sclerosis, 18% global sclerosis, moderate tubulointerstitial fibrosis, DNAJB9 – along occasional TBM	16.5	36	Significant drop in kidney function contributed by poorly controlled diabetes. Required dialysis 36 months after diagnosis	Yes	No
6	74/F			0.44	No	160	Yes	Established MPGN, segmental sclerosis, 33% global sclerosis, moderate tubulointerstitial fibrosis, no extraglomerular staining	18	69	Required dialysis 16 months after diagnosis. Developed myelodysplastic syndrome, aortic incompetence and cardiac failure. Died 7 years after diagnosis after withdrawal from dialysis	Yes	Yes
7	46/M			4.2	Yes	156	No	Established MPGN, 64% global sclerosis, severe tubulointerstitial fibrosis, no extraglomerular staining	18.1	3	Developed severe congestive cardiac failure and died 3 months after diagnosis	No	Yes

(Continues)

TABLE 3 | (Continued)

		Proteinuria						Kidney biopsy					
	Age/sex	Protein/creatinine ratio (mg/mmol)	Albumin/creatinine ratio (mg/mmol)	24h urine (g/24h)	Nephrotic range proteinuria	Serum creatinine (μmol/L) at presentation	Haematuria	Light microscopy	Mean fibril size (nm) on electron microscopy	Follow-up period (months)	Clinical course, therapy, associated conditions	Dialysis	Mortality
8	63/F			1	No	70	Yes	Established MPGN, segmental sclerosis, endocapillary proliferation, focal necrosis, 36% global sclerosis, mild tubulointerstitial fibrosis, no extraglomerular staining	20.9	25	Stable kidney function with no change, concomitant small joint seronegative deforming arthritis	No	No
9	61/F			2.11	No	99	Yes	Mesangial expansion with patchy increase in cellularity, capillary wall thickening, no global sclerosis, moderate tubulointerstitial fibrosis, no extraglomerular staining	18	72	Patient had diabetes, developed inflammatory bowel disease, and reactive arthritis, treated with cyclophosphamide and rituximab, developed end stage kidney disease 30 months after diagnosis	Yes	No
10	53/F		1058		Yes	560	Yes	Mesangial expansion, capillary wall thickening, 55% global sclerosis with significant tubulointerstitial fibrosis, no extraglomerular staining	13.88	60	Presentation with end stage kidney disease and initiated dialysis few days after presentation	Yes	No
11	72/F			2.77	No	346	Yes	Established MPGN—mesangial expansion with capillary wall thickening, segmental sclerosis, single cellular crescent, 84% global sclerosis, significant tubulointerstitial fibrosis, DNAJB9 along TBM	13.08	42	Patient had bronchiectasis, severe mitral regurgitation, dilated cardiomyopathy; started dialysis 2 months after presentation. ANCA+, MPO titre 11 U/mL	Yes	No
12	55/F	232.8			No	144	Yes	Mesangioproliferative, capillary wall thickening, segmental sclerosis, 67% global sclerosis, significant tubulointerstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	13.44	60	Slow progression of kidney disease. Creatinine 170 at last follow up	No	No
13	68/M	740			Yes	440	Yes	Established MPGN, segmental sclerosis, 39% global sclerosis, significant tubulointerstitial fibrosis, DNAJB9—along occasional TBM	16.44	28	End stage kidney disease needing dialysis 18 months after diagnosis	Yes	Yes

(Continues)

TABLE 3 | (Continued)

		Proteinuria						Kidney biopsy					
	Age/sex	Protein/creatinine ratio (mg/mmol)	Albumin/creatinine ratio (mg/mmol)	24h urine (g/24h)	Nephrotic range proteinuria	Serum creatinine (μmol/L) at presentation	Haematuria	Light microscopy	Mean fibril size (nm) on electron microscopy	Follow-up period (months)	Clinical course, therapy, associated conditions	Dialysis	Mortality
14	50/M			9.33	Yes	95	Yes	Mesangial expansion with patchy increase in cellularity, capillary wall thickening, congophilic deposits, 9% global sclerosis, moderate tubulointerstitial fibrosis, fibril deposition in TBM and interstitium on electron microscopy, DNAJB9 along TBM	20.39	54	Diagnosed to have biclonal gammopathy; (IgG and IgM Kappa, 2 g/L) received Rituximab therapy. Creatinine 180 at last follow up	No	No
15	67/M			4.27	Yes	110	No	Mesangial expansion, patchy increase in cellularity, capillary wall thickening, segmental sclerosis, congophilic deposits, 39% global sclerosis, moderate tubulointerstitial fibrosis, DNAJB9—along occasional TBM and peritubular capillaries	15.9	44	MGUS onset since 2019, IgM lambda paraprotein in serum –1.5 g/L. Treated with Rituximab followed by cyclosporine and prednisolone and subsequently cyclophosphamide with no response. Also had prostate cancer. Slow progression of kidney disease with GFR 28 at end of follow up period	No	No
16	39/F	180			No	61	N/A	Mesangial expansion, patchy increase in cellularity, occasional capillary wall thickening, segmental sclerosis 25% global sclerosis, mild tubulointerstitial fibrosis, DNAJB9 along TBM	18	30	No progression in kidney disease with normal kidney function at end of follow up	No	No
17	69/F	<0.8			No	140	Yes	Mesangial expansion with patchy increase in cellularity, capillary wall thickening, moderate tubulointerstitial fibrosis, 43% global sclerosis, no extraglomerular staining	16	36	Improvement in kidney function during follow up period with creatinine 90 at end of follow up. Concomitant diabetes mellitus type 2	No	No
18	57/M			5.62	Yes	101	N/A	Mesangial expansion, capillary wall thickening, congophilic deposits, segmental sclerosis, 24% global sclerosis, minimal tubulointerstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	14.3	24	No follow up data available	No	No

(Continues)

TABLE 3 | (Continued)

		Proteinuria						Kidney biopsy					
	Age/sex	Protein/creatinine ratio (mg/mmol)	Albumin/creatinine ratio (mg/mmol)	24h urine (g/24h)	Nephrotic range proteinuria	Serum creatinine (μmol/L) at presentation	Haematuria	Light microscopy	Mean fibril size (nm) on electron microscopy	Follow-up period (months)	Clinical course, therapy, associated conditions	Dialysis	Mortality
19	77/M				N/A	182	N/A	Mesangial expansion, focal capillary wall thickening, congophilic deposits, segmental sclerosis, 17% global sclerosis, moderate tubulointerstitial fibrosis, no extraglomerular staining	12.37	24	Had concomitant kappa light chain MGUS with bone marrow showing 2% plasma cells with 96% monoclonality and kappa light chain restriction. Additionally, marrow showed CMML—0. However fibrillary GN polyclonal in nature. Kidney disease stable at end of follow up with creatinine 150	No	No
20	63/F			6.82	Yes	192	Yes	Mesangial expansion, capillary wall thickening, concomitant diabetic nephropathy (nodular sclerosis), segmental sclerosis, no global sclerosis, significant tubulointerstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	26.5	0	Positive ANA at titre 1:2560. No change in kidney function. Died 2 months post diagnosis due to cerebrovascular episode. Had history of diabetes for at least 2 years prior to diagnosis	No	Yes
21	52/M			0.41	No	351	Yes	Established MPGN, single cellular crescent, segmental sclerosis, 13% global sclerosis, significant tubulointerstitial fibrosis	17.5	48	End stage kidney disease 1 month after diagnosis and started dialysis. Positive HCV serology with history of intravenous drug use. Died after asystolic cardiac arrest. ANCA+, PR3 14 U/mL, MPO 13 U/mL	Yes	Yes
22	51/F	327			Yes	130	No	Established MPGN—mesangial expansion, patchy increase in mesangial cellularity, necrotising lesions and two cellular crescents, segmental sclerosis, 67% global sclerosis with significant tubulointerstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	14.4	6	No progression in kidney disease. Creatinine 123 at end of follow up	No	No
23	39/F				N/A	240	Yes	Mesangial expansion with capillary wall thickening, 25% global sclerosis, mild tubulointerstitial fibrosis, DNAJB9—nonspecific staining in tubules, arterioles	23	75	Slow progression of kidney disease with creatinine 315 at end of follow-up period	No	No

(Continues)

TABLE 3 | (Continued)

		Proteinuria						Kidney biopsy					
	Age/sex	Protein/creatinine ratio (mg/mmol)	Albumin/creatinine ratio (mg/mmol)	24h urine (g/24h)	Nephrotic range proteinuria	Serum creatinine (μmol/L) at presentation	Haematuria	Light microscopy	Mean fibril size (nm) on electron microscopy	Follow-up period (months)	Clinical course, therapy, associated conditions	Dialysis	Mortality
24	66/M			0.93	No	156	Yes	Established MPGN, segmental sclerosis, 12% global sclerosis, significant tubulointerstitial fibrosis, no extraglomerular staining	16	1	Presented with acute kidney injury in the context of biliary sepsis and died 1 month after diagnosis	No	Yes
25	65/F			1.46	No	240	N/A	Increase mesangial matrix, mild increase in cellularity, capillary wall thickening, segmental sclerosis, 58% global sclerosis with significant tubulointerstitial fibrosis, no extraglomerular staining	15.8	13	Concomitant rheumatoid arthritis with anti Jo-1 and Ro-52 antibodies. Treated with prednisolone 5 mg daily. Creatinine 245 at end of follow up	No	No
26	62/F			3.18	No	444	Yes	Mesangial expansion, capillary wall thickening, 29% global sclerosis, significant tubulointerstitial fibrosis, DNAJB9—along occasional TBM	17	12	Long standing diabetes for 18 years at time of diagnosis. Progressed to end stage kidney disease requiring dialysis at end of follow up period	Yes	No

Abbreviations: ANA, anti-nuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; HCV, Hepatitis C virus; MGUS, monoclonal gammopathy of undetermined significance; MPGN, membranoproliferative glomerulonephritis; MPO, myeloperoxidase; PR3, proteinase 3; TBM, tubular basement membrane.

TABLE 4 | Differences in presentation parameters between patients with and without end-stage kidney disease (ESKD).

Clinical parameter	No ESKD ($N=16$)	ESKD ($N=7$)	p
Age	60	61	0.640[a]
Median (IQR)	(47–69)	(52–72)	
Sex	9	4	1.000[b]
Female (%)	(56.3)	(57.1)	
Presenting creatinine	135	346	0.009[a]
Median (IQR)	(97–190)	(160–440)	
Presenting protein/creatinine ratio	327.3	198.6	0.876[a]
Median (IQR)	(94.9–671.0)	(88.6–795.0)	
Glomerulosclerosis	27.9	38.9	0.403[a]
Median (IQR)	(13.5–54.5)	(13.3–77.8)	
Degree of interstitial fibrosis	2	3	0.084[a]
Median (IQR)	(1–3)	(2–3)	
Serum EPG/IEPG (%)	Insufficient sample size		

[a]Mann–Whitney *U* test.
[b]Fishers exact test.

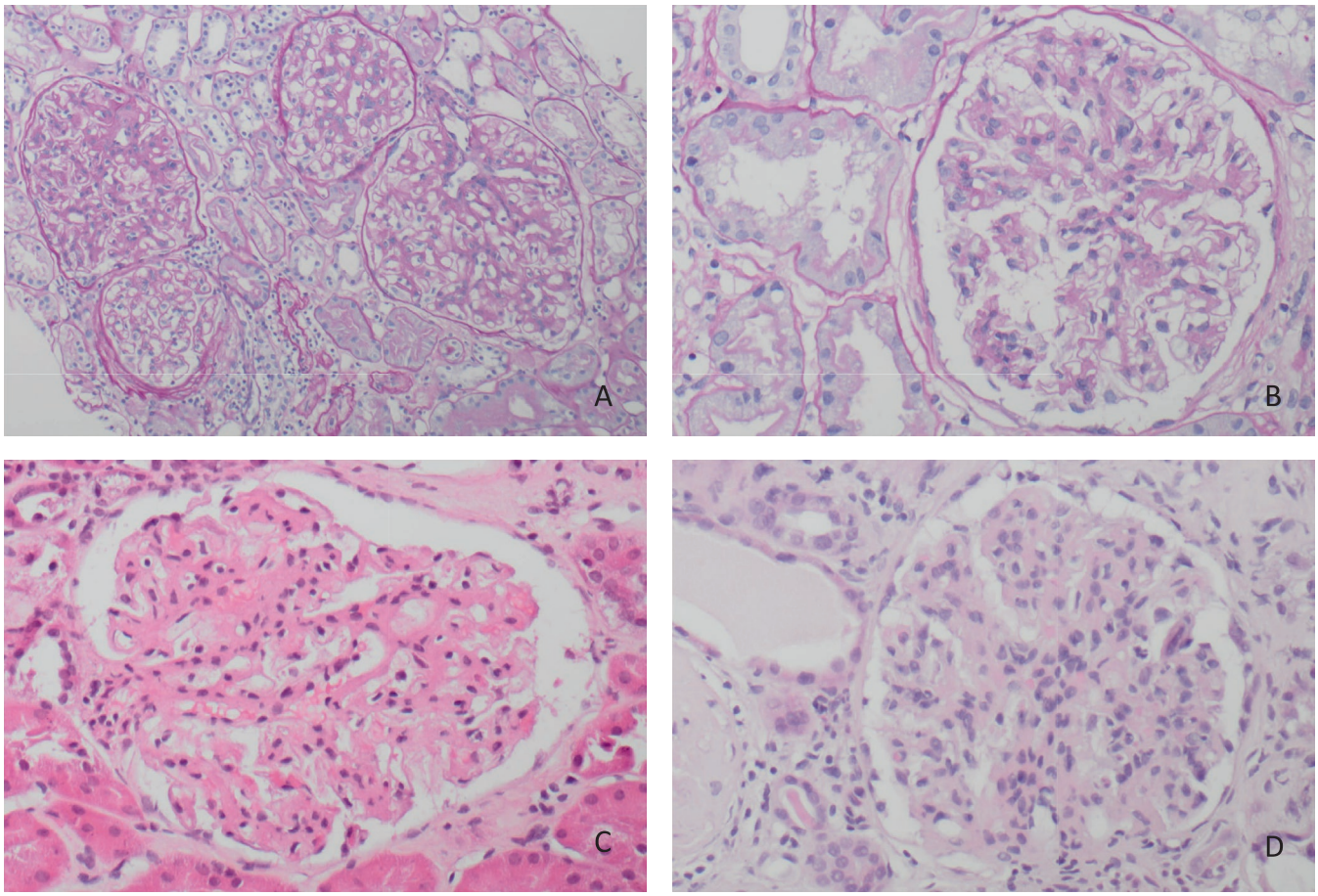

FIGURE 1 | (A–D) Patterns in fibrillary glomerulonephritis on light microscopy. (A) Glomeruli showing diffuse increase in mesangial matrix with amorphous glassy immune deposits (weakly positive for PAS original magnification ×100)—Case 18. (B) Glomerulus showing increase in mesangial matrix with variable mild increase in mesangial cellularity (PAS original magnification ×400)—Case 26. (C) Glomerulus showing diffuse increase in mesangial matrix with prominent capillary wall thickening (H&E original magnification ×400)—Case 22. (D) Glomerulus showing established membranoproliferative pattern with endocapillary hypercellularity and lobular accentuation (H&E original magnification ×400)—Case 21.

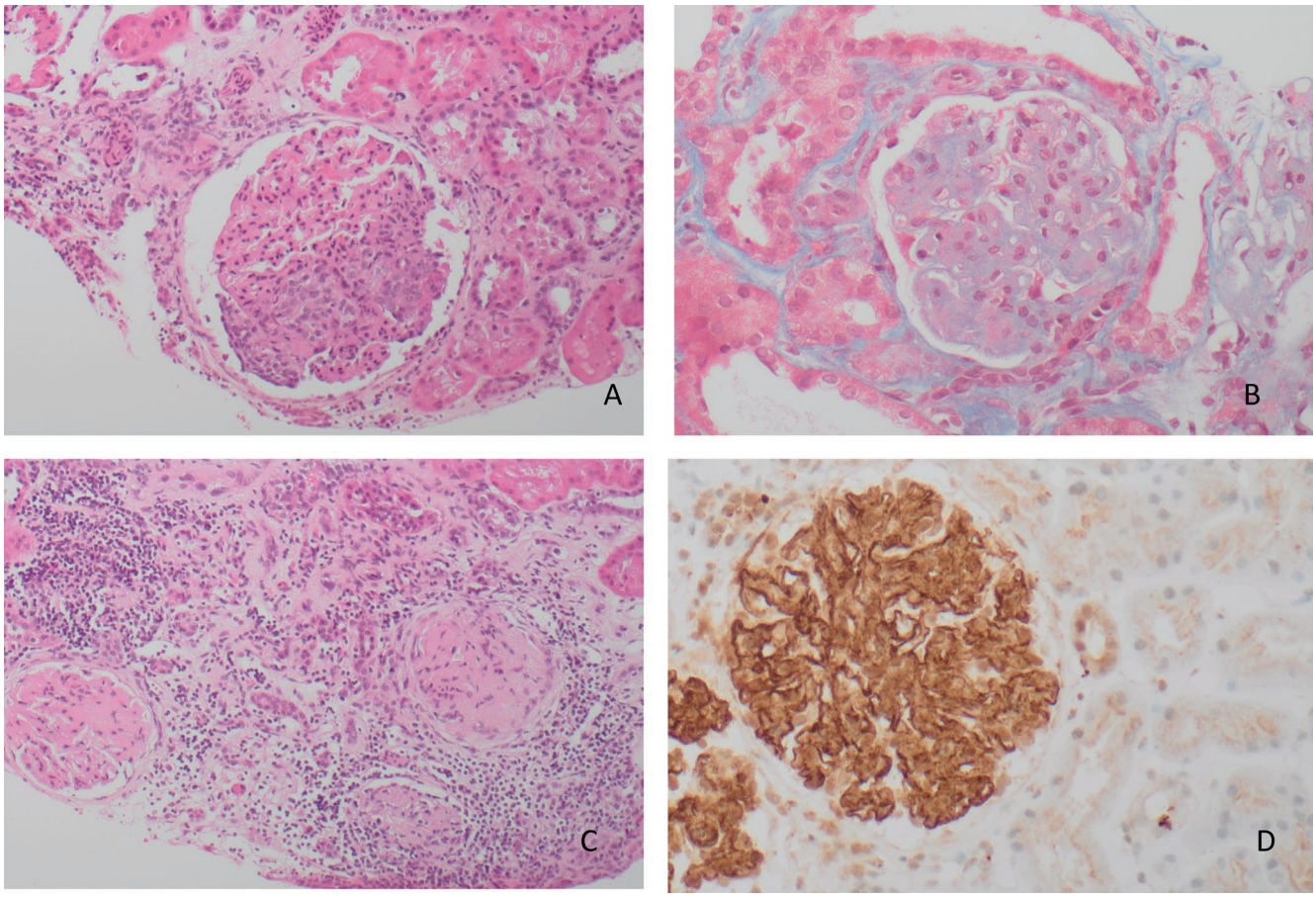

FIGURE 2 | (A–D) Patterns in fibrillary glomerulonephritis. (A) Glomerulus showing membranoproliferative pattern with global mesangial expansion with obliteration of capillary loops and a cellular crescent (H&E original magnification ×100)—Case 22 (B) Glomerulus showing chronic membranoproliferative pattern with segmental sclerosis (Gomori trichrome original magnification ×200)—Case 13. (C) Severe background scarring with segmentally and globally sclerosed glomeruli (H&E original magnification ×40)—Case 21. (D) Glomeruli showing positive staining for DNAJB9 (DAB original magnification ×200)—Case 19.

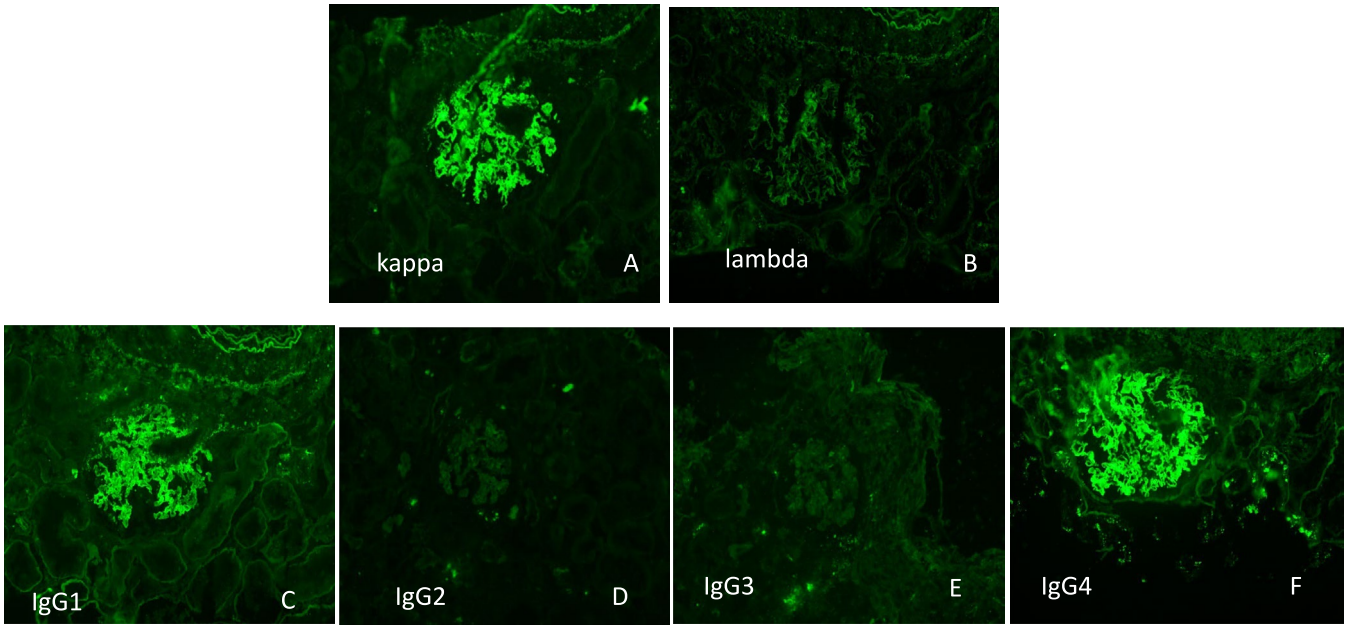

FIGURE 3 | (A–F) Case 19. (B) Bright smudgy mesangial and glomerular capillary wall staining for kappa light chain (×100). (C) Weak staining for lambda light chain (×100). (D) Bright staining for IgG subclass 1 (×100). (E) Negative staining for IgG subclass 2 (×100). (F) Negative staining for IgG subclass 3 (×100). (G) Bright staining for IgG subclass 4 (×100).

congo red positivity on immunofluorescence (Figure 4), with two of them also showing weak congo red staining on light microscopy with faint apple green birefringence on polarisation in one case. Interstitial fibrosis was absent or mild (< 25%) in five patients, moderate (25%–50%) in eight patients and severe (> 50%) in 13 patients.

Electron microscopy revealed deposition of fibrils measuring 12.37–26.5 nm in diameter predominantly in the mesangium (Figure 5). The mean fibrillary diameter was 15.85 nm in the congophilic group compared to 17.13 nm in the non-congophilic group. In 11/26 cases, there was heavy infiltration of the capillary basement membranes with extrusion of the fibrils into the urinary space.

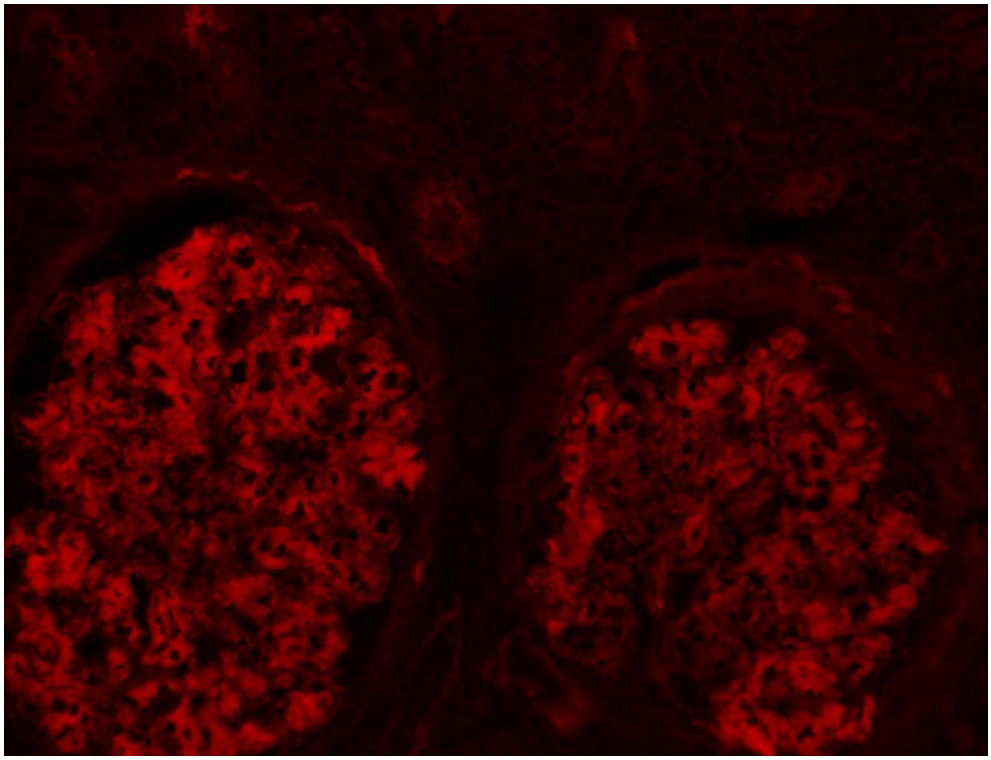

FIGURE 4 | Fluorescence staining for Congo red (original magnification ×200)—Case 14.

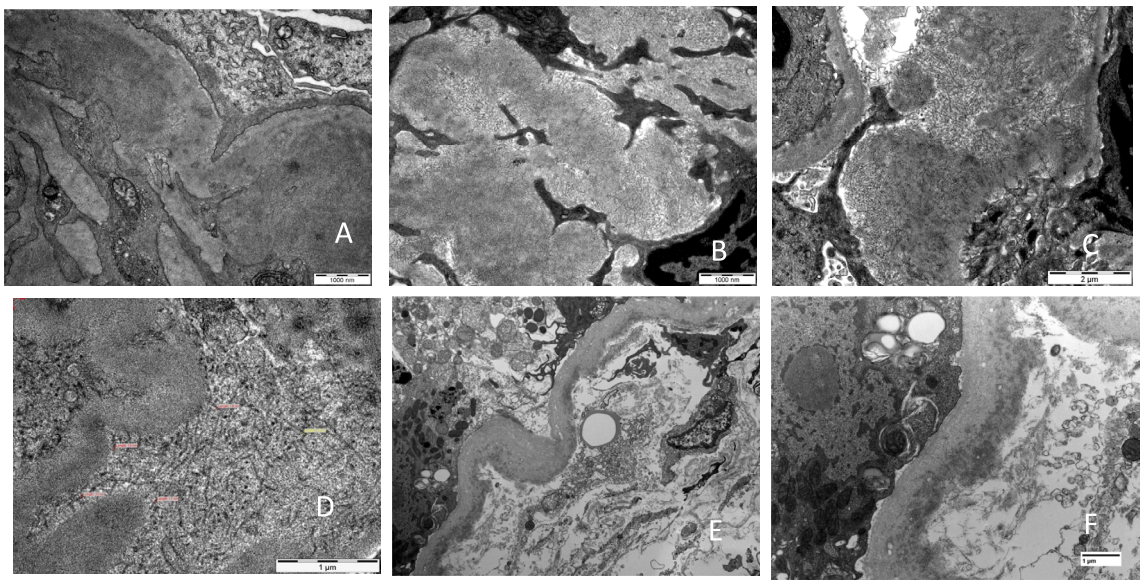

FIGURE 5 | (A–F) Electron microscopic findings in fibrillary glomerulonephritis (uranyl acetate and lead citrate). (A) Extensive deposits of randomly oriented straight fibrils seen expanding the mesangium and infiltrating the basement membrane in a sclerosed glomerulus—Case 7. (B) Randomly oriented fibrils expanding the mesangium—Case 8. (C) Randomly oriented fibrils diffusely and extensively infiltrating the basement membrane with extrusion into the urinary space—Case 9. (D) Higher magnification showing randomly oriented straight fibrils ranging in size from 17 to 23 nm—Case 9. (E, F) Randomly oriented fibrils infiltrating the tubular basement membrane with rupture and fibrils within the interstitium—Case 14.

3.3 | Follow Up and Outcome

The median follow-up period was 33 months with an interquartile range from 12.8 to 55.5 months (Figure 6). Three patients received immunosuppressive therapy directed at fibrillary GN. One patient received cyclophosphamide as per Eurolupus regimen followed by Rituximab. This did not prevent progression to end-stage kidney disease. The second patient received Rituximab, cyclosporine, and prednisolone followed by cyclophosphamide, and the third patient received low-dose prednisolone with ongoing progression of kidney disease in both patients (Table 3). Being a retrospective study on biopsy-based diagnosis, we do not have complete data on the reason for treatment decisions and choices of treatment for the patients who received immunosuppressive treatment in this study. Ten patients had significant progression of kidney disease manifested by progression to end-stage kidney disease. Seven of the nine patients developed ESKD primarily due to FGN, with two other patients developing end-stage kidney disease due to diabetes and one patient due to biliary sepsis respectively. The only significant factor identified as a risk factor for the progression of kidney disease was the degree of kidney dysfunction at presentation (Table 4). A total of six patients died during the follow-up period. Death was due to valvular heart disease in two patients, ischaemic heart disease in one patient, sudden cardiac death in one patient, cerebrovascular event in one patient, and biliary sepsis in one patient (Table 3).

4 | Discussion

This is one of the largest series of patients with fibrillary glomerulonephritis from Australia and the Asia Pacific region. This study reveals a middle-aged or older population with a slight female preponderance, which is consistent with other published studies [4, 14]. A summary of the key findings from some of the largest series has been presented in Table S1. However, our study demonstrated slightly different demographic characteristics. Previous studies have shown associations with other conditions, namely malignancies, Hepatitis C infection and autoimmune disorders [3, 14]. However, in our study, we had five patients with diabetes and a very limited number of patients with autoimmune disorders. We had two patients with Hepatitis C, comprising approximately 7% of our patient population. This may possibly be related to the different population composition in this region. The study by Andeen et al. demonstrated a higher incidence of Hepatitis C, paraproteinemia, malignancies and autoimmune disorders [3]. Similarly, the study by Nasr et al. demonstrated a higher incidence of associations with systemic illness [14]. This study did not use DNAJB9 as an ancillary test for FGN, as this was not yet developed. The authors identified DNAJB9 and developed immunohistochemistry to identify DNAJB9 and subsequently extended the case series [5]. In the updated series, the authors have identified numerous associated conditions, including malignancies in 10%, autoimmune disease in 14%, and hepatitis C in 7%. Most studies demonstrate that 10% of patients with FGN demonstrate paraproteinemia [15]. We had a slightly lower proportion of patients with paraproteinemia. Among the three patients in our study, there was one patient with monoclonal kappa light chain restriction with polyclonal IgG subclass staining. Although paraproteinemia is associated with FGN, true monoclonality and MGRS are rare, as demonstrated in previous studies [16, 17]. The pathophysiology of FGN has not been identified yet, and the lack of strong associations with autoimmune conditions or malignancy in our study suggests an as yet unidentified mechanism of production and deposition of these fibrils.

Most of the patients did not receive any targeted therapy except for three patients with no evidence of influence on the outcome. Complete remission was not seen in any of our patients. The course of the disease again is determined only to a small extent

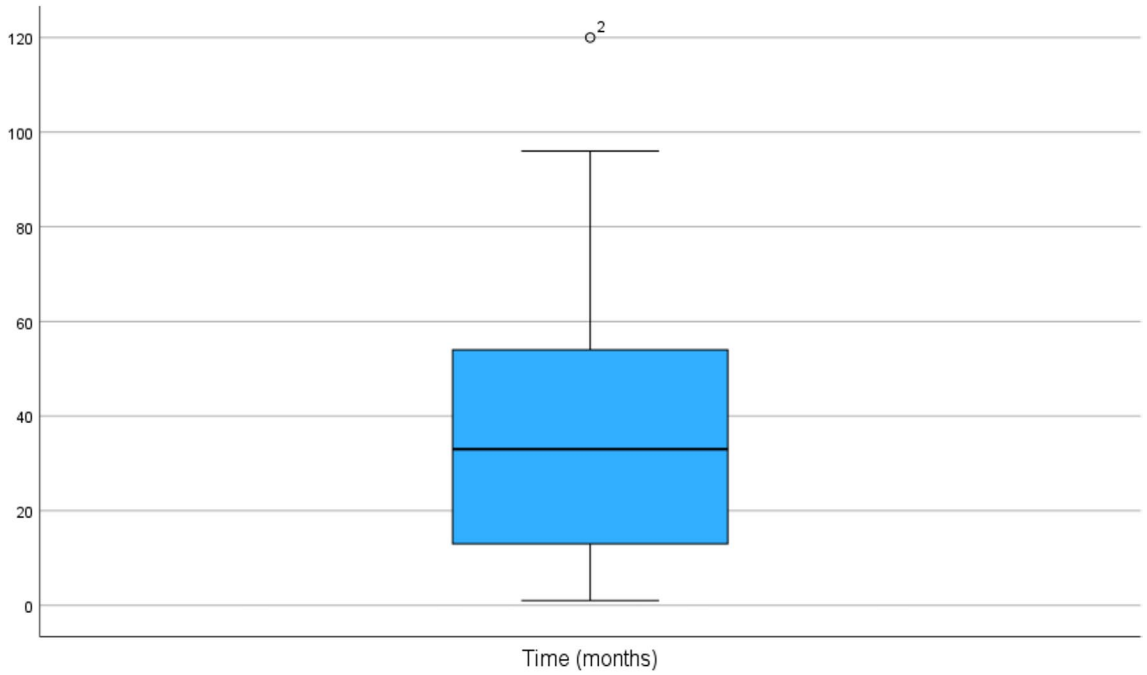

FIGURE 6 | Patient follow-up time. The median follow up time was 33 months, and the inter quartile range 12.8–55.5 months.

by other conditions, with most of the patients in our study developing end-stage kidney disease purely due to contribution from FGN and the rest developing end-stage kidney disease due to contribution from diabetes and sepsis. However, FGN was not the direct cause of death in the six patients who died during follow up, with ischaemic heart disease, valvular heart disease, and sepsis being the most likely causes. The kidney outcome and prognosis in our study are slightly better than the Columbia series and the Mayo series, possibly due to the fact that a large proportion of patients in our study had mesangial expansion with patchy cellularity or a mesangial proliferative pattern with varying degrees of capillary wall thickening, which is associated with better prognosis and is an earlier stage of FGN compared to other patterns such as membranoproliferative and diffuse glomerulosclerosis, which are later stages [18].

Hence the kidney prognosis of FGN is poor in a significant proportion of patients, with the most common outcome being slow progression of kidney disease in a 10-year period. The mortality and morbidity seen in some patients in our cohort were related to associated conditions. Presentation with significant renal dysfunction and a high proportion of sclerotic glomeruli seems to be associated with poor prognosis in terms of kidney survival [14]. Our study may only be reflecting the slower progression due to earlier identification of these patients.

One of the limitations in our study was the non-availability of ethnicity of all our patients. However, we have ethnicity data on more than half the patients, with a predominance of white patients similar to other reported studies listed previously [14]. Although there is no current evidence to suggest ethnicity has an impact on the severity of disease and outcomes, ethnicity data for all patients in this study would have provided an additional perspective on our patient profile. This small study also cannot make any inferences on the treatment outcomes in FGN.

Hence, in summary, a diagnosis of fibrillary glomerulonephritis is associated with poor kidney survival in a significant proportion of patients. Recurrence after transplantation is possible. Mortality is secondary to additional conditions rather than the FGN and end-stage kidney disease. More studies are required in the light of current diagnostic criteria to determine the clinical association, renal prognosis, post-transplant recurrence and patient survival.

Author Contributions

Research idea and study design: M.G.K. and S.V. Data acquisition: S.V. Data analysis and interpretation: M.G.K. and S.V. Supervision or mentorship: M.G.K. and S.V. Manuscript draft and editing: M.G.K. and S.V. Both M.G.K. and S.V. contributed equally to the preparation of this manuscript. Review of pathology cases: S.V. and A.B. Immunofluorescence interpretation and standardisation of paraffin immunofluorescence: A.Y.S.L. Clinical data collection: B.N. Imaging, data collection and technical support: L.N. Each author contributed important intellectual content during manuscript drafting or revision. S.V. accepts accountability for the accuracy of data. M.G.K. and S.V. accept accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.