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Kidney outcomes of immune-complex associated mesangiocapillary glomerulonephritis in patients with and without HIV

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ABSTRACT

Introduction: HIV-associated kidney diseases continue to be a major problem in South Africa.
Objectives: We aimed to determine the kidney outcomes of immune-complex associated mesangiocapillary glomerulonephritis (MCGN) in patients with and without HIV.
Patients and Methods: A retrospective cohort study was conducted on all adult patients with a kidney biopsy diagnosis of immune-complex associated MCGN from 1 January 2000 to 31 December 2016. We compared the proportion of HIV-positive and HIV-negative patients that reached the composite endpoint of either doubling of the serum creatinine or end-stage kidney disease. Cox proportional hazards models were employed to examine the association between the composite endpoint and predictor variables.
Results: A total of 79 patients were included of which 20 (25.3%) were HIV-positive. Twenty-four patients (30.4%) reached the composite endpoint. The cumulative proportions reaching the composite endpoint at one and four years were 25.3% and 30.4% with no difference between HIV-positive and HIV-negative patients (45.0% versus 25.4%, respectively; $P=0.10$). Multivariable Cox proportional hazards model identified estimated glomerular filtration rate at biopsy (hazard ratio [HR] = 0.92; 95% confidence interval [CI]: 0.84-1.00, $P=0.04$) and proteinuria at follow-up (HR = 1.60; 95% CI: 1.21-2.11, $P<0.01$) as predictors of the composite endpoint at one-year. On survival analysis, there was no difference in the composite endpoint for HIV status ($P=0.09$; log-rank).
Conclusion: Immune-complex associated MCGN continues to be a common histopathological pattern of injury at our center. Due to late presentation, kidney outcomes remain poor, regardless of HIV status.

Original Article

Implication for health policy/practice/research/medical education:
HIV immune-complex associated MCGN remains a common histopathological pattern of injury in developing countries with a high HIV prevalence. Due to late presentation of both the HIV diagnosis and the glomerular disease, the outcome is poor, regardless of the HIV status. Educating healthcare providers about chronic glomerular diseases along with frequent screening of at-risk populations should be prioritized so that early interventions can be instituted to prevent progression to end-stage kidney disease, particularly in countries where access to kidney replacement therapy is being rationed.

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Introduction

An association between HIV infection and kidney disease was reported since the 1980s when HIV-associated nephropathy was first described. Despite the introduction of antiretroviral therapy, kidney diseases continue to be a frequent complication in HIV patients living in South Africa (1). HIV infection has been associated with numerous immune-complex glomerular diseases, including mesangiocapillary glomerulonephritis (MCGN) (also known as membranoproliferative

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glomerulonephritis), IgA nephropathy, membranous nephropathy, lupus-like glomerulonephritis and post-infectious glomerulonephritis (2, 3). Immune-complex glomerulonephritis may be caused by circulating or in-situ immune complexes that become incorporated into glomerular tissue (4). Genetic susceptibility, environmental and also host-pathogen interactions promote the development of immune-complex glomerulonephritis (2).

MCGN is a histopathological pattern of injury that is characterized by the presence of mesangial and endocapillary cellular proliferation, double contours along the capillary walls and lobulated capillary tufts (5). It is classified histologically according to the presence or absence of immune complexes on immunofluorescence staining (5). Three categories have been described; 1) immunoglobulin plus C3 deposits (the immune-complex group), 2) exclusive C3 deposition and 3) absence of immunoglobulin and C3 deposits. The immune-complex group may be caused by autoimmune diseases such as systemic lupus erythematosus, paraproteinemia and chronic infections including hepatitis B, hepatitis C and HIV.

A kidney biopsy series from Cape Town, South Africa found 8.3% of biopsies in HIV positive patients had immune-complex kidney disease, 12.5% of which had an exclusive MCGN pattern of injury (6), while another study from South Africa only reported that 2% of kidney biopsies in HIV infected patients had an MCGN pattern (7). Data from other parts of Africa are scarce. In the Johns Hopkins HIV clinical cohort, immune-complex kidney disease accounted for nearly a third of all biopsies, with 7% revealing an MCGN pattern of injury (8). In a 20-year kidney biopsy series of HIV patients at a single center in Italy, immune-complex kidney diseases were observed in nearly 55% (9). Similarly, in Germany, HIV immune-complex glomerulonephritis was observed in 26.1% of HIV kidney biopsies (10).

A recent study of all kidney biopsies performed at our center over a 23-year period revealed MCGN as the most common primary glomerulonephritis and was associated with poor kidney and patient outcomes (11, 12). Although there are conflicting reports, antiretroviral therapy has been shown to improve survival in HIV patients with immune-complex kidney disease (6). There are concerns about the use of immunosuppressive agents in an already immunocompromised population (2).

Objectives

A comparison of the proportion of HIV-positive and HIV-negative patients with a biopsy confirmed diagnosis of immune-complex associated MCGN to reach the composite endpoint of either doubling of the serum creatinine or the development of end-stage kidney disease.

Patients and Methods

Study design

This was a retrospective cohort study of all HIV-positive and HIV-negative adult patients (18-years old or more) with a kidney biopsy confirmed diagnosis of immune-complex associated MCGN at Tygerberg Hospital (TBH), in Cape Town, South Africa, between 1 January 2000 to 31 December 2016. TBH is a 1380 bed facility that offers tertiary level care to nearly 2.5 million people dependent on the public sector for health care and is one of two hospitals to offer nephrology services in the public sector.

Patients were selected by reviewing histology records from the department of anatomical pathology. Clinical and laboratory data were extracted from electronic medical records and the national health laboratory service (NHLS), respectively.

Patients with documented or proven secondary causes of MCGN, other than HIV, including systemic lupus erythematosus, post-infectious glomerulonephritis, infective endocarditis, and other chronic viral infections such as hepatitis B and C, and also those with C3 glomerulopathy (C3GN) were excluded. Since our patient population was young, screening tests for monoclonal gammopathies such as serum or urine protein electrophoresis and serum free light chains were only conducted when the clinical index of suspicion was high.

Demographic data included age, gender and ethnicity. Clinical data included history of hypertension and diabetes mellitus, a history substance abuse or incarceration, indications for kidney biopsy, duration of follow-up from the date of kidney biopsy up until the time to reach the composite endpoint, blood pressure at presentation and pharmacological therapies received.

Laboratory data included serum albumin, cholesterol, creatinine, estimated glomerular filtration rate, proteinuria and complement components 3 and 4 levels at the time of biopsy and at follow-up.

Histological data included the number of glomeruli, proportion of interstitial fibrosis (graded as none, mild, moderate and severe), proportion of sclerosed glomeruli (graded as none, less than 50% and 50% or more) and proportion of crescents (graded as none, less than 50% and 50% or more), immunofluorescence staining for IgA, IgM, IgG and C3 (graded as absent, 1+, 2+ and 3+) and electron-microscopy features including mesangial, sub-epithelial and sub-endothelial electron-dense deposits, mesangial interposition, and the presence of tubulo-reticular inclusion bodies (TRIBS).

Statistical analysis

Descriptive data were reported as means and standard deviations if data were normally distributed, or median and interquartile ranges (IQR) if data were not normally

distributed. Chi-square and Fisher's exact tests were used to compare categorical variables. Student's t-test was utilized to compare continuous variables that were normally distributed while Mann-Whitney U test was applied for continuous variables that were not normally distributed. Univariable and multivariable Cox proportional hazards regression models were used to identify any associations with the composite endpoint and predictor variables at one-year. Kaplan-Meier survival analyses were employed and associated log-rank *P* values were reported. A *P* value <0.05 was considered statistically significant and 95% confidence intervals (95% CI) were used. Analysis was conducted using Stata IC version 16.1.

Results

A total of 144 kidney biopsies with a pathological diagnosis of MCGN were screened for inclusion. Sixty-five patients were excluded because 22 were considered to have C3GN, three patients had no HIV serology, seven had no immunofluorescence and 33 were lost to follow-up. Therefore, a total of 79 patients were included in the study of which 20 (25.3%) were HIV-positive. The median follow-up for the entire cohort was seven (IQR 3-12) months. Twenty-four patients (30.7%) reached the composite endpoint of which 15 (25.4%) were HIV-negative and nine (45.0%) were HIV-positive ($P=0.10$). The overall proportions reaching the endpoint at 1-year, 2-years, 3-year, and 4-years were 25.3%, 26.6%, 29.1% and 30.4%, respectively, with no statistical differences based on HIV status (Table 1).

Table 2 represents the demographic, clinical and laboratory data. The median age was 37 (IQR: 25-46) years. Most of the HIV negative patients were of mixed ancestry (58.2%), while most of the HIV positive patients were Black (80%), $P<0.01$. None of the HIV-positive patients had a history of substance abuse or incarceration (0% versus 34.8%; $P<0.01$).

There were no differences regarding baseline clinical data (Table 2). Regarding laboratory data, HIV-positive patients had a lower serum albumin concentration (26.4 g/L versus 20.2 g/L; $P<0.01$), higher serum creatinine concentration (172 µmol/L versus 354.5 µmol/L, $P=0.03$) and lower estimated glomerular filtration rate (eGFR) (40 mL/min/1.73 m^2 versus 20 mL/min/1.73 m^2; $P=0.04$) at the time of kidney biopsy. At follow-up, HIV-positive patients had a higher serum creatinine concentration (129 µmol/L versus 422 µmol/L; $P=0.03$), lower eGFR (55 mL/min/1.73 m^2 versus 22 mL/min/1.73m^2; $P=0.04$) and more proteinuria (2.1 g per day versus 6.5 g per day; $P<0.01$).

Table 3 represents the light microscopy, immunofluorescence and electron microscopy findings. On light microscopy, more HIV-positive patients had moderate to severe interstitial fibrosis (85% versus 55.7%; $P<0.04$). There were no differences with regards to C3, IgG, IgA or IgM deposits on immunofluorescence microscopy. On electron microscopy, HIV-positive patients had more tubulo-reticular inclusion bodies ($P<0.01$).

Table 4 shows the treatment received. More HIV-positive patients received dialysis (20% versus 1.7%; $P<0.01$). There were no differences with regards to the prescription of renin-angiotensin aldosterone system inhibitors (RAASi), oral or intravenous pulse steroids or oral cyclophosphamide administration.

Table 5 shows factors associated with the composite endpoint using Cox univariable and multivariable proportional hazard models. Serum creatinine concentration at biopsy (hazard ratio [HR]: 1.00, 95% CI: 1.00-1.00, $P<0.01$), eGFR at biopsy (HR: 0.97, 95% CI: 0.95-0.99, $P<0.01$), proteinuria at follow-up (HR: 1.35, 95% CI: 1.19-1.53, $P<0.01$), the presence of moderate to severe interstitial fibrosis (HR: 12.67, 95% CI: 1.71-93.94, $P<0.01$), 50% or more global glomerular sclerosis [HR: 5.73, 95% CI: 1.67-19.62, $P<0.01$) and the need for acute dialysis (HR: 3.27, 95% CI: 1.11-9.65, $P<0.03$) were predictors associated with the composite endpoint at one-year on univariable analysis; however, only eGFR at biopsy (HR: 0.92, 95% CI: 0.84-1.00, $P<0.04$) and proteinuria at follow-up (HR: 1.60, 95% CI: 1.21 -2.11, $P<0.01$] were associated with the composite endpoint at one-year on multivariable analysis.

On Kaplan-Meier survival analysis, severe interstitial fibrosis (log–rank; $P<0.01$), 50% or more global

Table 1. Proportion of patients reaching the composite endpoint by year following kidney biopsy

End of year	Composite endpoint of doubling of creatinine or ESKD, n (%)			*P* value	Cumulative percent (%)		
	All, n=24/79	HIV+, n=9/20	HIV-, n=15/59		All	HIV+	HIV-
1	20 (25.3)	7 (35.0)	13 (22.0)	0.24	25.3	35.0	22.0
2	1 (1.3)	1 (5.0)	0 (0)	0.25	26.6	40.0	22.0
3	2 (2.5)	1 (5.0)	1 (1.7)	1.00	29.1	45.0	23.7
4	1 (1.3)	0 (0)	1 (1.7)	-	30.4	-	25.4

Abbreviations: ESKD, end-stage kidney disease; HIV, human immunodeficiency virus.

Table 2. Comparison of demographic, clinical and laboratory data

	HIV-negative, n (%) = 59 (100)	HIV-positive, n (%) = 20 (100)	*P* value
Composite endpoint reached, n (%)	15 (25.4)	9 (45.0)	0.10
Demographic characteristics			
Age at biopsy in years, median (IQR)	37 (25-46)	33.5 (28.5-39)	0.40
Male, n (%)	37 (62.7)	10 (50)	0.32
Ethnicity, n (%)			
Black	17 (28.8)	16 (80)	**<0.01**
Mixed ancestry	42 (71.2)	4 (20)	
History of hypertension, n (%)	28 (47.5)	7 (35)	0.33
History of diabetes mellitus, n (%)	3 (5.1)	1 (5)	1.00
Antiretroviral therapy, n (%)	NA	12 (60.0)	-
History of substance abuse or incarceration	16 (34.8)	0 (0)	**<0.01**
Duration of follow-up (months), median (IQR)	8 (4-12)	5.5 (3-9.5)	0.15
Clinical characteristics			
Oedema, n (%)	48 (81.3)	18 (90.0)	0.57
Systolic blood pressure, median (IQR)	142 (130-157)	140.5 (130-165)	0.82
Diastolic blood pressure, median (IQR)	82 (76-91)	90 (80-95)	0.28
Mean arterial pressure, median (IQR)	103.3 (95-112.3)	107.5 (100-120)	0.55
Indications for biopsy, n%			
Acute kidney injury	5 (8.5)	1 (5)	0.08
Nephritic syndrome	1 (1.7)	0 (0)	
Nephrotic syndrome	6 (10.2)	7 (35)	
Nephritic-nephrotic syndrome	41 (69.5)	9 (45)	
Rapidly progressive glomerulonephritis	6 (10.2)	3 (15)	
Laboratory data			
CD4 count (cells per mm^3), mean ± SD	‡NA	263.1 ± 222.0	-
Serum albumin (g/L), mean ± SD	26.4 ±6.7	20.2±6.6	**<0.01**
Serum cholesterol (mmol/L), median (IQR)	5.7 (4.8-7.5)	5.0 (4.6-5.8)	0.17
Creatinine at biopsy (µmol/L), median (IQR)	172 (108-286)	354.5 (138-653.5)	**0.03**
eGFR at biopsy (mL/min/1.73 m^2), median (IQR)	40 (20-79)	20 (10-53)	**0.04**
Creatinine at follow-up (µmol/L), median (IQR)	129 (83-479)	422 (150-972.5)	**0.03**
eGFR at follow-up (mL/min/1.73 m^2), median (IQR)	55 (12-108)	22 (6-63)	**0.04**
Proteinuria at biopsy (g/d), median (IQR)	6.2 (4.9- 8.6)	8.9 (6-14.2)	**<0.01**
Proteinuria at follow-up (g/d), median (IQR)	2.1 (0.3-5.1)	6.5 (3.8 – 12.5)	**<0.01**
C3 at biopsy (g/L), mean ± SD	0.9 ± 0.4	0.8 ± 0.4	0.34
C4 at biopsy (g/L), mean ± SD	0.3 ± 0.1	0.3 ± 0.1	0.52

Abbreviations: HIV, Human immunodeficiency virus; NA, not applicable; IQR, Interquartile range; CD4, Cluster of differentiation 4 positive T-helper cells; eGFR, estimated glomerular filtration rate; C3, complement component 3; C4, complement component 4.

glomerular sclerosis (log-rank; $P<0.03$) and presence of any crescents (log-rank; $P<0.01$; Figure 1B-D) were associated with the composite endpoint. There were no differences regarding HIV status (log-rank; $P<0.09$; Figure 1A).

Discussion

To the best of our knowledge, this is the first study comparing the kidney outcomes of HIV-positive and HIV-negative patients with a biopsy-confirmed diagnosis of immune-complex associated MCGN. Nearly a third of patients reached the composite endpoint. Patients with more advanced kidney disease at the time of kidney biopsy were more likely to reach this outcome. Late presentation was probably the main reason for this poor outcome. Factors that may have contributed included lack of access to health care and delays in the recognition of glomerular disease at peripheral hospitals resulting

Table 3. Comparisons of histological data

	HIV-negative, n (%)	HIV-positive, n (%)	*P* value
Light microscopy			
Number of glomeruli	45 (29-59)	37 (31-50)	0.64
Globally sclerosed glomeruli			
Absent	15 (25.4)	2 (10.0)	0.38
<50%	25 (59.3)	14 (70.0)	
≥50%	9 (15.3)	4 (20.0)	
Interstitial fibrosis			
Absent to mild	25 (42.4)	3 (15.0)	**0.04**
Moderate to severe	34 (57.7)	17 (85.0)	
Crescents			
Absent	25 (42.4)	7 (35.0)	0.31
<50%	28 (47.5)	8 (40.0)	
≥50%	6 (10.2)	5 (25.0)	
Immunofluorescence			
C3 deposits			
Absent	4 (6.8)	0 (0)	0.78
1+	9 (15.3)	2 (10.0)	
2+	34 (57.6)	13 (65.0)	
3+	12 (20.3)	15 (25.0)	
IgG deposits			
Absent	14 (23.7)	9 (45)	0.18
1+	25 (42.4)	4 (20.0)	
2+	18 (30.5)	7 (35.0)	
3+	2 (3.5)	0 (0)	
IgM deposits			
Absent	18 (30.5)	5 (25)	0.96
1+	26 (44.1)	10 (50.0)	
2+	14 (23.7)	5 (25.0)	
3+	1 (1.7)	0 (0)	
IgA deposits			
Absent	31 (52.5)	12 (60)	0.37
1+	21 (35.6)	8 (40.0)	
2+	7 (11.9)	0 (0)	
3+	0 (0)	0 (0)	
Electron microscopy			
Subendothelial deposits			
Absent	2 (3.5)	0 (0)	1.00
Occasional	6 (10.3)	2 (10.0)	
Prominent	50 (86.2)	18 (90.0)	
Mesangial deposits			
Absent	28 (48.3)	7 (35.0)	0.30
Occasional	0 (0)	0 (0)	
Prominent	30 (51.7)	13 (65.0)	
Sub-epithelial deposits			
Absent	42 (72.4)	13 (65.0)	0.49
Occasional	15 (25.9)	6 (30.0)	
Prominent	1 (1.7)	1 (5.0)	
Mesangial interposition			
Absent	1 (1.7)	2 (10.0)	0.28
Occasional	9 (15.5)	2 (10.0)	
Prominent	48 (83.8)	16 (80.0)	
TRIBS			
Absent	50 (91.5)	12 (60.0)	**<0.01**
Present	5 (8.5)	8 (40.0	

Abbreviations: HIV, Human immunodeficiency virus; C3, complement component 3; IgG, immunoglobulin G; IgM, immunoglobulin M; IgA, immunoglobulin A; TRIBS, tubulo-reticular inclusion bodies.

Table 4. Comparison of treatments

	HIV-negative, n (%)	HIV-positive, n (%)	*P* value
Acute dialysis	1 (1.7)	4 (20.0)	**0.01**
RAASi	32 (54.2)	6 (30.0)	0.09
Oral prednisone	9 (15.2)	2 (10.0)	1.00
Intravenous pulse steroid	0 (0)	1 (5.0)	0.21
Oral cyclophosphamide	2 (3.4)	1 (5.0)	0.51

Abbreviations: RAASi, Renin-angiotensin-aldosterone system inhibitors including angiotensin-converting enzyme inhibitor and angiotensin receptor blocker.

in late referral to nephrology services (12). Although there was no difference between HIV-positive and HIV-negative patients reaching the composite endpoint, the severity of the kidney failure and the quantity of proteinuria at the time of kidney biopsy was greater in HIV patients. Despite South Africa having one of the largest antiretroviral therapy roll-out programmes in the world, many patients continue to be diagnosed late and therefore do not receive the antiretroviral therapy needed to prevent life-threatening conditions (13, 14). Although 60% of patients were receiving antiretroviral therapy at the time of kidney biopsy, most were initiated during the index presentation by referral centers. Since a direct role of HIV infection and immune-complex kidney disease has been postulated (4), earlier diagnosis and initiation of antiretroviral therapy may have reduced the burden of kidney disease in this patient population. The large proportion of patients reaching the composite endpoint is of concern, as many will not be accommodated on public sector chronic kidney replacement therapy programmes due to limited availability and rationing (15).

More black patients were found to be HIV-positive and is consistent with another study (6). This may reflect the overall higher HIV prevalence among the black population in South Africa (16). However, the apolipoprotein-L1 (APOL1) genetic risk variants have been identified as another risk factor for the excess development of non-diabetic kidney disease in black patients, particularly those of West African descent (17, 18). The association between APOL1 variants and immune-complex kidney diseases in HIV are poorly understood. A study could only identify one APOL1 risk allele in 47% of HIV infected patients with immune-complex kidney disease (19). Patients with two risk alleles had a three-fold greater risk for progression to end-stage kidney disease (ESKD) compared to those with zero or one risk allele.

More HIV-negative patients reported current or prior substance abuse or incarceration. A study found that more than half of methamphetamine abusers, colloquially referred to as 'tic', had a MCGN pattern of injury on

Table 5. Cox univariable and multivariable proportional hazards models of variables associated with the composite endpoint at 1-year following kidney biopsy

Variable	Univariable		Multivariable	
	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age(year)	1.00 (0.97-1.03)	0.87		
Female sex	0.86 (0.38-1.98)	0.73		
Mixed ancestry	1.80 (0.73-4.28)	0.20		
HIV positive	2.26 (0.98-5.18)	0.06	13.30 (0.49-359.52)	0.12
Creatinine at biopsy	1.00 (1.00-1.00)	**<0.01**	1.00 (0.99-1.00)	0.30
eGFR at biopsy	0.97 (0.95-0.99)	**<0.01**	0.92 (0.84-1.00)	**0.04**
Proteinuria at biopsy	1.10 (1.005-1.20)	**0.04**	0.85 (0.62-1.18)	0.34
Proteinuria at follow-up	1.35 (1.19-1.53)	**<0.01**	1.60 (1.21-2.11)	**<0.01**
Moderate to severe interstitial fibrosis	12.67 (1.71-93.94)	**0.01**	1.14 (0.03-43.45)	0.94
≥50% Globally sclerosed glomeruli	2.80 (1.19-6.58)	**0.02**	13.11 (0.73-235.48)	0.08
Crescents ≥50%	5.73 (1.67-19.62)	**<0.01**	18.37 (0.52-651.53)	0.11
Acute dialysis	3.27 (1.11-9.65)	**0.03**	0.99 (0.04-22.75)	1.00
RAASi	0.64 (0.21-1.93)	0.42		
Oral steroids	0.70 (0.20-2.43)	0.58		
Cyclophosphamide	1.79 (0.23-13.69)	0.57		

Abbreviations: HR, hazard ratio; eGFR; estimated glomerular filtration rate; RAASi, renin-angiotensin-aldosterone system inhibitors including angiotensin-converting enzyme and angiotensin receptor blocker; CI, confidence interval.

kidney biopsy (20). Although it was previously found that HIV infected patients with immune-complex glomerulonephritis reported drug abuse (8), others reported no association with HIV-associated kidney disease (6). Similarly, none of the HIV-positive patients in our study had a history of substance abuse or incarceration, while nearly a third of the HIV-negative patients reported prior or current exposures. Among substance abusers, MCGN may result from chronic exposure to antigens (5). These antigens may be transmitted during exposure to a yet unidentified infection or acquired through sharing of drug paraphernalia.

Multivariable Cox proportional hazards model identified eGFR at biopsy and proteinuria at follow-up as predictors of the composite endpoint. As with many other glomerular diseases, persistent nephrotic-range

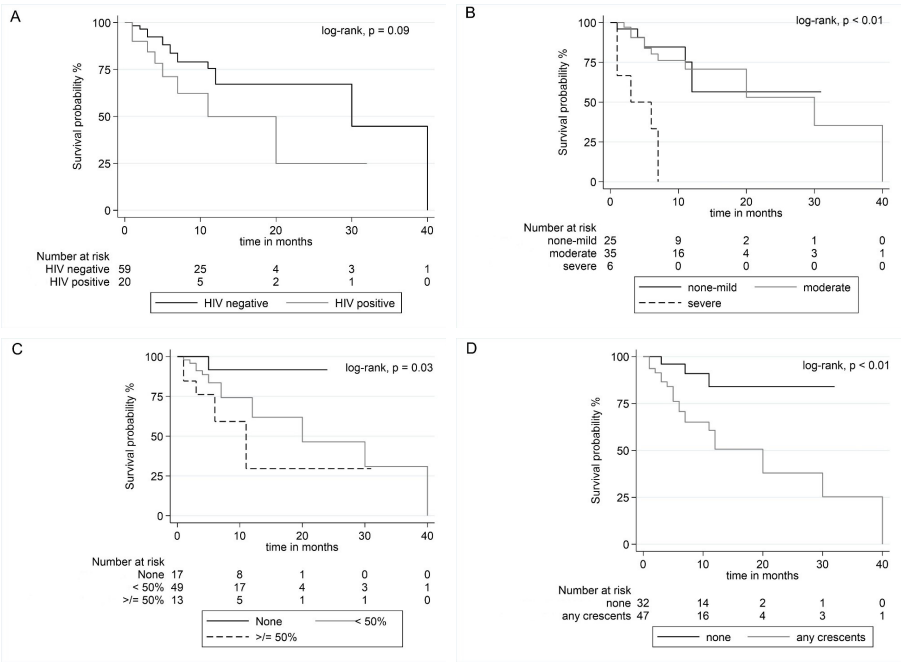

Figure 1. Kaplan-Meier survival estimates of the composite endpoint-free survival for HIV status (A), interstitial fibrosis (B), global glomerular sclerosis (C) and crescents (D).

proteinuria during follow-up is a powerful predictor of poor patient and kidney outcomes (21, 22). The presence of moderate to severe interstitial fibrosis, 50% or more global glomerular sclerosis and 50% or more crescents were histologic predictors associated with the composite endpoint on a univariable Cox proportional hazards model. These severe histological lesions are additional evidence of late presentation. Consequently, the initiation of any pharmacological therapies, including antiretroviral therapy, during this late stage was unlikely to alter the trajectory of kidney function decline. We have previously reported that patients treated with cyclophosphamide had poor kidney and patient survival and was thought to be related to late presentation with severe histopathological lesions (12).

Conclusion

Immune-complex associated MCGN continues to be a common histopathological pattern of injury at our center. Due to late presentation, kidney outcomes remain poor, regardless of HIV status.

Limitations of the study

This study had a retrospective design, small sample size and missing data which may have affected the robustness of the statistical analysis. Most secondary causes were excluded; however, monoclonal gammopathies could not be ruled out with certainty during the earlier period of the study. Since this was a single-center study, the findings may not be generalizable.

Authors' contribution

Conceptualization: MYC and AJI. Methodology: MYC, AJI, LC, WB. Validation: MYC and AJI. Formal Analysis: MYC and AJI. Investigation: AJI. Resources: AJI. Data Curation: AJI. Writing—Original Draft Preparation: AJI. Writing—Review and Editing: AJI, LC, WB, MYC. Visualization: MYC and AJI. Supervision: MYC. Project Administration: AJI

Conflicts of interest

None to declare.

Ethical issues

Ethics approval was obtained from Human Research Ethics Committee (HREC) at the Faculty of Medicine and Health Sciences of Stellenbosch University in Cape Town, South Africa (Project ID:18690, Reference No: S20/09/235). This included a waiver of informed consent due to the retrospective study design. This study was conducted in accordance with the Declaration of Helsinki. Besides, ethical issues (including plagiarism, data fabrication and double publication) were observed by the authors.

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