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Histopathological patterns of renal disease at Helen Joseph Hospital, South Africa: a 5-year retrospective review

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A Research Report in part fulfilment towards the degree of Master of Medicine in Internal Medicine.

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Histopathological patterns of renal disease at Helen Joseph Hospital, South Africa: a 5-year retrospective review.

Johannesburg, September 2022.

DECLARATION

I, Ahmed Mahomed Randeree, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



(signed by candidate)

21/09/2022 , Johannesburg

(date, place)

ABSTRACT

Introduction: The prevalence of chronic kidney disease and kidney failure has been on the rise globally. Early detection and appropriate management of renal disease is imperative for both patient outcomes, as well as to lessen the financial burden on the health sector which in South Africa is already resource constrained. Due to the paucity of data on histopathological patterns of renal disease in South Africa, this research was undertaken to assist with management of renal disease by establishing the spectrum of disease.

Objectives: The primary objective of this study was to describe the relative frequency of native kidney disease diagnosed at Helen Joseph hospital on renal biopsy.

Methods: A retrospective audit was undertaken of all patients that underwent native kidney biopsy at Helen Joseph hospital in Johannesburg during the period 1 January 2014 to 31 December 2018. Inclusion criteria for this study were: adults over the age of 14 and specimens with a definitive pathological diagnosis. Renal allograft biopsies were excluded. The following data was recorded for each patient: age, gender, ethnicity, indication for biopsy, urine protein: creatinine ratio, urine (microscopy, culture and sensitivity), blood results (creatinine, GFR, HIV status, CD4 count) and histopathological diagnosis.

Results: Data from 205 patients was extracted from clinical records. The cohort demonstrated a slight female preponderance (54.15%), with a median age of 36 years and of predominantly black ethnicity (82.93%). The most common primary glomerular diseases were focal segmental glomerulosclerosis (14.63%), membranous glomerulopathy (8.29%), minimal change disease (5.37%) and membranoproliferative glomerulonephritis (4.39%). The most common secondary glomerular diseases were lupus nephritis (26.83%), HIV associated nephropathy (10.24%), Hypertensive change (7.32%) and diabetic nephropathy (4.88%). Nephrotic syndrome was the most frequent indication for renal biopsy with 38.54%, followed by unexplained renal dysfunction with 36.10%, asymptomatic urine abnormalities 16.58% and the least frequent being nephritic syndrome with 8.78%.

Certain glomerular diseases appeared to show age clustering, with proliferative lupus nephritis tending to affect younger patients whilst membranous glomerulopathy was more common in older patients. A significant difference in the frequency of histological diagnoses was observed between ethnicities, with HIV associated nephropathy and proliferative lupus nephritis occurring more often in people of black African ethnicity. Lupus nephritis was statistically significantly more frequent amongst females ($p<0.001$). Results showed that (76.36%) of all lupus nephritis were female as compared to (23.64%) which were males. Males had a higher frequency of hypertensive change, diabetic nephropathy and membranoproliferative glomerulonephritis.

Discussion: NS was the most frequent indication for renal biopsy in this study and has been reported to be the most common indication for renal biopsy worldwide (10). LN was the most common histological finding overall and probably reflects the low threshold for renal biopsy in SLE patients as proteinuria of more than 500mg/day and / or deteriorating renal dysfunction are considered as indications for renal biopsy in these patients.

When comparing the frequency of native kidney disease by age in this study, it was found that LN, FSGS and ATN were more frequent in younger patients whilst primary MGN, DN and hypertensive change were more common in older patients. The global population of the elderly is steadily increasing which translates into more elderly patients with acute and chronic diseases and hence the increased frequency of DN and hypertensive change in this category (43). This can also be attributed to the fact that the renal effects of these diseases take time to manifest so they are more likely to be detected in older patients. In this study, it was found that males had a higher frequency of hypertensive change, DN and MPGN.

NS (47.62%) and unexplained renal dysfunction (52.38%) were the most frequent indications for biopsy in patients with HIVAN. This reflects the significant proteinuria associated with HIVAN. Unexplained renal dysfunction, which included AKI and CKD, was the most frequent presentation in patients with HIVAN (52.38%), hypertensive change (60%) and DN (80%). This probably reflects the significant target organ damage associated with these diseases as well as delayed

presentation due to progressive asymptomatic injury and hence poorer renal functions at presentation.

Conclusion: The data attained in this study is an important contribution to the patterns of renal disease particularly in the South African context. These findings could assist in the early detection and appropriate management of renal disease which would ultimately result in improved patient outcomes and decrease the financial burden on the health sector.

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My wife Anisa, for all the encouragement, motivation, patience and support.

My parents for their sacrifices, support and prayers.

LIST OF ABBREVIATIONS

ACR – American College of Rheumatology

AKI – Acute kidney injury

ARV – Antiretroviral therapy

ATN – Acute tubular necrosis

CD4 – Cluster of Differentiation 4

CKD – Chronic kidney disease

DN – Diabetic Nephropathy

FSGS – Focal segmental glomerulosclerosis

GFR – Glomerular filtration rate

GN - Glomerulonephritis

HJH – Helen Joseph Hospital

HIV – Human Immunodeficiency Virus

HIVAN – HIV Associated Nephropathy

HIV-ICD – HIV immune complex-mediated glomerular disease

IgAN – Immunoglobulin A Nephropathy

KDIGO – Kidney disease improving global outcomes

LN – Lupus Nephritis

MCD – Minimal change disease

MGN – Membranous glomerulopathy

MPGN – Membranoproliferative glomerulonephritis

MsPGN – Mesangioproliferative glomerulonephritis

NHLS – National Health Laboratory Service

NS – Nephrotic Syndrome

OR – Odds Ratio

SLE – Systemic lupus erythematosus

UPCR - Urine protein: creatinine ratio

USA – United States of America

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1. INTRODUCTION

1.1. Statement of the problem

Chronic kidney disease (CKD) and kidney failure are on the rise with a reported global prevalence of 1 million people in 2013 (1). In 2016 according to the South African Renal Registry data, 10257 people had access to dialysis and were on some form of renal replacement therapy (3). This gives rise to a prevalence of 183 per million population. Most of these patients were in the private sector which had a prevalence of 797.5 patients per million population compared to the public sector which had 67.5 patients per million population. This highlights the vast discrepancy between access to renal replacement therapy in the private versus the public sector healthcare system. Public sector access to dialysis has not increased to meet the growing needs of our society, and is actually less than figures noted in 1994 (3).

In cases where the cause of renal disease is not diagnosed timeously, kidney failure can ensue which will require renal replacement therapy. This places a financial burden on the healthcare budget in SA, which is already resource constrained.

Glomerular disease comprises 25-45% of kidney failure cases in developing countries. Many glomerular diseases are potentially treatable, so if we can timeously and appropriately diagnose and treat these cases, then we can avoid the development of progressive renal dysfunction which has an impact on both patient outcomes as well as the financial burden on the health sector. The definitive way to diagnose glomerulonephritis is by performing a renal biopsy.

Globally, the patterns of renal disease are well described, however in South Africa the data is limited. Understanding the patterns of glomerular disease will permit allocation of resources to the management thereof to prevent progression to kidney failure.

1.2 Justification of the research

Due to the paucity of data on histopathological patterns of renal disease in South Africa and specifically at HJH, this research will assist in management of renal disease by establishing the spectrum of disease.

2. LITERATURE REVIEW

2.1 Introduction

The prevalence and incidence of CKD and kidney failure is steadily increasing with more than 1 million kidney failure patients across the globe (1). The number of patients requiring chronic renal replacement therapy is expected to increase by 60% in the next 10 years (1). GN varies in incidence in different geographical areas due to different socioeconomic conditions and ethnicity, genetic variability and environmental factors (4). The knowledge of renal histology can guide the clinical management in patients with renal dysfunction (1, 5). In an observational study by Shah et al, renal biopsy led to therapeutic changes in 54% of cases (5).

The patterns of glomerular diseases have been widely reported from different regional and national biopsy registries worldwide. However, there have not been many studies of the epidemiology of biopsy-proven renal disease in Southern Africa (6). This could be due to the lack of availability of renal biopsy registries in many African countries or due to resource constraints (i.e., histopathology access and expertise as well as lack of equipment for renal biopsies).

If the cause of renal disease is not attained timeously it may result in renal failure that requires renal replacement therapy, which is extremely expensive and places a severe burden on the healthcare budget (6, 7). GN's are an important cause of morbidity and mortality and a potentially preventable cause of end-stage renal disease.

2.2 Renal biopsy

Percutaneous renal biopsy is the gold standard for the diagnosis, management and prognosis of renal disease (1).. A renal biopsy can provide information regarding the extent of disease activity (e.g., inflammatory cell proliferation, crescent formation, and necrosis) and chronicity (e.g., sclerosis and fibrosis), which may help guide prognosis and therapy, as well as establishing renal involvement of systemic diseases (9).

The most serious complication of performing a renal biopsy is haemorrhage with the rate of major bleeding reported around 0-6% (8). Perinephric haematomas are common post percutaneous renal biopsy but only a few are clinically significant that require further treatment (8). Infection has been reported in a few case series, but it's unlikely if sterile technique is followed, and unless bowel perforation occurs (9).

However, the use of modern techniques has led to an improvement in renal biopsy safety with minimal complications, as well as better diagnostic yields (9). Due to the invasive nature of the renal biopsy, there are recommended criteria that should be met in order to improve the risk : benefit ratio such as; the renal biopsy is required to diagnose and guide treatment, the suspected disease is associated with significant morbidity and mortality and there are treatment modalities available that can improve their outcome, the adverse effects of the treatments are acceptable to the patient in their current health condition and the risk of the procedure is acceptable to the patient (9).

2.3 Indications for renal biopsy

Renal disease may present with proteinuria, haematuria, reduced glomerular filtration rate (GFR) or may be detected during screening patients with a multi-system disease (10). Nephrotic Syndrome (NS) is defined by the presence of >3.5g proteinuria per day associated with hypoalbuminemia, peripheral oedema and hyperlipidaemia (7, 8). NS was found to be the most common indication for renal biopsy in studies that

reviewed renal histopathology worldwide (10). A study in Brazil by Polito et al(11) , found that NS was the main clinical indication for a renal biopsy in the study population (39%), followed by asymptomatic urinary abnormalities (20.7%), and renal dysfunction of unknown aetiology (16.8%) (11).

NS can be a result of a primary glomerular disease such as IgA nephropathy (IgAN) (10%) or other histopathological patterns of diseases including: focal segmental glomerulosclerosis (FSGS) (33%); membranous glomerulopathy (MGN) (33%); minimal change disease (MCD) (15%); membranoproliferative glomerulonephritis (MPGN) (2-5%) and other glomerulonephritis (GN) e.g., proliferative glomerulonephritis (5-7%) (12). The most common histological patterns related to primary NS in adults are MGN, FSGS and MCD (1). However, cases of NS are also found to be due to diabetes, systemic lupus erythematosus (SLE), infections, multiple myeloma, amyloidosis or neoplasias (1). The main causes of NS in a study at a tertiary hospital in Cape Town were lupus nephritis (LN) (17.2%), HIV associated nephropathy (HIVAN) (12.2%), MGN (11.6%), Crescentic GN (9.8%) and mesangioproliferative GN (MsPGN) (7.6%) (6).

Secondary causes of NS include: metabolic (amyloidosis, diabetes mellitus); immunologic (cryoglobinemia, erythema multiforme, Henoch- Schonlein purpura, polyarteritis nodosa, Sjogren syndrome, SLE); idiopathic/primary; neoplastic (carcinoma, leukaemia, lymphoma, multiple myeloma); medication/drug use (heroin, lithium, nonsteroidal anti-inflammatory drugs); infection (bacterial, protozoan, viral); allergic; genetic syndromes and other (Castleman disease, chronic allograft nephropathy, malignant hypertension, preeclampsia) (13). Diabetes mellitus and SLE are the most common secondary cause of NS (13).

Nephritic syndrome is defined by the presence of haematuria, oliguria, sub nephrotic proteinuria, oedema and hypertension. Haematuria is usually defined as the presence of >3 red blood cells per high power field using microscopy on a centrifuged urine specimen (14). Nephritic syndrome is most frequently caused by proliferative

glomerulonephritis, membranoproliferative glomerulonephritis and crescentic glomerulonephritis (15). Isolated microscopic haematuria results from glomerular diseases such as IgAN, Alport syndrome, thin basement membrane nephropathy and FSGS (1).

Renal disease can present in the form of AKI or CKD. If AKI or CKD is present without an identifiable cause, a renal biopsy is warranted. Kidney disease improving global outcomes (KDIGO) workgroups for AKI (2012) and CKD (2013) define AKI as either an increase in serum creatinine of ≥ 26.5 µmol/l within 48 hours, an increase in serum creatinine to ≥ 1.5 times the baseline creatinine or a urine volume of < 0.5ml/kg/hour for 6 hours (16). CKD is defined as abnormalities of kidney structure or function with markers of kidney damage (albuminuria ≥ 300mg/24h, urine sediment abnormalities, histological abnormalities, structural abnormalities on imaging or a history of renal transplantation) or a GFR <60ml/min/1.73m^2 present for >3 months, with implications for health (17). In a series of 259 patients with AKI undergoing renal biopsy, glomerular disease was the most recorded histological pattern, while tubulo-interstitial disease (acute interstitial nephritis and acute tubular necrosis) and vascular injury (atheroembolic disease) accounted for about 40 and 12% respectively of the remaining diagnoses (14).

Renal biopsies in patients with CKD are controversial due to high bleeding risk and low diagnostic success due to small and scarred kidneys (18). These cases should be considered as renal dysfunction of unknown aetiology. Diabetes and hypertension are the commonest causes of CKD, but recent evidence shows that glomerular disease is an increasing cause for patients requiring chronic renal replacement therapy (1). When the presentation of the renal disease was CKD, LN was the predominant diagnosis in young adults followed by FSGS and MCD; and LN also predominated in older adults, followed by FSGS and IgAN (11).

2.4 Use of Biomarkers in renal disease

Advances in clinical medicine has seen the arrival of new diagnostic tools. The detection of specific molecular ‘biomarkers’ in serum or urine could be of use in assisting with diagnosing, prognosticating and treating renal disease (19).

The detection of the serum auto-antibody to M-type phospholipase A2 receptor (PLA2R) protein correlates with the diagnoses of idiopathic primary MN (20). Serum soluble urokinase plasminogen activator receptor protein (suPAR) is another serum biomarker which has been detected in patients presenting with NS as a result of MCD or FSGS but studies do not at present support the use thereof in diagnosis of either condition (21). Galactose-deficient immunoglobulin A1 (Gd-IgA1) is known to play a key role in the pathogenesis of IgAN and its detection in serum could be used to diagnose the disease, but there is currently insufficient research on the correlation of serum levels with disease activity (22). Hence, there is still further research and testing required to validate the use of biomarkers in diagnosing renal disease and currently can only be used to supplement the renal biopsy and not replace it.

2.5 Pathological types of renal disease

2.5.1 Glomerular diseases

The nephron is the structural and functional unit of the kidney (23). The renal corpuscle is composed of a capillary network which is lined by a thin layer of endothelial cells; a central region of mesangial cells that is surrounded by a mesangial matrix material; the visceral epithelial cells and its associated basement membrane; and the parietal layer of Bowman's capsule with its basement membrane (24). The visceral epithelium is continuous with the parietal epithelium at the vascular pole, where the afferent arteriole enters and the efferent arteriole exits the glomerulus (24). Glomerular disease can be identified by the presence of glomerular haematuria, glomerular proteinuria, or both. Glomerular haematuria is caused by disruption to the glomerular filtration barrier which results in a urine sediment that contains an increased number of red cell

acanthocytes and the presence of cellular casts (7, 25). Glomerular proteinuria is the presence of plasma proteins in the urine, as a result of a disrupted glomerular filtration barrier (10).

Glomerular disease comprises 25-45% of kidney failure cases in developing countries (23, 25). It is considered to be primary when there is no associated disease elsewhere or secondary if glomerular involvement is part of a systemic disease, e.g., SLE. Primary GN can also be classified according to the clinical presentation, the histopathological appearance or the underlying aetiology (4).

According to Hebert et al (10), types of primary glomerulopathy include:

- MCD
- Idiopathic MGN
- IgAN
- Primary/Idiopathic FSGS
- Acute post-streptococcal GN
- Anti-GBM disease

Secondary glomerulopathy is a result of a multi-system disease that also causes a glomerulopathy, for e.g.

- DN
- LN
- ANCA-associated vasculitis
- Amyloidosis
- Infection related GN
- Cryoglobulinemias

Polito et al(11) found that in primary GN, macroscopic haematuria and NS predominated, while renal dysfunction or unknown aetiology and nephritic syndrome were the main manifestations in secondary GN.

MCD is defined by the absence of glomerular abnormalities on light microscopy but with evidence of podocyte foot process fusion on electron microscopy. There is a resultant loss of integrity of the glomerular filtration barrier which is potentially reversible in the case of MCD (25). MCD is predominantly idiopathic, but secondary causes, which include drugs (non-steroidal anti-inflammatory drugs, enalapril, lithium), malignancies, infections, atopy and SLE, should be excluded in adults. (15).

FSGS is evidenced on light microscopy by consolidation of the glomeruli with entrapment of plasma proteins. Morphological sub-types include the tip, perihilar, cellular, collapsing variants, and FSGS not otherwise specified. Electron microscopy shows extensive foot process effacement without other glomerular basement membrane involvement (15, 25) . FSGS accounts for approximately 40% of NS cases in adults at an incidence of 7 per million population. FSGS is idiopathic in 80% of cases, but may be adaptive, genetic or secondary to other disease processes. Secondary causes include viral infections (HIV, Parvovirus B19, Simian virus 40, Cytomegalovirus and Epstein-Barr virus) and drugs (heroin, lithium, pamidronate, sirolimus, interferon alpha, calcineurin inhibitors and anabolic steroids) (25).

MGN appears as a homogenous thickening of the glomerular capillary wall on light microscopy. MGN may be primary (70% of cases) or secondary. Secondary causes include drugs (gold, penicillamine), autoimmune disease (SLE), malignancies (particularly solid tumours) and infections (syphilis, Hepatitis B, Hepatitis C). MGN is the cause of NS in about 25% of adults (15).

MPGN is a pattern of glomerular injury that is characterised on light microscopy by mesangial hypercellularity, endocapillary proliferation and double-contour formation

along the glomerular capillary walls. MPGN arises as a result of either immune complex deposition that results in complement activation (classified as immune complex mediated MPGN) or dysregulation and continuous activation of the alternative complement pathway (classified as complement-mediated MPGN) (26). MPGN can be primary (that is, idiopathic) if no specific aetiology is found, or secondary due to auto-immune diseases (SLE, Rheumatoid arthritis), infections including Hepatitis B, Hepatitis C, endocarditis, visceral abscess malaria, schistosomiasis), cryoglobinemia, monoclonal gammopathy, neoplasia, chronic thrombotic microangiopathy and complement dysregulation (27).

The most common secondary glomerular diseases are LN, DN and post-infectious GN. About 35% of adults with SLE have clinical evidence of renal involvement at the time of diagnosis, and approximately 50-60% have renal involvement during the initial 10 years of disease. Males and patients of African ethnicity have higher prevalence of renal involvement in SLE (28). Overall, 5- and 10-year survival is significantly lower for SLE patients who also have Lupus Nephritis. According to the American College of Rheumatology (ACR), suggestive features of LN include persistent proteinuria of >0.5g/24h, or a protein-creatinine ratio (UPCR) >0.5 or >3+ protein on urine dipstick, and/or cellular casts. According to the Systemic Lupus International Collaborating Clinics (SLICC) group criteria, a renal biopsy confirming lupus nephritis with a positive test for antinuclear antibody or anti-double-stranded DNA antibody confirms the diagnoses of SLE (29).

The International Society of Nephrology / Renal Pathology Society (ISN/RPS) classification system divides LN into 6 classes which assist with prognostication and treatment decisions: (28):

- Class I: Minimal Mesangial LN – minimal mesangial deposits on immunofluorescence with normal light microscopy
- Class II: Mesangial proliferative LN – mesangial hypercellularity or matrix expansion on light microscopy with immune deposits confined to mesangium on immunofluorescence

- Class III: Focal LN – subendothelial immune deposits and proliferative changes in <50% of glomeruli
- Class IV: Diffuse LN - – subendothelial immune deposits and proliferative changes in >50% of glomeruli
- Class V: Membranous LN – subepithelial immune deposits and membranous thickening of glomerular capillaries
- Class VI: Advanced Sclerosing LN - >90% globally sclerosed glomeruli

Post-infectious GN presents clinically with features of the nephritic syndrome; namely oedema, hypertension, haematuria, proteinuria and renal dysfunction. On light microscopy, the glomeruli are enlarged with hypercellularity due to proliferation of glomerular cells as well as infiltration by leucocytes (28, 30). Granular deposits of IgG and complement are seen along the glomerular basement membrane and mesangium on immunofluorescence (28). Post-infectious GN has a high incidence in Africa and carries a poor prognosis with 30-70% of adults developing CKD (31). This poor prognosis is due to therapeutic challenges in the management of infectious causes such as HIV, Hepatitis B and Hepatitis C infections (28, 30).

DN is the leading cause of kidney failure in most of the developed world. Renal biopsy histopathology shows thickening of the glomerular basement membrane, mesangial expansion, nodular glomerulosclerosis and diffuse glomerulosclerosis in association with interstitial fibrosis and tubular atrophy (32).

2.5.2 Tubulointerstitial diseases

Tubulointerstitial disease includes tubulointerstitial nephritis, ATN, cortical necrosis, reflux nephropathy, oxalosis, nephrocalcinosis and myeloma cast nephropathy (11). Most primary tubulointerstitial diseases are due to apoptosis and necrosis of the tubular epithelium caused by drugs and toxins that accumulate in the tubules. Infection and inflammation of the tubulointerstitium, due to chronic pyelonephritis or urinary

reflux, is also common. Tubulointerstitial disease may also be idiopathic or secondary to an underlying genetic disease (33).

In a retrospective study in Cape Town, South Africa, ATN was the most frequent cause for patients presenting with AKI at 23.4% (6). The popular usage of herbal remedies prescribed by traditional healers, use of non-steroidal anti-inflammatory drugs or drugs used for the treatment of HIV and TB may cause ATN (6, 33).

2.5.3 Vascular diseases

Renal vascular diseases can be divided into hypertensive nephroangiosclerosis, which can be classified as benign or malignant; thrombotic microangiopathy and atheroembolic disease (6). Renal vascular disease may also be classified into micro or macrovascular disease (32, 34). Macrovascular diseases include acute arterial occlusion, aneurysms and thrombosis of the renal artery or vein (32, 34). These patients usually present with abdominal pain, macroscopic haematuria and AKI. Microvascular causes include thrombotic microangiopathy (e.g. malignant hypertension, thrombotic thrombocytopenic purpura) and small vessel vasculitides (33). These microvascular causes usually affect the glomerular capillaries and are occasionally characterised as glomerular diseases.

2.6 Impact of HIV in renal disease

HIVAN was described, clinically and histologically, as early as 1984 (34). Histological patterns from renal biopsies have been published from South Africa. Han et al. conducted a cross-sectional study of HIV reactive patients with varying degrees of proteinuria in Durban and found that HIVAN occurred in 83% of ambulatory patients with proteinuria and relatively preserved renal function (35). Gerntholtz et al reported HIVAN in 27% and HIV immune complex-mediated glomerular disease (HIV-ICD) in 21% of hospitalized patients with advanced kidney dysfunction in a retrospective

review of 99 renal biopsies in Soweto (Johannesburg) undertaken between 2003 and 2004 (36). Okpechi et al, in a 10-year review of 1284 renal biopsies in Cape Town from 2000 to 2009, showed that HIVAN was the predominant lesion (55%) and initiation of antiretroviral therapy (ART) in those with HIVAN and HIV-ICD significantly improved survival (6).

Patients with HIV are at risk of renal injury from many aetiologies, including systemic and renal infections, dehydration, and nephrotoxicity due to therapeutic agents. Autopsy studies in AIDS patients have reported a high incidence of tubulointerstitial disease, including acute tubular necrosis, interstitial nephritis, nephrocalcinosis, and renal involvement by neoplasms such as lymphoma and Kaposi's sarcoma (23, 26). HIVAN has traditionally been reported as the most common renal lesion affecting HIV infected patients but non-HIVAN lesions have shown to account for approximately (a) half of renal disease in these patients (37).

Clinical presentation of HIVAN includes severe proteinuria, rapid development of renal failure and occasionally hypertension (25). On histopathology, HIVAN is appreciated as a form of FSGS featuring global, prominent ‘collapse’ of the glomerular tuft, with visceral epithelial cells displaying striking changes including marked swelling and hypertrophy overlying the collapsed tufts and prominent tubulointerstitial disease, with less glomerular hyalinosis (25). In recognition of these findings, D’Agati et al (25) described HIVAN as diffuse sclerosing glomerulopathy rather than FSGS.. Risk factors that have been identified in the pathogenesis of HIVAN include comorbid diabetes and hypertension, low CD4 count, high HIV viral load, anaemia, infectious diseases and malnutrition (38).

Estrella et al (37) found that HIVAN was unlikely amongst patients with HIV RNA levels <400 copies/ml and was the main cause of secondary glomerular disease in the black population. HIVAN has been reported to be increasing, from 6.6% of all biopsies in 2000 to 25.7% in 2009 (6); however, recent analysis of the trends in the outcomes of kidney failure due to HIVAN has found that the incidence of kidney failure due to

HIVAN as well as mortality had decreased impressively due to the wide availability and usage of HAART (39).

The use of ART has resulted in an increase in the life expectancy and added exposure to nephrotoxic drugs to the HIV-infected population which has resulted in an increased prevalence of CKD from other causes (40). It is therefore important that patients who are diagnosed with HIV are screened at diagnosis and whilst on ART for renal dysfunction so that appropriate interventions are made to prevent progression of renal disease.

2.7 Global distribution of glomerular disease

Polito et al (11) undertook a retrospective study of 9617 renal biopsies in Brazil and found that primary GN was the most frequent histopathological finding (51% of biopsies) followed by secondary glomerular disease (22.6%) and tubulointerstitial disease (2.2%). FSGS and MGN were the leading causes of GN in this study (11). In Western Europe, Australia/New Zealand and some countries in Asia, IgAN is the leading cause of GN, in the Americas, data from the United States, Brazil and Uruguay show that FSGS is the most frequent GN whilst in most studies across Europe and the Americas, LN was the most frequent cause of secondary GN (11, 41).

In a five-year prospective study of kidney biopsies in Kuwait between 2009 and 2014, primary GN was reported in 46.7%, secondary GN was reported in 42.9% and tubulointerstitial disease was reported in 10.3% of kidney biopsies. Among primary GN, MGN was the most common lesion (12.1%), followed by IgAN (11.7%), MCD (9.8%) and FSGS (9.3%). Among biopsies that showed secondary GN, LN was the most common (11.7%), followed by hypertensive glomerulosclerosis (10.3%), crescentic GN (7.1%) and diabetic nephropathy (3.3%). The reason for the low rate of DN could be that diabetic patients do not undergo renal biopsy unless there is no evidence of other target organ damage, particularly diabetic retinopathy or the diagnosis is doubtful or there is a concern for another diagnosis suggested by an

active urinary sediment, rapidly declining renal function or positive serology. Among biopsies that showed tubulointerstitial disease, acute interstitial nephritis was the most common lesion (6.1%), followed by chronic interstitial nephritis (2.8%) and acute tubular necrosis (1.4%) (4).

Islam et al (23, 24), described the histopathological patterns of renal disease during a study in Dhaka. They reported NS as the most common clinical presentation (57.02%) followed by nephritic syndrome (33.19%). Histopathology showed that 95.19% were glomerular diseases, 3.37% were tubulointerstitial nephritis and 1.44% were ATN (23, 24). MPGN was the most common glomerular pathology followed by FSGS (23, 24).

In a 20-year review of renal biopsies in South Korea between 1992 and 2011, MsPGN and IgAN were the most frequent histopathological results, with lupus nephritis being the most common secondary glomerular disease. In the 5-year quartile comparison, the relative frequency of IgAN increased, while that of MsPGN and MPGN decreased significantly during the twenty year period (42).

The global population of the elderly is steadily increasing, especially in low- and middle-income countries. This translates into more elderly patients with acute and chronic diseases (43). Amongst all patients with CKD, the elderly constitutes the largest numbers. They are affected by the same types of renal diseases as younger individuals, but their clinical course and pathological manifestations are different (41). CKD has a greater impact on life expectancy in the elderly compared to the younger population. Cardiovascular disease is the leading cause of death in the CKD population. Therefore, early detection of renal disease and identifying the pattern from renal biopsy, can assist in targeted treatment which would improve cardiovascular outcome (41). Polito et al (11) have reported that gender distribution of patients undergoing biopsy was balanced (females in 51%) but males were more frequently diagnosed with primary GN, and secondary GN were more common in the elderly. In the elderly, the predominant renal diseases were idiopathic MGN, followed by FSGS and amyloidosis, as observed by the majority of the elderly registries.

2.8 South African distribution of glomerular disease

It is likely that South Africa's social inequalities may affect the pattern of glomerular disease in the country. As per the 'hygiene hypothesis', increased exposure to bacterial antigens in developing countries results in a different immune response which causes different glomerular diseases (higher prevalence of MPGN in developing areas, higher prevalence of IgAN and MCD in developed areas) (1).

In a 10-year retrospective study done at the Groote Schuur Hospital in Cape Town between January 2000 and December 2009, the reports of 1284 native renal biopsies were reviewed and the frequencies of primary GN were MPGN (20.4%), MsPGN (19.2%), MGN (18.5%), crescentic and necrotizing GN (11.4%), FSGS (10.5%), post-infectious GN (8.2%), MCD (6.0%) and IgAN (5.8%). Secondary glomerular diseases were more frequent in the young (<40 years) and middle aged (40–60 years) in all the ethnic groups, while primary glomerular diseases were more frequent in the elderly (6). Lupus nephritis was the most frequent secondary glomerular disease (39.0%) and was also the most frequent cause of nephrotic range proteinuria (17.2%). HIVAN increased from 6.6% in 2000 to 25.7% in 2009. The mean age of patients undergoing renal biopsy was 36.8 ± 14 years with 61.8% of patients being under 40 years of age. Their study saw a female preponderance of 54.8% with more mixed-race patients (53.7%), than black patients (42.2%), and Caucasian patients (3.9%) (6).

In a retrospective study reported from Bloemfontein, the nephrotic syndrome (which consisted of 16.7% of the study population) was the most common indication for renal biopsy, and histopathology revealed FSGS (3.8%) with the highest frequency followed by MPGN (3.0%), MN (2.3%) and MCD (1.9%) respectively (7).

Vermeulen et al conducted a retrospective analysis of 1848 adult renal biopsies at Chris Hani Baragwanath Academic Hospital from January 1982 to December 2011. In this predominantly (96.4%) black cohort, primary glomerular disease accounted for 39.7% of cases with FSGS being the most frequently observed GN (29.6%); MGN

accounted for 25.7%, MPGN 18.1% and MCD 14.3%. Secondary GNs comprised 49.3% of the total cases biopsied with LN being the most frequently seen (31%) followed by HIVAN (13.3%).

A systematic review and meta-analysis of the epidemiology of CKD in sub-Saharan Africa done between 1962 and 2011, analysed 17 articles from South Africa which included 5600 patients. The prevalence of CKD by disease-specific population was 18.9% in diabetics, 10% in HIV-infected patients and 24% in patients with hypertension (44). It can be concluded from the above review that both communicable and non-communicable diseases are risk factors for CKD, which has a great health burden throughout sub-Saharan Africa.

3. RESEARCH QUESTION

What is the epidemiology of renal disease in patients undergoing renal biopsy at Helen Joseph Hospital?

4. AIM

To describe the pattern of biopsy-proven renal disease at HJH over a five-year period (1st January 2014 to 31st December 2018) with respect to patient demographics, clinical presentation as indicated by indication for biopsy, and HIV infection status.

4.1 Objectives

- The primary objective of this study was to describe the relative frequency of native kidney disease diagnosed at HJH on renal biopsy.
- Secondary objectives of this study were:
    - To compare the frequency of native kidney disease diagnosis between age groups (15 – 25 years, 26 – 40 years, 41 – 60 years, and greater than 60 years), genders (male and female), and

ethnic groups (Caucasian, Black African, mixed ancestry and Asian; and Black and Non-Black groups).

- To compare the frequency of native kidney disease diagnosis between clinical presentation as indicated by indication to biopsy (nephrotic syndrome, nephritic syndrome, and unexplained renal dysfunction).
- To compare the frequency of native kidney disease diagnosis between HIV positive and HIV negative patients in this series.
- To compare the clinical presentation of glomerular disease in terms of urine protein: creatinine ratio, estimated GFR, and CD4 count (the latter applicable only in HIV positive patients) in this series.

5. METHODOLOGY

5.1 Research Design

A retrospective audit was undertaken of all patients undergoing native kidney biopsy at HJH during the period 1 January 2014 – 31 December 2018. Extracted data was subjected to descriptive and inferential analysis.

5.2 Study Population

The study included 205 patients who underwent native renal biopsy at HJH during the study period.

5.2.1 Inclusion and exclusion criteria

Inclusion criteria for this study were:

- Adults over the age of 14
- All specimens with a definitive pathological diagnosis

Exclusion criteria for this study were:

- Patients under the age of 14
- Renal allograft biopsy
- All specimens that yield inadequate samples for definitive histopathological diagnosis.

5.3 Study Location

The study was conducted at HJH, in Johannesburg, South Africa. HJH is a tertiary level teaching hospital affiliated to the University of the Witwatersrand.

5.4 Data Collection

Potential patients for inclusion in this study were identified through retrospective review of the HJH Division of Nephrology biopsy records. Pertinent data for those patients meeting inclusion criteria were extracted from clinical records and through review of the NHLS Labtrack system. Extracted data was collected using the attached datasheet (see appendix) and datasheets were used to populate a Windows Excel database. Patients included in this study were assigned a study number; identifying details such as patient name and hospital number were available only to the primary investigator and the final database contained only the relevant study number in order to maintain patient anonymity during statistical analysis.

The following data was recorded for each patient:

- Age
- Gender
- Ethnicity
- Indication for biopsy
- Urine protein: creatinine ratio (UPCR – g/mmol)
- Urine (microscopy, culture, sensitivity)

- Blood results (creatinine, GFR, HIV status, CD4 count)
- Histopathological diagnosis

5.5 Data Analysis

The resultant Excel database was imported into Statistica (Statsoft GmBH) for statistical analysis.

1.1 The frequency of native kidney disease diagnoses were compared between gender, ethnic groups and age using a frequency table and, where possible, a Chi-square test; for binomial categories with less than 10 valid data entries resort was made to the Fisher Exact test.

1.2 The frequency of native kidney disease diagnoses were compared across clinical presentation scenarios as evidence by indication to biopsy using the Chi-square test.

1.3 The frequency of native kidney disease diagnoses were compared between the HIV positive and negative patient cohorts in this series using the Chi-square test.

2. The frequency of native kidney disease diagnoses were analysed through the generation of a frequency table and represented graphically using a bar graph.

3. Continuous laboratory parameters urine protein: creatinine ratio, eGFR, and CD4 count were analysed for normality of distribution using the Shapiro Wilk W test and through visual inspection of the histogram plot; consideration was also given to the Central Limit Theorem. Parametric data were compared between native kidney disease diagnoses using the Student t-test. Since these analyses showed non-parametric distribution of data, the median and interquartile range were used to describe continuous variables, and comparison of these variables was undertaken using the Kruskall Wallis ANOVA test.

6. ETHICAL CONSIDERATIONS

The study commenced after approval by the Human Research Ethics Committee of the University of the Witwatersrand and the Helen Joseph Hospital Research Committee. All data was kept confidential and stored on a password-protected database, to which the author alone had access. Permission was obtained from the clinical and academic heads of department of Internal Medicine at HJH, as well as the CEO of HJH, and the head of department of the NHLS, to conduct the study and access the records.

7. RESULTS

7.1 Dataset

Data from 205 patients attending HJH over the five-year study period (1st January 2014 to 31st December 2018) was extracted from clinical records. Ninety-four (45.85%) of included patients were male whilst 111 (54.15%) were female. The majority of the patients were of Black African ethnicity (170, 82.93%), 16 (7.80%) were of mixed-race origin,14 (6.83%) Caucasian and 5 (2.44%) were Asian.

Table 7.1 Distribution by gender

Gender	Frequency	Percentage
Male	94	45.85%
Female	111	54.15%
Total	**205**	**100%**

Table 7.2 Distribution by ethnicity

Race	Frequency	Percentage
Black	170	82.93%
Caucasian	14	6.83%
Asian	5	2.44%
Mixed race	16	7.80%
Total	**205**	**100%**

The indications for biopsy recorded in this study comprised nephrotic syndrome in 79 (38.54%) cases, unexplained renal dysfunction in 74 (36.10%) cases, abnormalities of urinalysis in 34 (16.58%) cases, and nephritic syndrome in 18 (8.78%) cases.

Table 7.3 Frequency of the indications for biopsy

Indications for Biopsy	Frequency	Percentage
Nephrotic syndrome	79	38.54%
Unexplained renal dysfunction	74	36.10%
Abnormal urinalysis	34	16.58%
Nephritic syndrome	18	8.78%
Total	**205**	**100%**

Sixty-eight (33.17%) of included patients in this study were HIV reactive while 137 (66.83%) were HIV non-reactive.

Table 7.4 Frequency and percentages of HIV status

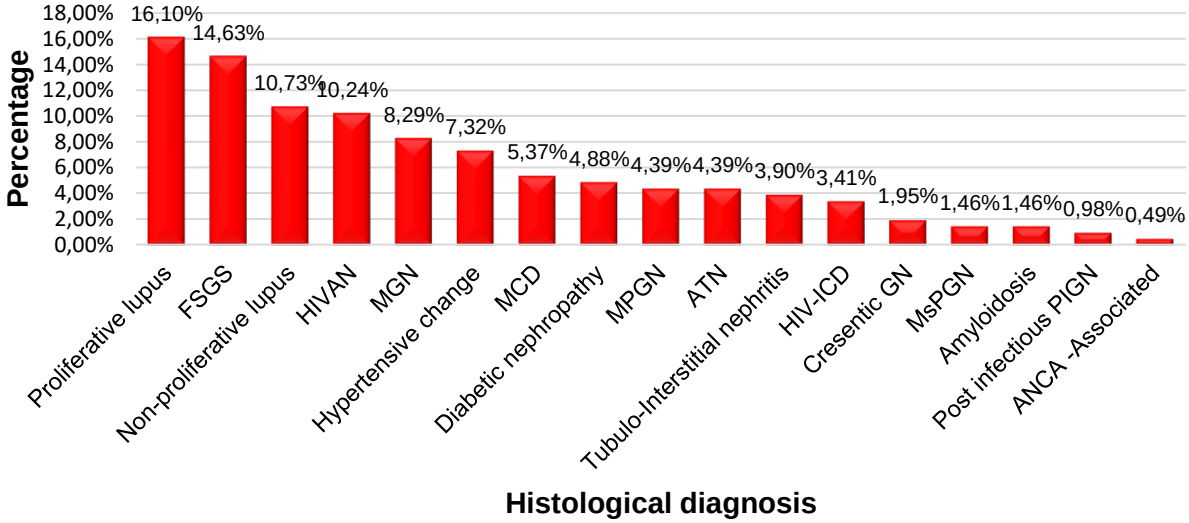
HIV Status	Frequency	Percentage
Reactive	68	33.17%
Non-reactive	137	66.83%
Total	**205**	**100.0%**

The frequencies of histologically diagnosed native kidney disease in this study are summarized in Table 7.5 below. For the purposes of this analysis, lupus nephritis classes III and IV were combined into the category of “proliferative lupus nephritis”, whilst lupus nephritis classes I, II, and V were combined into the category of “non-proliferative lupus nephritis”, and biopsies manifesting malignant hypertension and chronic hypertensive change were combined into the category of “hypertensive changes”. The most common histological diagnosis was that of proliferative lupus (33 cases, 16.10%); followed by FSGS (30, 14.63%); non-proliferative lupus (22, 10.73%); HIVAN (21, 10.24%); MGN (17, 8.29%); hypertensive changes (15, 7.32%); MCD (11, 5.37%) and DN (10, 4.88%).

Table 7.5 Frequency of native kidney disease

Category	Frequency	Percentage	Cumulative Percentage
Proliferative lupus	33	16.10%	16.10%
FSGS	30	14.63%	30.73%
Non-proliferative lupus	22	10.73%	41.46%
HIVAN	21	10.24%	51.71%
MGN	17	8.29%	60.00%
Hypertensive change	15	7.32%	67.32%
MCD	11	5.37%	72.68%
Diabetic Nephropathy	10	4.88%	77.56%
MPGN	9	4.39%	81.95%
ATN	9	4.39%	86.34%
Tubulo-Interstitial Nephritis	8	3.90%	90.24%
HIV-ICD	7	3.41%	93.66%
Crescentic GN	4	1.95%	95.61%
MsPGN	3	1.46%	97.07%
Amyloidosis	3	1.46%	98.54%
Post Infectious GN	2	0.98%	99.51%
ANCA-Associated	1	0.49%	100.00%
Total	**205**	**100.00%**	

Figure 7.1 Frequency of native kidney disease (combined categories)



7.2 Age

The frequencies of native kidney disease diagnoses between age groups (15 - 25 years, 26 - 40 years, 41- 60 years, and greater than 60 years) are summarized in Table 7.6 below. A significant number of patients undergoing native kidney biopsy in this series fell within the 26 – 40 years of age range (96, 46.83%). Chi-square testing suggested a significant difference in the frequency of native kidney disease by age group ($p < 0.001$). In general, lupus nephritis categories, primary FSGS, HIVAN, MsPGN and ATN were more frequent in younger patients; whilst membranous nephropathy, hypertensive and diabetic nephropathy, and tubulointerstitial nephritis were more frequent in older patients.

Table 7.6 Frequencies of native kidney disease by age groups

	15 – 25 N (%)[1]	**26 – 40 N (%)**	**41 – 60 N (%)**	**60+ N (%)**	**Total N (%)**
Proliferative lupus	10 (30.30)	18 (54.55)	5 (15.15)	0 (0.00)	**33 (16.10)**
FSGS	5 (16.67)	15 (50.00)	6 (20.00)	4 (13.33)	**30 (14.63)**
Non-proliferative lupus	2 (9.09)	13 (59.09)	7 (31.82)	0 (0.00)	**22 (10.73)**
HIVAN	0 (0.00)	15 (71.43)	6 (28.57)	0 (0.00)	**21 (10.24)**
MGN	2 (11.76)	3 (17.65)	11 (64.71)	1 (5.88)	**17 (8.29)**
Hypertensive change	0 (0.00)	5 (35.71)	6 (42.86)	3 (21.43)	**15 (7.32)**
MCD	3 (27.27)	3 (27.27)	3 (27.27)	2 (18.18)	**11 (5.37)**
Diabetic Nephropathy	0 (0.00)	2 (20.00)	5 (50.00)	3(30.00)	**10 (4.88)**
MPGN	3 (33.33)	3 (33.33)	3 (33.33)	0 (0.00)	**9 (4.39)**
ATN	0 (0.00)	6 (66.67)	2 (22.22)	1 (11.11)	**9 (4.39)**
Tubulo-Interstitial Nephritis	0 (0.00)	3 (37.50)	5 (62.50)	0 (0.00)	**8 (3.90)**
HIV-ICD	1 (14.29)	3 (42.86)	3 (42.86)	0 (0.00)	**7 (3.41)**
Crescentic GN	0 (0.00)	3 (75.00)	1 (25.00)	0 (0.00)	**4 (1.95)**
MsPGN	0 (0.00)	3 (100.00)	0 (0.00)	0 (0.00)	**3 (1.46)**
Amyloidosis	0 (0.00)	1 (33.33)	0 (0.00)	2 (66.67)	**3 (1.46)**
Post infectious GN	1 (50.00)	0 (0.00)	1 (50.00)	0 (0.00)	**2 (0.98)**
ANCA-Associated	0 (0.00)	0 (0.00)	0 (0.00)	1 (100.00)	**1 (0.49)**
Column Total	**27**	**96**	**65**	**17**	**205**

[1] % is the percentage of the total number in each diagnostic category

7.3 Gender

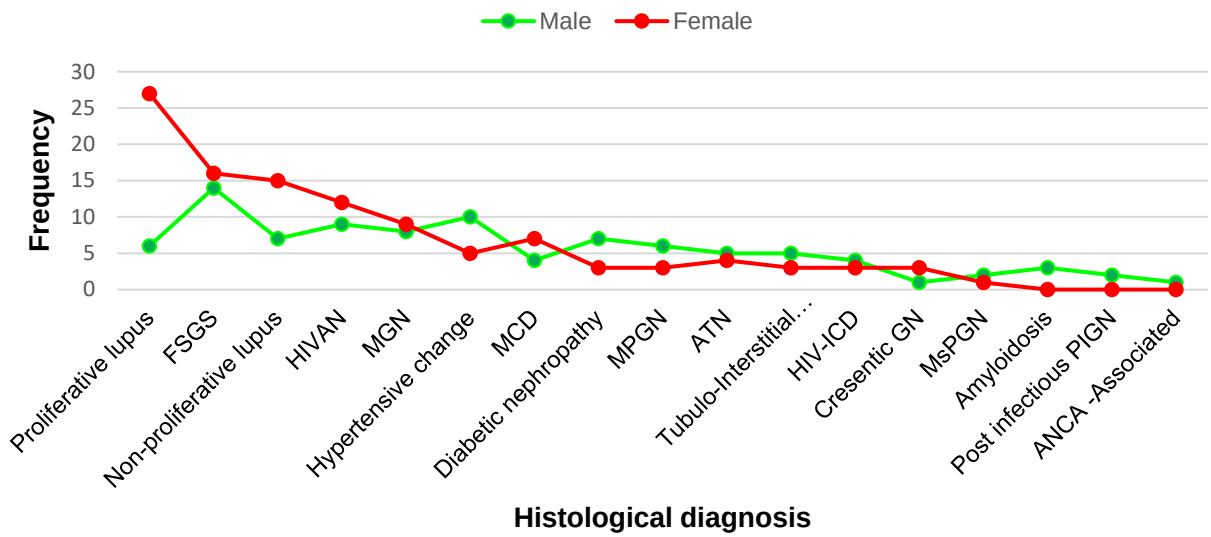
The frequencies of native kidney disease diagnoses by gender are summarized in Table 7.7 and Figure 7.2 below. Women comprised a slight majority of patients included in this study (111 patients, 54.15%). Chi-square testing suggested a significant difference in the distribution of histological diagnosis by gender (p = 0.007). Lupus nephritis diagnostic categories were more frequent in females; slightly higher frequencies of HIVAN, idiopathic crescentic glomerulonephritis and primary minimal change disease were also observed for women. In contrast, membranoproliferative glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, ATN and tubulointerstitial nephritis were more frequently diagnosed in males.

Table 7.7 Frequencies of native kidney disease by gender

Category	Male N(%) [2]	Female N(%)	Total N(%)
Proliferative lupus	6 (18.18)	27 (81.82)	**33 (16.10)**
FSGS	14 (46.67)	16 (53.33)	**30 (14.63)**
Non-proliferative lupus	7 (31.82)	15 (68.18)	**22 (10.73)**
HIVAN	9 (42.86)	12 (57.14)	**21 (10.24)**
MGN	8 (47.06)	9 (52.94)	**17 (8.29)**
Hypertensive change	10 (66.67)	5 (33.33)	**15 (7.32)**
MCD	4 (36.36)	7 (63.64)	**11 (5.37)**
Diabetic Nephropathy	7 (70.00)	3 (30.00)	**10 (4.88)**
MPGN	6 (66.67)	3 (33.33)	**9 (4.39)**
ATN	5 (55.56)	4 (44.44)	**9 (4.39)**
Tubulo-Interstitial Nephritis	5 (62.50)	3 (37.50)	**8 (3.90)**
HIV-ICD	4 (57.14)	3 (42.86)	**7 (3.41)**
Crescentic GN	1 (25.00)	3 (75.00)	**4 (1.95)**
MsPGN	2 (66.67)	1 (33.33)	**3 (1.46)**
Amyloidosis	3 (100.00)	0 (0.00)	**3 (1.46)**
Post infectious GN	2 (100.00)	0 (0.00)	**2) (0.98)**
ANCA-Associated	1 (100.00)	0 (0.00)	**1 (0.49)**
Total	**94**	**111**	**205**

[2] % is the percentage of the total number in each diagnostic category

Figure 7.2 Frequencies of native kidney disease by gender



Sub analysis confirmed a significantly higher prevalence of lupus nephritis in female patients undergoing biopsy. Chi square testing confirmed a higher frequency of all lupus nephritis categories in women (p = 0.0002, table 7.8 below), as well as a higher frequency of proliferative lupus nephritis classes in this group (p = 0.0009, table 7.9 below). No significant difference was however detected in the frequency of non-proliferative lupus nephritis classes between genders (p = 0.241, table 7.10 below).

Table 7.8 Comparison between all lupus nephritis and gender

Category	Male	Female	Row Total
All lupus nephritis	13	42	**55**
Row %	23.64%	76.36%	**26.83%**
Other	81	69	**150**
Row %	54.00%	46.00%	**73.17%**
Column Total	94	111	**205**
Column %	**45.85%**	**54.15%**	**100.00%**

Table 7.9 Proliferative lupus and gender

Category	Male	Female	Row Total
Proliferative lupus	6	27	**33**
Row %	18.18%	81.82%	**100.00%**
Other	88	84	**172**
Row %	51.16%	48.84%	**100.00%**
Column Total	**94**	**111**	**205**

Table 7.10 Non-proliferative lupus and gender

Category	Male	Female	Row Total
Non-proliferative lupus	7	15	**22**
Row %	31.82%	68.18%	**100.00%**
Other	87	96	**183**
Row %	47.54%	52.46%	**100.00%**
Column Total	94	111	**205**

7.4 Ethnicity

The frequency of native kidney disease by ethnicity is summarized in Table 7.11 and figure 7.3 below. The majority of patients included in this study were of black African ethnicity (170, 82.93%).

A Chi-square test for independence with simulated p-value (based on 10000 replicates) was performed to test for a significant relationship between ethnicity and histological diagnosis; no significant relationship was demonstrated in this analysis ($p = 0.6233$, $\chi 2 = 42.615$, $df = 48$).

Table 7.11 Frequency of native kidney disease by ethnicity

Category	Black	Caucasian	Asian	Mixed race	Row total
Proliferative lupus	22	5	3	3	**33**
N (%) [3]	66.67%	15.15%	9.09%	9.09%	**16.10%**
FSGS	26	1	0	3	**30**
N (%)	86.67%	3.33%	0.00%	10.00%	**14.63%**
Non-proliferative lupus	16	1	1	4	**22**
N (%)	72.73%	4.55%	4.55%	18.18%	**10.73%**
HIVAN	21	0	0	0	**21**
N (%)	100.00%	0.00%	0.00%	0.00%	**10.24%**
MGN	16	0	1	0	**17**
N (%)	94.12%	0.00%	5.88%	0.00%	**8.29%**
Hypertensive change	13	0	0	2	**15**
N (%)	86.67%	0.00%	0.00%	13.33%	**7.32%**
MCD	9	2	0	0	**11**
N (%)	81.82%	18.18%	0.00%	0.00%	**5.37%**
Diabetic Nephropathy	8	1	0	1	**10**
N (%)	80.00%	10.00%	0.00%	10.00%	**4.88%**
MPGN	7	1	0	1	**9**
N (%)	77.78%	11.11%	0.00%	11.11%	**4.39%**
ATN	7	2	0	0	**9**
N (%)	77.78%	22.22%	0.00%	0.00%	**4.39%**
Tubulo-Interstitial Nephritis	7	1	0	0	**8**
N (%)	87.50%	12.50%	0.00%	0.00%	**3.90%**
HIV-ICD	5	0	0	2	**7**
N (%)	71.43%	0.00%	0.00%	28.57%	**3.41%**
Crescentic GN	4	0	0	0	**4**
N (%)	100.00%	0.00%	0.00%	0.00%	**1.95%**
MsPGN	3	0	0	0	**3**
N (%)	100.00%	0.00%	0.00%	0.00%	**1.46%**
Amyloidosis	3	0	0	0	**3**
N (%)	100.00%	0.00%	0.00%	0.00%	**1.46%**
Post infectious GN	2	0	0	0	**2**
N (%)	100.00%	0.00%	0.00%	0.00%	**0.98%**
ANCA-Associated	1	0	0	0	**1**
N (%)	100.00%	0.00%	0.00%	0.00%	**0.49%**
Column Total	**170**	**14**	**5**	**16**	**205**
Column percentage	**82.93%**	**6.83%**	**2.44%**	**7.80%**	**100.00%**

[3] % is the percentage of the total number in each diagnostic category

Figure 7.3 Frequency of native kidney disease by ethnicity

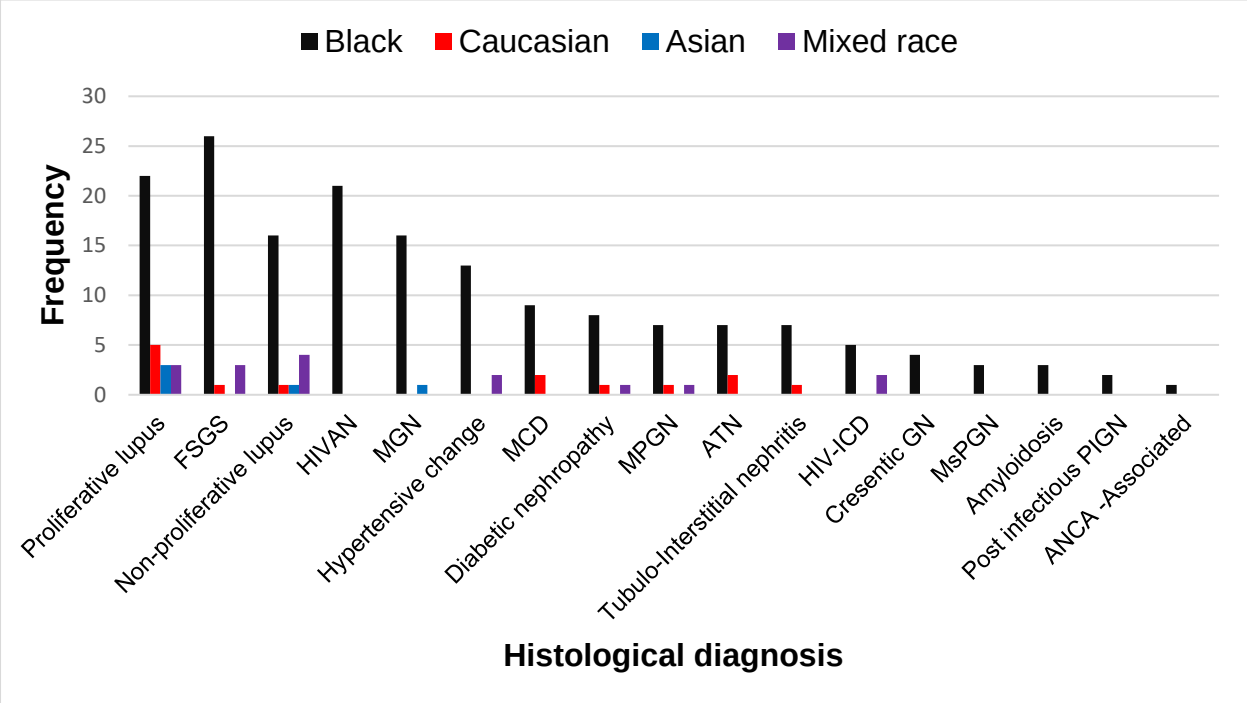
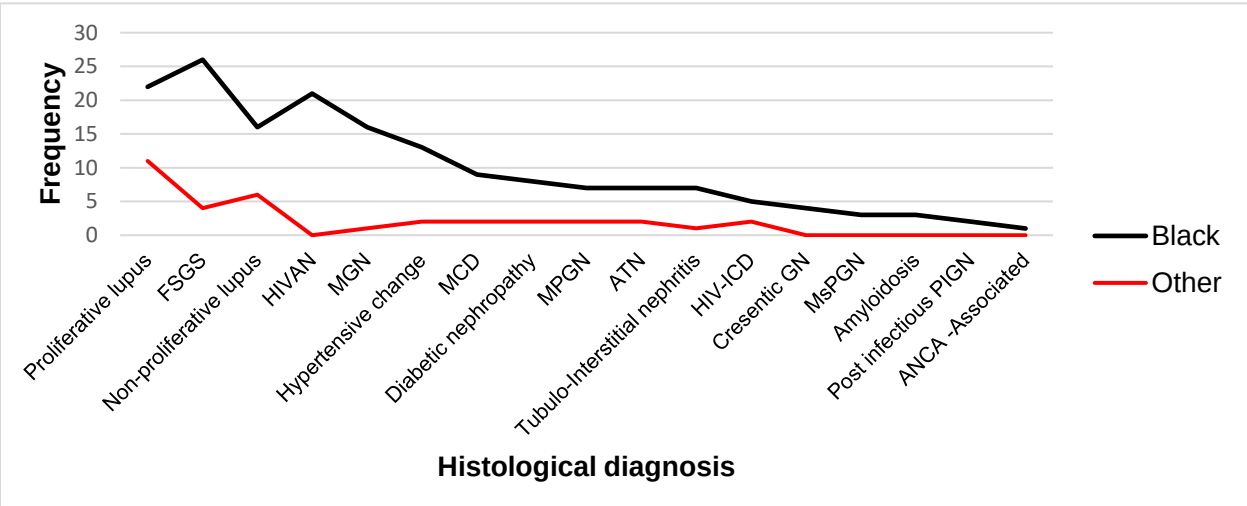


Figure 7.4 below shows the frequency of native kidney disease by ethnicity after combining non-black ethnicities. Chi-square testing for independence with simulated p-value (based on 10000 replicates) failed to demonstrate a significant relationship ($p = 0.3854$, $\chi^2 = 17.906$, $df = 16$).

Figure 7.4 Frequency of native kidney disease for Black vs other ethnic groups



Since visual inspection of the frequency plot appeared to show differences in the relative frequencies of proliferative lupus nephritis, HIVAN, primary FSGS, and primary membranous glomerulopathy between ethnicity groups, sub-analysis of the prevalence of each of these histological injuries between ethnic categories was performed using a Chi-square test. Amongst patients diagnosed with proliferative lupus, the majority (22, 66.67%) were of Black African ethnicity. The preponderance of patients of Black African descent over non-Black patients in this group was of statistical significance (p = 0.014).

Table 7.12 Comparison between Proliferative lupus and other histological diagnoses for Black and other ethnic groups

	Black		**Other ethnic groups**		**Row total**
Proliferative lupus	22	12.94%	11	31.43%	**33**
Other histological diagnoses	148	87.06%	24	68.57%	**172**
Column total	**170**	100%	**35**	100%	**205**

In comparison, no significant difference in the frequency of non-proliferative lupus nephritis was found between Black African and non-Black ethnic groups (p = 0.222).

Table 7.13 Comparison between Non-proliferative lupus and other histological diagnoses for Black and Other ethnic groups

Category	**Black**		**Other ethnic groups**		**Row total**
Non -proliferative lupus	16	9.41%	6	17.14%	**22**
Other histological diagnoses	154	90.59%	29	82.86%	**183**
Column total	**170**	100%	**35**	100%	**205**

All patients diagnosed with classic HIVAN during the course of this study were of Black African ethnicity. Chi-square testing indicated the preponderance of Black African ethnicity in the HIVAN group to be of statistical significance (p = 0.028).

Table 7.14 Comparison between HIVAN and other histological diagnoses for Black and other ethnic groups

Category	Black	Other ethnic groups			Row total
HIVAN	21	12.35%	0	0.00%	**21**
Other histological diagnoses	149	87.65%	35	100%	**184**
Column total	**170**	100%	**35**	100%	**205**

15.29% of Black African patients were diagnosed with primary FSGS during the course of this study, compared to 11.43% of non-Black patients. Chi-square testing showed no significant association between primary FSGS and ethnicity (p = 0.793).

Table 7.15 Comparison between FSGS and other histological diagnoses for Black and other ethnic groups

Category	Black		Other ethnic groups		Row total
FSGS	26	15.29%	4	11.43%	**30**
Other histological diagnoses	144	84.71%	31	88.57%	**175**
Column total	**170**	100%	**35**	**100.00%**	**205**

The freqeuncy of primary membranous glomerulopathy amongst patients of Black African ancestry was 9.41% compared to that of 2.86% amongst non-Black patients (p = 0.316).

Table 7.16 Comparison between MGN and other histological diagnoses for Black and other ethnic groups

Category	Black		Other ethnic groups		Row total
MGN	16	9.41%	1	2.86%	**17**
Other histological diagnoses	154	90.59%	34	97.14%	**188**
Column total	**170**	100%	**35**	**100.00%**	**205**

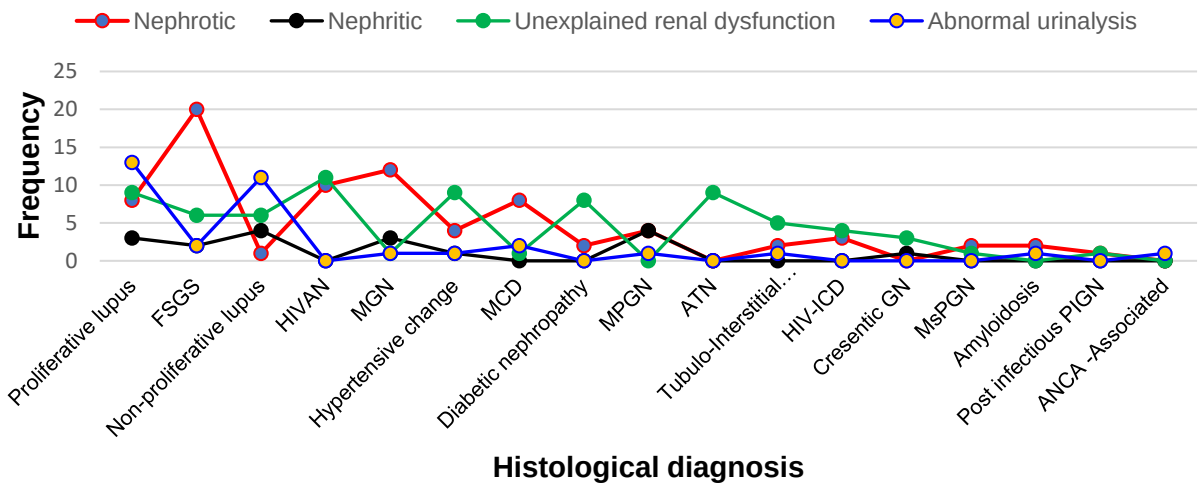
7.5 Clinical presentation / Indication to biopsy

The most frequent clinical scenario as an indication to biopsy in this study was nephrotic syndrome (38.54%), followed by unexplained renal dysfunction (36.10%), and abnormal urinalysis (16.59%), with nephritic syndrome (8.78%) being the least common indication for biopsy. Amongst all patients that underwent biopsy, the most frequent histological diagnoses for patients presenting with the nephrotic syndrome were FSGS (25.32%), MGN (15.19%), HIVAN (12.66%) and LN (11.40%). Amongst those undergoing biopsy for nephritic syndrome, the most frequent histological diagnoses were proliferative lupus (22.22%) and MPGN (22.22%). The most frequent histological diagnoses amongst patients biopsied for unexplained renal dysfunction was HIVAN (14.86%) followed by proliferative lupus, hypertensive change and ATN (each contributing 12.16%). Proliferative lupus (38.24%) and non-proliferative lupus (32.35%) were the most frequent diagnoses in those patients' undergoing biopsy for investigation of abnormal urinalysis. These differences in the frequency of histological findings by indication to biopsy were statistically significant in Chi-square testing ($p < 0.001$).

Table 7.17 - Comparison of native kidney disease by clinical presentation

	Nephrotic syndrome N (%) [4]	Nephritic syndrome N (%)	Unexplained renal dysfunction N (%)	Abnormal urinalysis N (%)	Totals
Proliferative lupus	8 (10.13)	3 (16.67)	9 (12.16)	13 (38.24)	33
FSGS	20 (25.32)	2 (11.11)	6 (8.11)	2 (5.88)	30
Non-proliferative lupus	1 (1.27)	4 (22.22)	6 (8.11)	11 (32.35)	22
HIVAN	10 (12.66)	0 (0.00)	11 (14.86)	0 (0.00)	21
MGN	12 (15.19)	3 (16.67)	1 (1.35)	1 (2.94)	17
Hypertensive change	4 (5.06)	1 (5.56)	9 (12.16)	1 (2.94)	15
MCD	8 (10.13)	0 (0.00)	1 (1.35)	2 (5.88)	11
Diabetic Nephropathy	2 (2.53)	0 (0.00)	8 10.81)	0 (0.00)	10
MPGN	4 (5.06)	4 22.22)	0 (0.00)	1 (2.94)	9
ATN	0 (0.00)	0 (0.00)	9 (12.16)	0 (0.00)	9
Tubulo-Interstitial Nephritis	2 (2.53)	0 (0.00)	5 (6.76)	1 (2.94)	8
HIV-ICD	3 (3.80)	0 (0.00)	4 (5.41)	0 (0.00)	7
Crescentic GN	0 (0.00)	1 (5.56)	3 (4.05)	0 (0.00)	4
MsPGN	2 (2.53)	0 (0.00)	1 (1.35)	0 (0.00)	3
Amyloidosis	2 (2.53)	0 (0.00)	0 (0.00)	1 (2.94)	3
Post infectious GN	1 (1.27)	0 (0.00)	1 (1.35)	0 (0.00)	2
ANCA-Associated	0 (0.00)	0 (0.00)	0 (0.00)	1 (2.94)	1
Total	79 (100.00)	18 (100.00)	74 (100.00)	34 (100.00)	205

Figure 7.5 Frequency of native kidney disease across clinical presentation scenarios



[4] % is the percentage of the total number within each clinical presentation

Further subanalysis was undertaken for those histological diagnosis categories where visual inspection of the frequency plot appeared to suggest significant association with an indication to biopsy.

In those patients diagnosed with proliferative lupus, 8 (24.24%) presented with nephrotic syndrome, 3 (9.09%) with nephritic syndrome, 9 (27.27%) had unexplained renal dysfunction while 13 (39.39%) had abnormality of urinalysis. The higher frequency of abnormality of urinalysis as an indication to biopsy in proliferative nephritis compared to other histological categories was statisitcally significant in Chi-square testing ($p = 0.002$).

Table 7.18 Histological diagnosis (proliferative lupus and other histologies) and clinical presentation

	Nephrotic syndrome	Nephritic syndrome	Unexplained renal dysfunction	Abnormal urinalysis	Totals
Proliferative lupus	8	3	9	13	33
N (%) [5]	24.24%	9.09%	27.27%	39.39%	16.10%
Other	71	15	65	21	172
N (%)	41.28%	8.72%	37.79%	12.21%	83.90%
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

In those patients diagnosed with non-proliferative lupus, 11 (50%) presented with abnormality of urinalysis, 6 (27.27%) had unexplained renal dysfunction, 4 (18.18%) manifested with nephritic syndrome and 1 (4.55%) presented with nephrotic syndrome. The pattern of biopsy indication in non-proliferative lupus nephritis compared to other categories of histological injury was clinically significant in Chi-square testing ($p < 0.001$).

[5] % is the percentage of the total number in each diagnostic category

Table 7.19 Histological diagnosis (Non-proliferative lupus / other histologies) and clinical presentation

	Nephrotic syndrome	Nephritic syndrome	Unexplained renal dysfunction	Abnormal urinalysis	Totals
Non-proliferative lupus	1	4	6	11	22
N (%) [6]	4.55%	18.18%	27.27%	50.00%	10.73%
Other	78	14	68	23	183
N (%)	42.62%	7.65%	37.16%	12.57%	89.27%
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

The apparent trend towards abnormality of urinalysis as an indication for biopsy in lupus nephritis was subjected to further subanalysis. Comparison of indication for biopsy between those patients diagnosed with any class of lupus nephritis compared to those with any other histological diagnosis revealed abnormality of urinalysis to be the most frequent indication to biopsy in lupus nephritis (44.44%), whilst nephrotic syndrome was the most common indication to biopsy in those patients diagnosed with other histological injury (46.36%) these differences in indication to biopsy were statistically signifiant ($p < 0.00001$).

Table 7.20 Histological diagnosis (all cases of lupus nephritis / other histologies) and clinical presentation

	Nephrotic syndrome	Nephritic syndrome	Unexplained renal dysfunction	Abnormal urinalysis	Totals
All lupus nephritis	9	7	14	24	22
N (%) [7]	16.67%	12.96%	25.93%	44.44%	10.73%
Other	70	11	60	10	183
N (%)	46.36%	7.28%	39.74%	6.62%	89.27%
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

[6] % is the percentage of the total number in each diagnostic category
[7] % is the percentage of the total number in each diagnostic category

The apparent association of abnormality of urinalysis over other indications to biopsy with subsequent diagnosis of lupus nephritis was confirmed through logistic regression analysis (odds ratio for the diagnosis of lupus nephritis in patients undergoing biopsy for abnormality of urinalysis of 11.28, 95%CI 4.89 – 26.03, $p < 0.000001$).

Eleven (52.38%) patients diagnosed with HIVAN underwent biopsy for unexplained renal dysfunction and 10 underwent biopsy for nephrotic syndrome (47.62%). There were no patients in this group that presented with nephritic syndrome or abnormal urinalysis. Chi-square testing suggested a signifcant difference in the frequency of indication to biopsy between HIVAN and non-HIVAN diagnoses ($p = 0.0426$). However, since HIVAN can only affect HIV positive patients, restriction of Chi-square testing for the frequency of unexplained renal dysfunction as an indication to biopsy in the HIVAN diagnostic category failed to show signficant difference with other biopsy indication ($p = 0.793$).

Table 7.21 Histological diagnosis (HIVAN / other histologies) and clinical presentation

	Nephrotic	Nephritic	Unexplained renal dysfunction	Abnormal urinalysis	Totals
HIVAN	10	0	11	0	21
N (%) [8]	47.62%	0.00%	52.38%	0.00%	10.24%
Other	69	18	63	34	184
N (%)	37.50%	9.78%	34.24%	18.48%	89.76%
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

The majority of patients diagnosed with primary FSGS (66.67%) presented with nephrotic syndrome, 20% of patients in this group presented with unexplained renal dysfunction; nephritic syndrome and abnormalities of urinalysis were rare in this cohort at 6.67% each. Chi-square testing appeared to show a statistically significant difference in the pattern of indication to biopsy between primary FSGS and other diagnostic categories ($p = 0.006$). The odds ratio for the diagnosis of primary FSGS in

[8] % is the percentage of the total number in each diagnostic category

biopsies undertaken for the indication of nephrotic syndrome was calculated using logistic regression modelling to be 3.93 (95% CI 1.73 – 8.94, p = 0.001).

Table 7.22 - Histological diagnosis (FSGS / other histologies) and clinical presentation

	Nephrotic	Nephritic	Unexplained renal dysfunction	Abnormal urinalysis	Totals
FSGS	20	2	6	2	**30**
N (%) [9]	66.67%	6.67%	20.00%	6.67%	**14.63%**
Other	59	16	68	32	**175**
N (%)	33.71%	9.14%	38.86%	18.29%	**85.37%**
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

As was the case with primary FSGS, the majority of patients diagnosed with primary membranous nephropathy presented with nephrotic syndrome (70.59%); nephritic syndrome was the indication to biopsy in 3 (17.65%) patients and 1 (5.88%) had abnormal urinalysis and unexplained renal dysfunction. Once again, Chi-sqaure testing appeared to suggest significant assoication between nephrotic syndrome as an indication to biopsy and the diagnosis of primary membranous nephropathy compared to other biopsy indications and histological categories (p = 0.003), which was further suggested by logistic regression modelling which found the odds ratio for the diagnosis of membranous nephropathy in patients biopsied for nephrotic syndrome to be 4.33 (95% CI 1.46 – 12.83, p = 0.008).

[9] % is the percentage of the total number in each diagnostic category

Table 7.23 Histological diagnosis (MGN / other histologies) and clinical presentation

	Nephrotic	Nephritic	Unexplained renal dysfunction	Abnormal urinalysis	Totals
MGN	12	3	1	1	**17**
N (%) [10]	70.59%	17.65%	5.88%	5.88%	**8.29%**
Other	67	15	73	33	**188**
N (%)	35.64%	7.98%	38.83%	17.55%	**91.71%**
Total	**79**	**18**	**74**	**34**	**205**
N (%)	**38.54%**	**8.78%**	**36.10%**	**16.59%**	**100.00%**

Thus, nephrotic syndrome was the most frequent indication to biopsy in both primary FSGS and primary membranous nephropathy, the two most commonly encountered primary podocytopathies in this series, confirmed by subanalysis using logistic regression modelling which found the odds of diagnosing either primary FSGS or membranous nephropathy in patients presenting with nephrotic syndrome in this series to be 3.93 (95% CI 1.73 – 8.94, p = 0.001). Although the frequency of nephrotic syndrome as the indication to biopsy was not significantly different between primary FSGS and membranous histological categories (p = 0.781 in Chi-square testing), univariate logistic regression modelling found the odds ratio for the diagnosis of primary membranous nephropathy on biopsy for nephrotic syndrome to be 5.67 (95% CI 1.89 – 16.99, p = 0.002) and that for FSGS to be 4.72 (95% CI 2.06 – 10.86, p = 0.0003). This latter analysis suggests the odds of diagnosing primary membranous nephropathy in the setting of nephrotic syndrome in this series to be slightly higher than that of diagnosing FSGS, and results from the higher frequency of cases of nephrotic syndrome in the former (70.59% compared to 66.67%).

[10] % is the percentage of the total number in each diagnostic category

7.6 HIV

The relative frequency of histological diagnoses in HIV positive and HIV negative patient cohorts in this series are plotted on Figure 7.6 below. Chi square testing suggested a significant difference in the frequency of histological diagnoses between these groups ($p < 0.001$). Visual inspection of the frequency plot indicated higher frequencies of HIVAN, HIV-immune complex kidney disease and tubulointerstitial nephritis amongst patients who were HIV positive.

Figure 7.6 Frequency of native kidney disease according to HIV status

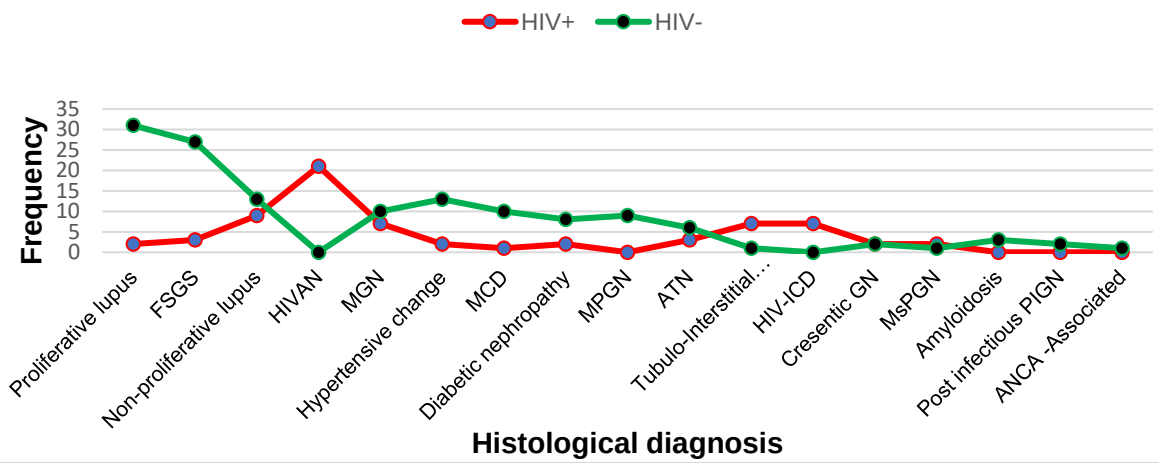


Table 7.24 Comparison of native kidney disease by HIV infection status

Category	HIV+	HIV-	Total
Proliferative lupus	2	31	33
N **(**%) [11]	6.06%	93.94%	
FSGS	3	27	30
N **(**%)	10.00%	90.00%	
Non-proliferative lupus	9	13	22
N **(**%)	40.91%	59.09%	
HIVAN	21	0	21
N (%)	100.00%	0.00%	
MGN	7	10	17
N (%)	41.18%	58.82%	
Hypertensive change	2	13	15
N (%)	13.33%	86.67%	
MCD	1	10	11
N (%)	9.09%	90.91%	
Diabetic Nephropathy	2	8	10
N (%)	20.00%	80.00%	
MPGN	0	9	9
N (%)	0.00%	100.00%	
ATN	3	6	9
N (%)	33.33%	66.67%	
Tubulo-Interstitial Nephritis	7	1	8
N (%)	87.50%	12.50%	
HIV-ICD	7	0	7
N (%)	100.00%	0.00%	
Crescentic GN	2	2	4
N (%)	50.00%	50.00%	
MsPGN	2	1	3
N (%)	66.67%	33.33%	
Amyloidosis	0	3	3
N (%)	0.00%	100.00%	
Post infectious GN	0	2	2
N (%)	0.00%	100.00%	
ANCA-Associated	0	1	1
N (%)	0.00%	100.00%	
Total	**68**	**137**	205
N (%)	33.17%	66.83%	

[11] % is the percentage of the total number in each diagnostic category

Since HIVAN and HIV-immune complex kidney disease can only be expected to occur in HIV-infected individuals, sub analysis of histological injury patterns by HIV infection status was restricted to the tubulointerstitial nephritis category. Tubulo-Interstitial nephritis cases were more frequent in HIV reactive patients (7 cases, 87.50%) than HIV non-reactive patients (12.50%), a difference which was statistically significant in Chi-square testing (p = 0.003).

Table 7.25 Tubulo-Interstitial nephritis vs. other histological diagnoses by HIV infection status

Category	HIV+	HIV-	Total
Tubulo-Interstitial Nephritis	7	1	**8**
N (%)	87.50%	12.50%	
Other	61	136	**197**
N (%)	30.96%	69.04%	
Total	**68**	**137**	**205**
N (%)	33.17%	66.83%	100.00%

7.7 Continuous parameters (UPCR/ Creatinine/ GFR)

Table 7.26 Descriptive statistics for continuous variables

	Age	UPCR	Creatinine	GFR	CD4
Median	36.00	0.43	163.00	49.00	212.50
Standard deviation	13.42	29.90	347.62	52.78	234.52

Table 7.27 UPCR, Creatinine and GFR results for each histological diagnosis

Hist. diagnosis	UPCR (Lower, Upper quartiles)	Creatinine (Lower, Upper quartiles)	GFR (Lower, Upper quartiles)
Proliferative lupus	0.336 (0.180 - 0.403)	80 (61.00 - 171.00)	92 (32.00 - 129.00)
FSGS	0.534 (0.34 - 0.96)	126.50 (79.00 - 223.00)	60.50 (25.00 - 104.00)
Non-proliferative lupus	0.15 (0.10 - 0.33)	71.00 (59.00 - 179.00)	107.00 (36.00 - 131.00)
HIVAN	0.744 (0.41 - 1.08)	556.00(393.00 - 850.00)	10.00 (6.00 - 18.00)
MGN	0.060 (0.50 - 1.10)	77.00 (65.00 - 127.00)	93.00 (55.00 - 123.00)
Hypertensive change	0.40 (0.20 - 0.55)	636.00 (340.00 - 957.00)	10.00 (7.00 - 47.00)
MCD	0.46 (0.35 - 0.59)	63.00 (54.00 - 73.00)	128.00 (84.00 - 168.00)
DN	0.75 (0.48 - 1.47)	374.00 (196.00 - 468.00)	13.50 (11.00 - 32.00)
MPGN	0.66 (0.45 - 0.77)	115.00 (91.00 (125.00)	74.00 (63.00 - 81.00)
ATN	0.33 (0.14 - 0.38)	298.00 (146.00 - 553.00)	16.00 (9.00 - 36.00)
Tubulo-Interstitial Nephritis	0.69 (0.28 - 0.78)	336.50 (190.00 - 849.50)	21.00 (6.50 - 51.00)
HIV-ICD	0.41 (0.27 - 0.64)	225.00 (171.00 - 956.00)	25.00 (7.00 - 49.00)
Crescentic GN	0.50 (0.20 - 1.27)	614.50 (246.00 - 980.00)	15.00 (6.00 - 26.00)
MsPGN	0.69 (0.22 - 1.48)	860.00 (121.00 - 1611.00)	8.00 (2.00 - 82.00)
Amyloidosis	0.57 (0.34 - 1.77)	109.00 (92.00 - 222.00)	77.00 (33.00 - 109.00)
Post infectious GN	0.44 (0.11 - 0.78)	260.00 (131.00 - 389.00)	37.00 (15.00 - 59.00)
ANCA-Associated	0.38 (0.38 - 0.38)	299.00 (299.00 -0299.00)	21.00 (21.00 - 21.00)

The Kruskal-Wallis ANOVA by ranks test shows that there was a significant difference in the continuous variables between histological categories (UPCR = 0.38, $p < 0.01$; Creatinine = 88.05, $p < 0.01$ and GFR = 87.41, $p < 0.01$).

7.8 CD4 count (cells/mm^3)

Analysis of CD4 count by histological category in HIV positive patients showed that higher CD4 counts were present in membranous nephropathy, non-proliferative LN, proliferative LN and HIV-ICD (241) whilst lower CD4 counts were present in patients with HIVAN and tubulo-Interstitial Nephritis, although this observed trend did not reach statistical significance (p = 0.556 in Kruskal Wallis ANOVA testing).

Table 7.28 CD4 count in HIV reactive patients for each histological diagnosis

Histological diagnosis	Median	Lower quartile	Upper quartile
Crescentic GN	409.50	158	661
MCD	405.00	405	405
MGN	343.00	245	908
Non-proliferative lupus	272.00	208	419
Proliferative lupus	248.50	160	337
HIV-ICD	241.00	105	533
MsPGN	218.50	58	379
DN	205.50	32	379
ATN	204.00	161	415
HIVAN	129.00	41	300
Tubulo-Interstitial Nephritis	156.00	67	444
Hypertensive change	123.50	53	194
FSGS	120.00	45	607

8. DISCUSSION

8.1 Dataset

Over the 5-year period of study, it can be noted from Table 7.1 that of the 205 total participants from HJH, there was about 8% more females than males (54.15% vs 45.85%). This is consistent with a study conducted in Brazil by Polito, et al (11) from 1993 to 2007, which found that women presented more frequently for renal biopsy than men. A study undertaken in Soweto, Johannesburg from 1982 to 2011 by Vermeulen et al (14) also reported a slight female preponderance (50.2% compared to 49.8%). The female preponderance probably reflects healthcare seeking behaviours. The 2011 General Household Survey in South Africa indicated that men are less likely than females to seek medical attention when ill (45). Factors that could be implicated in healthcare seeking behaviours include socio-economic status, demographic background, individual's attitudes and past experiences.

The majority of the participants in the study were of black ethnicity (82.93%), followed by mixed-race (7.80%), Caucasian (6.83%) and Asian (2.44%). This reflects the countries' demographics and access to health services in South Africa. According to Statistics South Africa's mid-year population estimates for 2021, the ethnic distribution was black African (80.9%), mixed-race (8.8%), Caucasian (7.8%) and Asian (2.6%) (46). The above findings also fit between the Vermeulen et al (14) study in Soweto, Johannesburg that consisted of predominantly black ethnic patients (96.4%) and the Okpechi et al (6) study in Cape Town that comprised of predominantly mixed-race patients (53.7%) followed by black patients (42.4%). The findings of the Cape Town study correlates with the Western Cape demographics as per Statistics South Africa which reported the demographical distribution of the Western Cape to consist of mixed-race (49%), black African (33%), Caucasian (17%) and Asian (1%) (45).

NS has been reported to be the most common indication for renal biopsy worldwide (10). Polito et al have reported from Brazil (11) that NS was the commonest clinical

indication for a renal biopsy in that population (39%), followed by AUA (20.7%), and acute and chronic renal failure (16.8%). Vermeulen et al reported from Soweto, South Africa (14) that the most common indication for renal biopsy were NS (47.7%), AKI (19.8%) and AUA (8.1%). Okpechi et al reported from Cape Town, South Africa (6) with similar findings of NS (52.5%), AKI (21.3%) and AUA (13.6%). In the present study, NS was the most prevalent indication to biopsy (38.54%), followed by unexplained renal dysfunction (36.10%), AUA (16.58%) and the least frequent indication was nephritic syndrome at 8.78%. These findings could be due to the lower number of acute GN cases that are seen in adults compared to the paediatric population, since post-infectious GN is more common in the latter and that renal biopsies at HJH are usually restricted to cases presenting with NS or nephritic syndrome as opposed to AUA.

The most common histological findings were lupus nephritis, 55 (26.83%); followed by FSGS, 30 (14.63%); HIVAN, 21 (10.24%); MGN, 17 (8.29%); Hypertensive change, 15 (7.32%); MCD, 11 (5.37%) and Diabetic Nephropathy 10 (4.88%). This probably reflects the low threshold for renal biopsy in SLE patients as proteinuria of more than 500mg/day, renal dysfunction or active urinary sediment are considered as indications for renal biopsy in these patients. HIVAN is often seen in the setting of untreated HIV, and these patients are not always suitable for renal biopsy due to presentation with advanced CKD where renal biopsy is not deemed safe.

Membranous GN is present because this is an adult cohort. In comparison to other local studies, the frequency of Membranous GN was 18.5% in the Cape Town study done by Okpechi et al (6) and 25.7% in the Soweto study by Vermeulen et al (14). Vermeulen et al (14) have previously reported LN as the most common cause of secondary GN with 31% of secondary GN cases (15.3% of all biopsies) with FSGS comprising 29.6% of primary GN cases. Okpechi et al (6) had also found LN to be the most common secondary cause of GN (39%) with the most common primary GN being MPGN (20.4%); FSGS was relatively uncommon in this group (10.5%). The lower frequency of FSGS reported in this (6) study could reflect study population demographics (mixed race predominance over patients of black ethnicity). There

were no recorded cases of IgA nephropathy in this study which is in keeping with the low incidence in other local studies with Vermeulen et al (14) recording 3.5% and Okpechi et al (6) recording 5.8% of all primary GN cases. This is in keeping with the epidemiology of the disease as IgA nephropathy appears to be rare in patients of African descent and more common in Western Europe, Australia/New Zealand and some countries in Asia (11). This also reflects the biopsy thresholds in our setting, where patients presenting with isolated microscopic haematuria with preserved renal function do not undergo renal biopsy.

8.2 Analysis of Age

When comparing the frequency of native kidney disease by age in this study (table 7.8), it was found that proliferative LN was more frequent in younger patients (15 - 25 years age group, 30.30% and 26 - 40 years age-group, 54.55%) with the OR for Proliferative lupus in patients younger than 33.68 years being 5.0189 (95%CI 2.1379 – 11.7827,p = 0.0002). Primary MGN was more common in older patients (70.59% affecting those above 40 years of age) with OR for MGN in patients older than 33.68 years being 2.7995 (95%CI 0.8805 – 8.9014, p = 0.0811). FSGS, non-proliferative lupus and ATN were also more frequent in younger age groups whilst DN and hypertensive change showed increased incidence in older age patients.

Similar findings of a higher frequency of MGN in older age groups have been reported by Polito et al (11) in Brazil, Okpechi et al (6) in Cape Town and Vermeulen et al (14) in Soweto, Johannesburg. The global population of the elderly is steadily increasing, especially in low- and middle-income countries. This translates into more elderly patients with acute and chronic diseases and hence the increased frequency of DN and hypertensive change in this category (43). This can also be attributed to the fact that the renal effects of these diseases take time to manifest so they are more likely to be detected in older patients.

8.3 Analysis of Gender

The comparison between histopathological diagnosis by gender revealed that LN was significantly more frequent amongst females ($p<0.001$). These figures mirror the prevalence of SLE which has a 9:1 female preponderance (29). Sub analysis suggests that the observed difference derives from differences in the frequency of proliferative LN between genders. Among proliferative lupus cases, 27 (81.82%) were female while 6 (18.18%) were male ($p<0.001$). The OR for proliferative LN in females in this cohort was 4.7143 (95% CI 2.8530 – 11.9936, $p = 0.0011$).

Vermeulen et al (14) also found a female predilection for LN with an OR of a female having LN being 11 times that of males. Abdallah et al (4), from Kuwait, reported LN as the most common cause of secondary GN (11.7%) and that LN constituted the most common lesion among female adults particularly in the middle-age groups.

In this study, it was found that males had a higher frequency of hypertensive change, DN and MPGN (table 9). These findings are similar to the Vermeulen et al (14) study, in Soweto, that reported a male preponderance of benign hypertensive nephroangiosclerosis and MPGN. Okpechi et al (6), from Cape Town, had reported a male preponderance for MPGN, MGN and post infectious GN whilst Abdallah et al (4), from Kuwait, reported a male preponderance for MPGN and FSGS.

8.4 Analysis of Ethnicity

Data in Table 7.13 shows the frequency of native kidney disease by ethnicity. The apparent significant difference is due to the predominantly black African population (82.93%) so that this ethnicity is more frequent and other ethnicities are relatively rare in almost all histological categories (i.e., sample bias). Further analysis comparing ethnicity and histological diagnosis after re-coding ethnicity as either black African or non-black showed that for proliferative LN ($p=0.014$) and HIVAN ($p=0.028$) were more frequent in patients of black ethnicity. The finding of higher frequencies of black African patients in the proliferative LN group could be due to the fact that LN is commonly

associated with more severe disease in black African patients (particularly male patients), although the possibility that it could be attributed to a possible selection bias due to the large number of black African patients in the study. The increased finding of HIVAN in patients of black ethnicity is consistent with the frequency of HIV positivity rates in black ethnic groups as compared to other ethnic groups (36). Genetic variants in APOL1, encoding apolipoprotein L1, in individuals of African descent have also shown to confer risk for HIVAN (40).

This study found no difference in non-proliferative LN (p=0.222), FSGS (0.616) and MGN (p=0.317) between ethnicities. The lack of significant association between FSGS and black ethnicity may have been affected by the low number of non-black patients for comparison. The most common primary GN amongst black patients in this study was FSGS followed by MGN and MCD. The study in Soweto, Johannesburg by Vermeulen et al (14) had found a similar pattern amongst the black population with FSGS and MGN being the most frequent cause of primary GN. This can be attributed to the presence of the G1 and G2 variants in the APOL1 gene amongst this population which has been reported to predispose to HIVAN, FSGS and other glomerular diseases (40). Individuals of African descent with these genetic variants are also at greater risk to develop CKD as opposed to the previously suggested MYH9 E1 haplotype (38). The study in Cape Town by Okpechi et al (6) recorded differing findings with MPGN and MsPGN predominating amongst black patients.

8.5 Analysis of Clinical presentation / Indication to biopsy

In the analysis of the indication for renal biopsy in this study, it was found that the most frequent clinical presentation was NS (38.54%), followed by unexplained renal dysfunction (36.10%), abnormal urinalysis (16.59%) and nephritic syndrome (8.78%). These findings are similar to those reported from Soweto, Johannesburg by Vermeulen et al (14) and from Cape Town by Okpechi et al (6), with NS, AKI and asymptomatic urine abnormalities being the most frequent indications for renal biopsy with 47.7%, 19.8% and 8.1% respectively in the Soweto study and 52.5%, 21.3% and

13.6% respectively in the Cape Town study. These findings probably reflect the presence of shared clinical practices between these renal units.

The most frequent histological diagnosis for patients presenting with NS was FSGS (25.3%), followed by MGN (15.2%), HIVAN (12.7%) and LN (11.4%). These findings are similar to those found by Vermeulen et al (14) where FSGS (19.8%), MGN (19.2%) and LN (12.3%) were the main histological patterns associated with NS. Okpechi et al (6), in their study in Cape Town, reported contrasting data with the most frequent causes of NS being HIVAN (25.2%), MPGN (7.8%) and LN (7.8%). However, cases of NS are also found to be due to diabetes, SLE, infections, multiple myeloma, amyloidosis or neoplasias (1).

NS (47.62%) and unexplained renal dysfunction (52.38%) were the most frequent indications for biopsy in patients with HIVAN. This reflects the significant proteinuria associated with HIVAN NS was also the most frequent indication for renal biopsy in patients with MGN (70.59%, p=0.007) and amongst FSGS patients (66.67%, p=0.006).

Abnormal urinalysis, which included patients with sub-nephrotic range proteinuria, haematuria, presence of cell fragments, casts or crystals, was the most frequent indication for renal biopsy in proliferative LN (39.39%) and non-proliferative LN (50%) compared to other indications which likely reflects the close surveillance of SLE patients and the low threshold for renal biopsy in these patients prior to developing overt nephrotic range proteinuria or renal dysfunction.

Unexplained renal dysfunction, which included AKI and CKD, was the most frequent presentation in patients with HIVAN (52.38%), hypertensive change (60%) and DN (80%). This probably reflects the significant target organ damage associated with these diseases as well as delayed presentation due to progressive asymptomatic injury and hence poorer renal functions at presentation.

8.6 Analysis of HIV

Sixty-eight HIV reactive patients were included amongst 205 total recruits (33.17%). The most frequent histological findings in HIV reactive patients were HIVAN (30.88%), non-proliferative LN (13.24%), HIV-ICD (10.29%), tubulo-interstitial nephritis (10.29%) and MGN (10.29%). Similar patterns amongst HIV reactive patients were noted in other South African studies. Vermeulen et al (14) found the most frequent histological diagnosis amongst HIV reactive patients to be HIVAN (32.7%), HIV-ICD (11.8%), FSGS (11.3%) and Tubulo-interstitial disease (9.1%). Okpechi et al (6), in Cape Town, found HIVAN (55.3%), ATN (8.0%) and kidney failure (7.2%) to be the most frequent diagnosis in HIV reactive patients.

Tubulo-Interstitial nephritis was more frequent (87.50%) in HIV reactive patients than HIV non-reactive patients when compared to other histological diagnoses (p=0.003). This is in keeping with results from other studies and various autopsy studies in AIDS patients that noted a high incidence of tubulointerstitial disease, (23, 26). HIV reactive patients are at risk of tubulo-interstitial disease from nephrotoxic drug side effects, especially Co-trimoxazole and Rifampicin, as well as direct effects from the HIV itself (6, 33).

8.7 Analysis of Continuous parameters (UPCR / Creatinine / GFR)

Median values for UPCR and GFR in this study were 0.43g/mmol and 49 ml/min/1.73m^2, respectively. This indicates that there was significant proteinuria within the biopsy population and is in keeping with NS being the most frequent indication for renal biopsy in many studies. In addition, patients undergoing biopsy usually had some degree of renal dysfunction as evidenced by a reduced median eGFR; severe renal dysfunction was unusual in this series as the increased risk of bleeding in such patients would have precluded biopsy.

Significant proteinuria was noted in patients with DN (0.746 g/mmol), HIVAN (0.744 g/mmol), MPGN (0.660 g/mmol) and MGN (0.600 g/mmol). This is in keeping with the pathophysiology of these conditions which are known to produce nephrotic range

proteinuria. eGFR was relatively preserved in proliferative LN (92 ml/min/1.73m^2) and non-proliferative LN (107 ml/min/1.73m^2), possibly reflecting close monitoring and a lower threshold to biopsy SLE patients prior to developing significant renal dysfunction. Other histological diagnoses that showed higher eGFR were MCD (128 ml/min/1.73m^2) and MGN (93 ml/min/1.73m^2). The above findings are in keeping with the pathogenesis of MCD and MGN which are associated with hyperfiltration due to the podocytopathy, without other structural damage to the glomerulus as is the case in FSGS and MPGN (15, 25). Histological diagnoses that presented with low eGFR values were HIVAN (10 ml/min/1.73m^2) and hypertensive change (10 ml/min/1.73m^2). This may indicate the tendency of these conditions to cause asymptomatic injury in their early stages leading to late presentation with advanced renal dysfunction.

8.8 Analysis of CD4 count (cells/mm^3)

In this study, higher CD4 counts were present in HIV reactive patients with MGN (343), non-proliferative LN (272), proliferative LN (249) and HIV-ICD (241). These findings reflect the immunological pathophysiology of the above conditions which are caused by immune complex formation and deposition in the glomerulus (28, 40).

Histological diagnoses in HIV reactive patients with lower CD4 counts were HIVAN (median CD4 count 129x10^6/mm^3) and tubulo-interstitial nephritis (median CD4 count 156x10^6/mm^3). This is in keeping with the fact that HIVAN is virus driven and hence a lower CD4 and simultaneous high HIV viral load would increase the possibility of developing HIVAN and similarly also be the cause in tubulo-interstitial nephritis. Tubulo-interstitial nephritis may also be caused by drugs (i.e., Co-trimoxazole, Rifampicin) that are commonly prescribed in patients with lower CD4 counts due to their increased risk to develop opportunistic infections. Husaina et al (38), in their description of HIVAN in Africa, noted a low CD4 count and high HIV viral load as risk factors for developing HIVAN.

8.9 Limitations

Data was obtained from a retrospective paper-based database at the renal unit at HJH. Due to the paper-based nature of the records and lack of any electronic back-up files, there was some missing data due to incomplete or inconsistent recording of patients that underwent renal biopsy as well as missing pages that had been lost with time. Despite this, every effort was made to obtain all data with the assistance of the NHLS LABTRAK system. Another limitation of this study is that patients with isolated microscopic haematuria as sole presentation usually do not undergo renal biopsy at HJH. This could have been a reason for not detecting any cases of IgA nephropathy and is in keeping with data from other South African renal studies.

The majority of the participants in the study were of black ethnicity (82.93%) which could have resulted in over-estimation of renal diseases that are more common in this ethnic group. However, the overall frequency of each ethnic group in this study is representative of the demographics of South Africa, so the results in this study may be generalisable within the South African context. There could have been misrepresentation of data since conditions such as DN may be under-represented since not all diabetics with proteinuria undergo renal biopsy, whilst LN could be over-represented due to renal biopsies in SLE patients being undertaken at low levels of proteinuria.

9. CONCLUSION

This study reviewed the renal histopathology of 205 patients at HJH with a slight female preponderance (54.15%) and of predominantly black ethnicity (82.93%), which is in keeping with the demographics of the general South African population. The most common primary GNs reported were FSGS (14.63%), MGN (8.29%), MCD (5.37%) and MPGN (4.39%) whilst the most common secondary GNs were LN (26.83%), HIVAN (10.24%), Hypertensive change (7.32%) and DN (4.88%). LN was the most common histological finding overall and probably reflects the low threshold for renal

biopsy in SLE patients as proteinuria of more than 500mg/day and / or deteriorating renal dysfunction are considered as indications for renal biopsy in these patients.

The cohort of this study consisted of patients that were young (median age 36), had significant proteinuria on presentation (UPCR of 0.43 g/mmol), and with relatively preserved renal function (GFR of 49ml/min/1.73m^2). Proliferative LN tended to affect younger patients, whilst MGN was more common in older patients. There was a significant association between histological diagnoses and ethnicity with black ethnic predominance noted for proliferative LN (p=0.014) and HIVAN (p=0.028).

NS was the most frequent indication for renal biopsy comprising 38.54% of patients, followed by unexplained renal dysfunction with 36.10%, AUA 16.58% and the least frequent being nephritic syndrome with 8.78%. The most frequent histological diagnoses for patients presenting with NS was found to be FSGS (25.3%), MGN (15.2%), HIVAN (12.7%) and LN (11.4%).

There were 68 HIV reactive patients (33.17% of study population) with the most frequent histological findings amongst these patients being HIVAN (30.88%), non-proliferative LN (13.24%), HIV-ICD (10.29%), Tubulo-Interstitial nephritis (10.29%) and MGN (10.29%). Higher CD4 counts (cells/mm^3) were present in HIV reactive patients with MGN (343), non-proliferative LN (272), proliferative LN (249) and HIV-ICD (241) with lower CD4 amongst HIVAN (129) and Tubulo-Interstitial Nephritis (156) patients.

The data attained in this study is an important contribution to the patterns of renal disease particularly in the South African context. These findings could assist in the early detection and appropriate management of renal disease which would ultimately result in improved patient outcomes and decrease the financial burden on the health sector.

References

1. Fiorentino M, Bolignano D, Tesar V, Pisano A, Van Biesen W, D''Arrigo G, et al. Renal Biopsy in 2015 - From Epidemiology to Evidence-Based Indications. American Journal of Nephrology. 2016;43(1):1-19.
2. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. PLoS ONE. 2016;11(7):e0158765.
3. Davids R, Jardine T, Marais N, Jacobs JC. South African Renal Registry Annual Report 2016. African Journal of Nephrology. 2018;21(1):61-72.
4. Abdallah E, Al-Helal B, Asad R, Kannan S, Draz W, Abdelgawad Z. Analysis of histopathological pattern of kidney biopsy specimens in Kuwait: A single-center, five-year prospective study. Saudi Journal of Kidney Diseases and Transplantation. 2015;26(6):1223-31.
5. Shah R, Vathsala A, Chiang G, Chin Y, Woo K. The impact of percutaneous renal biopsies on clinical management. Annals of the Academy of Medicine, Singapore. 1993;22(6):908-11.
6. Okpechi I, Swanepoel C, Duffield M, Mahala B, Wearne N, Alagbe S, et al. Patterns of renal disease in Cape Town South Africa: a 10-year review of a single-centre renal biopsy database. Nephrology Dialysis Transplantation. 2010;26(6):1853-61.
7. Van Rensburg BWJ, Van Staden AM, Rossouw GJ, Joubert G. The profile of adult nephrology patients admitted to the Renal Unit of the Universitas Tertiary Hospital in Bloemfontein, South Africa from 1997 to 2006. Nephrology Dialysis Transplantation. 2009;25(3):820-4.
8. Carrington CP, Williams A, Griffiths DF, Riley SG, Donovan KL. Adult day-case renal biopsy: a single-centre experience. Nephrology Dialysis Transplantation. 2010;26(5):1559-63.
9. Hogan JJ, Mocanu M, Berns JS. The Native Kidney Biopsy: Update and Evidence for Best Practice. Clinical journal of the American Society of Nephrology : CJASN. 2016;11(2):354-62.
10. Hebert LA, Parikh S, Prosek J, Nadasdy T, Rovin BH. Differential diagnosis of glomerular disease: a systematic and inclusive approach. American Journal of Nephrology. 2013;38(3):253-66.
11. Polito MG, De Moura LAR, Kirsztajn GM. An overview on frequency of renal biopsy diagnosis in Brazil: clinical and pathological patterns based on 9617 native kidney biopsies. Nephrology Dialysis Transplantation. 2009;25(2):490-6.
12. Koenig K, Bolton W, Neilson E, Couser W. Clinical evaluation and treatment of haematuria and proteinuria. Philadelphia: Lippincot-Raven Publishers; 1997.
13. Kodner C. Diagnosis and management of nephrotic syndrome in adults. American Family Physician. 2016;93(6):479-85.
14. Vermeulen A, Menezes CN, Mashabane M, Butler OK, Mosiane P, Goetsch S, et al. Patterns of renal disease: A 30-year renal biopsy study at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg, South Africa. South African Medical Journal. 2019;109(7):486-92.
15. Nachman P, Jennette J, Falk R. Primary Glomerular Disease. In: Brenner B, editor. Brenner and Rector's The Kidney. 9th ed. Philadelphia: Elsevier; 2012. p. 1100-91.
16. Kidney Disease: Improving Global Outcomes (KDIGO), Group AKIW. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International. 2012;Suppl. 2012(2):1-138.
17. Kidney Disease: Improving Global Outcomes (KDIGO), Group CW. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International. 2013;Suppl. 2013(3):1-150.
18. Joseph A, Compton S, Holmes L, Annand A, Self S, Fitzgibbon W, et al. Utility of percutaneous renal biopsy in chronic kidney disease. APSN. 2010;15(5):544-8.

19. Glassock RJ. Con: Kidney biopsy: an irreplaceable tool for patient management in nephrology. Nephrology Dialysis Transplantation. 2015;30(4):528-31.
20. J.Glassock R. Antiphospholipase A2 Receptor Autoantibody Guided Diagnosis and Treatment of Membranous Nephropathy: A New Personalized Medical Approach. Clinical Journal of the American Society of Nephrology. 2014;8(9):1341-3.
21. Spinale J, Mariani L, Kapoor S, Zhang J, Weyant R, Song P, et al. A reassessment of soluble urokinase-type plasminogen activator receptor in glomerular disease. Kidney International. 2015;87(3):564-74.
22. Moldoveanu Z, Wyatt R, Lee J, Tomana M, Julian B, Mestecky J, et al. Patients with IgA nephropathy have increased serum galactose-deficient IgA1 levels. Kidney International. 2007;71(11):1148-54.
23. Islam SMJ, Haque WS, Akhter S, Alam SMM. Histomorphological pattern of renal biopsy in Dhaka: A single center study. Saudi Journal of Kidney Diseases and Transplantation. 2018;29(5):1159.
24. Nielson S, Kwon T, Fenton R, Pretorius J. Anatomy of the kidney. In: Brenner B, editor. Brenner and Rector's The Kidney. 9th edition. Philadelphia: Elsevier; 2012. p. 31 - 93.
25. D'Agati V, Suh J-I, Carbone L, Cheng J-T, Appel G. Pathology of HIV-associated nephropathy: a detailed morphologic and comparative study. Kidney international. 1989;35(6):1358-70.
26. Sethi S, Fervenza FC, Zhang Y, Zand L, Vrana JA, Nasr SH, et al. C3 glomerulonephritis: clinicopathological findings, complement abnormalities, glomerular proteomic profile, treatment, and follow-up. Kidney international. 2012;82(4):465-73.
27. Rennke H. Secondary membranoproliferative glomerulonephritis. Kidney International. 1995;47(2):643-56.
28. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012;64(6):797-808.
29. Petri M, Orbai A, Alarcon G, Gordon C, Merrill J, Fortin P. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64(8):2677-86.
30. Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, et al. A new classification of diabetic nephropathy 2014: a report from Joint Committee on Diabetic Nephropathy. Journal of diabetes investigation. 2015;6(2):242-6.
31. Naicker S, Fabian J, Naidoo S, Wadee S, Paget G, Goetsch S. Infection and glomerulonephritis. Seminars in Immunopathology. 2007;29(4):397-414.
32. Zelmanovitz T, Gerchman F, Balthazar AP, Thomazelli FC, Matos JD, Canani LH. Diabetic nephropathy. Diabetology & metabolic syndrome. 2009;1(1):10.
33. Lopez-Novoa JM, Rodriguez-Pena AB, Ortiz A, Martinez-Salgado C, Lopez Hernandez FJ. Etiopathology of chronic tubular, glomerular and renovascular nephropathies: clinical implications. Journal of translational medicine. 2011;9:13.
34. Fabian J, Naicker S, Goetsch S, Venter WDF. The clinical and histological response of HIV-associated kidney disease to antiretroviral therapy in South Africans. Nephrology Dialysis Transplantation. 2013;28(6):1543-54.
35. Han TM, Naicker S, Ramdial PK, Assounga AG. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney International. 2006;69(12):2243-50.
36. Gerntholtz TE, Goetsch SJ, Katz I. HIV-related nephropathy: a South African perspective. Kidney International. 2006;69(10):1885-91.
37. Estrella M, Fine DM, Gallant JE, Rahman MH, Nagajothi N, Racusen LC, et al. HIV type 1 RNA level as a clinical indicator of renal pathology in HIV-infected patients. Clinical Infectious Diseases. 2006;43(3):377-80.
38. Husaina N, Ahmed M, Almobarak A, Noor S, Elmadhoun W, Awadalla H, et al. HIV-Associated Nephropathy in Africa: Pathology, Clinical Presentation and Strategy for Prevention. Journal of Clinical Medicine Research. 2018;10(1):1-8.

39. Razzak-Chaudhary S, Workeneh B, Montez-Rath M, Zolopa A, Klotman P, Winkelmayer W. Trends in the outcomes of end-stage renal disease secondary to human immunodeficiency virus-associated nephropathy. Nephrology Dialysis Transplantation. 2015;10:1734-40.
40. Naicker S, Rahmania S, Kopp J. HIV and chronic kidney disease. Clinical Nephrology. 2015;83(1):S32-S8.
41. Perkowska-Ptasinska A, Deborska-Materkowska D, Bartczak A, Stompor T, Liberek T, Bullo-Piontecka B, et al. Kidney disease in the elderly: biopsy based data from 14 renal centers in Poland. BMC nephrology. 2016;17(1):194.
42. Shin HS, Cho DH, Kang SK, Kim HJ, Kim SY, Yang JW, et al. Patterns of renal disease in South Korea: a 20-year review of a single-center renal biopsy database. Renal failure. 2017;39(1):540-6.
43. Zhu P, Zhou F-d, Zhao M-h. The renal histopathology spectrum of elderly patients with kidney diseases: a study of 430 patients in a single Chinese center. Medicine (Baltimore). 2014;93(28):e226.
44. Stanifer J, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet. 2014;2(3):174-81.
45. Statistics South Africa (2013). Mid-year population estimates. Pretoria: Statistics South Africa.
46. Statistics South Africa (2021), Mid-year population estimates, Statistical Release P0302, Statistics South Africa, Pretoria.

Appendix A – Data collection sheet

Patient Details:	
Age	
Gender	Male ☐ Female ☐
Ethnicity	Mixed Race☐ Asian☐ Black☐ Caucasian☐
Indication for biopsy:	
Acute kidney injury ☐	Haematuria ☐
Chronic kidney disease ☐	Asymptomatic urine abnormalities ☐
Nephritic syndrome ☐	Nephrotic syndrome ☐
UPCR :	
Urine MC+S:	
Serum:	
Creatinine	
GFR	
HIV	Reactive ☐ Non-Reactive ☐
CD4	
Histopathological diagnosis:	
Minimal change disease (MCD) ☐	Lupus Nephritis class 4 ☐
Membranous Nephropathy (MN) ☐	Lupus Nephritis class 5 ☐
Focal segmental glomerulosclerosis (FSGS) ☐	Lupus Nephritis class 6 ☐
IgA Nephropathy (IgAN) ☐	Amyloidosis ☐
Mesangioproliferative GN (MsPGN) ☐	Cryoglobinemia ☐
Membranoproliferative GN (MPGN) ☐	ANCA-associated ☐
Crescentic GN ☐	ATN ☐
Post Infectious GN ☐	Tubulointerstitial nephritis ☐
HIVAN ☐	Myeloma cast nephropathy ☐
HIV-immune complex disease (HIV-ICD) ☐	Benign hypertensive nephroangiosclerosis ☐
Lupus Nephritis class 1 ☐	Malignant Hypertension ☐
Lupus Nephritis class 2 ☐	ANCA-associated ☐
Lupus Nephritis class 3 ☐	ATN ☐

Appendix B – Ethics Approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Ahmed Mahomed Randeree

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M200219

NAME: (Principal Investigator)	Dr Ahmed Mahomed Randeree
DEPARTMENT:	Internal Medicine Helen Joseph Hospital
PROJECT TITLE:	Histopathological patterns of Renal disease at Helen Joseph Hospital, South Africa: a 5 year retrospective review
DATE CONSIDERED:	28/02/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/03/2020

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **February** and will therefore be due in the month of **February** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date 13/05/2022

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C – Turnitin report

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by Ahmed Randeree

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