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Patterns of biopsy-proven kidney disease among South African adults from 1995 to 2017

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ABSTRACT

Introduction: Few data are available on biopsy-proven kidney disease in African countries. In this study, we describe the patterns of biopsy-proven kidney disease among South African adults encountered over a 23-year period and report whether these have changed over time.

Methods: This retrospective study included all adults who underwent a native kidney biopsy at Tygerberg Hospital in Cape Town, from January 1995 to December 2017. Only the first biopsy for each patient was included in the analysis. From patient records, we extracted demographic and clinical information and details of the kidney biopsies, including the indications and the final histopathological diagnosis.

Results: During the study period, 2 227 first native kidney biopsies were performed. The median age of the patients was 38.0 years (interquartile range 30.0–48.1 years), and 53.3% were female. The most common indication for biopsy was nephrotic syndrome (38.6%). Glomerulonephritis (GN) was the most common pattern of kidney disease, with similar numbers of cases of primary and secondary glomerular disease. Among the primary glomerular diseases, mesangiocapillary GN (34.5%) was the most common, followed by focal segmental glomerulosclerosis (22.3%) and membranous nephropathy (15.8%). Among the secondary glomerular diseases, lupus nephritis was the most common (39.1%), followed by human immunodeficiency virus-associated nephropathy (HIVAN, 22.1%), and diabetic nephropathy (14.4%). IgA nephropathy was uncommon, accounting for only 2.0% of cases of glomerular disease, as was hypertensive kidney disease, which was diagnosed in only 1.3% of all our biopsies.

Conclusions: Over the last two decades, mesangiocapillary GN was the most common primary glomerular disease and lupus nephritis the most common secondary glomerular disease. There was a steady increase in the number of patients with HIVAN. Hypertensive nephropathy was an uncommon histological diagnosis, and IgA nephropathy remains rare.

Keywords: kidney biopsy; histopathology; glomerular disease; South Africa.

INTRODUCTION

The global prevalence of chronic kidney disease (CKD) is estimated at 8–16% [1], with diabetes and hypertension being major contributors, and glomerulonephritis (GN) also an important cause. There is much variation in the spectrum of kidney diseases reported [2] and the causes, prevalence and outcomes in developing countries may differ compared to developed countries.

In most African countries, data on the topic are sparse because of limited kidney biopsy services and a lack of renal registries. The available data suggest that the causes of kidney failure are similar to those reported from developed countries, with hypertension, diabetic nephropathy and glomerular disease being the most common. The latest report from the South African Renal Registry [3] lists the most common causes of kidney failure as hypertensive kidney disease (36.6%), kidney failure of unknown cause (30.4%), diabetic nephropathy (14.3%) and glomerular disease (11.0%). Most of the

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patients included in this registry presented late and their diagnoses were never confirmed histologically.

Regarding glomerular disease in African countries, secondary glomerular diseases predominate. A systematic review of histologically proven glomerular disease in Africa reported minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS) and mesangiocapillary GN as the most common causes [4]. Hepatitis B-related glomerulonephritis and lupus nephritis were the most common forms of secondary glomerular disease, with the former more prevalent in sub-Saharan Africa and the latter in North Africa [4].

HIV infection is a major cause of kidney disease in sub-Saharan Africa, with the spectrum of kidney diseases including conditions directly associated with the virus, those linked to the systemic response to infection, complications of treatment and coincidental diseases such as diabetic nephropathy or lupus nephritis [5]. Classic HIV-associated nephropathy (HIVAN) is a collapsing form of FSGS with microcystic renal tubular dilatation, interstitial inflammation, fibrosis and tubulo-reticular inclusion bodies in endothelial cells [6]. HIVAN accounted for only 1.0% of cases of secondary glomerular diseases in the review by Okpechi et al. [4], whose authors suggest that limited kidney biopsy services leads to underreporting of this entity in many African countries.

Table 1 summarises the common patterns of glomerular disease previously reported in South Africa. Among the primary glomerular diseases, mesangiocapillary GN was the most common from another centre in Cape Town [7], whereas FSGS was the most common in the Johannesburg region [8,9]. IgA nephropathy was uncommon. The most common cause of secondary glomerular disease in all areas of the country was lupus nephritis [7-9].

Given the limited African data on the spectrum of kidney disease, we describe here the causes of biopsy-proven kidney disease we managed in Cape Town from 1995 to 2017 and also report whether disease patterns have changed over this period.

METHODS

Tygerberg Hospital (TBH) is a 1380-bed academic institution in Cape Town, South Africa, which provides tertiary renal services to approximately 2.5 million people in the Western Cape province. We conducted a retrospective study that included all adults (aged 20 years and older) who underwent kidney biopsy at TBH from January 1995 to December 2017. Transplant biopsies and biopsies that were reviewed by the Division of Anatomical Pathology at Tygerberg Hospital but had been performed at other hospitals were excluded from the study.

Kidney biopsies are usually performed with patients in the prone position, targeting the lower pole of the left kidney. In the early part of the period described in the study, biopsies of patients with normal kidney function were performed with the aid of radiocontrast screening; in patients with raised creatinine levels, they were conducted under ultrasound guidance. Conventional Tru-Cut® cutting needles were used initially, but more recently, the use of spring-loaded needles has been the norm, with all biopsies performed under direct, real-time ultrasound guidance.

All kidney tissue was evaluated by light microscopy, immunofluorescence and electron microscopy. The biopsy material was received fresh and unfixed, then divided under a dissecting microscope to provide optimal numbers of glomeruli for light and electron microscopy as well as immunofluorescence studies. The material for ultrastructural examination was fixed in 2.5% glutaraldehyde in 0.1 M

Table 1. Common patterns of glomerular disease in South Africa.

Region	Study	Period	Total biopsies	PGN	SGN
Bloemfontein	Van Rensburg, 2009 [10]	1997–2006	1216	FSGS, 19.0% Mesangiocapillary GN, 14.9% Membranous nephropathy, 11.5%	Lupus nephritis, 14.5%
Cape Town	Okpechi, 2011 [7]	2000–2009	1753	Mesangiocapillary GN, 20.4% Mesangioproliferative GN, 19.2% Membranous nephropathy, 18.5%	Lupus nephritis, 39.0% Infection-related GN, 30.1%
Johannesburg	Patchapen, 2017 [9]	2001–2010	1495	FSGS, 29.8% Membranous nephropathy, 19.5% Mesangiocapillary GN, 18%	Lupus nephritis, 55.8% Diabetic nephropathy, 9.6%
Johannesburg	Vermeulen, 2014 [8]	1982–2011	1848	FSGS, 29.6% Membranous nephropathy, 25.7% Mesangiocapillary GN, 18.1%	Lupus nephritis, 31.0% HIVAN, 13.3%

Abbreviations: FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; PGN, primary glomerulonephritis; SGN, secondary glomerulonephritis.

phosphate buffer, whereas the light microscopy material was fixed in buffered formalin. For light microscopy, serial two- to three-micrometre sections were stained with haematoxylin and eosin and other special stains as appropriate. Material for immunofluorescence was frozen, cryostat sections cut and labelled for IgA, IgG, IgM and C3. Electron microscopy specimens were post-fixed in osmium tetroxide embedded in Spurr's resin.

All biopsies were reviewed at weekly meetings between the nephrology team and the pathologist. In each case, the clinical information and the special investigations were presented by the clinicians involved, highlighting any information that would point to a multisystem disease or a secondary cause for the kidney disease. After reviewing the biopsy, a final clinico-pathological diagnosis was then made and the pathology report finalised.

Cases were identified from our REDCap [11] database, which was developed to hold data from the histopathology request forms and the final pathology reports. We extracted demographic and clinical information, including information on comorbidities, the clinical presentation and laboratory workup, as well as details of the kidney biopsies, including the final histopathological diagnosis.

Statistical analysis

Descriptive statistics were used to summarise the patient demographics and biopsy data, including the indications for the biopsy and the frequencies of each type of kidney disease. Means and standard deviations were used to summarise normally distributed numerical data, and medians and interquartile ranges for nonparametric data. Frequencies and percentages were used to describe categorical data.

Ethical approval to conduct the study was obtained from the Stellenbosch University Health Research Ethics Committee (reference no. N19/03/039).

RESULTS

The total number of biopsies performed at TBH from January 1995 to December 2017 was 2 888. During this 23-year period, 2 781 of the biopsies (96.3%) were reported by a single nephropathologist (WDB). The overwhelming majority were native kidney biopsies (2 684, 92.9%), including 308 which were biopsies performed on children (≤19 years of age), 59 which were repeat or follow-up biopsies, and 90 biopsies that were inconclusive due to inadequate tissue samples. There were 204 transplant biopsies, including 14 repeat biopsies. Transplant rejection was the most common histopathological diagnosis in the transplant biopsies. The 2 227 native adult kidney biopsies, which were the first biopsies for each patient, is the sample on which this report is based (Figure 1).

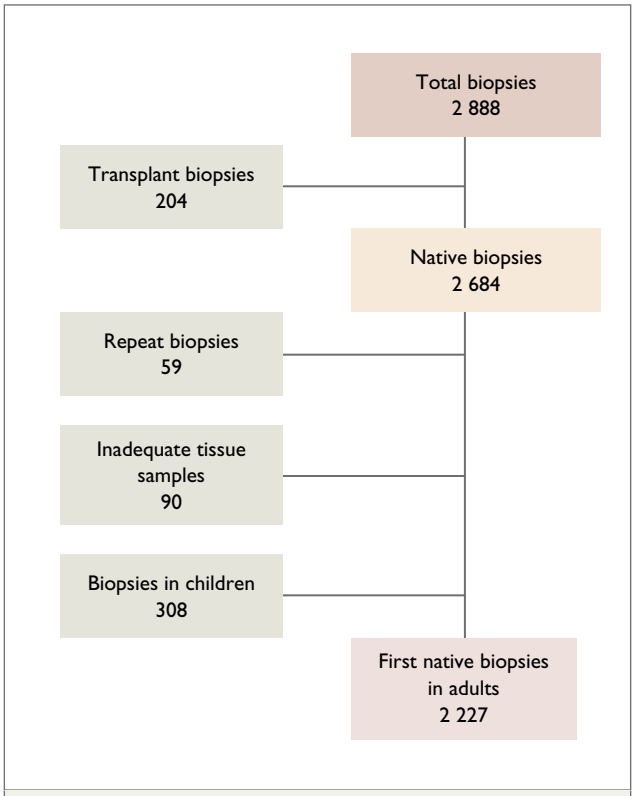

Figure 1. Study flow chart. Kidney biopsies performed at Tygerberg Hospital from 1995 to 2017.

The 23 years of the study were divided into four equal periods, each consisting of 69 months (5.75 years). Over time, the annual number of biopsies performed steadily increased, with almost twice as many biopsies performed over the last quartile compared to the first. Slightly more biopsies were performed on females (53.3%). The median age of the patients was 38.0 years (interquartile range (IQR) 30.0–48.1 years).

The most common indication for kidney biopsy was nephrotic syndrome (38.6%), followed by unexplained acute kidney injury (AKI, 30.9%) and nephritic syndrome (18.8%). This finding was consistent in all four periods. Subnephrotic proteinuria and haematuria were the least common indications. Patients with isolated haematuria were seldom biopsied (median 1, range 0–4 per year).

Overall, the most common pattern of kidney disease observed was glomerulonephritis, followed by HIVAN, acute tubular necrosis, tubulointerstitial nephritis and diabetic nephropathy (Table 2). Hypertensive nephropathy was an uncommon diagnosis, accounting for 1.3% of cases. Some patients had more than one histological diagnosis, as indicated in the relevant tables.

Among the glomerular diseases (Table 3), lupus nephritis was the most common (20.4%). This was followed by mesangiocapillary GN (15.5%), FSGS (10.7%) and membra-

nous nephropathy (7.6%). The proportions of primary and secondary glomerular diseases were similar at 47.9% and 52.1%, respectively, and this trend was observed throughout the study period. Diabetic nephropathy and HIVAN were included among the secondary glomerular diseases.

Among the primary glomerular diseases (Figure 2), mesangiocapillary GN (34.5%) was the most common followed by FSGS (22.3%), MGN (15.8%) and mesangioproliferative glomerulonephritis (12.8%). FSGS was the most common pattern in the first quartile, but thereafter mesangiocapillary GN was consistently the most common pattern by a steadily increasing margin.

Among the cases of secondary glomerular diseases (Figure 3), lupus nephritis was consistently the most common (39.1%), followed by HIVAN (22.1%), diabetic nephropathy (14.4%) and PIGN (11.2%). From the second quartile, HIVAN was consistently the second-most common of the secondary glomerular diseases. PIGN showed a steady decrease in frequency over time.

The most common histological class of lupus nephritis was class IV (57.0%), followed by class III (21.3%). There were no cases of class I or class VI reported.

There was a total of 106 cases of crescentic glomerulonephritis. The most commonly identified underlying cause was mesangiocapillary GN (17.0%), followed by pauci-immune GN in patients who were positive for anti-neutrophil cytoplasmic antibody (11.3%).

IgA nephropathy accounted for only 2.0% of all cases of glomerular diseases. It was predominantly diagnosed amongst individuals of mixed ancestry. Minimal change disease (MCD) accounted for 1.9% of all cases of glomerular diseases.

Of the 2 227 biopsies, 504 (22.6%) were from HIV-infected patients, and 44.2% of these had HIVAN, either alone or in combination with one or more additional diagnoses (Table 4). The number of HIV-infected patients biopsied increased steadily over the study period, from only 2 in 1995 to 36 in 2017. This was mirrored by the increase in

Table 2. Patterns of biopsy-proven kidney disease, in order of frequency.

Pattern of kidney disease	n	% of all biopsies*
Glomerulonephritis	1 568	70.4
HIVAN	223	10.0
Acute tubular necrosis	165	7.4
Tubulointerstitial nephritis	161	7.2
Diabetic nephropathy	145	6.5
End-stage kidney	75	3.4
Myeloma kidney	40	1.8
Malignant hypertension	30	1.3
Amyloidosis	28	1.3
Thrombotic microangiopathy	15	0.7

*Some patients had more than one histological diagnosis.

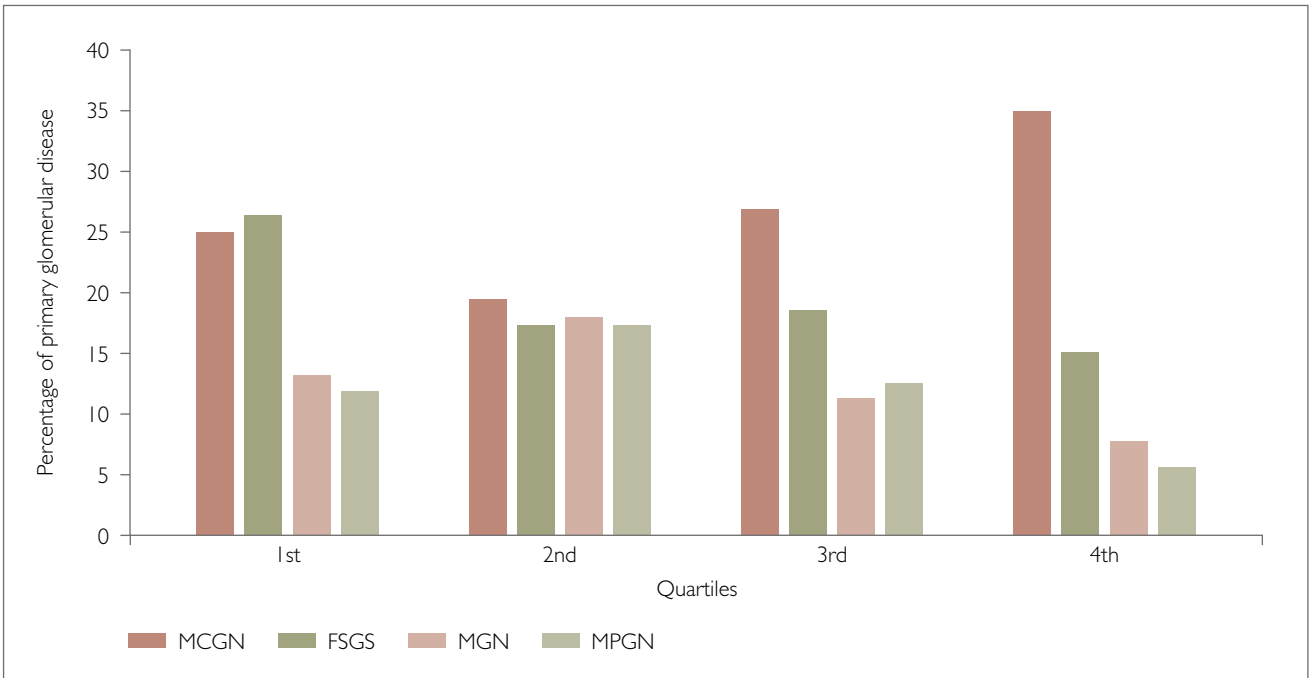

Figure 2. Frequency of common primary glomerular diseases over the quartiles of the study period.
Abbreviations: MCGN, mesangiocapillary glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MGN, membranous nephropathy; MPGN, mesangioproliferative glomerulonephritis.

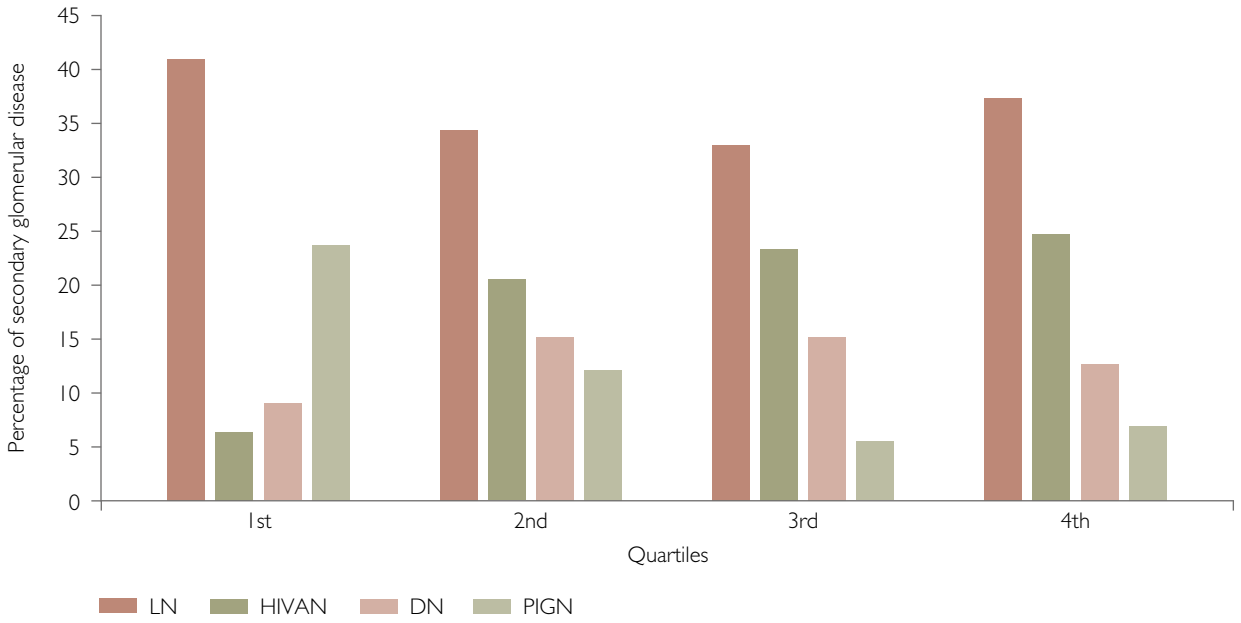

Figure 3. Frequency of cases of common secondary glomerular diseases over the quartiles of the study period.
Abbreviations: LN, lupus nephritis; HIVAN, HIV-associated nephropathy; DN, diabetic nephropathy; PIGN, post-infectious glomerulonephritis.

Table 3. Causes of primary and secondary glomerular diseases.

Pattern	n	% of all glomerular diseases (n = 1 936)	% of primary glomerular diseases (n = 928)	% of secondary glomerular diseases (n = 1 008)
Mesangiocapillary GN	320	16.5	34.5	
FSGS	207	10.7	22.3	
Membranous nephropathy	147	8.9	15.8	
Mesangioproliferative GN	119	6.1	12.8	
Crescentic GN	68	3.5	7.3	
IgA nephropathy	39	2.0	4.2	
Minimal change disease	36	1.9	3.9	
Lupus nephritis	394	20.4		39.1
HIVAN	223	11.5		22.1
Diabetic nephropathy	145	7.5		14.4
Post-infectious GN	113	5.8		11.2
ANCA-associated GN	31	1.6		3.1
Hepatitis B-related MCGN	29	1.5		2.9
Hepatitis B-related MGN	12	0.6		1.2
IE-related GN	7	0.4		0.7
GBM disease	4	0.2		0.4
RA-related MGN	1	<0.1		<0.1
Syphilis-related MGN	1	<0.1		<0.1
Syphilis-related MCD	1	<0.1		<0.1

Abbreviations: GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; ANCA, anti-neutrophil cytoplasmic antibody; MCGN, mesangiocapillary glomerulonephritis; MGN, membranous nephropathy; IE-related GN, infective endocarditis-related glomerulonephritis; GBM, glomerular basement membrane disease; RA, rheumatoid arthritis.

Table 4. Patterns of kidney disease among HIV-infected patients undergoing biopsy (n = 504). In many patients more than one kidney disease was present.

Pathology	n	% of HIV-positive patients
HIVAN	223	44.2
Other glomerular diseases	233	46.2
Mesangiocapillary GN	62	12.3
Mesangioproliferative GN	34	6.7
FSGS	26	5.2
Membranous nephropathy	25	5.0
Crescentic GN	20	4.0
End-stage kidney disease	19	3.8
PIGN	16	3.2
Lupus nephritis	12	2.4
Minimal change disease	4	0.8
IgA nephropathy	2	0.4
Other immune complex GN	9	1.8
Acute tubular necrosis	202	40.1
Tubulointerstitial nephritis	54	10.7

Abbreviations: HIVAN, HIV-associated nephropathy; GN, glomerulonephritis; FSGS, focal segmental glomerulosclerosis; PIGN, post-infectious glomerulonephritis.

Table 5. Uncommon diseases diagnosed on kidney biopsy.

Diseases	n	% of all biopsies
Myeloma cast nephropathy	40	1.8
Amyloidosis	28	1.3
HUS/TTP	10	0.4
Granulomatous interstitial nephritis	8	0.4
Infective endocarditis-related GN	7	0.3
Pyelonephritis	7	0.3
Goodpasture's disease	4	0.2
Scleroderma renal crisis	4	0.2
Malignancy other than myeloma	3	0.1
Dense deposit disease	2	<0.1
Cholesterol emboli	1	<0.1
Alport syndrome	1	<0.1

Abbreviations: HUS/TTP, haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura; GN, glomerulonephritis.

the cases of HIVAN. Other kidney diseases encountered among the HIV-positive patients included other glomerulonephritides, acute tubular necrosis, and tubulointerstitial nephritis secondary to anti-retroviral therapy (ART) or anti-tuberculosis drugs.

Hepatitis B was more common than hepatitis C seropositivity, and was documented for 88 and 9 patients, respectively. Hepatitis B was predominantly associated with mesangiocapillary GN (28 cases) and membranous nephropathy (11 cases), accounting for 8.8% of all mesangiocapillary GN and 7.5% of all membranous nephropathy cases. In the 9 patients with hepatitis C seropositivity, one had mesangiocapillary GN, one had idiopathic crescentic GN, and one had an end-stage kidney. In the remaining 6 cases, the pathology was another obvious condition, such as diabetic nephropathy or lupus nephritis.

A total of 213 patients had diabetes, mostly type 2 (85%), with diabetic nephropathy identified in 68%. Kidney disease other than diabetic nephropathy was present in 32%, and there was a combination of diabetic nephropathy and another disease in 20% of cases.

Hypertension was documented in half of the patients; however, hypertensive kidney disease was diagnosed on histopathology in only 30 patients (1.3%).

Myeloma cast nephropathy and amyloidosis were the most prevalent among the rare causes of kidney disease, accounting for 1.8% and 1.3% of total biopsies, respectively (Table 5).

DISCUSSION

Glomerulonephritis was the most frequently diagnosed kidney disease on biopsy in our study, with the proportions of primary and secondary glomerular diseases being almost equal. Among the primary diseases, mesangiocapillary GN was the most common, similar to the findings of another study from Cape Town [7] and in contrast to the reports from Bloemfontein and Johannesburg, in the provinces of the Free State and Gauteng, where FSGS was predominant [8-10].

We speculate that environmental and/or genetic factors may play a role in the high prevalence of idiopathic mesangiocapillary GN in the Western Cape province [12]. People of mixed ancestry make up the largest population group in the Western Cape, whereas Black South Africans are the largest group in the provinces reporting FSGS as the most common primary glomerular disease. At Groote Schuur Hospital in Cape Town, Jones et al. [13] reported on patients with kidney disease and a history of methamphetamine use. Kidney biopsies, performed in 24 patients, showed mesangiocapillary GN in 58% and hypertensive changes in 50%, suggesting an association between methamphetamine use and mesangiocapillary GN and severe hypertension. Other environmental factors noted to be

common in patients with mesangiocapillary GN in our region include exposure to tattoo ink or previous incarceration in a correctional facility [12]. A recent report from our centre [14] confirmed poor outcomes in patients with immunoglobulin-associated mesangiocapillary GN, with 81% reaching the composite outcome of doubling of creatinine and/or end-stage renal disease and/or death at five years.

IgA nephropathy was an uncommon cause of glomerular disease, as reported by other South African and African studies, and quite different from the findings in Europe, where it is the most common [2]. This could be explained partly by the low number of biopsies performed on patients with isolated haematuria.

Among the secondary glomerular diseases, lupus nephritis was the most common, as it was in most other South African studies. Class IV lupus nephritis was the predominant histological pattern, followed by class III. These proliferative forms of lupus nephritis were also found to be the most common and associated with the worst prognosis in previous studies [15]. Brijlal and colleagues [16] have studied the patients with lupus nephritis seen at our centre in more detail and reported an overall 5-year survival rate of 67%.

The number of HIV-infected patients having kidney biopsies increased sharply over the period of the study, in line with the increasing burden from HIV over the last 20 years [17]. HIVAN was the most common kidney pathology and was the second-most common secondary glomerular disease reported in our study. It is interesting that the number of HIV-positive patients having biopsies, and consequently the diagnosis of HIVAN, dropped off after 2015. This could potentially be explained by the widespread use of ART. The proportion of South Africans with HIV on ART has increased from 23% in 2010 to 70% in 2019 [18].

Certain variants of the APOL1 gene which are common among Africans confer increased risk of CKD, HIVAN, primary FSGS and other non-diabetic kidney disease [17]. A study from Johannesburg has reported a strong association between lupus nephritis and *APOL1* risk alleles in Black South Africans [18].

Diabetic nephropathy accounted for 14.4% of all cases of secondary glomerular diseases, making it the third-most common after lupus nephritis and HIVAN. According to the South African Renal Registry, diabetes is the cause of kidney failure in 14.3% of South Africans on KRT [3]. Kidney disease other than diabetic nephropathy was diagnosed in 32% of the patients with diabetes in our study, highlighting the importance of performing kidney biopsies in patients with diabetes who have an atypical clinical presentation.

Hepatitis B virus (HBV) infection remains highly endemic in Africa. Bates et al. [19] and van Buuren et al. [20] have studied South African and Namibian children with HBV-associated membranous nephropathy and found that they frequently had features of mesangiocapillary GN and tubuloreticular inclusion bodies, in addition to the typical subepithelial deposits. Routine HBV immunisation was introduced in South Africa in 1995, resulting in a significant decline in the numbers of new cases of HBV-associated MGN [21]. The latest data from the South African Renal Registry indicate that 2.3% of all patients on KRT are hepatitis B positive [3]. In the present study, 4% of the patients were seropositive for hepatitis B, with mesangiocapillary GN the most common pattern of kidney disease in these patients, followed by membranous nephropathy.

Hypertensive kidney disease is one of the most commonly reported causes of kidney failure worldwide. In many cases, however, the diagnosis is presumed and not proven histologically. Hypertensive kidney disease was diagnosed in only 1.3% of our biopsies despite half of the patients being hypertensive. This is similar to the findings of the Bloemfontein study [10], where CKD in the majority of the patients was thought to be related to hypertension, but only 2.8% were proven histologically. The role of mild-to-moderate hypertension as a cause of advanced CKD or kidney failure remains debatable [22]. Certain genetic variants, such as the APOL1 variants, may cause glomerular disease (often with FSGS) and secondary hypertension. Many cases of CKD in patients with mild-to-moderate hypertension may be misclassified as "hypertension-attributed nephropathy" whereas it may be due to primary glomerular disease [22]. We diagnosed hypertensive kidney disease on the basis of arteriolar lesions such as intimal thickening, an "onion skin" pattern and luminal narrowing, sometimes accompanied by ischaemic wrinkling of the glomerular basement membrane, and an absence of immune complex deposits or pathology suggesting another kidney disease. This was usually in the setting of patients with severe hypertension and acute kidney injury.

Among the rare diseases reported in our study, myeloma cast nephropathy and amyloidosis were the most prevalent. The cases of renal amyloidosis seen at our centre over three decades have been described in more detail by Hassen et al. [23]. In their study, AL amyloidosis was the most common type (26 of 46 cases) and AA amyloidosis was seen in the 20 other cases. Tuberculosis was the most frequent underlying disease in the cases of AA amyloidosis (60% of these cases).

One of the limitations of our study is that we had no reliable data on the ethnicity of the patients as this is not routinely captured by our hospital patient administration

systems or by our clinicians. For context, the distribution of population groups in the Western Cape in the 2011 census was mixed ethnicity ("Coloured") 49%, Black/African 33%, White 16% and Indian/Asian 1% [24].

CONCLUSIONS

This study has provided valuable information regarding patterns of kidney disease in South Africa over the last two decades. It is the largest South African study of its kind, with more than 90% of the biopsies reported by a single nephropathologist, ensuring a high level of consistency in reporting. Nephrotic syndrome was the most common indication for kidney biopsy. Mesangiocapillary GN was the most common primary glomerular disease and lupus nephritis the most common secondary glomerular disease. There was a significant increase in the number of HIV-infected patients having biopsies over the course of the study, with HIVAN the most frequent pattern and with combinations of diagnoses common in this group of patients. Almost one-third of the diabetic patients who were biopsied had a kidney disease other than diabetic nephropathy. Hypertensive nephropathy was an uncommon histological diagnosis and IgA nephropathy was rare.

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Conflicts of interest

No conflicts of interest to declare.

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