NEPHROLOGY

Clinical presentation, treatment and outcome of focal segmental glomerulosclerosis in Far North Queensland Australian adults

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Abstract

Aim: To describe the clinical features, treatment and outcomes in Australian adults with focal segmental glomerulosclerosis and identify predictors of disease progression and all-cause mortality.

Methods: The study included all patients with biopsy confirmed focal segmental glomerulosclerosis between January 1997 and June 2014 at participating hospitals. Clinical factors, histopathological findings, biochemical markers and treatments were analysed and potential predictors of doubling serum creatinine, end stage kidney disease or death identified.

Results: 98 patients were included with a median follow-up of 4.3 years. 34 (35%) patients were Aboriginal or Torres Strait Islander. Focal segmental glomerulosclerosis not-otherwise-specified was the most common variant. 17 (59%) patients initially treated with immunosuppression experienced an improvement in renal function. At the end of follow-up 43 (44%) patients had progressed to the composite outcome. Baseline tubulointerstitial scarring and lower haemoglobin predicted shorter time to doubling serum creatinine. Dual diagnosis, higher serum creatinine, lower estimated glomerular filtration rate and doubling creatinine were associated with shorter time to end stage kidney disease with remission the only protective factor. Age was the only variable associated with all-cause mortality.

Conclusion: Focal segmental glomerulosclerosis holds serious implications for patients. Concomitant diabetic nephropathy, higher serum creatinine and lower estimated glomerular filtration rate at renal biopsy were associated with poorer renal prognosis. Indigenous people had a female predominance and are over-represented in relation to their population size, however were not associated with poorer prognosis. Remission was the only modifiable variable and thus should be at the forefront of patient management goals and future studies.

Key words: Focal segmental glomerulosclerosis, nephrotic syndrome, end stage kidney disease, adult, prognosis

Introduction

Focal Segmental Glomerulosclerosis (FSGS) is a pathologic term that is characterised by the presence of focal and segmental glomerular sclerotic lesions. It has a complex aetiology and can be classified into primary and secondary FSGS. Primary FSGS is diagnosed in over 80% of cases, and is a diagnosis of exclusion.[1] The disease trends towards progressive decline of renal function to end stage kidney disease (ESKD) within 5-10 years in over 50% of cases.[2, 3]

In 2011, FSGS was the second leading cause of all new glomerulonephritis cases resulting in ESKD in Australia.[4] These rates are on the rise internationally with some countries reporting a 3-13 fold increase in incidence over the past two decades.[5-8]

The increasing incidence of ESKD attributable to FSGS and its associated burden on patients and their families that has prompted renewed interest in this disease.

The purpose of the study was to describe the clinical features, treatment and outcomes of primary and secondary FSGS in Far North Queensland Australian adults and to identify any predictors of disease progression and all-cause mortality.

Methods

The human research ethics committee for the participating hospitals (HREC/13/QHC/031) and affiliated university (H5707) approved the study. A retrospective review was conducted of patients' medical records and pathology reports to record clinical, histopathological,

biochemical and medication details. Informed patient consent was waived due to the retrospective nature of the study.

Settings and patients

All incident patients with biopsy proven FSGS at Cairns and Townsville Hospitals between January 1997 and June 2014 were included. Patients younger than 18 years old were excluded. We analysed the FSGS cases as a single group due to difficulty distinguishing between primary and secondary cases.

Clinical presentation, disease profile and study endpoints

The following baseline clinical variables were recorded at the time of renal biopsy: patient age, gender, ethnicity, BMI, comorbidities (diabetes, cerebrovascular disease, hypercholesterolemia, hypertension and infection), smoking status, haematuria (macro- and microscopic findings) and oedema.

Histopathological findings including variant (Columbia Classification), additional diagnosis and degree of tubulointerstitial scarring were obtained from biopsy results reported at the Princess Alexandra Hospital pathology department. [9] Degree of tubulointerstitial scarring was based on the scoring system which has been better defined in transplant biopsies; mild (≤25), moderate (26-50%) and severe (>50%). [10]

A retrospective review of the electronic pathology system was performed to record the following baseline biochemical parameters: haemoglobin, platelets, total white cell count and differential, serum creatinine, serum albumin, estimated glomerular filtration rate, albumin-creatinine ratio, protein-creatinine ratio and 24 hour urinary protein. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. Nephrotic range proteinuria was classified as >3g protein/day. [11]

Medication information was retrieved from patient records. The use of the following medications was recorded: diuretics, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, immunosuppression (prednisolone, cyclosporine A, cyclophosphamide) as was subsequent treatment response. Complete remission was defined as a daily urine protein excretion of <0.3 g/d, partial remission was defined as ≥50% reduction of proteinuria from baseline. Relapse was defined by a single proteinuria value ≥3 g/d after any remission.[12]

Patients were followed until June 2014, death or lost to follow-up. The primary endpoint of the study was a composite outcome of doubling of serum creatinine, progression to ESKD or all-cause mortality. Each of these three separate outcomes was also investigated as secondary endpoints. Baseline patient and biochemical characteristics were recorded at the time of renal biopsy. ESKD was defined as eGFR <15mL/min/1.73m^2 or commencement of dialysis. Kidney transplantation was intentionally excluded due to an incomplete data set, with a significant proportion of the cohort transplant status unknown. None of the transplants received were pre-emptive, hence transplant status was not relevant when it came to reaching the endpoint of ESKD.

Statistical analysis

All data were recorded and analysed using SPSS (IBM, Version 22). Descriptive statistics were calculated for the study cohort and reported as mean +/- standard deviation or median and range for continuous data, depending on distribution, and frequency (%) for categorical variables. All decimal values were rounded to two significant figures.

Comparison of Aboriginal and Torres Strait Islander and non-Aboriginal and Torres Strait Islander patients at baseline was made using Students two sample t-test for continuous variables and chi square for observations measured with a nominal scale.

The association of clinical, biochemical and treatment related variables with progression to the composite and secondary study endpoints were analysed using unadjusted (univariate) Cox regression analysis. P values <0.05 were considered significant. Significant variables in univariate analysis were entered into a correlation matrix to evaluate zero order correlations. If two independent variables correlated with a Pearson correlation coefficient of greater than 0.6 (with $p<0.05$), one of them was excluded. Remaining independent variables were entered into adjusted (multivariate forward stepwise) Cox regression model to determine the final predictors of progression to the composite outcome.

Results

During the study period, 98 patients had biopsy proven FSGS. 10 were lost to follow-up. The remaining patients were followed-up for a median of 4.32 years (range 0-16.5 years).

Baseline characteristics

There was an equal gender distribution with a median age of 45 years. Approximately one third of patients were Aboriginal or Torres Strait Islanders who had statistically significant greater rates of comorbidities including diabetes, hypertension, cardiovascular disease and dyslipidaemia (Table 1). Nephrotic range proteinuria was observed in 50 (51%) patients. The median serum creatinine and eGFR at the time of biopsy was 131µmol/L and 53ml/min respectively (Table 2).

Histopathological findings

Mild tubulointerstitial scarring was present in 46 (47%) patients and another 18 (20%) had severe scarring. FSGS not-otherwise-specified (NOS) was the most common variant identified in 85 (87%) patients. Dual diagnosis was identified in 22 (22%) of patients; the

most common underlying renal disease was diabetic nephropathy which affected 8 (8.2%) patients within the cohort.

Treatment modalities

Immunosuppression was given to 30 (30%) patients initially. Of these, 24 (80%) received prednisolone at an average dose of 1mg/kg/day for a duration of six weeks. Over half of these patients improved their renal function by the end of the follow-up period, with only 29 (43%) patients receiving conservative management alone improving their renal function. Complete remission was achieved in one- third of the entire cohort. Conservative management with diuretics, angiotensin-converting-enzyme inhibitors and angiotensin II receptor blockers were used in 26 (88%) patients receiving immunosuppression with angiotensin-converting-enzyme inhibitors the most commonly used agent. Approximately 70% of the patients that received immunosuppression suffered a relapse.

Treatment outcomes

At the end of follow-up, 43 (44%) patients had progressed to the composite outcome. One-third doubled their serum creatinine within a median time of 2.9 years (range 0.2-11.3 years). Progression to ESKD occurred in 37 (38%) patients in a median period of 1.6 years (range 0-12.4 years). Death from any cause occurred in 18 (19%) patients during the follow-up period.

Predictors of renal outcomes

Indicators of more severe disease at baseline as well as failure to achieve or sustain a remission were the only prognostic factors identifiable. A worse prognosis was associated with histopathological findings of diabetic nephropathy (Table 3), tubulointerstitial scarring (Table 4) or "dual diagnosis" (Table 5). A worse prognosis was also linked to baseline

increased serum creatinine (Table 3), reduced eGFR (Table 3+5) and anaemia (Table 4). As expected higher age at baseline was linked to earlier death (Table 6).

Discussion

Studies involving primary FSGS in adults have shown it to be a disease encompassing different demographic characteristics, clinical manifestations, treatment regimens and outcomes. We examined these aspects in an attempt to identify clinically important variables which may guide management and further improve our understanding of this disease in the Australian population, particularly with its unique Aboriginal and Torres Strait Islander population.

The cohort included in our study *is* unique. The catchment of hospitals involved encompasses Aboriginal and Torres-Strait Islanders from remote and very remote locations. The Indigenous population was over-represented accounting for one-third of the cohort despite comprising only 7.8% and 5.5% of the Cairns and Townsville populations respectively. Surprisingly, ethnicity was not identified as a significant predictor towards poorer outcomes. Regardless, the Indigenous population did show marked increased rates of comorbidities (diabetes, cardiovascular disease, hypertension, hypercholesterolaemia), diabetic nephropathy and severe tubulointerstitial scarring which in itself hold implications for morbidity and mortality.[13-15]

Within our study 21% of the ATSI participants had a dual histological diagnosis, of which only 15% was diabetic nephropathy. This is an important observation as renal disease within Indigenous Australians is frequently attributed to Type 2 Diabetes. Whilst nearly half of the Indigenous patients within the study had diabetes, fewer than half of these had diabetic nephropathy on biopsy. Hoy et al. reports a similar finding with only one quarter of the remote/very remote Aboriginal people having definitive diabetic change on biopsy.[13] This

highlights the important role of renal biopsies even within diabetic populations, where diabetic nephropathy may not be the primary cause of renal disease.

The female excess within our Indigenous cohort is consistent with the analyses of remote and very remote Indigenous biopsies by Hoy et al. This pattern of disease differs from that witnessed within urban Indigenous Australians and is likely related to a combination of socioeconomic and environmental conditions. Female predominance is difficult to explain but may be related to lower female birth weight – associated with nephropenia and compensatory glomerulomegaly. Female gender is itself associated with lower nephron number.[13, 16] High rates of diabetes until mid-life and greater central fat distribution may also contribute.[13]

The Columbia classification is a widely used system to classify FSGS into five histological variants based entirely on light microscopic findings; tip, perihilar, cellular, collapsing and not-otherwise specified. [17] Several studies have analysed differences in clinical characteristics and outcomes between these variants.[18] It has been reported that the collapsing variant confers poorer prognosis whilst the tip variant has better survival and remission rates. [19, 20] Cellular and collapsing variants have also been shown to be more common in African-Americans. [21] In this study the collapsing and cellular variants were only identified in two biopsies each. Due to the small number of these histological variants in our cohort we were unable to comment on the prognostic significance of any of the variants.

The proportion of patients given immunosuppression was lower in this population compared to previous studies which averaged over 60%.[21-23] This may be due to the fact that previous studies consisted of entirely primary FSGS cohorts in which immunosuppression is considered the mainstay of treatment.[11] This study made no differentiation between primary and secondary FSGS due to the difficulty in clinically distinguishing between the two in a

retrospective setting. No single test exists to differentiate primary and secondary FSGS with the exclusion of secondary causes being particularly challenging in this population given the frequency of comorbidities and dual diagnoses. Furthermore defining primary and secondary FSGS based purely on treatment is not sufficient, and was consequently decided against.

It has been documented that 50% of patients with nephrotic-range proteinuria develop ESKD within 6-8 years.[23] In this study, 38% developed ESKD over a median period of 1.6 years. This may have been foreshortened due to the exclusion of the period between the incident presentation with FSGS to the time it was confirmed by renal biopsy. Additionally late presentation to the participating health centre may have been influenced by such factors as travel time, cost and health care accessibility from more remote areas.

Lower haemoglobin and high serum creatinine were associated with significant progression of renal disease. Interestingly, lower haemoglobin was found to be a biochemical marker of time for progression to doubling of serum creatinine. Whilst anaemia has long been associated with chronic kidney disease, few authors, including have Chou *et al.* have demonstrated any relationship between lower haemoglobin and doubling of serum creatinine.[24] The pathophysiology behind this finding requires further investigation. Stirling *et al*. reported that patients with serum creatinine >100μmol/l at disease onset had a significantly poorer prognosis than those whose creatinine was <100μmol/l.[25] In our study, the prognostic value of serum creatinine at biopsy with respect to ESKD was strengthened only when tubulointerstitial scarring was included. .

In multivariate Cox regression analysis, age was only a predictor of death and did not predict the composite outcome, doubling of serum creatinine, or progression to ESKD. Whilst age is a component of the CKD-EPI formula for estimating glomerular filtration rate, any relationship between age, eGFR and the measured outcomes is adjusted for through

multivariate Cox regression analysis. For example, whilst age was a significant predictor of the composite outcome in univariate analysis, this became non-significant compared to baseline serum creatinine in the adjusted Cox regression analysis (Table 3).

Several studies have demonstrated that achievement of remission confers favourable prognosis.[26-28] This study strengthens this observation with remission found to be the only protective variable. The large, multi-centre study by Troyanov *et al.* found that immunosuppression through high-dose prednisolone was associated with a higher rate of partial and complete remission.[29] Whilst there was a trend towards steroid responsiveness and reduced risk of ESKD in our study (p=0.052) it was likely that the small number of primary FSGS cases limited the study's statistical power to demonstrate this association.

There are several limitations of our study that challenge the interpretation of our results. Our study was retrospective in design, with all the inherent drawbacks of such an approach. The other limitation related to potential sample bias. Patients were only included in the study if they underwent a renal biopsy. This may have led to under representation as not all patients with FSGS underwent biopsies for reasons such as geographic location, failure to attend or a clinical decision that biopsy was unnecessary.

To the best of our knowledge, this is the first study of its kind in patients with FSGS in North Queensland. In addition it is also valuable due to the significant portion of Aboriginal or Torres Strait Islander patients. This study may improve the understanding of the disease profile of FSGS and identification of risk factors for poor renal outcomes in this unique patient population. It underscores the need to ensure appropriate exclusion of secondary causes to enable suitable treatment with immunosuppression to optimize remission rates.

Further work to elucidate the underlying pathophysiology of these prognostic variables may enhance our understanding of this disease in addition to guiding future trial priorities and treatment regimes.

Conclusion

Concomitant diabetic nephropathy, higher serum creatinine and lower eGFR at renal biopsy were associated with poor renal prognosis. Aboriginal or Torres Strait Islander people are over-represented in relation to their population size, and more females were affected but there was no difference in potential for progression to outcomes. Achievement of remission remains the single most important modifiable variable for renal survival and thus should be at the forefront of patient management goals.

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Conflict of Interest: All authors declare no competing interests.

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Table Legend

Table 1. Baseline characteristics at time of FSGS diagnosis and follow-up period

Table 2. Biochemical results at time of FSGS diagnosis

Table 3. Predictors towards the composite event of worsening of any outcome parameter

Table 4. Predictors towards the event of doubling serum creatinine

Table 5. Predictors towards the event of end stage kidney disease

Table 6. Predictors towards the event of death

Table 1. Baseline characteristics at time of FSGS diagnosis and follow-up period

Clinical Variable	All (n = 98)	Non- Aboriginal and Torres Strait Islander (n = 64)	Aboriginal and Torres Strait Islander (n = 34)	P value
Age (median) (years)	45 (range 20-88)	46 (range 20—88)	44 (range 20-70)	0.28
Male (%)	50	61	29	0.003
Body mass index[1] (%)				0.16
Underweight	28	33	20	
Average	28	27	30	
Overweight	35	35	37	
Obese	8.2	5.5	13	
Comorbidities (%)				
Diabetes	29	20	47	0.01
Cardiovascular disease	27	19	43	0.02
Hypercholesterolemia	66	57	83	0.01
Hypertension	78	72	90	0.04
Infection	4.4	1.7	9.7	0.08
Smoking status (%)				0.81
Never smoked	41	44	37	
Ever smoked	59	56	63	
Clinical findings (%)				
Haematuria[2]	45	46	42	0.76
Oedema[3]	49	49	49	0.96
Follow-up (median) (years)	4.3 (range 0-17)	3.5 (range 0-17)	4.8 (range 0-15)	0.47

[1]Body mass index: underweight (BMI <18.5), average (BMI 18.5-24.9), overweight (BMI 25.0-29), obese (BMI >30)

[2]Haematuria: included both micro and macroscopic haematuria

[3]Oedema: clinically noted, degree unspecified

Table 2. Biochemical results at time of FSGS diagnosis

Biochemical Marker	Median	Range
Haemoglobin (g/L)	129	81-172
White cell count (10^9/L)	8.9	4-27
Neutrophils (10^9/L)	5.9	2-6.4
Lymphocytes (10^9/L)	1.8	0-1
Platelets (10^9/L)	258	132-1852
Serum protein (g/dL)	68	9-88
Serum albumin (g/dL)	34	15-46
Serum creatinine (μmol/L)	131	0-1450
PCR (mg/mmol)	291	7-1700
ACR (mg/mmol)	240	2-1100
24hr urinary protein (mg/24hr)	3100	70-18000
eGFR (mL/min)	53	2-134

Table 3. Predictors towards the composite event of worsening of any outcome parameter

Independent variable	Unadjusted Cox regression Numbers	p-value	Hazards ratio (95% CI)	Adjusted Cox regression‡ p-value	Hazards ratio (95% CI)
Clinical factors					
Age in decades	98	**0.001**	1.5 (1.2-1.9)	-----	-----
				-----	-----
Male gender	98	0.90	1.0 (0.57-1.9)		
Ethnicity	98	0.51	0.81 (0.42-1.5)		
Diabetes	93	**0.03**	2.1 (1.1-3.9)	-----	-----
				-----	-----
Hypertension	91	0.64	1.3 (0.45-3.7)		
Hypercholesterolemia	90	0.54	1.3 (0.61-2.6)		
Cardiovascular disease	88	**0.004**	2.6 (1.4-5.1)	-----	-----
				-----	-----
Ever smoked	87	0.56	1.2 (0.62-2.4)		
Infection	90	0.58	1.5 (0.36-6.3)		
Body mass index	98	0.22	0.79 (0.55-1.2)		
Haematuria	92	0.32	1.4 (0.73-2.6)		
Oedema	88	0.07	1.9 (0.94-3.7)		
Lesion factors					
Dual diagnosis	98	**0.003**	2.8 (1.4-5.5)	-----	-----
				-----	-----
Diabetic nephropathy	98	**0.004**	3.4 (1.5-7.8)	-----	-----
				0.021	**11 (1.4-87)**
IgA nephropathy	98	0.43	0.44 (0.06-3.3)		
Acute tubular necrosis	98	**0.006**	5.6 (1.7-19)	-----	-----
				-----	-----
NOS variant	98	0.09	3.5 (0.83-15)		
Tip variant	98	0.29	0.34 (0.05-2.5)		
Perihilar variant	98	0.84	0.05 ($5.3x10^{-15}$ – $4.5x10^{11}$)		
Collapsing variant	98	0.63	0.05 ($2.0x10^{-7}$ - $11.5x10^{3}$)		
Cellular variant	98	0.29	0.33 (0.04-2.6)		
Tubulointerstitial Scarring	98	**<0.001**	1.9 (1.4-2.7)	-----	-----
				-----	-----
Biochemical factors					
Haemoglobin (g/L)†	91	**0.001**	0.78 (0.67-0.91)	-----	-----
				-----	-----
White cell count (10^9/L)	91	0.079	1.1 (0.99-1.2)		
Platelets (10^9/L)†	90	0.15	0.97 (0.92-1.0)		
Neutrophils(10^9/L)	89	0.44	1.0 (1.0-1.0)		
Lymphocytes (10^9/L)	89	0.602	0.99 (0.97-1.0)		
Serum creatinine (μmol/L)†	92	**<0.001**	1.0 (1.0-1.0)	**0.001**	**1.3 (1.1-1.5)**
				-----	-----
Serum albumin (g/dL)†	77	0.23	0.71 (0.41-1.2)		
Serum protein (g/dL)†	70	0.14	1.0 (0.99-1.1)		
Albumin creatinine ratio (mg/mmol)†	57	**0.045**	1.0 (1.0-1.0)	-----	-----
				-----	-----
Protein creatinine	81	0.21	1.0 (1.0-1.0)		

ratio (mg/mmol)[†]					
24hr urinary protein (mg/24hr)[†]	81	0.23	1.0 (1.0-1.0)		
eGFR (mL/min)[†]	91	<**0.001**	0.74 (0.65-0.86)	-----	-----
				0.001	**0.54 (0.37-0.78)**
Treatment					
Angiotensin-converting-enzyme inhibitor	85	0.84	0.93 (0.46-1.9)		
Angiotensin II receptor blocker	81	0.12	0.37 (0.11-1.3)		
Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker	84	0.06	0.49 (0.23-1.0)		
Diuretics	83	0.73	1.1 (0.57-2.2)		
Immunosuppression	83	0.024	2.4 (1.1-5.0)		
Remission	91	**0.003**	0.48 (0.29-0.78)	**0.045**	**0.29 (0.09-0.97)**
				0.037	**0.29 (0.09-0.93)**
Complete remission	91	**0.006**	0.13 (0.03-0.56)	-----	-----
				-----	-----
Partial remission	91	0.63	1.2 (0.55-2.6)		
Relapse	50	0.20	0.57 (0.24-1.3)		
Steroid response	22	0.12	0.34 (0.09-1.3)		

Table 4. Predictors towards the event of doubling serum creatinine

		Unadjusted Cox regression		Adjusted Cox regression‡	
Independent variable	Numbers	p-value	Hazards ratio (95% CI)	p-value	Hazards ratio (95% CI)
Clinical factors					
Age in decades	80	**0.01**	1.4 (1.1-1.8)	-----	-----
				-----	-----
Male gender	80	0.38	1.4 (0.68-2.8)		
Ethnicity	80	0.78	0.90 (0.43-1.9)		
Diabetes	79	**0.01**	2.6 (1.3-5.3)	-----	-----
				-----	-----
Hypertension	78	**0.03**	8.6 (1.2-63)	-----	-----
				-----	-----
Hypercholesterolemia	79	0.67	1.2 (0.53-2.7)		
Cardiovascular disease	77	0.05	2.1 (1.0-4.3)		
Ever smoked	76	0.96	0.98 (0.48-2.0)		
Infection	78	0.09	3.5 (0.81-15)		
Body mass index	74	0.75	0.94 (0.64-1.4)		
Haematuria	76	0.82	1.1 (0.53-2.3)		
Oedema	74	0.12	1.9 (0.86-4.0)		
Lesion factors					
Dual diagnosis	80	**0.04**	2.2 (1.0-4.8)	-----	-----
				-----	-----
Diabetic nephropathy	80	**0.02**	3.4 (1.3-9.2)	-----	-----
				-----	-----
IgA nephropathy	80	0.59	0.58 (0.08-4.3)		
Acute tubular necrosis	80	0.68	1.5 (0.21-11)		
NOS variant	80	0.36	2.0 (0.47-8.3)		
Tip variant	80	0.41	0.43 (0.06-3.2)		
Perihilar variant	80	0.85	0.05 ($3.6x10^{-15}$ – $6.6x10^{10}$)		
Collapsing variant	80	0.53	0.05 ($3x10^{6}$-$7x10^{2}$)		
Cellular variant	80	0.55	1.8 (0.25-13)		
Tubulointerstitial Scarring	80	**<0.001**	2.9 (1.8-4.5)	**0.005** -----	**2.5 (1.3-4.9)** -----
Biochemical factors					
Haemoglobin (g/L)†	78	**0.004**	0.76 (0.64-0.92)	**0.004** **0.006**	**0.62 (0.45-0.86)** **0.64 (0.47-0.88)**
White cell count (10^9/L)	78	0.35	0.95 (0.85-1.1)		
Platelets (10^9/L)†	77	0.53	0.99 (0.95-1.0)		
Neutrophils(10^9/L)	76	0.09	1.0 (1-1.0)		
Lymphocytes (10^9/L)	76	0.67	1.01 (1.0-1.0)		
Serum creatinine (μmol/L)†	80	0.09	1.01 (1.0-1.0)		
Serum albumin (g/dL)†	64	0.11	0.62 (0.35-1.1)		
Serum protein (g/dL)†	60	**0.01**	1.1 (1.0-1.1)	-----	-----
				-----	-----
Albumin creatinine	34	0.22	1.01 (0.99-1.03)		

ratio (mg/mmol)[†]					
Protein creatinine ratio (mg/mmol)[†]	66	**0.03**	1.01 (1.0-1.0)	----- -----	----- -----
24hr urinary protein (mg/24hr)[†]	66	**0.03**	1.0 (1-1.0)	----- -----	----- -----
eGFR (mL/min)[†]	79	**<0.001**	0.73 (0.63-0.84)	----- -----	----- -----
Treatment					
Angiotensin-converting-enzyme inhibitor	73	0.68	0.85 (0.40-1.8)		
Angiotensin II receptor blocker	71	0.63	1.3 (0.48-3.3)		
Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker	73	0.92	0.95 (0.39-2.3)		
Diuretics	71	0.45	1.3 (0.64-2.8)		
Immunosuppression	72	0.77	1.1 (0.50-2.6)		
Remission	76	**0.01**	0.50 (0.30-0.84)	----- -----	----- -----
Complete remission	76	**0.02**	0.24 (0.07-0.83)	----- -----	----- -----
Partial remission	75	0.93	0.96 (0.41-2.3)		
Relapse	43	0.07	0.40 (0.15-1.1)		
Steroid response	18	0.31	0.45 (0.10-2.1)		

[†] Hazards ratio per 10 unit increase

‡ Within the multivariate analysis two analysis were made (due to Pearson correlation coefficient of greater than 0.6, $p<0.05$). The first analysis included tubulointerstitial scarring however excluded eGFR, with the second analysis vice versa.

Table 5. Predictors towards the event of end stage renal disease

	Unadjusted Cox regression			Adjusted Cox regression‡	
Independent variable	Numbers	p-value	Hazards ratio (95% CI)	p-value	Hazards ratio (95% CI)
Clinical factors					
Age in decades	92	**0.01**	1.4 (1.1-1.7)	-----	-----
				-----	-----
Male Gender	92	0.52	1.2 (0.64-2.4)		
Ethnicity	92	0.20	0.62 (0.29-1.3)		
Diabetes	90	**0.049**	2.0 (1.0-3.9)	-----	-----
				-----	-----
Hypertension	88	0.26	1.8 (0.64-5.3)		
Hypercholesterolaemia	86	0.80	1.1 (0.51-2.4)		
Cardiovascular disease	85	0.35	1.4 (0.68-2.9)		
Ever smoked	84	0.75	1.1 (0.55-2.3)		
Infection	87	0.15	2.9 (0.67-12)		
Body Mass Index	82	0.38	0.84 (0.57-1.2)		
Haematuria	87	0.078	1.9 (0.93-3.7)		
Oedema	84	0.12	1.8 (0.86-3.8)		
Lesion factors					
Dual diagnosis	92	**0.007**	2.7 (1.3-5.5)	**0.006**	**3.5 (1.4-8.4)**
				0.027	**2.8 (1.1-6.9)**
Diabetic nephropathy	92	**0.002**	4.3 (1.7-10.8)	-----	-----
				-----	-----
IgA nephropathy	92	0.58	0.57 (0.077-4.2)		
Acute Tubular	92	**0.034**	3.7 (1.1-12)	-----	-----
Necrosis				-----	-----
NOS variant	92	0.201	2.5 (0.61-10)		
Tip variant	92	0.27	3.08 (0.42-22)		
Perihilar variant	92	0.78	0.049 ($2.8x10^{-11}$ – $8.5x10^{6}$)		
Collapsing variant	92	0.54	0.048 ($3.0x10^{-6}$- $8.9x10^{2}$)		
Cellular variant	92	0.83	1.2 (0.17-9.2)		
Tubulointerstitial	92	**<0.001**	3.04 (2.01-4.6)	-----	-----
Scarring				-----	-----
Biochemical factors					
Haemoglobin (g/L)†	87	**<0.001**	0.61 (0.51-0.74)	-----	-----
				-----	-----
White cell count (10^{9}/L)	87	0.703	1.02 (0.92-1.1)		
Platelets (10^{9}/L)†	86	0.47	0.99 (0.94-1.03)		
Neutrophils (10^{9}/L)	85	0.16	1.002 (1.0-1.0)		
Lymphocytes (10^{9}/L)	85	0.98	1.0 (0.98-1.02)		
Serum creatinine (μmol/L)†	88	**<0.001**	1.03 (1.02-1.04)	**<0.001**	**1.04 (1.02-1.05)**
				-----	-----
Serum albumin (g/dL)†	73	0.12	0.65 (0.38-1.1)		
Serum protein (g/dL)†	66	0.101	1.04 (0.99-1.08)		
Albumin creatinine ratio (mg/mmol)†	38	0.39	1.009 (0.99-1.03)		
Protein creatinine ratio (mg/mmol)†	76	**0.033**	1.009 (1.001-1.02)		
24hr urinary protein	76	0.053	1.001 (1.0-1.002)		

(mg/24hr)[†]					
eGFR (mL/min)[†]	87	**<0.001**	0.49 (0.38-0.63)	-----	-----
				<0.001	**0.57 (0.45-0.72)**
Treatment					
Angiotensin-converting-enzyme inhibitor	82	0.32	0.69 (0.34-1.4)		
Angiotensin II receptor blocker	80	0.97	1.02 (0.39-2.7)		
Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker	82	0.26	0.64 (0.29-1.4)		
Diuretics	81	0.64	0.83 (0.38-1.8)		
Immunosuppression	81	0.33	1.5 (0.69-3.1)		
Remission	87	**0.001**	0.43 (0.25-0.72)	**0.031**	**0.53 (0.301-0.95)**
				0.005	**0.43 (0.45-0.72)**
Complete remission	87	**0.006**	0.13 (0.031-0.56)	-----	-----
				-----	-----
Partial remission	86	0.92	1.04 (0.46-2.3)		
Relapse	48	0.087	0.42 (0.16-1.1)		
Steroid response	22	0.052	0.24 (0.056-1.01)		
Outcomes					
Doubled creatinine	91	**<0.001**	5.4 (2.4-11)	**<0.001**	**5.3 (2.09-13)**
				-----	-----

[†] Hazards ratio per 10 unit increase

‡ Within the multivariate analysis two analysis were made (due to Pearson correlation coefficient of greater than 0.6, $p<0.05$). The first analysis included tubulointerstitial scarring however excluded eGFR, with the second analysis vice versa.

Table 6. Predictors towards the event of death

Independent variable	Unadjusted Cox regression Numbers	p-value	Hazards ratio (95% CI)	Adjusted Cox regression‡ p-value	Hazards ratio (95% CI)
Clinical factors					
Age in decades	87	**<0.001**	2.3 (1.6-3.4)	**0.030**	**3.4 (1.1-10.5)**
				0.030	**3.4 (1.1-10.5)**
Gender	87	0.31	0.601 (0.22-1.6)		
Ethnicity	87	0.71	0.83 (0.31-2.2)		
Diabetes	80	0.15	2.07 (0.78-5.5)		
Hypertension	78	0.39	2.5 (0.32-18)		
Hypercholesterolaemia	79	0.52	0.72 (0.26-2.0)		
Cardiovascular disease	77	**0.002**	5.7 (1.9-17)	-----	-----
				-----	-----
Ever smoked	76	0.82	1.1 (0.402-3.2)		
Infection	78	0.59	1.8 (0.23-14)		
Body mass index	74	**0.029**	0.53 (0.30-0.94)	-----	-----
				-----	-----
Haematuria	82	0.14	2.06 (0.80-5.3)		
Oedema	78	0.74	1.2 (0.45-3.1)		
Lesion factors					
Dual diagnosis	87	0.30	1.8 (0.61-5.03)		
Diabetic nephropathy	87	0.089	3.0 (0.85-10.5)		
IgA nephropathy	87	0.99	0.99 (0.13-7.6)		
Acute tubular necrosis	87	0.25	3.4 (0.43-27)		
NOS variant	87	0.32	25 (0.047-13046)		
Tip variant	87	0.46	0.044 ($1.3x10^{5}$ -158)		
Perihilar variant	87	0.88	0.049 (6.3×10^{-19} - $3.8x10^{15}$)		
Collapsing variant	87	0.72	0.048 ($3.6x10^{-9}$ – $6.3x10^{5}$)		
Cellular variant	87	0.61	0.046 ($3.7x10^{-7}$ – $5.7x10^{3}$)		
Tubulointerstitial Scarring	87	**0.001**	2.5 (1.4-4.3)	-----	-----
				-----	-----
Biochemical factors					
Haemoglobin (g/L)†	82	**0.001**	0.69 (0.56-0.87)	-----	-----
				-----	-----
White cell count (10^{9}/L)	82	0.051	1.1 (1.0-1.3)		
Platelets (10^{9}/L)†	81	**0.04**	0.92 (0.85-1.0)	-----	-----
				-----	-----
Neutrophils (10^{9}/L)	80	0.56	1.0 (0.98-1.009)		
Lymphocytes (10^{9}/L)	80	**0.001**	0.21 (0.09-0.51)	-----	-----
				-----	-----
Serum creatinine (μmol/L)†	84	**0.002**	1.02 (1.0-1.03)	-----	-----
				-----	-----
Serum albumin (g/dL)†	70	0.43	0.73 (0.33-1.6)		
Serum protein (g/dL)†	64	**0.02**	1.1 (1.0-1.1)	-----	-----
				-----	-----
Albumin creatinine ratio (mg/mmol)†	58	**0.04**	1.0 (1.0-1.1)	-----	-----
				-----	-----
Protein creatinine ratio	67	0.97	1.0 (0.99-1.0)		

(mg/mmol)[†]					
24hr urinary protein (mg/24hr)[†]	67	0.66	1.0 (1.0-1.0)		
eGFR (mL/min)[†]	83	<**0.001**	0.62 (0.48 – 0.80)	----- -----	----- -----
Treatment					
Angiotensin-converting-enzyme inhibitor	73	0.039	0.33 (0.11-0.94)		
Angiotensin II receptor blocker	70	0.85	0.86 (0.19-3.9)		
Angiotensin-converting-enzyme inhibitor/ angiotensin II receptor blocker	72	**0.02**	0.26 (0.089-0.78)	----- -----	----- -----
Diuretics	70	0.77	1.2 (0.39-3.5)		
Immunosuppression	72	0.35	1.8 (0.54-5.7)		
Remission	81	0.094	0.56 (0.28-1.1)		
Complete remission	81	0.21	0.38 (0.09-1.7)		
Partial remission	81	0.55	0.68 (0.19-2.4)		
Relapse	48	0.64	0.74 (0.21-2.6)		
Steroid response	15	0.19	0.20 (0.02-2.2)		
Outcomes					
ESKD	78	0.09	2.7 (0.87-8.6)		
Doubled creatinine	84	0.50	1.4 (0.53-3.7)		

[†] Hazards ratio per 10 unit increase

‡ Within the multivariate analysis two analysis were made (due to Pearson correlation coefficient of greater than 0.6, $p<0.05$). The first analysis included tubulointerstitial scarring however excluded eGFR, with the second analysis vice versa.