Patterns of biopsy-proven renal disease in Cape Town, South Africa, from 1995 to 2017

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ABSTRACT

Introduction: The causes, prevalence and outcomes of renal disease in developing countries may differ compared to developed countries. In most African countries, little data on the topic is available because of the lack of renal biopsy and chronic kidney disease (CKD)/end stage renal disease (ESRD) registries. In view of the limited African data on the spectrum of renal disease, we have described the causes of biopsy-proven renal disease encountered at Tygerberg Hospital (TBH), in Cape Town, over a 23-year period and examined whether patterns have changed over this period.

Methods: This retrospective study included all patients who underwent renal biopsies at TBH from January 1995 to December 2017. Cases were identified from the records of the Division of Anatomical Pathology, where biopsy records are stored in paper files. From these files, we created an electronic database using REDCap™, to digitize this archive.

Results: This report is based on a total of 2564 native kidney biopsies, which were the first biopsies for each patient. Slightly more biopsies were performed on females (53%). The majority of the patients were between the ages of 20-39 (48.5%), while patients over 60 years and under 20 years accounted for 6.6% and 13.3% respectively. The most common indication for biopsy was nephrotic syndrome (42.4%). Overall, the most common pattern of kidney disease observed was glomerulonephritis. Lupus nephritis (LN) was the most common glomerular disease (20.9%), followed by mesangiocapillary glomerulonephritis (MCGN, 16.4%), Focal segmental glomerulosclerosis (FSGS, 10.8%) and membranous nephropathy (MGN, 7.9%). The number of cases of primary and secondary glomerular diseases were similar. Among the primary glomerular disease, MCGN (32.2%) was the most common, followed by FSGS (21.2%), MGN (15.4%) and mesangioproliferative GN (14.5%). Among the secondary glomerular diseases, LN was the most common (42.4%), followed by Human immunodeficiency virus associated nephropathy (HIVAN, 20.1%), diabetic nephropathy (DN, 13.7%) and Post infectious glomerulonephritis (PIGN, 13.3%). IgA nephropathy was uncommon, accounting for only 2.4% of all glomerular disease. The number of HIV-positive patients biopsied increased steadily over the study period, from only 2 in 1995 to 40 patients in 2017. Of the total of 519 HIV-positive patients, 44.1% had HIVAN. Of 218 patients identified as diabetics, diabetic nephropathy was identified in 68.3% and another renal disease was diagnosed in 32%. Hypertensive renal disease was diagnosed in only 2.7% of all our biopsies. Myeloma kidney and amyloidosis were the most prevalent among the less common causes of renal disease, accounting for 1.5% and 1.1% of total biopsies, respectively.

Conclusion: An electronic renal registry was successfully established which will serve to facilitate good patient management and further research. Valuable new information has been generated regarding the patterns of renal disease in the Western Cape over the last two decades.

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LIST OF ABBREVIATIONS

ANA - Anti-neutrophil antibody
ANCA - Anti-neutrophil cytoplasmic antibody
APOL1 - Apolipoprotein L1
ART- Anti retroviral therapy
CKD - Chronic kidney disease
DN - Diabetic nephropathy
ESRD - End stage renal disease
FSGS - Focal segmental glomerulosclerosis
GBM - Glomerular basement membrane
GN - Glomerulonephritis
HBV - Hepatitis B virus
HCV - Hepatitis C virus
HIV - Human immunodeficiency virus
HIVAN - Human immunodeficiency virus associated nephropathy
HIVICK - Human immunodeficiency virus immune complex kidney disease
HUS - Hemolytic uremic syndrome
LN - Lupus nephritis
MCD - Minimal change disease
MCGN - Mesangiocapillary glomerulonephritis
MGN - Membranous glomerulonephritis/Membranous nephropathy
PGN - Primary glomerulonephritis
PIGN - Post infective glomerulonephritis
SGN - Secondary glomerulonephritis
SLE - Systemic lupus erythematosis
TTP - Thrombotic thrombocytopenic purpura

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INTRODUCTION

The global prevalence of chronic kidney disease (CKD) is estimated to be around 8-16%.[1] The causes, prevalence and outcomes of renal disease in developing countries may differ compared to developed countries. The major contributors of end stage renal disease (ESRD) in many developed countries are diabetes, hypertension and glomerulonephritis.[2] Glomerular diseases are an important contributor to CKD worldwide.[3] There is geographic and temporal variation in the spectrum of glomerular diseases reported, and this has been attributed to various demographic, economic and healthcare factors.[3] In Europe, primary glomerular disease (disease confined to the kidney) is more common than secondary glomerular disease occurring as part of a multisystem disease. IgA nephropathy is the most common form of glomerular disease in Western Europe, Australia and some Asian countries, while focal segmental glomerulosclerosis (FSGS) is the most common form in South America.[3]

In most African countries, little data on the topic is available because of the lack of renal biopsy and CKD/ESRD registries. Where data is available, it suggests that the causes of ESRD are similar to those reported from developed countries, with hypertension, diabetic nephropathy and glomerular disease being the most common.[4] The 2016 annual report of the South African Renal Registry lists the most commonly reported causes for ESRD as hypertensive renal disease, ESRD of unknown cause, diabetic nephropathy and glomerular disease (Table 1).[5] Many of these common causes for ESRD presented late and diagnosis never confirmed histologically.

Table 1. Most common reported causes of ESRD from the South African Renal Registry Annual Report 2016.

	% of total
Hypertensive renal disease	34.7
Cause unknown	32.4
Diabetic nephropathy	15.2
Glomerular disease	9.9
Cystic kidney disease	3.0
Obstruction and reflux	1.7

The total number of patients was 10257.

Regarding glomerular disease in African countries, secondary glomerular diseases predominate and have been increasing in step with the human immunodeficiency virus (HIV) epidemic. A systematic review of histologically-proven glomerulonephritis in Africa reported minimal change disease (MCD), FSGS and mesangiocapillary glomerulonephritis (MCGN) as the most common causes.[6] Hepatitis B-related glomerulonephritis and lupus nephritis (LN) were the most common forms of secondary glomerular disease, with the former more prevalent in sub-Saharan Africa and the latter in North Africa. This is not surprising considering the highest prevalence of hepatitis B virus (HBV) infection is in the sub-Saharan African region.[6,17] A systemic review of worldwide prevalence of chronic hepatitis virus infection,[17] published in 2015, found that many African countries have prevalence rates of greater than 8%.

HIV is a major cause of renal disease in sub-Saharan Africa and it is estimated that less than half of affected individuals are receiving anti-retroviral therapy (ART).[7,8] In South Africa it has an

estimated prevalence of 13.1%.[9] The spectrum of kidney disease includes conditions directly associated with the virus, those linked to the systemic response to infection, complications of treatment,[7] and coincidental renal disease such as diabetic nephropathy (DN) or LN occurring in an HIV positive patient.[12] 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.[7] HIVAN accounted for only 1.0% of secondary glomerular diseases in an African systemic review by Okpechi et al., which may reflect under-reporting of this entity across Africa.[6] In contrast, a study from Groote Schuur Hospital in Cape Town[10] showed an increase in the frequency of HIVAN as a percentage of all biopsies, from 6.6% in 2000 to 25.7% in 2009. HIVAN was the main cause of secondary glomerular disease among younger black patients. In this study, classical HIVAN was also reported as the most common pattern of renal disease among HIV positive individuals.[10] Similar results were reported from two other studies from Johannesburg, where HIVAN was the most commonly identified renal pathology.[11,12] In the Vermeulen study from 2014,[11] HIVAN was the second most common cause of secondary glomerular diseases, accounting for 13.3% (LN was the most common), and accounting for 6.5% of all biopsies. In the Gerntholtz study,[12] HIVAN accounted for 27.3% of total biopsies.

In a study from Bloemfontein between 1997 and 2006,[13] the majority of the patients included had CKD. Hypertension was presumed the likely underlying cause in most but only 2.8% were histologically proven. Among those with renal histology, glomerular disease was the most common diagnosis, accounting for almost 20%, with FSGS being the most common pattern and IgA nephropathy the least.

The Cape Town study[10] reported MCGN as the most common primary glomerular disease. Primary glomerular disease was more common among the elderly whereas secondary glomerular disease was more common among younger and middle-aged individuals. LN was the most common secondary glomerular disease among patients of mixed ancestry (“Coloured”) and HIVAN the predominant cause among young Black patients.

The Vermeulen study from Johannesburg, from 1982 to 2011, reported secondary glomerular disease as more prevalent than primary disease,[11] and over the study period its frequency continued to rise, a finding also reported from Cape Town. The main causes of secondary glomerular disease in the Johannesburg study were LN and HIVAN, and the main cause of primary glomerular disease was FSGS.[11]

The other study from Johannesburg, from 2001 to 2010, showed a similar increasing frequency of secondary glomerular disease. The most common primary glomerular disease was FSGS, followed by membranous nephropathy (membranous glomerulonephritis, MGN), while IgA nephropathy was relatively uncommon. Among the secondary glomerular diseases, LN was by far the most common, accounting for more than half of cases, followed by DN and post-infective glomerulonephritis (PIGN).[14] Table 2, below, summarizes the common patterns of glomerular disease in South Africa.

Table 2. Common patterns of glomerular disease in South Africa.

Study	Region	Period	Total biopsies	PGN	SGN
Patchapen, 2017[14]	Johannesburg	2001-2010	1495	FSGS 29.8% MGN 19.5% MCGN 18%	LN 55.8% Diabetic nephropathy 9.6%
Vermeulen, 2014[11]	Johannesburg	1982-2011	1848	FSGS 29.6% MGN 25.7% MCGN 18.1%	LN 31.0% HIVAN 13.3%
van Rensburg, 2009[13]	Bloemfontein	1997-2006	1216	FSGS 19.0% MCGN 14.9% MGN 11.5%	LN 14.5%
Okpechi, 2011[10]	Cape Town	2000-2009	1753	MCGN 20.4% Mesangioproliferative GN 19.2% MGN 18.5%	LN 39.0% Infection-related GN 30.1%

FSGS, focal segmental glomerulosclerosis; MGN, membranous nephropathy; MCGN, mesangiocapillary GN; LN, lupus nephritis; HIVAN, HIV-associated nephropathy. PGN, primary glomerulonephritis; SGN, secondary glomerulonephritis.

In view of the limited African data on the spectrum of renal disease, we have described the causes of biopsy-proven renal disease encountered at Tygerberg Hospital from 1995 to 2017, and examined whether patterns have changed over this period.

METHODS

Tygerberg Hospital (TBH) is a 1380-bed tertiary hospital in Cape Town, South Africa, which provides tertiary renal services to approximately 2.5 million people from the region. The predominant ethnic group in South Africa is Black/Africans (80.8%) followed by people of mixed ancestry ("Coloured", 8.8%)[9]. In the Western Cape, however, people of mixed ancestry predominate, accounting for 48.8%, followed by Blacks (32.9%), Whites and Indian/Asians (Table 3).

Table 3. Ethnic distribution in South Africa and Western Cape[9,16].

Population group	South Africa (%)	Western Cape (%)
Black	80.8	32.9
Coloured	8.8	48.8
White	8.0	15.7
Indian/Asian	2.5	1.0

We conducted a retrospective study that included all patients, adults and children, who underwent renal biopsies at TBH from January 1995 to December 2017. Biopsies that were reviewed at Tygerberg Hospital but had been performed at other hospitals were excluded from the study.

Renal 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 in patients with normal renal function were performed with the aid of radiocontrast screening, and in patients with raised creatinine levels they were done under ultrasound guidance. Conventional Tru-Cut

cutting needles were used initially, but recently the use of spring-loaded needles has been the norm, with all biopsies performed under direct, real-time ultrasound guidance.

All renal tissue was evaluated by light microscopy, immunofluorescence and electron microscopy. Renal biopsy material was received fresh and unfixed, and evaluated and divided under a dissecting microscope to provide optimal numbers of glomeruli for light and electron microscopy as well as immunofluorescent studies. The ultrastructural material was then fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffer, while the light microscopy material was fixed in buffered formalin. For light microscopy, serial two- to three-micron sections were stained with hematoxylin and eosin and other special stains as appropriate, including Congo Red. Material for immunofluorescence was frozen, cryostat sections cut and labeled for IgA, IgG, IgM and C3. Electron microscopy (EM) specimens were post-fixed in osmium tetroxide embedded in Spurr's resin.

All biopsies were reviewed at a weekly meeting which includes the nephrology team and the pathologist before a final diagnosis was made and the pathology report finalized.

Cases were identified from the records of the Division of Anatomical Pathology, where biopsy records are stored in paper files. These records consist of the renal histopathology request forms and the final pathology report. Request forms are completed by the nephrology team and contain key demographic and clinical information, as well as a provisional clinical diagnosis. From these files, we created an electronic database using REDCap[15], a secure web application designed to support data capture for research, to digitize this archive.

The measures implemented to improve data quality included the small dataset and the use of the REDCap system. REDCap facilitates easy and accurate data entry through the use of drop-down lists, radio buttons and checkboxes, and data validation. For example, date fields have a calendar control, and will only accept valid dates in the format year-month-day. Another example is the setting of a maximum valid values for albumin and haemoglobin concentrations. New users were trained on the REDCap system by Prof Davids using PDF versions of the online forms (Appendix 1) as well as the data dictionary (Appendix 2) as training materials.

From the REDCap database, we extracted demographic and clinical information, including information on comorbidities, the clinical presentation and laboratory workup, as well as details of the renal biopsies including the final histopathological diagnosis.

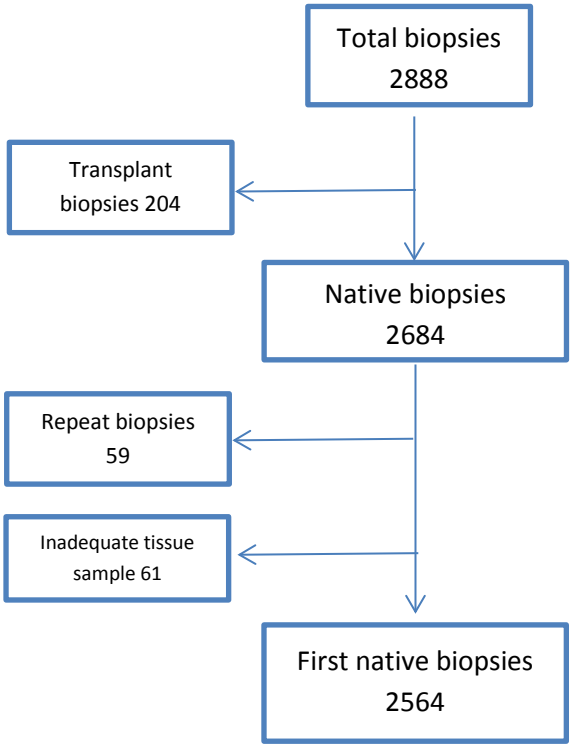
Descriptive statistics were used to summarize the patient demographics and biopsy data, including the indications for renal biopsy and the frequencies of each type of renal disease. Means and standard deviations were used to summarize normally distributed numerical data, and medians and interquartile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

Ethics approval, which included a waiver of individual informed consent, was obtained from the Stellenbosch University Health Research Ethics Committee (reference no. N19/03/039).

RESULTS

The total number of biopsies performed at Tygerberg Hospital (TBH) from January 1995 to December 2017 was 2888. During this 23-year period, 2781 of the biopsies (96.3%) were reported by a single nephropathologist (WB). The overwhelming majority were native biopsies (2684, 92.9%), including 59 which were repeat or follow-up biopsies; and 61 biopsies that were either inconclusive due to inadequate tissue or normal histology. There were 204 transplant biopsies, including 14 repeat biopsies. Transplant rejection was the most common histopathological diagnosis in the transplant biopsies. The 2564 native kidney biopsies which were the first biopsies for each patient is the sample on which this report is based, see Figure 1.

Figure 1. Study flow chart.



Slightly more biopsies were performed on females (53%). The age distribution of the patients is summarized in Table 4. Biopsies in children (using the WHO definition of ≤19 years of age) accounted for 13.1% of all biopsies, and biopsies in children under 13 years of age accounted for 3.9% of all biopsies.

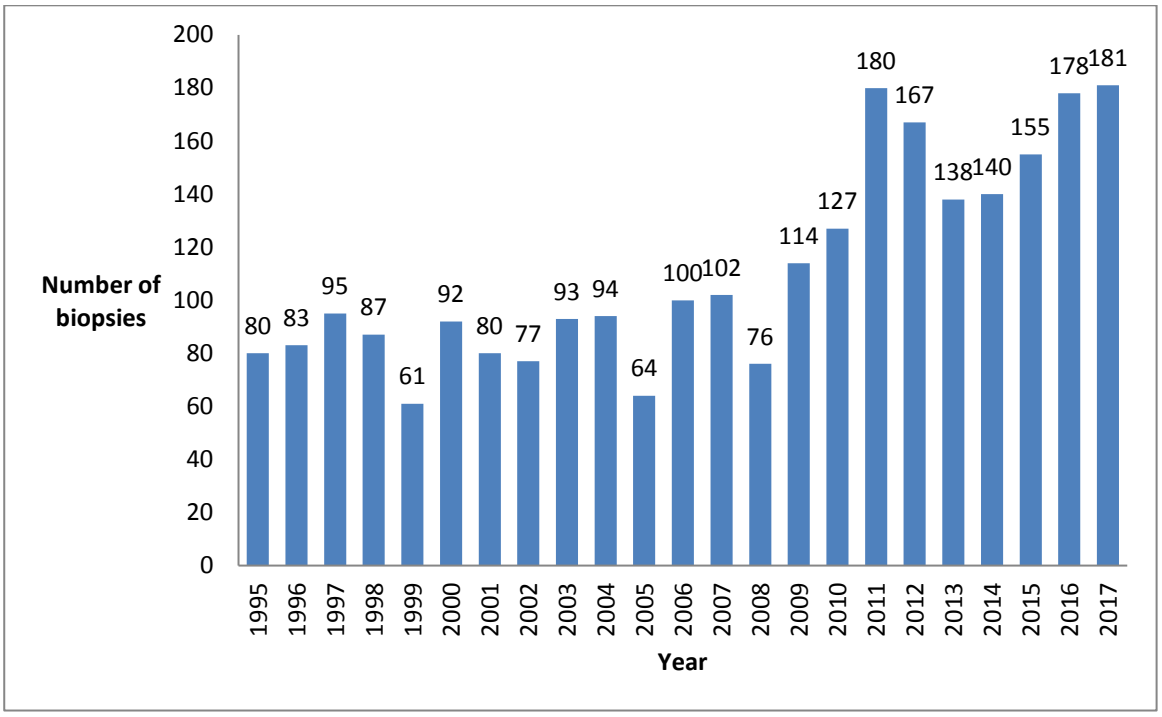
Table 4. Age distribution of patients undergoing renal biopsy at Tygerberg Hospital.

Age (years)	*N*	% of total biopsies
0-19	341	13.3
20-39	1243	48.5
40- 59	811	31.6
>60	169	6.6
Total	2564	100.0

No data on ethnicity was available for the majority of patients (60.3%). Where ethnicity was recorded, mixed ancestry ("Coloured") and Black patients were the predominant groups, comprising 17.6% and 16.6% of the total patients, respectively.

We divided the 23 years of the study into 4 equal periods, each consisting of 69 months (5.75 years). Over time, the number of biopsies performed annually steadily increased (Figure 3), with almost twice as many biopsies performed over the last quartile (average 166 biopsies per annum) compared to the first (84 per annum).

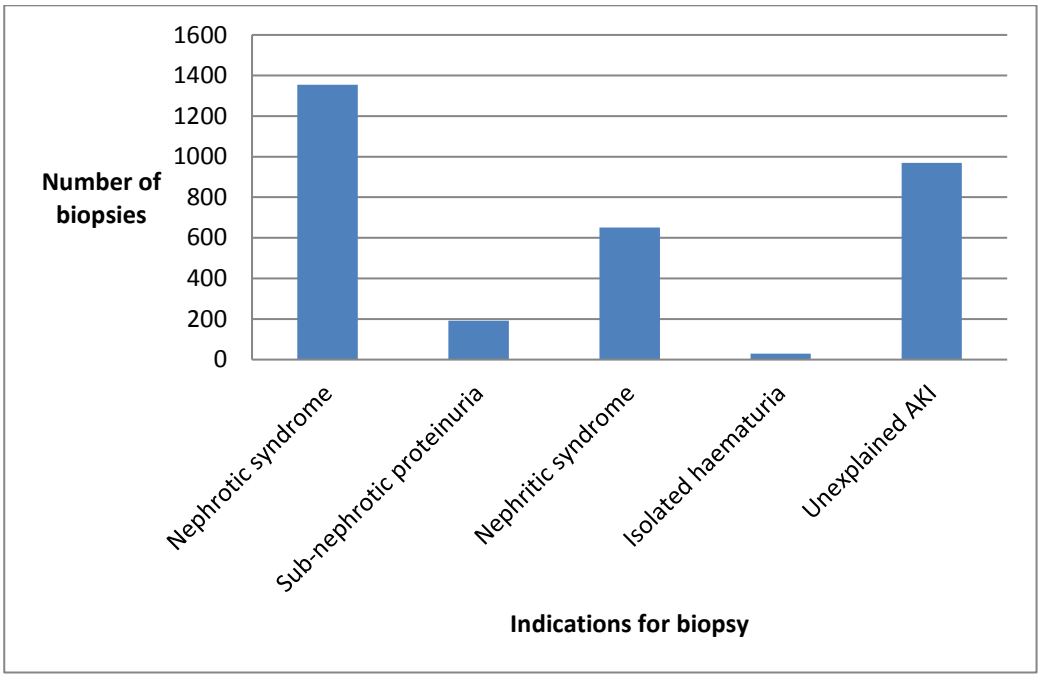
Figure 2. Number of renal biopsies performed per year, from 1995-2017.



The most common indication for biopsy was nephrotic syndrome (42.4%) followed by unexplained acute kidney injury (AKI, 30.3%) and nephritic syndrome (20.4%). These indications remained the most common throughout the study period. Sub-nephrotic proteinuria and haematuria were the least common indications in all four quartiles; however, the number of biopsy for sub-nephrotic proteinuria increased by a small margin, accounting for 6.7% of all indications for biopsy in the

first quartile and 9.1% in the fourth quartile of the study. Patients with isolated haematuria were seldom biopsied (median 1, range 0-4 per year).

Figure 3. Indications for renal biopsy.



Overall, the most common pattern of kidney disease observed was glomerulonephritis, followed by HIVAN, tubular necrosis, tubulointerstitial nephritis and diabetic nephropathy (DN). Hypertensive nephropathy was an uncommon diagnosis, accounting for around 1%.

Table 5. Patterns of biopsy-proven kidney disease, in order of frequency.

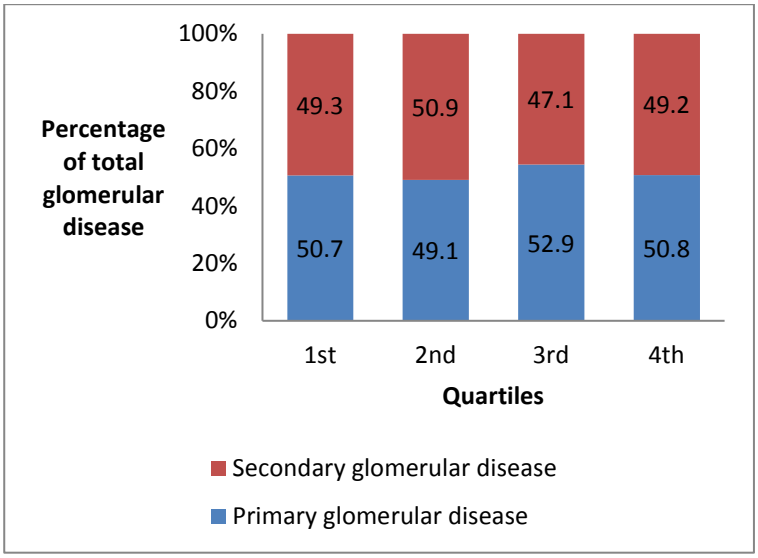
Pattern of kidney disease	*N*	% of all biopsies*
Glomerulonephritis	1836	71.6
HIVAN	230	9.0
Tubular necrosis	174	6.8
TIN	168	6.6
Diabetic nephropathy	149	5.8
ESRD	82	3.2
Myeloma kidney	40	1.6
Malignant hypertension	30	1.2
Amyloidosis	28	1.1
Thrombotic microangiopathy	15	0.6
Other	36	1.4

* Some patients had more than one histological diagnosis.

Amongst the glomerular diseases, LN was the most common (20.9%). This was followed by MCGN (16.4%), FSGS (10.8%) and MGN (7.9%). We included DN and HIVAN among the secondary glomerular diseases. The overall number of cases of primary and secondary glomerular diseases

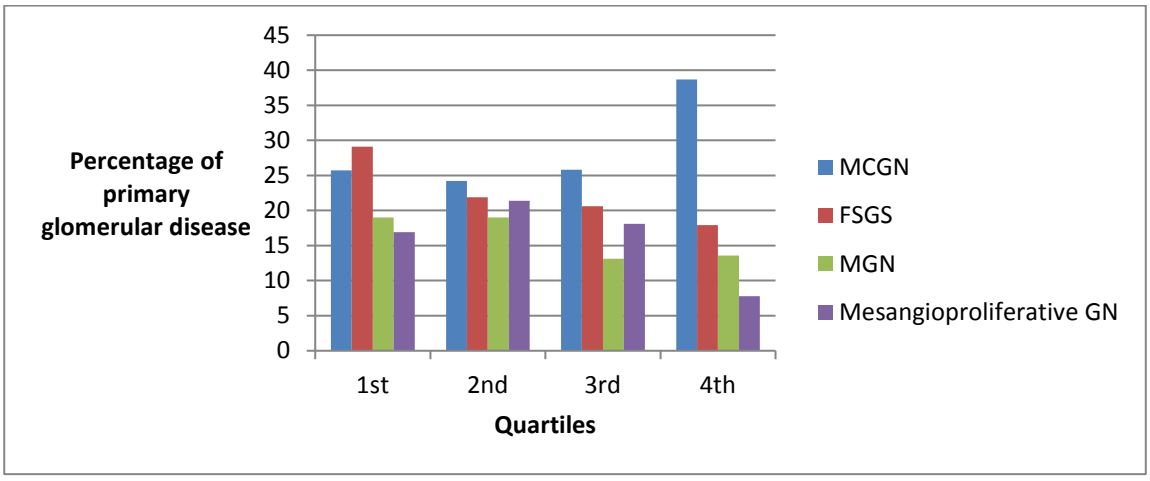
were similar, 50.8% and 49.2%, respectively. This trend was similarly observed throughout the study period, with exception to the third quartile where primary glomerular disease was slightly more prevalent.

Figure 4. Proportion of primary and secondary glomerular disease over the 4 quartiles of the study period.



Among the primary glomerular diseases, MCGN (32.3%) was the most common followed by FSGS (21.2%), MGN (15.4%) and mesangioproliferative GN (14.5%). FSGS was the most common pattern in the first quartile, thereafter MCGN was consistently the most common pattern by a gradually increasing margin.

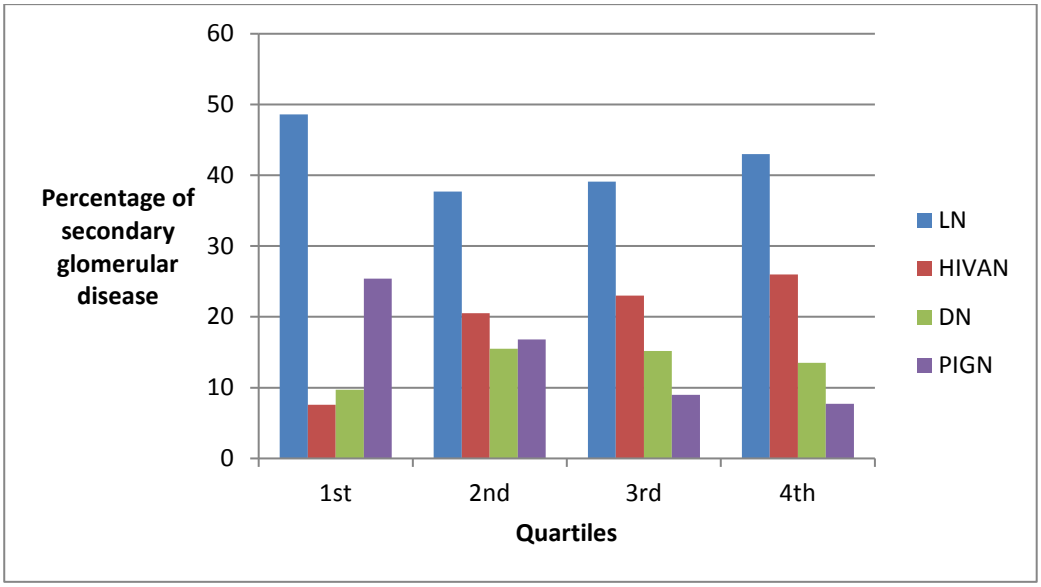
Figure 5. Frequency of common primary glomerular diseases over the quartiles of the study period.



MCGN, mesangiocapillary GN; FSGS, focal segmental glomerulosclerosis; MGN, membranous nephropathy.

Among the secondary glomerular diseases, LN was consistently the most common over the 23 years (42.4%), followed by HIVAN (20.1%), DN (13.7%) and PIGN (13.3%). From the second quartile, HIVAN was consistently the second most common of the secondary glomerular diseases. PIGN showed a steady decrease in frequency over the four quartiles of the study.

Figure 6. Frequency of common secondary glomerular diseases over the quartiles of the study period.



LN, lupus nephritis; HIVAN, HIV associated nephropathy; DN, diabetic nephropathy; PIGN, post infective glomerulonephritis

The most common class of LN was class IV (55.0%), followed by class III (21.4%). There were no cases of class I, and class VI (1.8%) was rarely reported.

A total of 122 cases of crescentic glomerulonephritis were identified, with idiopathic glomerulonephritis diagnosed in the majority of these. The most commonly identified underlying cause was MCGN, followed by pauci-immune glomerulonephritis. All the cases of pauci-immune glomerulonephritis were positive for anti-neutrophil cytoplasmic antibody (ANCA). See Table 8.

Table 6. Causes of primary and secondary glomerular disease.

Type	*N*	% of all glomerular disease (n=2215)	% of primary glomerular disease (n=1126)	% of secondary glomerular disease (n=1089)
MCGN	364	16.4	32.3	-
FSGS	239	10.8	21.2	-
MGN	173	7.9	15.4	-
Mesangioproliferative GN	163	7.4	14.5	-
Idiopathic crescentic GN	68	3.1	6.0	-
MCD	65	3.0	5.8	-
IgA nephropathy	54	2.4	4.8	-
LN	462	20.9	-	42.4
HIVAN	230	10.4	-	20.1
DN	149	6.7	-	13.7
PIGN	144	6.5	-	13.2
Pauci-immune GN	47	2.1	-	4.3
Hepatitis B-related MCGN	29	1.3	-	2.7
Hepatitis B-related MGN	14	0.6	-	1.3
IE-related GN	7	0.3	-	0.6
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

* Note the inclusion of HIVAN and DN in this table. MCGN, mesangiocapillary glomerulonephritis; MGN, membranous glomerulopathy; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; PIGN, post-infectious glomerulonephritis; LN, lupus nephritis; DN, diabetic nephropathy; HIVAN, HIV-associated nephropathy; IE related GN, infective endocarditis-related glomerulonephritis; GBM, glomerular basement membrane disease; RA, rheumatoid arthritis.

Table 7. Causes of crescentic glomerulonephritis.

Underlying cause	*N*	% of all crescentic glomerulonephritis
Idiopathic crescentic GN	68	48.0
MCGN	29	34.6
Pauci-immune, ANCA+ GN	13	8.7
LN (class IV)	4	3.1
PIGN	4	2.4
GBM disease	3	1.6
MGN	1	0.8
Total	122	100

MCGN, mesangiocapillary glomerulonephritis; MGN, membranous glomerulopathy; FSGS, focal segmental glomerulosclerosis; PIGN, post infective glomerulonephritis; LN, lupus nephritis; GBM, glomerular basement membrane, ANCA-anti-neutrophil cytoplasmic antibody.

IgA nephropathy was uncommon, accounting for only 2.4% of all glomerular disease. It was predominantly diagnosed amongst Coloured individuals and was rare in Black patients.

Of the 2564 biopsies, 519 (20.2%) were from HIV-positive patients, and 44.1% had HIVAN. The number of HIV-positive patients biopsied increased steadily over the study period, from only 2 in 1995 to 40 patients in 2017. This was mirrored by the increase in the cases of HIVAN. Other renal diseases encountered among the HIV-positive patients included other glomerulonephritides, acute tubular necrosis, and TIN secondary ART or anti-tuberculosis drugs. Among the glomerulonephritides, MCGN was the most common, followed by mesangioproliferative glomerulonephritis, FSGS and MGN. In many patients more than one renal diagnosis was made.

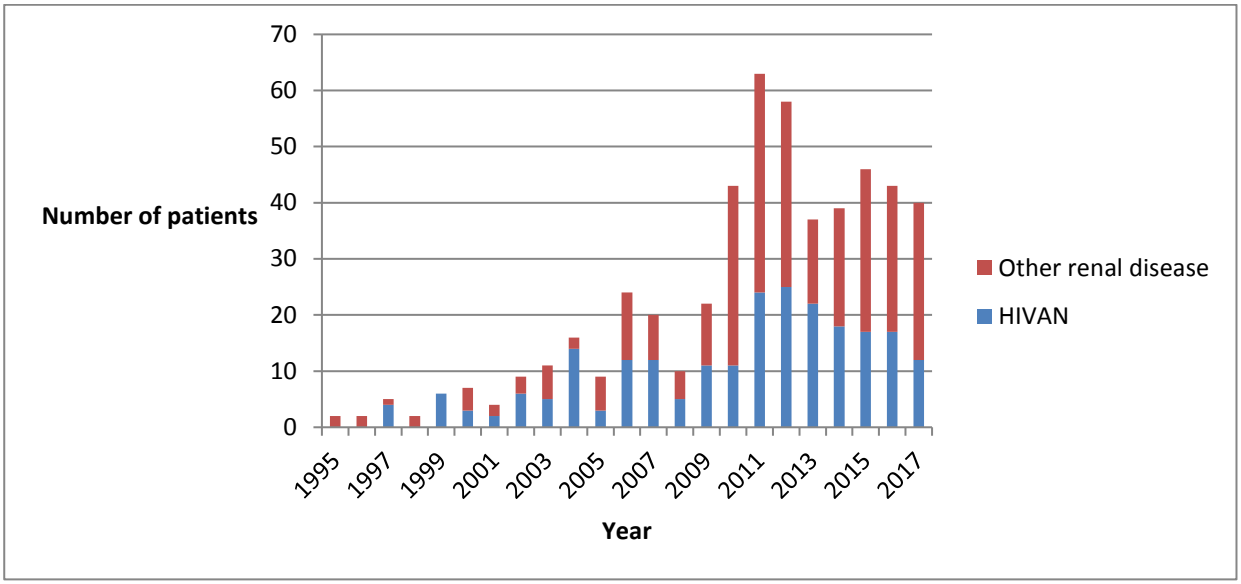
Table 8. Distribution of renal pathologies among HIV-positive patients undergoing renal biopsy.

Renal pathology	N	% of HIV patients (n=519)
HIVAN	229	44.1
Other glomerular diseases	242	46.6
• Mesangioproliferative GN	40	7.7
• PIGN	18	3.5
• FSGS	26	5.0
• MCGN	63	12.1
• MGN	25	4.8
• MCD	4	0.8
• LN	12	2.3
• Immune complex GN	5	1.0
• IgA nephropathy	2	0.4
• HIVICK	4	0.8
• Glomerulosclerosis	19	3.7
• Crescentic GN	20	3.9
Tubular necrosis	202	38.9
TIN	54	10.4

Note that in many patients more than one renal disease was present.

MCGN, mesangiocapillary glomerulonephritis; MGN, membranous nephropathy; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; PIGN, post infective glomerulonephritis; LN, lupus nephritis; TIN, tubulointerstitial nephritis; HIVAN, HIV associated nephropathy; HIVICK, HIV immune complex kidney disease.

Figure 7. Frequency of HIVAN among HIV-positive patients undergoing renal biopsy.



Hepatitis B was more common than hepatitis C seropositivity, and was documented for 97 and 9 patients, respectively. Hepatitis B was predominantly associated with MGN (14 cases) and MCGN (29 cases), accounting for 7.5% of all MGN and 7.8% of all MCGN. In the 9 patients with hepatitis C, one had MCGN, the other had idiopathic crescentic GN, and one had ESRD of unknown cause. In the remaining 6 cases, the renal pathology was attributed to another obvious condition, such as diabetes or SLE.

A total of 218 patients were identified as diabetics, mostly type 2 (83.5%). Among them, 68.3% had diabetic nephropathy, 32% had a renal disease other than diabetic nephropathy and 20% had a combination, as shown in Figure 8. The number and proportion of diabetic patients having renal biopsies steadily increased over the four quartiles from 4.6% in the first quartile, to 9.7% in the third and 10.1% in the fourth.

Figure 8. Renal diseases among diabetics.

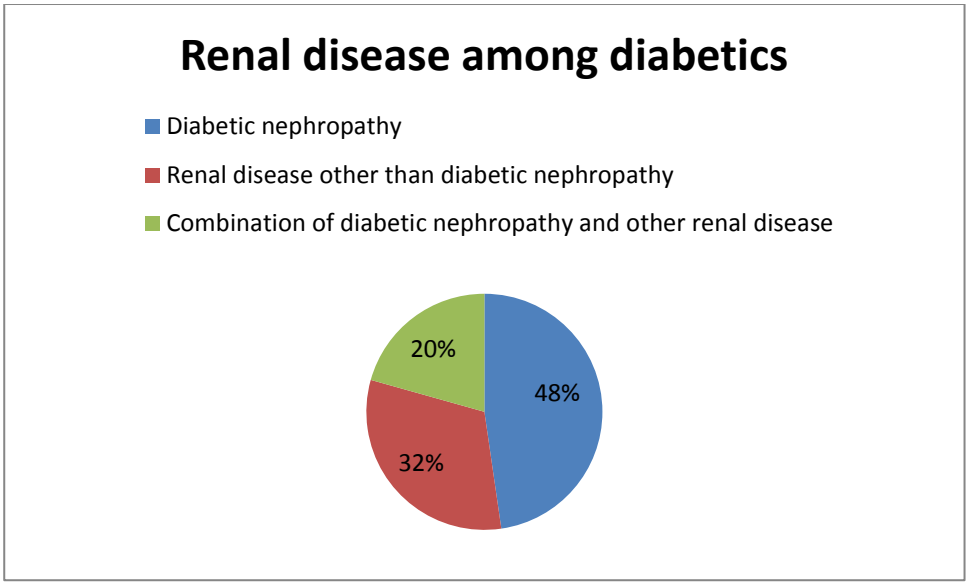


Table 9. Renal diseases among diabetics.

	N	% of total diabetics (218)
Diabetic nephropathy	149	68.3
Glomerular disease*	88	40.4
• MCGN	23	10.6
• FSGS	18	8.3
• Glomerulosclerosis	12	5.5
Tubulo-interstitial nephritis	17	7.8
Tubular necrosis	9	4.1

* Only the three most common causes of glomerular disease in diabetic patients are listed. MCGN, mesangiocapillary glomerulonephritis; FSGS, focal segmental glomerulosclerosis.

Hypertension was documented in almost half of the patients (48.2%); however, hypertensive renal disease was diagnosed in only 37 patients (2.7%).

Myeloma kidney and amyloidosis were the most prevalent among the less common and rare causes of renal disease, accounting for 1.6% and 1.1% of total biopsies, respectively. Other causes included malignancies other than myeloma, infective endocarditis-related glomerulonephritis, haemolytic-uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Table 10. Uncommon diseases diagnosed on kidney biopsy.

Diseases	*N*	% of all biopsies (n=2564)
Myeloma kidney	40	1.6
Amyloidosis	28	1.1
HUS/TTP	10	0.4
Granulomatous interstitial nephritis	8	0.3
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

HUS/TTP- haemolytic-uraemic syndrome/thrombotic thrombocytopenic purpura.

DISCUSSION

The most common indication for renal biopsy in Tygerberg Hospital over the study period was nephrotic syndrome, in line with other South African and international studies. The least common indication was microscopic haematuria and asymptomatic urine abnormalities such as the presence of an active urine sediment. This is in contrast to international reports, particularly from Europe and North America.[3]

Glomerulonephritis was the most commonly diagnosed renal disease on renal biopsy. The distribution of primary and secondary glomerular diseases was almost equal. Among the primary glomerular diseases, MCGN was the most common, similar to the findings of another study conducted in Cape Town[10] and in contrast to the reports from Bloemfontein and Johannesburg, where FSGS was predominant.[11,13] The reasons for this geographical variation are not clear. Among the factors that may be relevant is the different ethnic distribution of the population in the Western Cape, where persons of mixed ancestry make up the largest group. Another factor is the increasing use of crystal meth, the primary illicit drug used in the Western Cape.[19] At Groote Schuur Hospital, Cape Town, Jones et al.[27] reported that renal biopsies in patients with a history of methamphetamine use revealed MCGN in 58.3%, suggesting an association. Anecdotally, and in common with the findings of the Groote Schuur group, [28] we have also noted MCGN to be a common renal diagnosis in individuals who have been incarcerated, and also speculate that it may be related to exposure to drugs, infections or tattoo ink in prison.

IgA nephropathy was the least common glomerular disease, as reported by other South African and African studies, but quite different from the findings in Europe, where it is the most common.[3] This could possibly be explained by the low number of biopsies performed on patients with

isolated hematuria. Among the secondary glomerular diseases, LN was the most common, as it was in most other South African studies. Despite no clear data regarding the prevalence of SLE in Africa and South Africa, the Western Cape is considered to have a high prevalence of systemic lupus erythematosis (SLE). Renal complication is a common manifestation of SLE and also associated with a poorer prognosis.[18,25,26] Up to 50% of SLE patients have abnormalities in renal function or urine, and up to 80% will develop abnormalities at some point during the course of the disease.[25] Class IV lupus nephritis was the predominant histological pattern, followed by class III. Similar results were obtained from another study conducted at Tygerberg Hospital which included LN cases diagnosed between 1983 and 2012. In that study, class IV was also the most common, followed by class III and no cases of class I or VI were reported.[18] These proliferative forms of LN were also found to be more common and associated with worst prognosis in other Cape Town studies.[18,25]

The number of HIV-positive patients having renal biopsies increased sharply over the period of the study. This was in keeping with data from Statistics South Africa which clearly shows an increase in the total number of HIV patients over the last 20 years.[9] HIVAN was the most commonly identified pathology and was the second most common secondary glomerular disease reported in our study. HIV-associated immune complex disease was uncommon. It is interesting that the number of HIV-positive patients having biopsies, and consequently the diagnosis of HIVAN, dropped off after 2013. This could potentially be explained by increases in HIV awareness and use of ART and therefore less renal complications. The UNAIDS target for 2020 is to achieve a 90% rate of diagnosis in HIV positive individuals, and South Africa is well on its way to achieving those targets.[24] There has been a more than two-fold increase in the number of people on ART from 2010 to 2015 in South Africa, as well as in the Western Cape.[24]

Certain variants of the APOL1 gene which are common among Africans confer increased risk of CKD.[7] HIVAN, primary FSGS, and other non-diabetic renal disease are related to the “risk” alleles.[7] A study from Johannesburg has reported an association between lupus nephritis and APOL1 risk alleles in black South Africans.[20]

Diabetic nephropathy accounted for 13.7% of all secondary glomerular disease, making it the third most common after LN and HIVAN. According to the South African Renal Registry, diabetes is the cause of ESRD in 15.2% of South Africans on RRT. Renal disease other than diabetic nephropathy were diagnosed in 32% of the diabetics in our study. In another study conducted at Tygerberg Hospital, [22] non-diabetic renal disease was found in 45% of diabetics who were biopsied between 2003 and 2012. These findings highlight the importance of performing renal biopsies in diabetic patients who have renal disease and a clinical picture which is not typical of diabetic nephropathy.[23]

Hypertensive renal disease is one of the most common reported causes of ESRD worldwide; however, in many cases the diagnosis is presumed and not proven histologically. In our study hypertensive renal disease was diagnosed in only 2.7% of all our biopsies despite approximately half of our patients being hypertensive. This finding is similar to that of the Bloemfontein study, where CKD in the majority of the patients was thought to be related to hypertension but only 2.8%

were proven histologically. It is generally agreed that malignant hypertension can lead to irreversible kidney failure; however, the role of mild-to-moderate hypertension as a cause of ESRD remains debatable.[21] 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 systemic hypertension may be misclassified as being due to "hypertension-attributed nephropathy" whereas it may be due to primary glomerular disease.[21]

Regarding the strengths and limitations of our study, most of the renal biopsies (greater than 90%) were reported by a single nephropathologist, ensuring a high level of consistency in the reporting. Some of the limitations involved missing data, for example, data on ethnicity and serological tests.

Conclusions

This study served two main purposes, to provide information regarding patterns of renal disease in the Western Cape over the last two decades, as well as to create an electronic renal database for good patient management and from which further studies will be performed more readily. Nephrotic syndrome was the most common indication for renal biopsy and glomerulonephritis was the most common pattern of renal disease reported. MCGN was the most common primary glomerular disease and LN the most common secondary glomerular disease. IgA nephropathy was rare. We noticed a significant increase in the number of HIV-positive patients having biopsies over the course of the 23 years, which correlated with increases in the cases of HIVAN. Almost one-third of the diabetic patients who were biopsied had a renal disease other than diabetic nephropathy. Hypertensive nephropathy was an uncommon histological diagnosis.

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