A RETROSPECTIVE STUDY EVALUATING THE PATTERNS OF PRIMARY GLOMERULAR DISEASE AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Dr Yvette Patchapen MBBCh (Wits) FCP (SA)

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfillment of the requirements for the degree of Masters in Medicine (Internal Medicine)

Johannesburg 2017

TABLE OF CONTENTS

2. METHODS AND RATIONALE

3. RESULTS

6. STUDY LIMITATIONS AND STRENGTHS

7. REFERENCES 77

8. APPENDICES

DECLARATION

I, Yvette Patchapen, declare that this research report is my own work. It is being submitted for the degree of Masters in Medicine in Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been previously submitted for any degree or examination at this or any other University.

Signed

day of May 2017

ETHICAL CONSIDERATIONS

Permission for this retrospective study was obtained from Prof S. Naicker (Head of Department, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital), Dr. T. E. Selebano (Chief Executive Officer, CMJAH), Prof M. Hale (Head of Anatomical Pathology CMJAH) and the Ethics Committee of the University of the Witwatersrand (Clearance number M122146). See appendix. Informed consent was not required as no identifiable patient information was used in analysis.

DEDICATED TO

God,

my husband Wesley Lazarus,

my parents and family for their love and support.

ACKNOWLEDGEMENTS

Dr Malcolm Davies for his academic expertise, supervision and guidance, without which this study would not have been possible.

All the renal patients whose biopsy reports were used in this study.

Prof Sarala Naicker and Prof Graham Paget - Heads of Division of Nephrology.

My husband and parents for their continued support.

Mitan Nana for his technical expertise and time.

PUBLICATIONS AND PRESENTATIONS

Poster presentation to the South African Renal Congress, Cape Town 9-11 September 2016. Abstract to be published in African Journal of Nephrology.

LIST OF ABBREVIATIONS

- AKI Acute Kidney Disease
- Anti GBM Anti Glomerular Basement Membrane
- ANA Anti Nuclear Antibodies
- ANCA Anti neutrophil cytoplasmic antibodies
- ANOVA Analysis of variance
- APOL 1 Apolipoprotein L1 gene
- ATIN Acute Tubulointerstitial nephritis
- ATN Acute Tubular Necrosis
- BFH Benign Familial Haematuria
- CHBAH Chris Hani Baragwanath Academic Hospital
- CMJAH Charlotte Maxeke Johannesburg Academic Hospital
- CKD Chronic Kidney Disease
- DDD Dense Deposit Disease
- DPGN Diffuse Proliferative Glomerulonephritis
- EM Electron Microscopy
- eGFR Estimated Glomerular Filtration Rate
- ESRD End Stage Renal Disease
- FSGS Focal Segmental Glomerulosclerosis
- GGS Global Glomerulosclerosis
- GN Glomerulonephritis
- Hb Haemoglobin
- HT Hypertension
- IgA Immunoglobulin A

- IMF Immunofluorescence
- JHB Johannesburg
- KDIGO Kidney Disease Improving Global Outcome
- MCD Minimal Change Disease
- MesPGN Mesangioproliferative glomerulonephritis
- MGN Membranous Glomerulonephritis
- MPGN Membranoproliferative Glomerulonephritis
- MYHC 9 Myosin Heavy Chain 9
- NS Nephrotic Syndrome
- NV Necrotising Vasculopathy
- NHLS National Health Laboratory Services
- NSAIDS Non-Steroidal Anti Inflammatory Drugs
- PCR Protein: Creatinine Ratio
- PLA2R1 M Type Phospholipase A2 Receptor
- PRB Percutaneous Renal Biopsy
- SADTR South African Dialysis and Transplant Registry
- SD Standard Deviation
- SLE Systemic Lupus Erythematosus
- SuPAR Soluble Plasminogen Activating Receptor
- Thin GBM Thin Glomerular Basement Membrane
- TNF Tumour Necrosis factor
- TRAIL TNF related apoptosis inducing ligand
- USRDS United States Renal Data System

ABSTRACT

Background

Glomerular disease is a frequent and important cause of renal dysfunction. Current data on the patterns of glomerular disease in South Africa is lacking. The aim of this study was to characterize the prevalence and nature of presentation of primary glomerular disease at Charlotte Maxeke Johannesburg Academic Hospital.

Materials And Methods

This single center, retrospective observational study was performed on adult native renal biopsies over a 10 year period from 2001 - 2010. A total of 1495 native renal biopsies were reviewed. After exclusion of common secondary causes, the results of 194 patients with primary glomerular disease were evaluated.

Results

The most frequent primary glomerular disease was FSGS (29.8%) followed by MN (19.5%), MPGN (18%), MCD (17%) and IgAN (3%). Nephrotic range proteinuria (60.5%) and unexplained renal dysfunction (24.2%) were the most common indications for biopsy. There was a 59.4% male predominance. From the 73.9 % of patients of African descent, 34.1% presented with FSGS. The majority of patients (62.9%) were aged between 18-49 years with 30.3% of them presenting with FSGS. FSGS presented with a median creatinine 183.5 [101 - 476] mmol/l and mean UPCR (0.89 ± 0.66) g/mmol. There were no statistically significant differences in albumin, haemoglobin and triglycerides between the glomerular disease subtypes. The highest urine leucocytes and dysmorphic red cells were from the IgAN subtype. Most patients, 56.8% had no casts observed, and 39.1% were hypertensive. No change in the pattern of glomerular injury was observed over the course of the study.

Conclusion

Glomerular pathology is more common in younger patients. FSGS is more common than other glomerular pathologies in our setting; which may partly be due to local biopsy practices and patient demographics. Clinical parameters do not adequately predict biopsy findings.

1. INTRODUCTION

1.1 Background

Current renal histological data demonstrates temporal and regional variation in the patterns of primary glomerulonephritis (GN)[1]. Whilst some of this variation may be explained by differences in locally accepted indications for biopsy, there appears to be a role for certain patient-related factors (such as age, sex, and race) in determining the patterns of glomerular disease.

True geographic variation in the pattern of glomerular disease may exist between the various populations of the world, due to differences in the native environment, socioeconomic status, and prevalence of certain infections[2]. Such geographic variation may partially be explained by the hygiene hypothesis in which a persistence of the Th2 response is proposed to explain the marked increase in allergies that has been observed in industrialized societies. Certain types of glomerular pathology are postulated to be caused by an overzealous Th2 immune response, (membranous nephropathy MN, minimal change disease MCD, and immunoglobulin A nephropathy IgAN). The higher prevalence of IgAN and MCD in industrialized countries would thus be in keeping with the hygiene hypothesis[2].

From available data it appears that glomerular disease is more prevalent in developing countries such as South Africa where patients have a poorer response to therapy and a greater rate of progression to end stage renal disease (ESRD). This is of particular concern because of the limited availability of renal replacement therapies in the developing world[3].

1.2 Renal anatomy and classification

A nephron is comprised of a renal tubule and its glomerulus. Each kidney has approximately 1.3 million nephrons. The glomerulus is formed by the invagination of capillaries into the dilated, blind end of the nephron known as the Bowmans capsule. The glomerulus is supplied by an afferent arteriole and drained by an efferent arteriole. The capillary endothelium and the podocytes separate glomerular filtrate from blood[4]. The stability of the glomerulus depends on the integrity of the basement membrane, mesangial cells and podocytes. Disruption of this structure leads to predictable architectural lesions[5].

Renal dysfunction may be classified as acute kidney injury (AKI) or chronic kidney disease (CKD). Irrespective of the underlying pathology, once a considerable portion of renal tissue has been destroyed, a continued deterioration in the glomerular filtration rate over time is related to a loss of viable nephrons[5].

Various aetiologies may be implicated in the progression of renal dysfunction including:

- pre-renal causes such as hypovolaemia, cardio renal, hepato-renal syndromes and non-steroidal anti-inflammatory drugs (NSAIDS)
- intrinsic renal vascular causes which include nephrosclerosis secondary to hypertension and microangiopathic haemolytic anaemia

- intrinsic glomerular disease which may be subcategorized as primary (idiopathic, not associated with systemic disease) or secondary (such as paraneoplastic, drug induced, systemic auto immune disorder)
- intrinsic tubular and interstitial causes, including:
    - acute - acute tubular necrosis (ATN), acute interstitial necrosis (AIN), cast nephropathy
    - chronic - polycystic kidney disease (PCKD), nephrocalcinosis, sarcoidosis
- obstructive nephropathy such as prostatic disease and renal calculi[6]

1.3 Primary glomerular disease

Glomerular diseases have a variety of clinical presentations including:

- Asymptomatic
- Hypertension
- Oedema
- Haematuria
- Proteinuria (normal excretion is < 150mg/24hrs)
- Urinary abnormalities such as casts, dysmorphic red cells and leucocyturia
- Acute kidney injury[7]

Proteinuria is the hallmark of glomerular disease[8]. Glomerular disease may be classified as either primary or secondary. Primary disease may be idiopathic or restricted to the kidneys, whilst secondary is usually associated with more systemic or generalized disease[9].

Irrespective of the initial insult, inflammatory pathways are activated leading to complement activation, coagulation cascades and overproduction of pro-inflammatory cytokines. This leads to chemotaxis, cell lysis, fibrin deposition and apoptotic failure. Cytokine release results in cellular proliferation of parietal cells and acute glomerular crescent formation. Overproduction of proteases and antioxidants lead to fibrosis stimulated by platelet derived growth factor (PDGF) and transforming growth factor beta (TGF β). After prolonged injury, haemodynamic alteration leads to hyperfiltration and intraglomerular hypertension with sclerosis. Thus, the initial inflammatory process may progress to fibrosis and irreversible scarring[9].

1.3.1 Proliferative glomerulonephritis

1.3.1.1 IgA nephropathy / Mesangioproliferative glomerulonephritis

IgA nephropathy (IgAN) was first recognized in 1968 by Jean Berger and is therefore also known as Berger's disease[10]. IgAN is the commonest of all glomerulonephritides in the United States of America (USA)[11]. Micro or macroscopic haematuria is the usual presentation but no clinical pattern is pathognomonic. Peak incidence is between the second and third decades with a female: male ratio of 1:2. The gross histological pattern associated with IgAN is classically that of mesangioproliferative GN with cellular proliferation predominantly affecting the mesangium and paramesangial deposition of IgA together with alternative pathway complement components[9].

IgAN is unique amongst the glomerulonephritides as it is identified by the presence of an immune reactant instead of any morphological finding on renal biopsy. An infectious source has long been suspected however no organism has been consistently implicated[10].

IgA is the most common immunoglobulin in the body and is primarily associated with mucosal defense. Two subclasses of IgA are produced, namely IgA1 and IgA2 [10]. Overproduction of systemic IgA1 polymers by plasma cells is associated with deposition in the kidney. Abnormal glycosylation of IgA may facilitate this deposition by promoting self-aggregation forming immune complexes with mesangial affinity. Serum IgA levels are raised in 50% of patients with normal serum complement, as complement activation is confined to the kidneys[9]. Studies of renal biopsies support a role for PDGF and TGF β. These features are not exclusive to IgAN and are likely involved in all forms of mesangioproliferative GN[10].

The hallmark on immunofluorescence is diffuse mesangial polymeric IgA with C3 being deposited in about 90% of cases. Electron microscopy shows dense deposits restricted to mesangial and paramesangial areas[10].

1.3.1.2 Membranoproliferative glomerulonephritis (MPGN) / Mesangiocapillary glomerulonephritis

MPGN types 1 and 2 are the commonest subtypes of this infrequent form of glomerular disease. Children ranging from 8 - 16years old are usually affected[12]. Clinical presentation includes microhaematuria and sub-nephrotic range proteinuria (35%), nephrotic syndrome with mild renal dysfunction (35%), chronically progressive GN (20%), or nephritic syndrome with rapidly declining renal function with proteinuria and red blood cell casts (10%). Hypertension is present in 50 - 80% of patients[13].

Type 1

Features on light microscopy include diffuse capillary wall thickening, increased mesangial matrix and endocapillary hypercellularity with a hypersegmented or lobular appearance to the glomerulus[12]. Immunofluorescence staining reveals peripheral granular or band-like staining for complement factor C3 and immunoglobulin. The ultra structural hallmark on electron microscopy is mesangial interposition in an expanded sub endothelial region containing electron dense immune deposits[12].

The pathophysiology highlights the immune complex-mediated nature of type 1, however the identity of the nephrogenic antigen is still unknown. Sources of antigen may include infections, neoplasms, hereditary diseases and autoimmune diseases[12]. Type I MPGN has similar findings to lupus nephritis (LN). Activation of the classical complement pathway with decreased serum C4 levels is found in idiopathic type 1 MPGN[9].

Type II

Type II MPGN is known as dense deposit disease (DDD) as the classical finding is that of dense material deposited within the membranes of glomeruli, Bowmans capsule and tubules[12]. Activation of the alternative complement pathway results in decreased serum C3 levels associated with C3 nephritic factor (an antibody leading to unregulated initiation of the complement cascade). The pathogenesis is not well understood but likely implicates intensive cellular proliferation of mesangial cells in response to injury. Histologically both type I and II display mesangial expansion and thickening of the capillary walls; the distinction between them being made on electron microscopy, specifically by the location of subendothelial immune deposits[12,13].

1.3.2 Non-proliferative glomerulonephritis

1.3.2.1 Minimal change disease (MCD)

MCD is implicated in the aetiology of nephrotic syndrome in about 90% of children under 10years. A cardinal clinical feature is the fairly acute onset of proteinuria / nephrotic syndrome. Haematuria and hypertension are unusual[12]. It is characterised by an absence of gross histological glomerular abnormalities; however, electron microscopy shows evidence of fusion and effacement of epithelial cell foot process. The degree of effacement appears to relate more with the timeline of active nephrotic syndrome rather than the level of proteinuria. The most common feature on immunofluorescence is low-level mesangial staining of IgM[14].

The pathogenesis is unclear but is probably a consequence of dysregulation of a T cell subset. This is supported by the knowledge that a glomerular permeability factor is created by human T cell hybridomas. Lymphocytes have sub optimal reactivity when confronted with mitogens. T cells produce a lymphokine that increases glomerular permeability protein[15]. Haemopexin is a protein normally present, but an active isoform increases glomerular permeability due to enhanced protease activity. Interferon α, β and interleukin 12 are important inducers of T helper cell development, immunity, inflammation and delayed hypersensitivity. Patients with MCD frequently display a delayed type hypersensitivity response[15].

The immune system is complex and dysregulation seems to be more diverse than just T cells[16]. Further research is required in this area. There have, for example, been suggestions of a modification in tumor necrosis factor (TNF) related apoptosis inducing ligand (TRAIL) in peripheral serum mononuclear cells. Genetic factors include heterozygous amino acid changes in nephrin and podocin[12].

1.3.2.2 Focal segmental glomerulosclerosis (FSGS)

FSGS is a histological pattern of glomerular injury that may be primary (idiopathic) or secondary to various aetiologies including genetic mutations, circulating permeability factors, viral infections, drug toxicities and haemodynamic stress[17]. The aetiology of idiopathic FSGS is unknown; however, genetic mutations regulating the cytoskeletal framework of the podocyte are likely to be responsible for many such cases that remain “idiopathic” due to lack of genetic testing[17].

Five different gross histological patterns have been identified:

- Perihilar variant
- Cellular variant
- Tip variant
- Collapsing variant
- Not otherwise specified[18]

Podocyte injury is a central pathogenic mediator leading to altered cell signaling, reorganization of actin skeleton and resultant foot process effacement. FSGS is thus considered a podocytopathy. Podocyte injury is multifactorial and may occur in response to reduction in support factors like nephrin signaling, or increase in angiotensin II or mechanical strain. Angiogenic factors like TGF α, PDGF and vascular endothelial growth factor (VEGF) recruit monocytes, macrophages and T cells that release additional cytokines like IL 1 and TNF α. This inflammation, coupled with mechanical stress and plasma proteins directly injures the tubulointerstitium and leads to glomerular collapse. Cell to cell spread of podocyte injury explains the characteristic segmental nature of the sclerosing lesion[17,19].

Myosin heavy chain 9 (MYHC 9) encodes for the heavy chain of non-muscle myosin IIA that is a component of the podocyte cytoskeleton involved in contractility. MHYC 9 is ubiquitous in glomeruli and podocytes and loss of this gene leads to glomerular injury and kidney disease[20].

African Americans have long been known to have a greater risk of idiopathic FSGS when compared to their Caucasian counterparts. Recent studies have

identified an association between the apolipoprotein 1 (APOL 1) gene (specifically the risk-associated allele variants G1 and G2) on chromosome 22q13 and primary FSGS, HIV-associated nephropathy and hypertensive nephropathy (all of which histologically share an FSGS morphology) in these patients[21].

Both MYHC 9 and APOL 1 are genetic factors that are recognized as prominent risk factors for FSGS in patients of African descent[17]. Risk variants in MYHC 9 and APOL 1 are in strong linkage disequilibrium; the two APOL 1 risk alleles are common in African chromosomes but absent from European chromosomes[12]. Genetic variation at the MYHC 9 locus assists in explaining the burden of FSGS and hypertensive end stage renal disease amongst African Americans[12].

The APOL 1 gene however has a stronger association with non-diabetic chronic kidney disease than MYHC 9. APOL 1 is involved in lysis of Trypanosoma brucei rhodensiense, a known culprit for sleeping sickness, which is common in Africa. This APOL 1 gene has likely evolved under selective pressure to convey a survival advantage to offspring carrying the mutation by early red cell lysis preventing maturation of the red cell [22].

Clinical presentation includes varying degrees of proteinuria, nephrotic syndrome, haematuria, hypertension and renal dysfunction[17].

1.3.2.3 Membranous glomerulonephritis (MN)

MN is one of the most frequent causes of nephrotic syndrome in adults aged 40-50 years. Primary/ idiopathic disease accounts for the majority of cases. Secondary causes include autoimmune diseases, infections, malignancy and drugs[12]. Primary MN is an immune complex glomerular disease with IgG and complement deposits developing predominantly beneath podocytes. The podocyte injury results in increased glomerular permeability leading to varying degrees of proteinuria[23].

Light microscopy shows thickening of the glomerular capillary wall. Immunofluorescence and electron microscopy reveal diffuse finely granulated immune deposits and electron dense deposits respectively in the sub epithelial space that are regarded as pathognomonic[23].

Antibodies directed to M type phospholipase A2 receptor (PLA2R) on podocytes is the favored hypothesis for primary MN. These antibodies are predominantly IgG4. AntiPLA2R antibodies are found in serum of 70-75% of all patients with primary disease but are rarely seen in secondary forms[12].

Nephrotic syndrome occurs in 70-80% of patients at clinical presentation with the remainder presenting as subnephrotic or asymptomatic proteinuria. Although microscopic haematuria is common (30-40%), red cell casts are rare. Serum complement levels and renal function are usually normal at presentation[23].

1.4 Epidemiology

1.4.1 South African experience

Available literature pertaining to the pattern of renal disease in South Africa (SA) suggests that glomerular disease is more frequent in patients of black African descent. This may reflect a background milieu of chronic parasitic, bacterial and viral infections produced by socio-economic and geographical factors superimposed on a genetic susceptibility[24,25].

The South African Dialysis and Transplant Registry in 1994 reported the causes of ESRD to be secondary to glomerulonephritis in 52.1% of patients[25].

In a study carried out at Chris Hani Baragwanath Hospital (CHBAH) between October 1972 and December 1976 chronic GN was found to be the cause of biopsy confirmed ESRD in 40 % of cases[26].

In Bloemfontein between 1997- 2006, 1216 biopsies were reviewed. Nephrotic syndrome was the most common indication for renal biopsy, with the histology showing FSGS to be most common primary glomerular disease followed by MPGN, MN and MCD. IgAN was the most infrequent finding[27].

A retrospective study of 1284 native biopsies from Cape Town between January 2000 to December 2009 found mesangiocapillary GN 20.4% to be the most frequent histological finding followed by mesangioproliferative 19.2%, MN 18.5%, crescentic and necrotizing GN 11.4%, FSGS 10.5%, post-infectious GN 8.2%,

MCD 6.0% and lastly IgAN 5.8% [28]. Notably, that sample population (53.7% coloured, 42.2% black and 3.9% white) was different to this study.

Available data on the patterns of glomerular disease in South Africa and the Gauteng province in particular is nevertheless scanty, and where available, outdated. The aim of this study is to improve available data regarding the prevalence and nature of glomerular disease in this area.

1.4.2 African experience

Accurate and comprehensive statistics regarding the pattern of glomerular disease is lacking in Africa. This represents an important area of research since glomerular disease is believed to be both more prevalent and more severe in Africa than in Western countries[25,29].

Available data suggests that 2 to 3% of medical admissions may be attributed to renal related complaints, with a large proportion being due to glomerular disease, which is often characterized by poor response to treatment and progression to CKD[25]. Although there is lack of registry data in sub-Saharan Africa, CKD seems to be 3-4 times more frequent in developing countries than in the developed world[30].

A cross sectional study in Sudan in 2010 - 2011 reviewed 83 adult patients. The findings revealed a diagnosis of primary GN in 71 patients (85.5%) with the major indication for biopsy being nephrotic syndrome 46.5% followed by unexplained

elevations in renal parameters 33.8%. FSGS was the most common biopsy finding in 29.6%, followed by MPGN 26.8%, MCD 16.9% and least common IgAN 5.6% [31]. Primary GN remains a leading cause of end-stage renal disease (ESRD) in many developing countries and is likely under reported with many patients being undiagnosed due to late presentation or unavailable diagnostics.

1.4.3 International experience

The most significant contributors to ESRD in the USA as reported by the United States Renal Data System (USRDS) are diabetes 37%, hypertension 25% and GN 14% [32]. In European biopsy studies, primary GN is present in up to 49%, with the most frequent subtypes being IgAN 38.8%, MN 29.4%, MCD 9.8%, MPGN type 1 9.6% and FSGS 5.7% [1].

In the USA, analysis of data suggests that IgAN is the most frequently found primary glomerular pathology and the most frequent cause of ESRD amongst young adult Caucasians, whilst FSGS is more common in African Americans[11,33,34]. Such data indicates that different racial groups may have different prevalence's of primary GN.

Data from Europe and the USA such as that reported above is reflective of the prevalence of GN within an urbanized and industrialized population. However, as previously indicated, socio-economic conditions may play an integral role in determining the prevalence and types of primary GN within a population.

Brazil has features of both a developed and developing country similar to South Africa. Studies from Brazil indicate that primary GN is detected in about half of all native renal biopsies. FSGS is the most frequent primary glomerular lesion in this population followed by MN and IgAN. Analysis of this study population has also shown variation in glomerular disease patterns based on patient age, with FSGS being the most frequently detected lesion in children, adolescents, young adults and adults; whilst MN predominated in elderly patients[33,35].

Patterns of primary glomerular disease were evaluated in an Indian study of 75 biopsies in 2013, with primary disease detected in 80%. MCD was the most common histological pattern followed by IgAN, crescentic GN, FSGS and mesangiocapillary GN. Lupus nephritis was the most common aetiology in the secondary glomerulonephritis group. This study however also included children, which may have resulted in the higher incidence of MCD. The most common presentations were oedema 62.7%, haematuria 46.7%, nephrotic syndrome and renal impairment 30.7% each[36].

1.5 Biopsy Practices

Prior to the advent of renal biopsy, insight into clinicopathological correlation was suboptimal. Iversen and Brun performed percutaneous native renal biopsy in 1951 using an aspiration needle technique, which yielded an adequate sample in about 53%. Drs. Robert Kark and Robert Muehrcke improved on this technique using a Franklin-modified Vim-Silverman needle (a precursor to the current needle) that

collected tissue and sheared it off. In 1954, they reported a success rate of 96% with no major complications[37].

Modifications and updates in imaging and biopsy needles have resulted in acquiring optimal renal tissue in 95% of biopsies[37]. Current practice at CMJAH involves use of the spring-loaded tru-cut biopsy needle.

In a systematic review of 34 retrospective and prospective studies, which included 9474 native kidney biopsies, the approximate incidence of complications using real-time ultrasonic guidance was as follows:

- Transient macroscopic hematuria - 3.5 %
- Requirement for transfusion - 0.9 %
- Requirement for angiographic intervention to control bleeding - 0.6 %
- Requirement for nephrectomy to control bleeding - 0.01 %
- Death - 0.02 % [38]

The complication rate resulting in death declined from 0.12% to 0.02% during the preceding 50 years, with some studies reporting no deaths[39].

Renal biopsy is a vital procedure in the diagnosis, prognosis, and management of patients with renal pathology. This procedure has proven invaluable not only by the ability to obtain tissue but also by the safety profile[40].

For interpretation of biopsy an adequate sample consisting of two cylinders of tissue of minimum length 1cm and diameter of 1.2mm is required; there should be adequate cortical tissue in the samples – for glomerular lesions a minimum of 5 glomeruli are needed, and for tubular interstitial lesions a minimum of 6 – 10 are required[41].

Contraindications to renal biopsy may be sub classified as absolute or relative:

1. Absolute

- Small kidney size
- Coagulopathy
- Uncontrolled hypertension (>160/95 mmHg)

2. Relative

- Solitary kidney
- Uncooperative patient
- Patient who is unable to lie supine[41]

Renal biopsy may be considered as a diagnostic procedure in the following clinical situations:

- nephrotic syndrome (NS)
- prolonged non-resolving acute renal failure
- rapidly progressive renal failure
- systemic diseases with co-existent renal dysfunction

- non-nephrotic range proteinuria
- isolated microscopic hematuria
- unexplained chronic renal failure
- renal transplant dysfunction
- patients with a history of familial renal disease[42]

The most common indications for biopsy in a retrospective review at a tertiary hospital in South India over 19 years between 1990 and 2008 were nephrotic syndrome 49%, chronic renal failure 13.6% and rapidly progressive renal failure 12% [43].

Indications for biopsy in Sudan in 2011 were reported as nephrotic syndrome 46.5%, unexplained renal impairment 33.8%, asymptomatic microscopic hematuria with minimal non-nephrotic range proteinuria 8.5%, nephritic syndrome 7%, and isolated non-nephrotic range proteinuria 4.2% [31].

In Johannesburg at Chris Hani Baragwanath Hospital, a study evaluating biopsy practices for the period 1982 - 2011, reported the most common indications for biopsy to be nephrotic syndrome 47.1%, acute kidney injury 19.8%, asymptomatic urinary abnormalities 8.1% and nephrotic / nephritic syndrome 6.2% [44].

2. METHODS AND RATIONALE

2.1 Aim

There is currently a lack of data regarding the prevalence of primary glomerular disease in the South African context. The aim of this study was therefore to characterize the prevalence and nature of presentation of glomerular disease in the patients undergoing native kidney biopsy at Charlotte Maxeke Johannesburg Academic Hospital.

2.2 Study objectives

2.2.1 Primary objective

1. To determine the overall prevalence of primary glomerular disease in the population of patients undergoing native kidney biopsy at Charlotte Maxeke Johannesburg Academic Hospital.

2.2.2 Secondary objectives

1. To characterize the types of primary glomerular disease in the context of the locally practised indications for native kidney biopsy.
2. To determine the association of patient factors such as age, sex, and race on the prevalence and relative frequencies of primary glomerular disease in this patient population.

3. To characterize the clinical presentation of glomerular disease within this population and evaluate the differences (if any) in clinical presentation in the various types of primary glomerular diseases.

2.3 Study description

This is a single center retrospective observational study conducted on all patients who underwent native kidney biopsies at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) during the period 2001-2010. The study contains descriptive and comparative elements.

2.4 Study population

All native renal biopsies undertaken on patients aged 18 years and older between the years 2001 and 2010 were considered for inclusion in this study.

2.5 Inclusion criteria

All patients who underwent kidney biopsy during the period 1/1/2001 – 31/12/2010 at CMJAH were included in this study if the following criteria were met:

1. Native renal biopsy was performed.
2. Biochemical, serological and histopathological evaluation indicated the presence of primary glomerular disease.
3. All patients with renal histopathological evidence of primary glomerular disease and sufficient biochemistry for analysis.
4. Patients were 18 years or older.

2.6 Exclusion criteria

Patients were excluded from this study if the following criterion were met:

1. Retrospective review of clinical and / or histopathological data indicated the possibility of a secondary cause for the glomerular lesion diagnosed.

   Secondary glomerular diseases excluded from analysis after clinical review and biochemical / histological parameters included:

   - Lupus nephritis
   - Diabetic nephropathy
   - Hypertensive nephropathy
   - HIV associated nephropathy

2.7 Site of study

This study was undertaken in the Division of Nephrology, Department of Internal Medicine, CMJAH, South Africa. CMJAH is a quaternary level hospital that serves as a referral hospital in Johannesburg. The patient population resident in these areas is heterogeneous and includes patients of African, Indian, Caucasian and Coloured (mixed race) ancestry.

2.8 Method

Records from all patients diagnosed with primary glomerular disease on native kidney biopsy at CMJAH between 1/1/2001 – 31/12/2010 and meeting the inclusion criteria were analyzed.

1. The prevalence of primary glomerular disease overall was determined as a percentage of all native kidney biopsies performed regardless of indication for biopsy

1.1 The prevalence of the various forms of primary glomerular disease, for example, FSGS, MN, MPGN, MCD, IgAN was determined as a percentage of the total number of diagnoses of primary glomerular disease as a whole.

1.2 Since patterns of glomerular disease may be affected by local biopsy practices, the prevalence of the various forms of primary glomerular disease was further characterized in the context of the indication for biopsy. For example, the prevalence of primary FSGS, MN, MPGN, and MCN were determined within the subgroup of patients undergoing native kidney biopsy for investigation of the nephrotic syndrome, as well as for those undergoing biopsy for evaluation of unexplained proteinuria, or urinary abnormalities, or renal dysfunction.

2. The effect of patient factors on the prevalence of primary glomerular disease was determined by evaluation of the relative frequencies of each of the subtypes of primary glomerular disease encountered within the patient subgroups of sex, race, and age.

3. The indication for renal biopsy was analyzed in respect of the following 6 main categories:

- Nephrotic range proteinuria
- Sub nephrotic range proteinuria
- Nephrotic /nephritic features
- Nephritic features
- Unexplained renal dysfunction
- Abnormal urine sediment (See definitions in 2.9 below)

Many patients had more than one indication for biopsy but the most prominent indication was used in this study. This was ascertained by reviewing the notes from the renal biopsy summary; in cases where this was not clear, the laboratory findings closest to the renal biopsy date that showed the greatest derangement from normal were used as indicators.

2.9 Definitions

As per the 2012 KDIGO Clinical Practice Guidelines on Glomerulonephritis, the following definitions were applied:

- Nephrotic range proteinuria was defined as a spot uPCR > 0.3-0.35 g/mmol
- Sub-nephrotic proteinuria was defined as a spot uPCR > 0.03g/mmol but < 0.3g/mmol
- Nephrotic syndrome was defined by the presence of:
    - proteinuria > 3.5g/day or spot UPCR > 0.3g/mmol
    - hypoalbuminaemia < 30g/l
    - oedema
    - dyslipidaemia[45]

- Nephritic syndrome was defined by the presence of:
    - microhaematuria
    - hypertension
    - proteinuria usually non nephrotic range,
    - abnormal renal function[45]

- Microhaematuria was defined by the presence of more than two red blood cells (RBCs) per high-power field in a spun urine sediment or more than 10 × 10 ^{6} RBCs/l ^{7}.

- Unexplained renal dysfunction – acute or chronic
    - Acute kidney injury - A rise in the serum creatinine concentration that has developed within hours to days. The criteria includes an increase in serum creatinine by 27 micromol/L or ≥1.5 times the baseline value within 48 hours (Acute Kidney Injury Network [AKIN] criteria), or an increase ≥1.5 times the baseline value within seven days (RIFLE criteria and Kidney Disease: Improving Global Outcomes [KDIGO]-AKI)
    - Chronic kidney disease - The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) and the KDIGO CKD guidelines define CKD as being present if glomerular filtration rate (GFR) has been recorded as being persistently below 60 mL/min/1.73 m2 or if abnormalities of urinalysis or histology or renal imaging have been present for three months or more.

- Estimated GFR was determined using the Modification of Diet in Renal Disease (MDRD) Study Group formula.

  eGFR = 32788 × standardized creatinine $^{-1.154}$ × age$^{-0.203}$ × 1.212 [if black] × 0.742 [if female], where GFR is expressed as mL/min/1.73 m2 of body surface area, and creatinine is expressed in µmol/L [46].

- Abnormal urine sediment
  - Proteinuria and haematuria as above
  - Leucocyturia
  - Dysmorphic red cells
  - Casts: granular, hyaline, waxy, red cell, cellular and combination

2.10 Variables

The clinical presentation of the various forms of primary glomerular disease was evaluated in the context of the following parameters:

2.10.1 serum creatinine

2.10.2 serum albumin

2.10.3 serum total cholesterol and triglyceride concentration

2.10.4 haemoglobin

2.10.5 urine white cell count

2.10.6 urine dysmorphic red cells

2.10.7 urine casts

2.10.8 urine protein: creatinine ratio

2.10.9 non-invasive arterial blood pressure

2.11 Data analysis

All continuous variables were tested for normality of distribution by visual inspection of frequency plot and the Shapiro-Wilk W test. The mean and standard deviations were used as the central and dispersal measurements for normally distributed data and the median and interquartile range were used for non-parametric data. Frequencies and percentages were used to describe categorical data. Differences in the various forms of primary glomerular disease with regards to demographics (patient age, sex, and race) and clinical presentation were analyzed using the ANOVA (parametric data), Friedman (non-parametric) tests; a Chi squared test was used for categorical variables.

3. RESULTS

3.1 Overview of records

A total of 1495 renal biopsies were performed at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2001 and 31 December 2010. Of these, 1135 biopsies were excluded from analysis at initial record review for the following reasons:

- Patients under 18 years
- Transplant kidney biopsies
- Patients diagnosed with HIV
- Insufficient records available for analysis of clinical and biochemical data

The remaining 360 records were subdivided into primary, secondary and non-glomerular pathology.

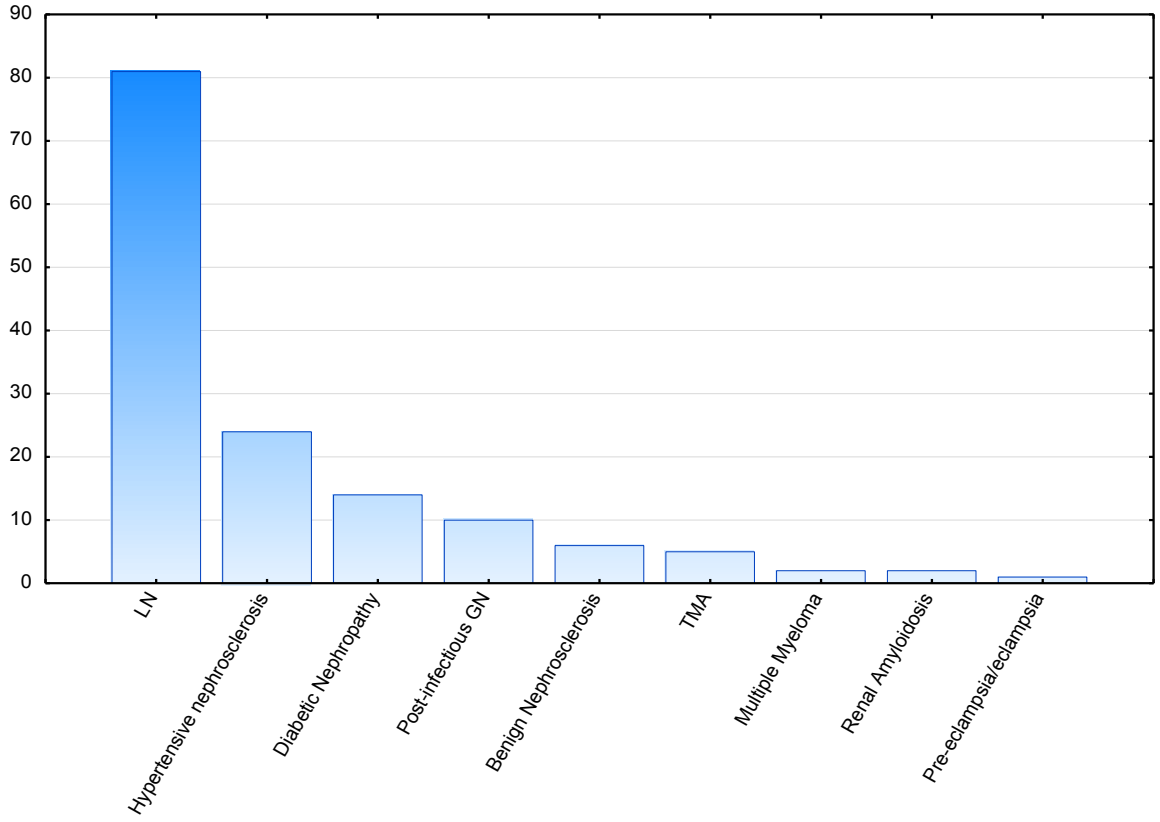
Table 3.1.1 Incidence of primary glomerular disease

Category	Count	Percentage
Primary	194	53.8%
Secondary	145	40.2%
Non-glomerular	21	5.8%
Total	**360**	**100%**

Table 3.1.2 Secondary causes of glomerular disease

Category	Count	Percentage
Lupus nephritis (LN)	81	55.8%
Hypertensive (HT) Nephrosclerosis	24	16.5%
Diabetic Nephropathy	14	9.6%
Post-infectious Glomerulonephritis	10	6.8%
Benign Nephrosclerosis	6	4.1%
Thrombotic microangiopathy (TMA)	5	3.4%
Primary renal Amyloidosis	2	1.3%
Multiple Myeloma (MM)	2	1.3%
Pre-eclampsia /Eclampsia	1	0.6%
Total	**145**	**100%**

Figure 3.1.1 Secondary glomerular diseases



The most common secondary cause for glomerular disease in this study was LN (55.8%), followed by HT nephrosclerosis (16.5%), diabetic nephropathy (9.6%), post-infectious GN (6.8%), benign nephrosclerosis (4.1%) and TMA (3.4%). The incidence of LN far out-weighs HT nephrosclerosis and the other histological sub types. Biopsy assists with classification of lupus nephritis which impacts on treatment and outcomes. Hypertensive and diabetic nephropathy are relatively easily diagnosed on clinical grounds and treatment and outcomes are not as varied as is the case with LN and so do not always require biopsy. Thus, local biopsy practices may have affected this analysis.

Table 3.1.3 Non-Glomerular Reasons for Exclusion

Category	Count	Percent
Acute Tubular Necrosis	11	52.3%
Chronic Interstitial Nephritis	6	28.5%
Chronic Pyelonephritis	2	9.5%
Acute Pyelonephritis	1	4.7%
Normal Biopsy	1	4.7%
Total	**21**	**100%**

The frequency of primary glomerular disease (53.8%) was higher than that of secondary (40.2%) and non-glomerular causes (5.8%). This trend may reflect local biopsy practices in our resource-limited setting where patients with known underlying aetiologies for the renal abnormalities are not readily biopsied.

The patterns of primary glomerular disease in the 194 biopsies included in this analysis are tabulated in Table 3.1.4.

Table 3.1.4 Subtypes of primary glomerular disease

Category	Count	Percent
Focal Segmental Glomerulosclerosis (FSGS)	58	29.8%
Membranous Glomerulonephritis (MN)	38	19.5%
Membrano Proliferative GN (MPGN)	35	18.0%
Minimal Change Disease (MCD)	33	17.0%
Global Glomerular Sclerosis of unknown aetiology (GGS)	7	3.6%
Mesangio-Proliferative GN (MesPGN)	6	3.0%
IgA Nephropathy (IGAN)	6	3.0%
Thin GBM Disease (Thin GBM)	3	1.5%
Diffuse Proliferative GN (DPGN)	1	0.5%
Immunotactoid Glomerulopathy (Immunotactoid GN)	1	0.5%
Necrotising Vasculopathy (NV)	1	0.5%
Anti-GBM Disease (Anti GBM)	1	0.5%
ANCA Vasculitis (ANCA vasc)	1	0.5%
Benign Familial Haematuria (BFH)	1	0.5%
Idiopathic crescentic Glomerulonephritis (Crescentic GN)	1	0.5%
Dense Deposit Disease (DDD)	1	0.5%
Total	**194**	**100%**

FSGS (29.8%) was found to be the most common cause of primary glomerular disease in this study followed by MN (19.5%), MPGN (18%), MCD (17%), GGS (3.6%), IgAN (3%) and MesPGN (3%).

3.2 Glomerular disease by indication to biopsy

Table 3.2.1 Indication to biopsy

Category	Count	Percentage
Nephrotic Range Proteinuria	157	43.6%
Unexplained Renal Dysfunction	115	31.9%
Lupus Nephritis	40	11.1%
Nephrotic / Nephritic Features	25	6.9%
Abnormal Urine Sediment	11	3.1%
Sub-nephrotic Range Proteinuria	10	2.8%
Nephritic Features	2	0.6%
Total	**360**	**100%**

The most common indication for renal biopsy at CMJAH for the period 2001-2010 amongst patients with primary glomerular, secondary glomerular, and non-glomerular patterns on renal biopsy (360 records) were nephrotic range proteinuria (43.6%) followed by unexplained renal dysfunction (31.9%), nephrotic / nephritic features (6.9%), abnormal urinary sediment (3%), sub nephrotic range proteinuria (2.7%) and lastly, nephritic features (0.5%).

Figure 3.2.1 Indication for biopsy

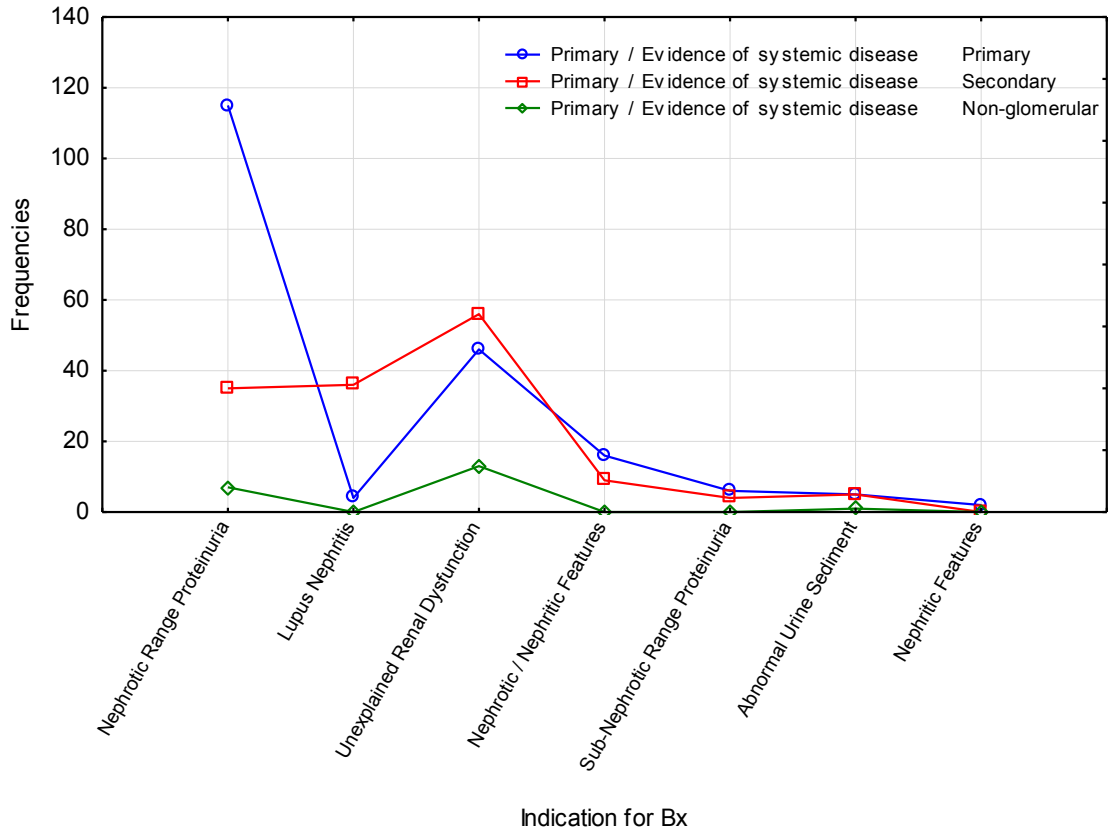
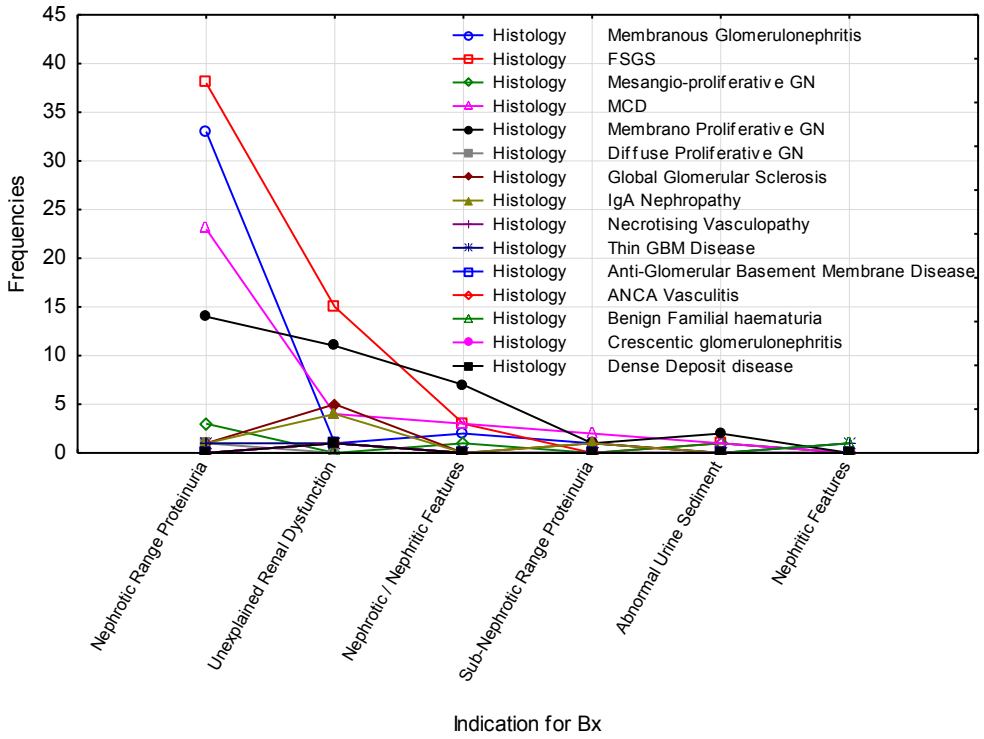


Figure 3.2.1 highlights the differences in frequency of the primary, secondary and non-glomerular histological patterns diagnosed on biopsy with respect to the indication to biopsy. Nephrotic range proteinuria was the indication for biopsy in (60.5%) patients with primary glomerular pathology, (24.1%) with secondary glomerular pathology and (33.3%) with non-glomerular pathology. Unexplained renal dysfunction was the most common indication for biopsy amongst the secondary glomerular (38.6%) and non-glomerular (61.9%) histopathology groups. These figures may infer a trend for primary glomerular disease to be more frequent in the nephrotic range category. There was a difference in the frequency of disease category (primary/ secondary and non glomerular) by indication to biopsy ($p < 0.001$ Pearson Chi Square).

Figure 3.2.2 Primary glomerular disease and indication for biopsy



The most common indication for biopsy across most of the subclasses of primary glomerular pathology was nephrotic range proteinuria, except for IgAN and GGS in which unexplained renal dysfunction was the most common indication for biopsy as illustrated in Figure 3.2.2.

Table 3.2.2 Indication for biopsy amongst the primary glomerular pathologies

Histology	Nephrotic Range Proteinuria	Unexplained Renal Dysfunction	Nephrotic Nephritic Features	Sub Nephrotic Proteinuria	Abnormal Urine Sediment	Nephritic	Total
FSGS	38	15	3	0	1	0	57(30%)
%	66.6%	26.3%	5.2%	0.0%	1.7%	0.0%	100%
MN	33	1	2	1	0	0	37(19.4%)
%	89.1%	2.7%	5.4%	2.7%	0.0%	0.0%	100%
MPGN	14	11	7	1	2	0	35(18.4%)
%	40.0%	31.4%	20.0%	2.8%	5.7%	0.0%	100%
MCD	23	4	3	2	1	0	33(17.3%)
%	69.7%	12.1%	9.0%	6.0%	3.0%	0.0%	100%
IgAN	1	4	0	1	0	0	6(3.1%)
%	16.6%	66.6%	0.0%	16.6%	0.0%	0.0%	100%
MesPGN	3	0	1	0	1	0	5(2.6%)
%	60.0%	0.0%	20.0%	0.0%	20.0%	0.0%	100%
NV	0	1	0	0	0	0	1
Thin GBM	1	1	0	0	0	1	3
Anti-GBM	0	1	0	0	0	0	1
ANCA Vasc	0	1	0	0	0	0	1
BFH	0	0	0	0	0	1	1
DPGN	1	0	0	0	0	0	1
GGS	1	5	0	1	0	0	7
Crescentic	0	1	0	0	0	0	1
DDD	0	1	0	0	0	0	1
Total	**115**	**46**	**16**	**6**	**5**	**2**	**190**
%	**60.5%**	**24.2%**	**8.4%**	**3.1%**	**2.6%**	**1.0%**	**100%**

Table 3.2.2 demonstrates the variation in indication for biopsy amongst the most frequent types of primary glomerular pathology.

Nephrotic range proteinuria (60.5%) followed by unexplained renal dysfunction (24.2%) and nephrotic / nephritic features (8.4%) were the most common indications for native renal biopsy in patients with primary glomerular pathologies.

Abnormal urinary sediment (2.6%) and nephritic features (1%) were relatively rare indications for biopsy in this series.

Nephrotic range proteinuria was the most common indication for biopsy amongst MN (89.1%), FSGS (66.6%), MCD (69.7%), MesPGN (60%) and MPGN (40%). Unexplained renal dysfunction was the most common indication for biopsy in IgAN (66.6%). Indication for biopsy was significantly associated with the different histological subtypes ($p < 0.001$ Pearson Chi square).

Figure 3.2.3 Podocytopathies and indication for biopsy

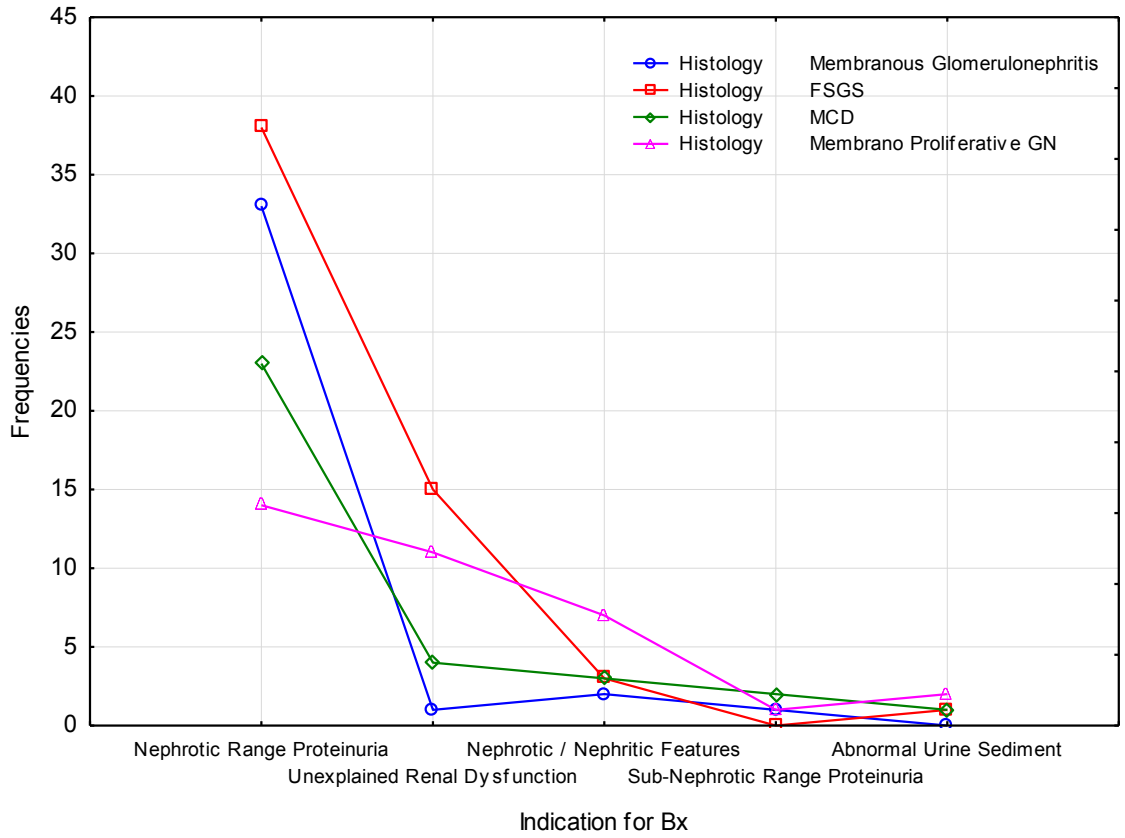


Table 3.2.3 Podocytopathies and indication to biopsy

	Nephrotic Range Proteinuria	Unexplained Renal Dysfunction	Nephrotic / Nephritic Features	Sub-Nephrotic Range Proteinuria	Abnormal Urine Sediment	Row Total
FSGS	38	15	3	0	1	57
%	66.7%	26.3%	5.3%	0.0%	1.8%	
MN	33	1	2	1	0	37
%	89.2%	2.7%	5.4%	2.7%	0.0%	
MCD	23	4	3	2	1	33
%	69.7%	12.1%	9.1%	6.1%	3.0%	
MPGN	14	11	7	1	2	35
%	40.0%	31.4%	20.0%	2.9%	5.7%	
Total	**108**	**31**	**15**	**4**	**4**	**162**
%	**66.7%**	**19.1%**	**9.3%**	**2.5%**	**2.5%**	**100%**

Amongst the 57 patients with FSGS, nephrotic range proteinuria and renal dysfunction was the indication to biopsy in (66.7% and 26.3%) respectively. Among the 37 patients with MN, nephrotic range proteinuria (89.2%) was the most common indication for biopsy followed by nephrotic / nephritic features (5.4%).

Nephrotic range proteinuria (40%), unexplained renal dysfunction (31.4%), and nephrotic / nephritic features (20.0%) were the dominant indications to biopsy in MPGN.

Nephrotic range proteinuria (66.7%) was the most common indication for biopsy amongst the podocytopathies overall, followed by unexplained renal dysfunction (19.1%). Sub-nephrotic range proteinuria and abnormal urine sediment were the least documented indications for renal biopsy in this analysis. Most patients with FSGS, MCD and MPGN presented with nephrotic range proteinuria and unexplained renal dysfunction. The differences in indication to biopsy amongst the podocytopathies were significantly different by histological subtype ($p = 0.004$ Pearson Chi-square).

3.3 Primary glomerular disease and gender

Table 3.3.1 Observed frequencies of histological subtypes and gender

Gender	MN	FSGS	MesPGN	MCD	MPGN	DPGN	GGS	IgAN	Immunotactoid	NV	Thin GBM	Anti-GBM	ANCA Vasc	BFH	Crescentic GN	DDD	Total
Male	19	32	4	16	24	1	5	6	1	1	0	1	1	1	0	1	113
Female	18	25	2	16	10	0	2	0	0	0	3	0	0	0	1	0	77
Total	**37**	**57**	**6**	**32**	**34**	**1**	**7**	**6**	**1**	**1**	**3**	**1**	**1**	**1**	**1**	**1**	**190**

The incidence of glomerular disease relative to gender is tabulated in Table 3.3.1. There was an overall male preponderance (59.5%) compared to females (40.5%). This male dominance was mainly a result of FSGS, MPGN and IgAN; as a similar male to female ratio was noted in MN, MCD and MesPGN. There were no significant differences in patterns on histological biopsy with respect to gender on Pearson Chi square testing p = 0.19

3.4 Primary glomerular disease and ethnicity

Table 3.4.1 Observed frequencies of primary glomerular disease and ethnicity

Race	MN	FSGS	MesPGN	MCD	MPGN	DPGN	GGS	IgAN	Immuno GN	NV	Thin GBM	Anti-GBM	ANCA Vasc	BFH	Crescentic GN	DDD	Total
Black	27	43	5	27	29	1	5	2	1	0	0	1	1	0	0	0	142 (73.9%)
%	19	30.3	3.5	19	20.4	0.7	3.5	1.4	0.7	0	0	0.7	0.7	0	0	0	100%
White	6	8	1	4	2	0	2	3	0	0	3	0	0	1	1	0	31 (16.1%)
%	19.4	25.8	3.2	12.9	6.5	0	6.5	9.7	0	0	9.7	0	0	3.2	3.2	0	100%
Indian	5	4	0	2	2	0	0	1	0	1	0	0	0	0	0	1	16 (8.3%)
%	31.3	25.0	0	12.5	12.5	0	0	6.3	0	6.3	0	0	0	0	0	6.3	100%
Total	**38**	**57**	**6**	**33**	**34**	**1**	**7**	**6**	**1**	**1**	**3**	**1**	**1**	**1**	**1**	**1**	**192**
%	**19.8**	**29.7**	**3.1**	**17.2**	**17.7**	**0.5**	**3.7**	**3.1**	**0.5**	**0.5**	**1.6**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**100%**

Table 3.4.1 demonstrates that the majority of all patients biopsied were of black ethnicity (73.9%), followed by white (16.1%) and indian (8.3%) patients. Included in this series but not tabulated for purposes of simplicity were two coloured patients (one diagnosed with FSGS and one with MPGN) and one asian patient diagnosed with FSGS.

The percentage of black vs white patients with FSGS, MCD, MPGN MN and MesPGN were 30.2% vs. 25.8%, 19% vs 12.9%, 20.4% vs 6.4%, 19.1% vs. 19.5% and 3.5% vs. 3.2%, respectively.

In patients presenting with MPGN, 93.5% were black vs 6.5% white, MCD 87% black vs 13% white, FSGS 84.3% black vs 15.6% white and MN 81.8% black vs 18.2% white. In black patients FSGS 30.3% was the most common subtype followed by MPGN 20.4% and MCD and MN 19% each.

The study population was predominantly from the black ethnic group and most histological subtypes had more patients in the black ethnic group, except for IgAN, thin GBM, BFH and Crescentic GN.

Overall, there was no statistical significance in the distribution of histological patterns between the ethnic groups ($p = 0.242$ Pearson Chi-square).

Figure 3.4.1 Podocytopathies and ethnicity

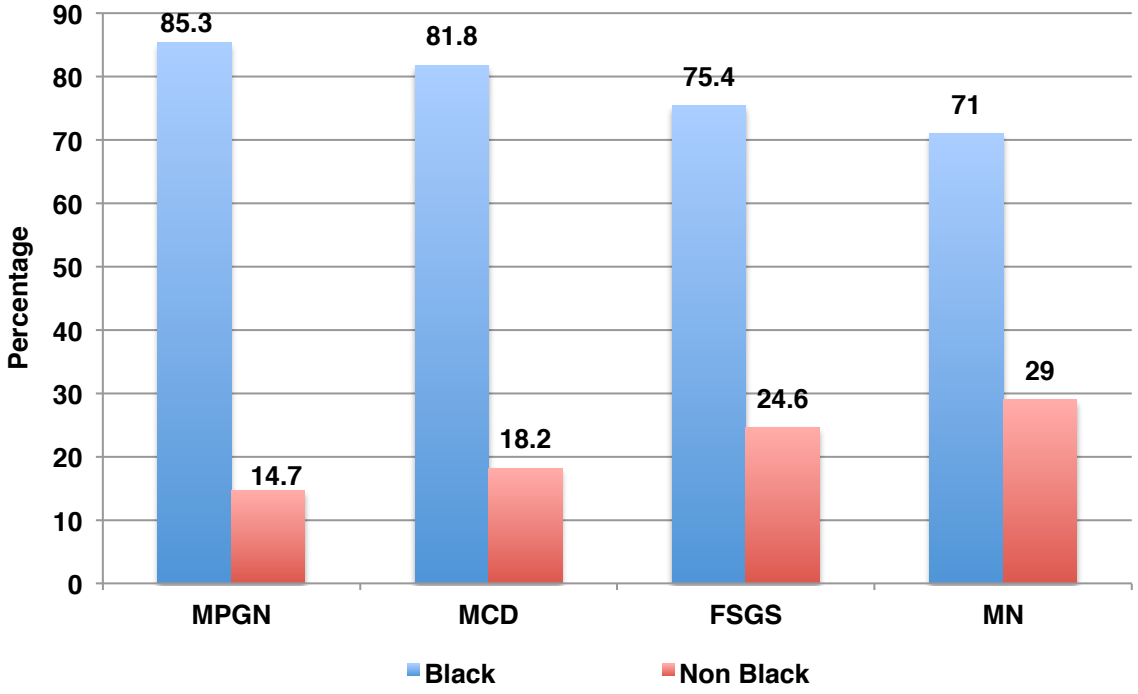


Figure 3.4.1 illustrates podocytopathy subtype between black and non-black ethnic groups. The black to non-black ratios amongst the podocytopathies were MPGN (85.3% vs 14.7%), and MCD (81.8% vs 18.2%), FSGS (75.4% vs 24.6%), and MN (71% vs 29%).

The distribution of podocytopathy amongst black patients was FSGS (34.1%), MPGN (23.0%), MN (21.4%), and MCD (21.4%), compared to non-black patients FSGS (38.9%), MN (30.6%), MPGN (17.9%), and MPGN (13.9%). There was no statistical significance between the podocytopathy histological subtype and black vs non-black patients p = 0.46 Pearson Chi Square.

3.5 Primary glomerular disease and age group

Figure 3.5.1 Primary glomerular disease and age

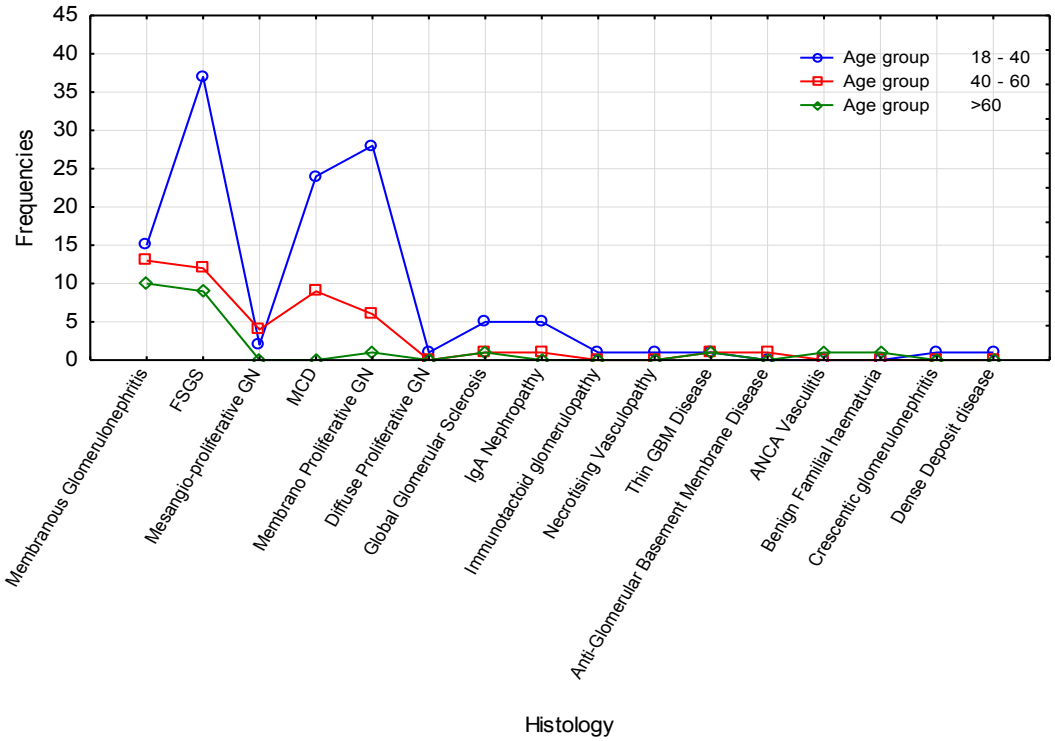


Table 3.5.1 Primary glomerular pathology in relation to age group

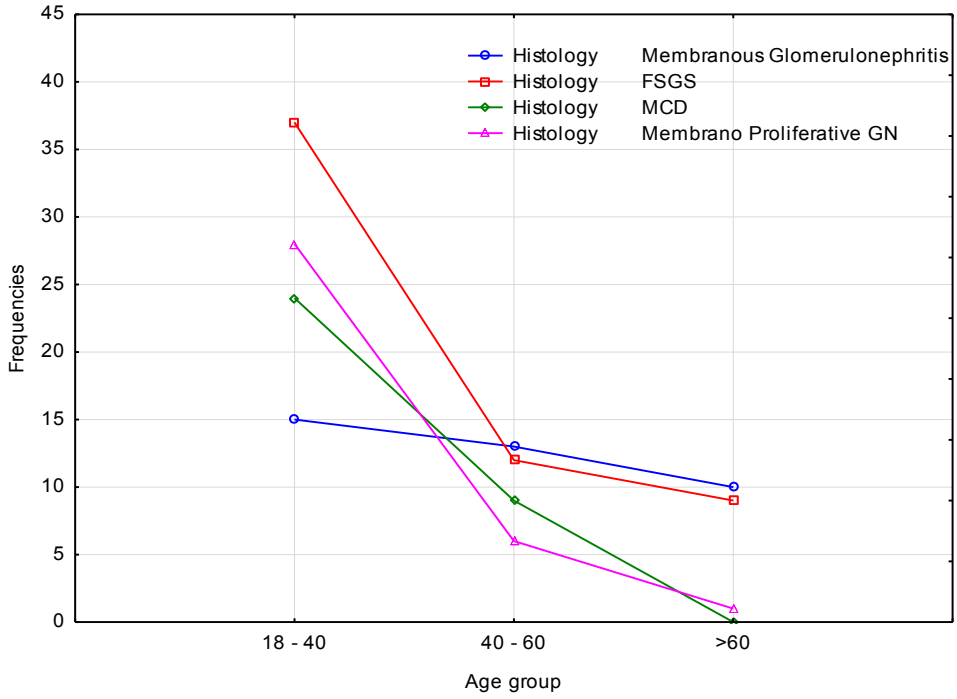
Age group	MN	FSGS	MesPGN	MCD	MPGN	DPGN	GGS	IgAN	Immuno GN	NV	Thin GBM	Anti-GBM	ANCA Vasc	BFH	Crescentic GN	DDD	Row Total
18- 40	15	37	2	24	28	1	5	5	1	1	1	0	0	0	1	1	122
%	12.3	30.3	1.6	19.7	23.0	0.8	4.1	4.1	0.8	0.8	0.8	0	0	0	0.8	0.8	62.9% 100
40- 60	13	12	4	9	6	0	1	1	0	0	1	1	0	0	0	0	48
%	27.1	25.0	8.3	18.8	12.5	0	2.1	2.1	0	0	2.1	2.1	0	0	0	0	24.7% 100
>60	10	9	0	0	1	0	1	0	0	0	1	0	1	1	0	0	24
%	41.7	37.5	0	0	4.2	0	4.2	0	0	0	4.2	0.0	4.2	4.2	0	0	12.4% 100
Total	38	58	6	33	35	1	7	6	1	1	3	1	1	1	1	1	194
%	19.6	29.9	3.1	17.0	18.0	0.5	3.6	3.1	0.5	0.5	1.6	0.5	0.5	0.5	0.5	0.5	100%

The mean age of all patients was 37.13 years. From Figure 3.5.1 and Table 3.5.1, it is noted that the majority of patients were from the 18 - 40 year old age group

(62.89%), followed by the 40 - 60 year subgroup (24.74%); and the least number of patients from the above 60 year old age group (12.37%).

The most frequent histological subtype in the 18 - 40 age group was FSGS (30.3%) followed by MPGN (23%), MCD (19.7%), and MN (12.3%). In the 40 – 60 year old sub group, MN (27.1%) was the most frequent, closely followed by FSGS (25%). Patients in the 60 years and above age group had MN (41.7%) as the most frequent glomerular pathology, followed by FSGS (37.5%). The majority of patients with MPGN (80%), MCD (72.7%) and FSGS (63.3%) were from the 18 - 40 year group. The Pearson Chi Square test indicated a statistically significant difference in the frequency of histological patterns of primary glomerular disease and age group p = 0.01. This probably reflects the higher numbers of patients in the 18 – 40 year group. This was not unexpected as primary GN is more common in younger patients.

Figure 3.5.2 Primary podocytopathies and age groups



The frequencies of histological pattern of injury per age group are illustrated in the line graph Figure 3.5.2. Although all the frequencies were high amongst the patients aged 18 – 40, which were highly represented in the sample, it is noted that FSGS was most prevalent within the 18 – 40 year age group while MN was most prevalent in the 40 – 60 and above 60 year age group. There were no patients with MCD above 60 years.

Table 3.5.2 Podocytopathies and age groups

Age group	MN	FSGS	MCD	MPGN	Row Total
18 - 40	15	37	24	28	104
%	14.4	35.6	23.1	26.9	100
Total %	9.2	22.6	14.6	17.1	63.4
40 - 60	13	12	9	6	40
%	32.5	30.0	22.5	15.0	100
Total %	7.9	7.3	5.5	3.7	24.4
>60	10	9	0	1	20
%	50.0	45.0	0	5.0	100
Total %	6.1	5.5	0	0.6	12.2
Total	**38**	**58**	**33**	**35**	**164**
%	**23.2%**	**35.4%**	**20.1%**	**21.3%**	**100%**

Among patients aged 18 – 40 years, FSGS (35.6%) was the most common histological pattern followed by MPGN (26.9%). MN (34.5%) was the most common glomerular pattern among the 40 – 60 years age group followed by FSGS (30.0%). MN (50%) followed by FSGS (45%) were the most common histological patterns in the 60 years and above age group. On review of the podocytopathies, histological subtypes were significantly different amongst the three age groups (p = 0.002 Pearson Chi Square).

3.6 Primary glomerular disease and creatinine/ eGFR

Table 3.6.1 Creatinine and histological subtypes

Histology	Creatinine	
	N	Median [Interquartile range]µmol/l
Crescentic GN	1	2154
NV	1	1009
GGS	4	510 [232 - 844.5]
IgAN	5	488 [315 - 694]
Anti-GBM	1	408
FSGS	54	183.5 [101 - 476]
MPGN	34	156.5 [104 - 239]
MN	32	92.5 [63 - 140]
Immunotactoid GN	1	90
MCD	29	79 [65 - 103]
MesPGN	4	76 [66 - 177.5]
Thin GBM	3	76 [75 - 137]
DPGN	1	76
BFH	1	76

The total mean creatinine was 261.3 ± 352.6 µmol/l. The creatinine value used was the one stated on the histology request form or the closest value to the renal biopsy date. In histological subtypes with only one patient, no IQR is documented. Poor documentation and inadequate records form the majority of the undocumented results. Amongst the commoner subtypes, the highest median and IQR for creatinine was recorded in patients diagnosed with IgAN 488 [315 - 694] µmol/l followed FSGS 183.5 [101 - 476] µmol/l, MPGN 156.5 [104 - 239], MN 92.5 [63 - 140], MCD 79 [65 - 103] and MesPGN 76 [66 - 177.5] µmol/l). A significant difference was noted in the mean creatinine amongst the histological subtypes ($p < 0.001$ Kruskall - Wallis), which suggests that the severity of renal dysfunction at presentation is disparate between the histological subtypes.

Table 3.6.2 Estimated Glomerular Filtration rate (eGFR) amongst podocytopathies

Histology	N	Median [Interquartile Range] mL/min/1.73m^2
FSGS	52	40.9 [12.6 – 86.9]
MPGN	34	57.4 [30.6 – 77.9]
MN	30	85.4 [50.6 – 131.5]
MCD	29	111.7 [79.9 – 137.8]

The median and interquartile range (IQR) for eGFR amongst the podocyopathies FSGS, MPGN, MN, MCD were 40.9 [12.6 – 86.9], 57.4 [30.6 – 77.9], 85.4 [50.6 – 131.5], 111.7 [79.9 – 137.8] mL/min/1.73m^2 respectively. The highest median eGFR was found in MCD 111.7 mL/min/1.73m^2 which is more than twice the value for FSGS 40.9 mL/min/1.73m$^{2.}$. A significant difference in the median EGFR was found amongst the podocytopathies ($p < 0.001$ Kruskall- Wallis), which suggests that the severity of renal dysfunction at presentation is disparate between the histological subtypes.

3.7 Primary glomerular disease and albumin

Table 3.7.1 Albumin and histological subtypes

Histology	Albumin	Albumin
	N	Mean ± Std.Dev g/L
IgAN	2	32.5 ± 14.8
MCD	13	26.2 ± 9.4
MPGN	9	24.8 ± 7 .2
MN	16	24.5 ± 9.8
FSGS	18	24.3 ± 10.3
Total	**67**	**26.3 ± 9.7**

A total of 67 values for albumin were found. The mean albumin was 26.3 ± 9.7 g/L. FSGS had the lowest mean albumin at 24.3 ± 10.3 g/L, followed very closely by MN, MPGN, MCD. IgAN was closest to that of healthy individuals (35-52 g/L at

National Health Laboratory Service used by CMJAH). The albumin value used was the one stated on the histology request form or the closest value to the renal biopsy date. Poor documentation and inadequate records form the majority of the undocumented results. Only values for the most common subtypes have been shown for purposes of simplicity. Mean albumin values were not significantly different amongst the histological subtypes (p = 0.366 on ANOVA).

3.8 Primary glomerular disease and haemoglobin

Table 3.8.1 Glomerular disease and haemoglobin (Hb)

Histology	N (Hb)	Mean ± Std dev g/dL
IgAN	3	9.93 ± 1.45
FSGS	52	11.59 ± 3.15
MPGN	33	12.0 ± 2.24
MN	33	12.79 ± 2.20
MCD	28	13.2 ± 2.52
MesPGN	4	13.35 ± 1.54
Gender		
Male	94	12.65 ± 2.8
Female	69	11.49 ± 2.42

A total of 167 results were found for analysis of Hb. The total mean Hb for the study was 12.14 ± 2.7 g/dL. Amongst the most common types of primary GN, the highest mean Hb was observed in patients diagnosed with MesPGN (13.3 ± 1.54), followed by MCD (13.2 ± 2.5), MN (12.78 ± 2.2) g/dL, MPGN (12.0 ± 2.24), FSGS (11.59 ± 3.15) and IgAN (9.93 ± 1.45) g/dL respectively. A significant difference in Hb was noted amongst the histological subtypes (p = 0.02 ANOVA). Females (11.49 ± 2.42) g/dL had a lower mean Hb than males (12.65 ± 2.8) g/dL (p = 0.004 Chi Square).

3.9 Primary glomerular disease and dyslipidaemia

Table 3.9.1 Cholesterol and histological subtypes

Histology	Cholesterol	Cholesterol mmol/l
	N	Mean ± Std.Dev
FSGS	45	9.9 ± 5.3
MCD	23	9.8 ± 4.6
MN	30	7.7 ± 3.4
MesPGN	3	7.6 ± 3.9
MPGN	30	6.2 ± 2.9
Thin GBM	2	6.0 ± 2.1
GGS	3	5.1 ± 1.1
IgAN	2	4.7 ± 2.1
Total	**143**	**8.2 ± 4.4**

A total of 143 values for cholesterol were analysed. In histological subtypes with only one patient, the recorded value was omitted from the table. The highest cholesterol levels were recorded amongst those with FSGS (9.9 ± 5.3) mmol/l followed by MCD (9.8 ± 4.6) mmol/l and MN (7.7 ± 3.4) mmol/l. Cholesterol levels tended to be within the normal range for patients diagnosed with Anti-GBM Disease, crescentic GN, immunotactoid GN, IgAN and GGS but the sample size in these subtypes were small. Measured cholesterol levels were significantly different between the histological subtypes ($p = 0.022$ on ANOVA).

Table 3.9.2 Triacylglycerol (TG) and histological subtypes

Histology	Triacylglycerol	mmol/L
	N	Mean (Std.Dev)
FSGS	40	3.2 ± 2.3
MesPGN	3	2.9 ± 1.9
MCD	20	2.7 ± 1.9
GGS	2	2.6 ± 0.8
MN	23	2.4 ±1.5
MPGN	27	1.8 ± 1.3
IgAN	2	1.6 ± 0.6
Total	**123**	**2.6 ± 1.9**

The highest TG levels were recorded among those patients diagnosed with FSGS (3.2 ± 2.3), MesPGN (2.9 ± 1.9), MCD (2.7 ± 1.9), MN (2.4 ± 1.5), and MPGN (1.8 ± 1.3) mmol/L. Subtypes with only one patient were omitted from Table 3.9.2. The TG values tended to be in the normal range amongst patients with immunotactoid GN, anti GBM, DPGN and IgAN, but these sample sizes were small. ANOVA testing did not demonstrate a statistically significant difference in TG levels between the various histological subtypes (p = 0.289).

3.10 Primary glomerular disease and urine white cell count

Table 3.10.1 Urine white cell counts and histological subtypes

Histology	UWCC	UWCC
	N	Median [Interquartile Range]
IgAN	4	115 500 [38 250 – 321 000]
MPGN	21	46 000 [12 000 – 117 000]
FSGS	29	33 000 [7 000 – 77 000]
MCD	15	18 000 [7 500 – 28 000]
MN	16	15 500 [6750 – 56 250]
MesPGN	2	4 500 [2750 – 6250]

The highest UWCC was observed in patients with IgAN 115 500 [38 250 – 321 000] followed by those with MPGN 46 000 [12 000 – 117 000], FSGS 33 000 [7

000 – 77 000], MCD 18 000 [7 500 – 28 000], MN 15 500 [6750 – 56 250] and MesPGN 4 500 [2750 – 6250]. No significant difference in UWCC was noted between histological subtypes (p = 0.234 ANOVA). It should be noted that patients with values < 1000 or > 750 000 as reported by the NHLS were excluded from this analysis. Only histological sub types with more than one record were documented on the table above.

3.11 Primary glomerular disease and urine dysmorphic red cells

Table 3.11.1 Urine dysmorphic cells and histological subtypes

Histology	Urine dysmorphic RC Recorded	No dysmorphic cells seen	Dysmorphic RC (%)
	N	N	Mean ± Std Dev
IgAN	5	4	80
MN	24	20	40 ± 39
MCD	26	19	34 ± 32
FSGS	39	21	33 ± 27
MPGN	21	9	24 ± 16
ANCA Vasc	1	0	10
GGS	4	4	-
MesPGN	3	3	-
Thin GBM	2	2	-
DPGN	1	1	-
Immunotactoid GN	1	1	-
NV	1	1	-

A total of 128 records for urine dysmorphic red cells were found. 85 patients had no dysmorphic red cells seen. Amongst patients with urinary dysmorphic red cells seen on microscopy, the highest mean was recorded in patients with IgAN (80%) followed by those with MN (40 ± 39), MCD (34 ± 32), FSGS (33 ± 27), and MPGN (24 ± 16%). No dysmorphic red cells were seen in MesPGN, DPGN, GGS, Immunotactoid GN, NV and thin GBM disease. This result may be skewed due to

small patient numbers in these categories. No significant difference in urinary dysmorphic red cell percentage was noted between the histological subtypes (p = 0.989 ANOVA).

3.12 Primary glomerular disease and urine casts

Table 3.12.1 Casts and histological subtypes

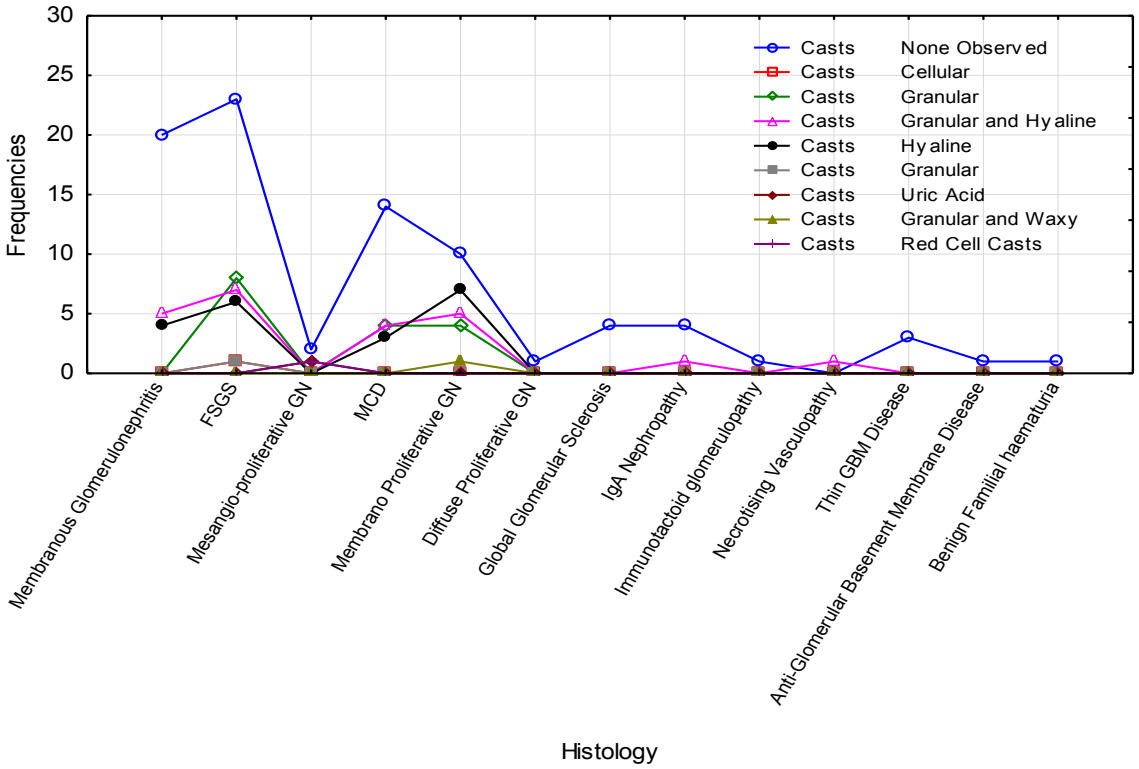
Casts	MN	FSGS	MesPGN	MCD	MPGN	DPGN	GGS	IgAN	Immuno GN	NV	Thin GBM	Anti-GBM	BFH	Total
None Observed	20	23	2	14	10	1	4	4	1	0	3	1	1	84 (56.8%)
%	23.8	27.4	2.4	16.7	11.9	1.2	4.8	4.8	1.2	0	3.6	1.2	1.2	100%
Granular	0	9	0	4	4	0	0	0	0	0	0	0	0	17 (11.5%)
%	0.0	52.9	0.0	23.5	23.5	0	0	0	0	0	0	0	0	100%
Granular & Hyaline	5	7	0	4	5	0	0	1	0	1	0	0	0	23 (15.5%)
%	21.7	30.4	0	17.4	21.7	0	0	4.4	0	4.4	0	0	0	100%
Hyaline	4	6	0	3	7	0	0	0	0	0	0	0	0	20(13.5%)
%	20	30	0	15	35	0	0	0	0	0	0	0	0	100%
Total	**29**	**46**	**4**	**25**	**27**	**1**	**4**	**5**	**1**	**1**	**3**	**1**	**1**	**148**
%	**19.6**	**31.1**	**2.7**	**16.9**	**18.2**	**0.7**	**2.7**	**3.4**	**0.7**	**0.7**	**2.0**	**0.7**	**0.7**	**100%**

Table 3.12.1 demonstrates the types of urinary cast detected on urinalysis by histological category. (56.8%) of patients had no casts observed, (0.6%) had cellular, (11.5%) granular, (15.5%) a combination of granular and hyaline, (13.5%) hyaline, and (0.7%) granular and waxy combination and (0.7%) red cell casts. Granular and waxy combination and red cell casts were found in one patient each with MPGN and MesPGN and were not tabulated for purposes of simplicity.

For the patients presenting with MN, (69.0%) had no casts, (17.2%) had granular and hyaline casts, and (13.8%) had hyaline casts. In patients who presented with FSGS, (50%) had no casts, granular (19.6%), granular and hyaline (15.2%), hyaline (13%) and (2.2%) had cellular casts observed. Of the patients diagnosed with MCD, (56%) had no casts; granular casts were present in (16%), granular and hyaline casts were present in (16%), and hyaline casts were present in (12%).

No casts were observed for patients that presented with DPGN, immunotactoid GN, thin GBM, Anti-GBM and benign familial haematuria. This is likely as a result of the small sample sizes in these subtypes or laboratory error. Urinary casts were not significantly different amongst the different histological subtypes ($p = 0.155$ Pearson Chi Square). The line graph in Figure 3.12.1 illustrates the frequency of casts and histology.

Figure 3.12.1 Primary glomerular disease and casts



3.13 Primary glomerular disease and urine protein: creatinine

Table 3.13.1 UPCR and histological subtypes

Histology		UPCR
	N	Mean (Std. Dev.)
Thin GBM	2	2.1 ± 2.1
MN	35	0.94 ± 0.74
FSGS	52	0.89 ± 0.66
MPGN	28	0.66 ± 0.46
IgAN	3	0.62 ± 0.42
MCD	26	0.60 ± 0.38
MesPGN	4	0.4 ± 0.5
GGS	4	0.2 ± 0.2
Immunotactoid GN	1	0.7
Anti-GBM	1	0.4
DPGN	1	0.3
ANCA Vasculitis	1	0.1
Total	**158**	**0.8 ± 0.6**

A total of 158 cases with recorded UPCR were analysed. In histological subtypes with only one record, only the actual value is documented on the table as no standard deviation was calculated. The highest mean UPCR value was recorded

among those with MN (0.94 ± 0.74) g/mmol followed by FSGS at (0.89 ± 0.66), MPGN (0.66 ± 0.46), IgAN (0.62 ± 0.42) and MCD (0.60 ± 0.38) g/mmol. Analysis by ANOVA demonstrated that UPCR was significantly different by histological subtype (p = 0.017). This result may be biased in the groups with small patient numbers. The differences are illustrated on the means and confidence interval plot in Table 3.14.1.

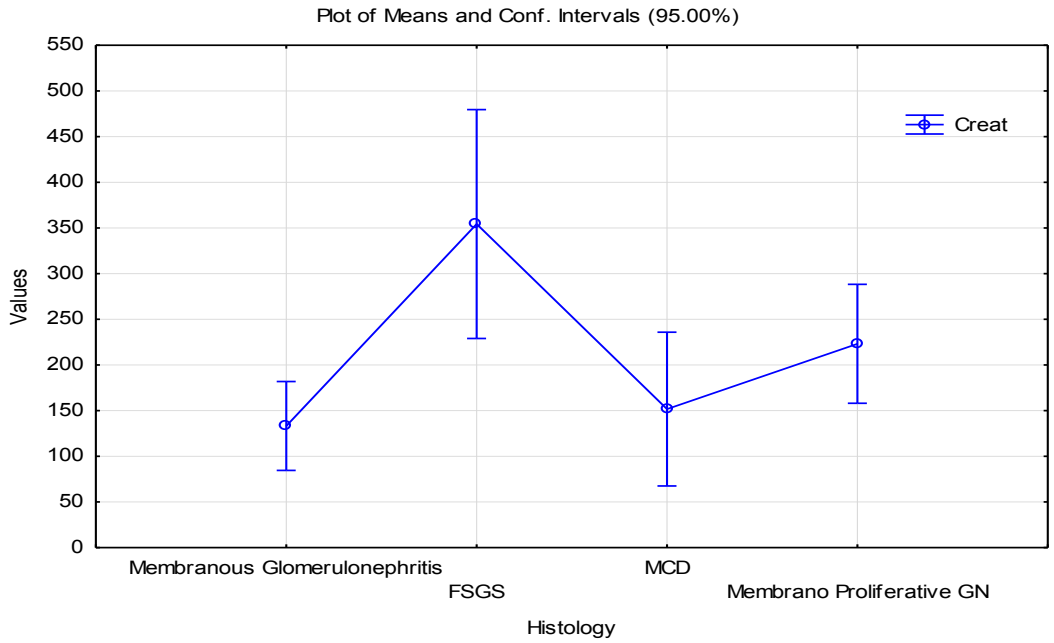
3.14 Podocytopathies and biochemical presentation

Table 3.14.1 Histology and biochemical presentation

Histo	Creatinine		Cholesterol		UWCC	
	N	Median [IQR]	N	Mean ± Std.Dev	N	Median [IQR]
FSGS	54	183.5 [101 - 476]	45	9.9 ± 5.3	29	33 000 [7 000 – 77 000]
MPGN	34	156.5 [104 - 239]	30	6.2 ± 2.9	21	46 000 [12 000 – 117 000]
MN	32	92.5 [63 - 140]	30	7.7 ± 3.4	16	15 500 [6750 – 56 250]
MCD	29	79 [65 - 103]	23	9.8 ± 4.6	15	18 000 [7 500 – 28 000]

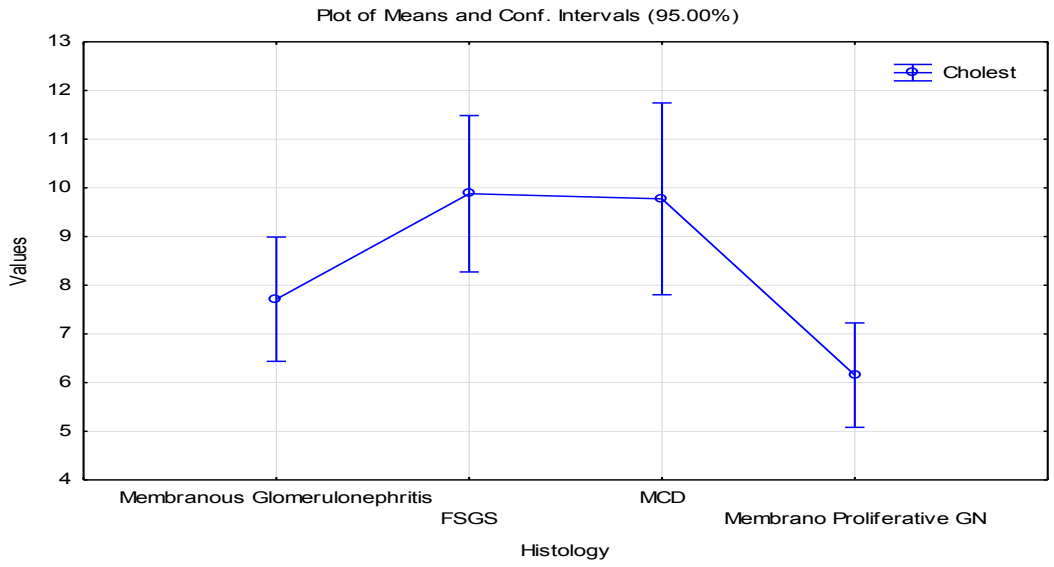
The median creatinine value was highest in the FSGS group 183.5 [101 - 476] µmol/l, followed by MPGN 156.5 [104 - 239] µmol/l, MN 92.5 [63 - 140] µmol/l; the lowest median creatinine value was for MCD79 [65 - 103] µmol/l). These values are also seen on the plot of means and confidence intervals in Figure 3.14.1. Creatinine levels were significantly different by podocytopathy subtype (p = 0.005 ANOVA).

Figure 3.14.1 Means and confidence intervals of creatinine



The highest mean cholesterol value was observed for FSGS (9.9 ± 5.3µmol/L), followed by MCD (9.8 ± 4.6), MN (7.7 ± 3.4) and the lowest were for MPGN (6.2 ± 2.9µmol/L). This is also seen on the plot of means and confidence intervals showing wide confidence intervals throughout the podocytopathies, Figure 3.14.2. Cholesterol varied by histological subtype (p = 0.001 ANOVA).

Figure 3.14.2 Means and confidence intervals of cholesterol



The highest UWCC median and IQR was found in MPGN 46 000 [12 000 – 117 000 followed by FSGS 33 000 [7 000 – 77 000], MCD 18 000 [7 500 – 28 000] and MN 15 500 [6750 – 56 250] had the lowest UWCC value. The difference in the UWCC by podocytopathy histology was not statistically significant (p-value = 0.132 ANOVA).

3.15 Primary glomerular disease and blood pressure (BP)

Table 3.15.1 Blood pressure and histological subtypes

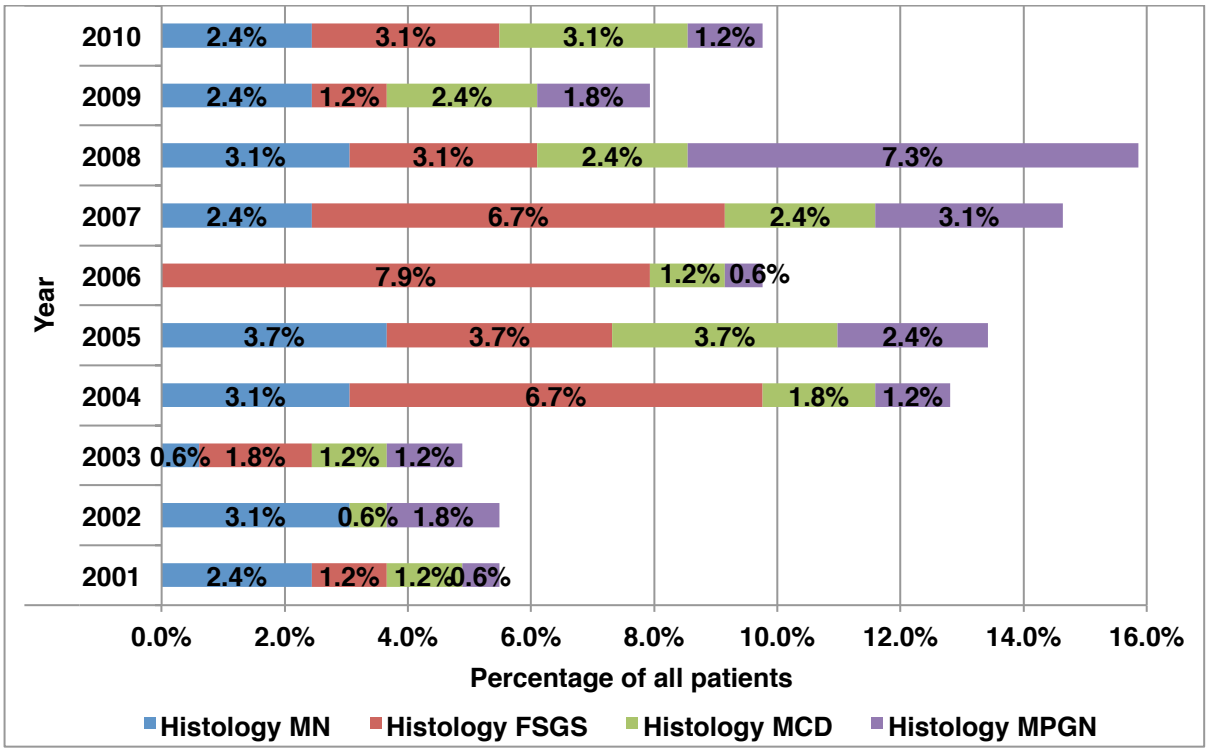
Histology	Hypertension		
	Yes	No	Row Total
MN	1	1	2
Row %	50	50	100
Total %	4.35	4.35	8.7
FSGS	3	2	5
Row %	60	40	100
Total %	13.0	8.7	21.7
MesPGN	1	1	2
Row %	50	50	100
Total %	4.35	4.35	8.7
MCD	0	6	6
Row %	0	100	100
Total %	0	26	26
MPGN	4	3	7
Row %	57.1	42.9	100
Total %	17.4	13	30.4
Immunotactoid GN	0	1	1
Row %	0	100	100
Total %	0	4.35	4.35
Totals	**9**	**14**	**23**
Total %	**39.1%**	**60.9%**	**100%**

23 records for BP were found. 39.1% of patients had hypertension at the time of biopsy. None of the patients biopsy-proven MCD had hypertension. The highest frequency of hypertension was observed in the MPGN group. 60% of patients with FSGS had hypertension. There is no significant difference between hypertension

and histological sub-types (p = 0.969 by Pearson Chi square). This is likely due to the very small sample size as a result of inadequate documentation of BP.

3.16 Primary glomerular disease patterns over time

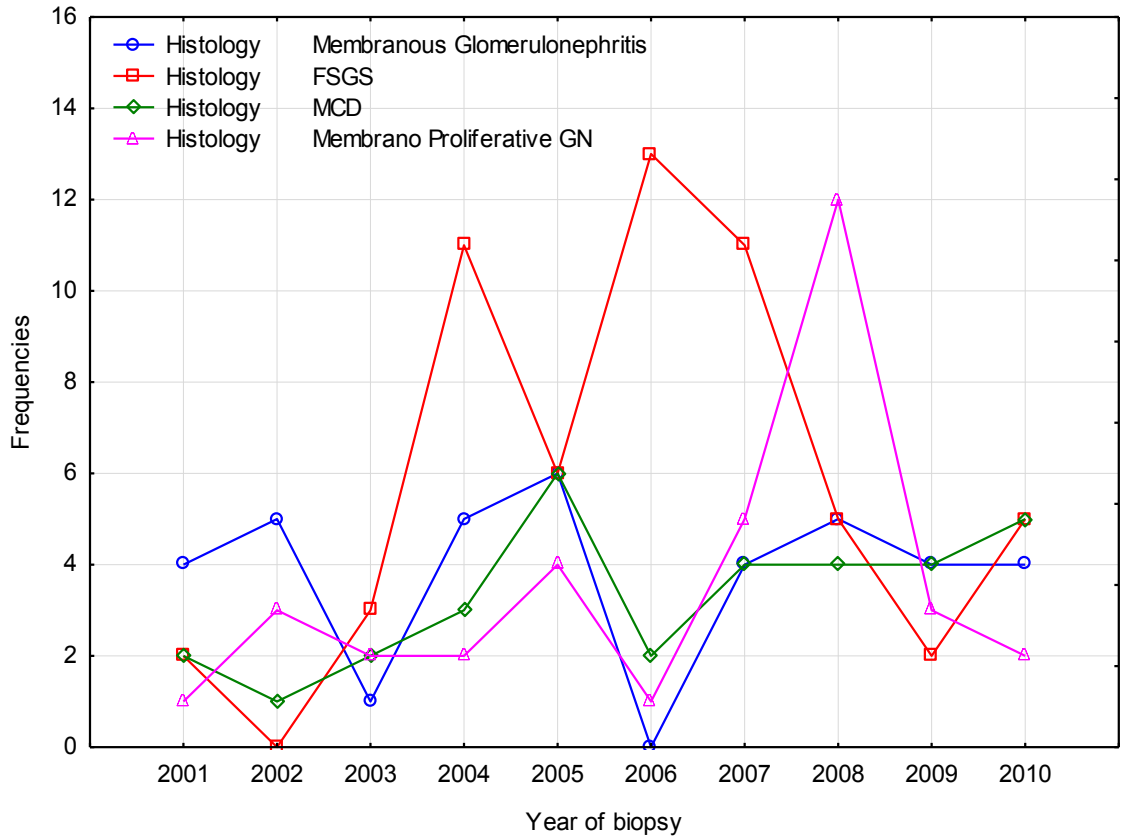
Figure 3.16.1 Histological subtypes by years



The results show that 5.5% of the patients had their biopsy done in 2001, 5.5% in 2002, 4.9% in 2003, 12.8% in 2004, 13.4% in 2005, 9.8% in 2006, 14.6% in 2007, 15.9% in 2008, 7.7% in 2009, and 9.8% in 2010. The most biopsies were done in 2008. It was noted that MN had the highest frequency during the periods 2001 to 2002, then FSGS dominated in the period 2003 to 2007. In 2008 MPGN was the most prominant type. In 2009 it was MPGN and MCD and in 2010 the highest frequency was for FSGS and MCD. The distribution of podoctyopathy histology over the years is statistically significant Pearson Chi-square p-value = 0.01. This is

also noted on the frequency plot Figure 3.16.2 that shows that FSGS is amongst the most common subtypes in most years, however there is no discernable trend.

Figure 3.16.2 Podocytopathies over time



4. DISCUSSION

4.1 Overview of records

A total of 1495 renal biopsies were done at Charlotte Maxeke Johannesburg Hospital between 1 January 2001 and 31 December 2010. 1135 biopsies were excluded from analysis at initial record review for the following reasons:

- Patients under 18 years
- Transplant kidney biopsies
- Patients diagnosed with HIV
- Insufficient records available for analysis of clinical and biochemical data

The incidence of primary glomerular disease (53.8%) was higher than that of the secondary (40.2%) and non-glomerular pathologies (5.8%).

In 2014 at Chris Hani Baragwanath Hospital (CHBAH), the incidence of primary glomerular disease was found to be (39.7%) and secondary (49.3%)[44]. In Cape Town in 2001-2009, a similar time line to this study, the incidence of primary and secondary glomerular disease was found to be (31.2%) and (49.0%) respectively, which is similar to the results at CHBAH[28].

In the current study patients that were HIV positive were excluded at initial review, and this may play some part in the lower numbers for secondary glomerular disease, as HIV is an ubiquitous infectious agent in South Africa and a well documented cause of glomerular disease. This result may also be skewed by local biopsy practices, which eschew biopsy in cases of clear diabetic and hypertensive nephropathy, and biopsy is usually performed in patients with unclear diagnosis.

Hence the rate of secondary pathologies may be under reported. Patients with lupus nephritis (LN) were excluded from the primary disease cohort after confirmation on renal histology.

The most common secondary cause of glomerular disease in the current study was LN (55.8%) followed by hypertensive nephrosclerosis (16.5%), diabetic nephropathy (9.6%) and post-infectious GN (6.8%).

The high incidence of LN as the most common secondary GN worldwide has been extensively documented. Recent data include CHBAH in 2014 (31%), Cape Town in 2011 (39%), Oman in 2013 (36.1%), China in 2012 (53.2%) and Brazil in 2010 (45.5%) [44,28,47,48,34]. The above data supports this study. CMJAH is a referral hospital for SLE patients and intensive monitoring of patients is practiced as renal involvement is independently associated with poor outcome[49], hence the early detection rate and high referral for renal biopsy, which generally alters treatment protocols.

4.2 Glomerular disease by indication to biopsy

The most common indications for biopsy in primary glomerular disease were nephrotic range proteinuria (60.53%) followed by unexplained renal dysfunction (24.2%), a combination of nephrotic / nepritic features (8.4%), sub nephrotic range proteinuria (3.2%) and abnormal urinary sediment (2.6%).

Nephrotic range proteinuria is overwhelmingly the most common indication for biopsy in this study. These results have been echoed in other studies in South Africa, Africa, and the rest of the world. There are however contrasting studies

where abnormal urine findings, renal dysfunction and nephritic syndrome are more prominent. These differences are multifactorial in aetiology. Indication to biopsy is under influence of geographic location, expected histological outcomes, biopsy practices in different regions, clinical skills, experience of nephrologists and financial constraints. Environmental factors, genetics and infections may also play a role.

Table 4.2.1 Nephrotic syndrome as the most common indication for biopsy

Area	Year of study	Frequency	Reference
Johannesburg	2001- 2010	59.2 %	Current study
Johannesburg	1982 - 2011	47.7 %	44
Cape Town	2000 - 2009	52.5 %	28
Bloemfontein	1997 - 2006	unknown	27
Senegal	1993 - 1998	67 %	50
Morocco	2000 - 2007	60.3 %	51
China	2000 -2010	52.5 %	48
Pakistan	1995 - 2008	49.9 %	52
India	1990 - 2008	49 %	43
Sudan	2010 - 2011	46.5 %	31
Brazil	1993 - 2007	39 %	34
Spain	1994 - 1999	35.2 %	53
Egypt	1998 - 1999	31.9 %	54

Table 4.2.2 Non nephrotic indications for biopsy

Area	Year of study	Indication for bx	Frequency	Reference
Belgium	1991 - 2006	Urinary abnormalities	53.5 %	55
Finland	1976 - 2000	Urinary abnormalities	38.7 %	56
Italy	1996 - 2000	Urinary abnormalities	53.2 %	57
France	1976 - 2002	CKD	36 %	58
Japan	2007 - 2008	Nephritic syndrome	48.2 %	59

Nephrotic range proteinuria was the most common indication for biopsy in patients subsequently diagnosed with MN (89.1%), FSGS (66.6%), MCD (69.7%),

MesPGN (60%), MPGN (40%). Unexplained renal dysfunction was the most common indication for biopsy in patients subsequently diagnosed with IgAN (66.6%). These findings are consistent with the clinical presentation of non-proliferative disorders like MN, FSGS and MCD, which usually present with nephrotic features and proliferative disorders such as IgAN which usually present with haematuria / nephritic features, renal dysfunction or nephrotic syndrome.

4.3 Most frequent primary histological pattern

FSGS (29.8%) was found to be the most common cause of primary glomerular disease in this study followed by MN (19.5%) and MPGN (18%), MCD (17%), IgAN (3%) and MesPGN (3%). This trend mirrors previous studies undertaken in SA and other parts of the developing world. This may be due to the higher incidence of non-proliferative GN especially FSGS in developing worlds compared to proliferative IgAN first world countries. Genetic factors involving APOL 1 / MYHC 9 gene penetrance in black patients and a second hit being poor nephron mass especially in low socio economic settings like ours are contributing factors.

Table 4.3.1 FSGS as the most frequent primary glomerulopathy

Area	Year of study	Frequency	Reference
Johannesburg	2001- 2010	29.8 %	Current study
Johannesburg	1982 - 2011	29 %	44
Bloemfontein	1997 - 2006	unknown	27
Senegal	1993 - 1998	47 %	50
Columbia	1998 - 2007	37.7 %	60
Belgium	1991 - 2006	30.3 %	55
Sudan	2010 - 2011	29.6%	31
Pakistan	1995 - 2008	29 %	52
Brazil	1993 - 2007	24 %	34
Egypt	1998 - 1999	22.6 %	54

This may be in part reflective of local practice, which considers isolated haematuria an indication for renal biopsy, and good urinary surveillance[1] with urine dipstix and blood pressure monitoring. Diseases that present with isolated haematuria are more likely to be asymptomatic in comparison with gross clinical features with nephrotic syndrome. Doctors and nephrologists in various parts of the world are also aware of the most common histological variants in their geographic location, and surveillance and biopsy practice is likely based on these patterns. Studies confirming this have been done in Europe, America and Australia.

Table 4.3.2 Non FSGS most frequent primary glomerular disease

Area	Year of study	Histology	Frequency	Reference
France	1976-2002	IgAN	73.4 %	58
Ireland	1976 - 2005	IgAN	38.8%	1
Finland	1976 - 2000	IgAN	34.9%	56
Italy	1996 - 2000	IgAN	34.5%	57
Australia	1995 - 1997	IgAN	34.1 %	61
Korea	1987 - 2006	IgAN	28.3 %	62
Japan	2007 - 2008	IgAN	27.6 %	59
USA	1974 - 2003	IgAN	22 %	35
Spain	1994 - 1999	IgAN	17.2 %	53
Cape Town	2000 - 2009	MPGN	20.4 %	28
Morocco	2000 - 2007	MCD	26 %	51
India	1990 - 2008	MCD	21.8 %	43
China	2000 - 2010	MN	31.7 %	48
Iran	1998 - 2007	MN	26.8 %	63

In developing worlds like SA, the increased incidence of FSGS may be as a result of the aggressive nature of the clinical presentation i.e. gross oedema and renal derangement in FSGS likely prompting more urgent investigation and referral for biopsy than the patients presenting with isolated haematuria. CMJAH is a public centre tertiary hospital hence the patient population is usually from the lower income sector. These patients do not have medical insurance and are required to attend their primary health care facility and then be referred to a secondary level hospital prior to being referred to a tertiary or quartenary level hospital for consideration of biopsy. Delays occur at most levels due to late presentation of patients, poor resources, referral systems and transport issues.

Although patients with HIV were excluded from this study, to not mention the high burden of disease in SA would be an oversight. In resource limited settings renal biopsy is usually limited to the more acute patients, those requiring diagnosis and patients in whom prompt intervention is required. There is a high incidence of HIV infection in SA and this predisposes patients to a more aggressive form of secondary FSGS. The late presentation of patients at our center, delayed referral from some peripheral care facilities and poor surveillance of urinary sediment may also play a role in the frequency of FSGS in this study.

Other postulations include underlying genetic factors like APOL 1 and MYHC 9 gene, which has been found to be a risk factor for the development of FSGS. These alleles are present in patients of African descent and their family members and absent from their Caucasian counterparts[20,21].

The underlying population at CMJAH is predominantly from African origin. Further evidence for genetic variation is found in a 30 year retrospective review in Ireland, in an over 99% Caucasian population documenting a 49% incidence in IgAN[1].

In 1988, Brenner proposed that babies born with low birth weight or intra uterine growth retardation had an increased susceptibility to hypertension, reduced sodium excretory capacity, progressive renal insufficiency and chronic kidney disease[64]. This may be a risk factor for the development of FSGS considering that in 2013, Statistics South Africa reported that 53.9% of babies were born with low birth weights less than 2500g [65]. Patients born with low birth weight are also more common amongst the lower socio economic income groups and African origin in South Africa due to previous political injustices, and many of these patients access state hospitals like CMJAH more frequently.

4.4 Primary glomerular disease and gender

There was an overall male preponderance, 59.5% vs females 40.5%. This male dominance is mainly as a result of FSGS, MPGN and IgAN as a similar male to female ratio was noted in the MN, MCD and MesPGN. According to statistics SA, there is a fairly equal distribution in gender in Johannesburg with 50.2% males[65]. The results in this study echo a very large study in Brazil reviewing 9617 renal biopsies over 15 years showing a 54% overall male predominance in primary glomerular disease[34].

4.5 Primary glomerular disease and ethnicity

The majority of all patients biopsied were of black ethnicity (73.9%), followed by white (16.1%) and indian (8.3%) patients. This distribution of ethnic variation reflects the population base at CMJAH, which is a state facility. The trend also mirrors the numbers quoted by Statistics SA in 2013 with (79.8%) of Gauteng being of black African descent, (8.9%) coloured, (8.7%) white and (2.6%) Indian[65].

The percentage black vs white patients with FSGS, MCD, MPGN MN and MesPGN, were 30.2% vs. 25.8%, 19% vs 12.9%, 20.4% vs 6.4% 19.1% vs. 19.5% and 3.5% vs. 3.2% respectively. The black to non-black ratios amongst the podocytopathies were MPGN (85.3% vs 14.7%), and MCD (81.8 vs 18.2%), FSGS (75.4% vs 24.6%), and MN (71% vs 29%). There is likely some selection bias as the study population was predominantly of black ethnicity and most histological subtypes had more patients in the black ethnic group. There was no statistical significance in the distribution of histological patterns between the ethnic groups ($p = 0.242$).

In Cape Town between 2000 – 2009, a similar time line to the current study, mesangiocapillary / MPGN was found to be the most common primary glomerular disease (20.4%) [28]. The percentage black vs white patients for MPGN, MesPGN, MN, FSGS and MCD were (20.6% vs 16.7%), (17.7% vs 27.8%), (16% vs 22%), (13.1% vs 5.6%), (6.3% vs 5.6%) respectively. Mixed ancestry patients who

formed the majority were documented separately. These results were not statistically significant.

Ethnic variation is important in susceptibility for glomerular subtypes. There is substantial evidence that an African population is at higher risk for primary and secondary FSGS due to multiple variables including hypertension, diabetes, HIV, and genetic risk. Our study showed FSGS to be the most common type in a largely African population. In a study looking at APOL genotype amongst patients of different ethnic groups, a recessive model conferred a 17 fold higher odds for patients with the APOL variant and FSGS. FSGS associated with the APOL risk alleles were also associated with a younger age of onset and faster progression to renal failure[66]. Further evidence for genetic variation and histological subtypes is found in a 30 year retrospective review in Ireland in an over 99% Caucasian population documenting a 49% incidence in IgAN[1]. Pure genetics is not enough to cause FSGS and it is likely a second hit hypothesis may be involved especially after reviewing the results of the current study.

4.6 Primary glomerular disease and age groups

The majority of patients were in the 18-40 year old age group (62.89%), followed by the 40-60 year subgroup (24.74%); the least number of patients were from the above 60year old age group (12.37%). This is consistent with published data showing that primary glomerular pathology is more common amongst younger patients.

The most frequent histological subtype in the 18 – 40 age group was FSGS (30.3%), in the 40 – 60 year old sub group and above 60 year old subgroup, MN was most frequent at (27.1% and 41.7%) respectively.

Age groups between the primary glomerular pathologies from the recent study in Johannesburg at Chris Hani Baragwanath Hospital found similar results to this study. FSGS and MN were the most common subtypes in patients aged 20 – 39 years, 40 – 59 years and above 60 years[44].

A large Indian study reviewing 1849 patients confirmed the above results showing a mean age of 32.77 years. This Indian study also documented the mean age for FSGS, MCD, MPGN and MN to be 25, 26, 27 and 40 years respectively, highlighting the younger age of presentation for the first three and the slightly older age of presentation of MN[43]. In the current study, most patients over 60 years presented with MN (41.67%). The peak incidence of MN is known to be 40- 50 years old[12].

4.7 Primary glomerular disease and biochemical parameters

Amongst the commoner subtypes, the highest median and IQR for creatinine were recorded in patients diagnosed with IgAN 488 [315 - 694] µmol/l followed by FSGS 183.5 [101 - 476] µmol/l, MPGN 156.5 [104 - 239], MN 92.5 [63 - 140], MCD 79 [65 - 103] and MesPGN 76 [66 - 177.5] µmol/l). A significant difference was noted in the mean creatinine amongst the histological subtypes ($p < 0.001$ Kruskall - Wallis).

The median and IQR for eGFR amongst the podocyopathies FSGS, MPGN, MN, MCD were 40.9 [12.6 – 86.9], 57.4 [30.6 – 77.9], 85.4 [50.6 – 131.5], 111.7 [79.9 – 137.8] mL/min/1.73m^2 respectively. The highest median eGFR was found in MCD 111.7 mL/min/1.73m^2 which is more than twice FSGS 40.9 mL/min/1.73m^2. The severity of renal dysfunction at presentation is different between the histological subtypes ($p < 0.001$ Kruskall - Wallis).

Renal insufficiency is known to be common at presentation with FSGS, occurring in about 30-45% of cases; the level of serum creatinine at biopsy is also predictive of progression to ESRD[67]. The mean eGFR at presentation of MCD patients is usually preserved or slightly deranged unless poor prognostic features like advanced age, hypertension or extremes in albumin or proteinuria is present[68]. Other causes of renal dysfunction in MCD are pre renal azotaemia due to intravascular contraction from hypoalbuminaemia, renal vessel thrombosis, over diuresis, nephrotoxins and intra renal parenchymal oedema.

A Chinese study[69] evaluating the metabolomics (quantitative measurement of the dynamic multi parametric metabolic response of living systems to pathophysiological stimuli or genetic modification) of primary GN in 2013 found that the mean eGFR was reduced in GN versus healthy participants in whom the mean eGFR was 120mL/min/1.73m^2. The most affected was FSGS 94 ± 33.1, followed by IgAN 99 ± 22.3, MCD 101 ± 32.4 and MN 108 ± 45.3 ml/min/1.7m^2 .

The GN progress trial reviewed 339 white patients in Paris, and recorded the eGFR median and IQR of FSGS 56 [36-83], IgAN 70 [42-92], MN 79 [61-95] mL/min/1.73m^2 [70]. The values for FSGS are similar to the Chinese and the current study, which also highlights the severity of renal dysfunction in FSGS compared to the other GN due its underlying physiology irrespective of ethnicity. Of note, is that in the GN progress trial, all patients with eGFR <15 ml/min/1.73m^2 were excluded.

All these studies show greater derangement in eGFR for FSGS with more preserved levels for MN and MCD. These results support the findings in the current study. Similar values were seen in MN and MCD in my study and the Chinese study. FSGS is known to have greater renal impairment at presentation compared to the fairly well preserved renal function of MCD and MN, this is known and is due to the basic underlying pathophysiology of each disease process.

Amongst the podocytopathies, FSGS had the lowest mean albumin at 24.3 ± 10.2 g/L, followed closely by MN, MPGN, MCD (24.5 ± 9.8, 24.8 ±7.1, 26.2 ± 9.4 g/L) respectively. Mean albumin in IgAN 32.5 ± 14.8 was closest to that of healthy individuals, although these observations did not reach statistical significance (p = 0.366). This current study correlated closely to the study in China mentioned above which showed the mean albumin levels for MN, MCD and IGAN to be (20 ± 7.21, 23 ± 11.2, 34.9 ± 4.67g/L), The mean albumin for FSGS (36.05 ± 7.76g/L) however was higher in China[69]. This difference may in part be due to later presentation, delayed referral for biopsy in our setting, a more aggressive type of FSGS and differences in dietary protein intake.

In the current study, amongst the most common types of primary glomerulopathies, the highest mean Hb was observed in patients diagnosed with MesPGN (13.3 ± 1.54), followed by MCD (913.2 ± 2.5) followed by MN (12.7 ± 2.2) g/dL, MPGN (12.0 ± 2.2), FSGS (11.6 ± 3.1) and (IgAN 9.93 ± 1.45) g/dl respectively. Males had a higher mean Hb (12.65 ± 2.82) compared to females (11.4 ± 2.4) g/dL.

The GN PROGRESS trial in 2008 reviewed clinical and biochemical data in 536 patients with FSGS, MN or IgAN. The mean Hb amongst women in FSGS, IgAN and MN were (12.6 ± 1.6, 12.3 ± 1.4, 12.0 ± 1.5 respectively) [70]. The mean Hb amongst men was approximately 1.5 g/dL higher in each category. This result supports the results in my study and it is well known that males have a mean Hb about 12% higher than their female counterparts[71]. These results are comparative to the results in the current study, except that the Hb for IgAN was lower in the current study. These patients with IgAN also presented with the lowest eGFR and low Hb's which may be as a result of the renal dysfunction or later presentation.

The highest cholesterol levels were recorded in those patients with non-proliferative glomerular pathology FSGS (9.9 ± 5.3) mmol/L, MCD (9.8 ± 4.5) and MN (7.7 ± 3.4) followed by proliferative MPGN and IgAN (6.15 ± 2.8), (4.65 ± 2.0) mmol/L respectively with a significant p-value of 0.022.

These findings correlate with the Chinese study reviewing 89 patients with primary GN, which demonstrated an elevated total cholesterol and range amongst MCD

9.62 [3.9-13.9mmol/L] and MN 7.3 [3.3-14.5mmol/L/]; interestingly, the cholesterol levels in FSGS 5.2 [8-10mmol/L] in the Chinese study were lower than those seen in the CMJAH cohort[69].

A Saudi Arabian retrospective review of 120 patients with primary GN found a mean total cholesterol of 5.9 ± 1.4 [72], which is lower than that of this study (8.2 ± 4.4) mmol/L. The difference was mainly due to higher FSGS and MN in our study (9.9 ± 5.3 and 7.7 ± 3.4 vs 5.6 ± 1.2 and 5.4 ± 1.2 mmol/ L). The values for MCD and IgAN 8.0 ± 3.3, 6.0 ± 1.6mmol/L respectively were similar. This is again likely due to late presentation and hence increased severity of disease on presentation and probably more aggressive underlying disease. It is also interesting to note, that in the current study, the non-proliferative GN being FSGS, MCD and MN had the highest total cholesterol and the lowest albumin levels. These clinical parameters are linked to the underlying disease process and the nephrotic syndrome presentation.

The mean triacylglycerol (TG) level for the 123 records was (2.6 ± 1.9)mmol/L. Amongst the most frequent GN, the highest levels were recorded among those with FSGS (3.2 ± 2.3)mmol/L followed by MesPGN (2.9 ± 1.8)mmol/L, MCD (2.7 ±1.9) mmol/L, MN (2.4 ± 1.4)mmol/L, MPGN (1.8 ± 1.2)mmol/L with IgAN having the lowest TG levels (1.6 ± 0.5)mmol/L. There were no significant differences in the mean TG values among the histological subtypes ($p = 0.289$). These results are similar to the findings of the Chinese study discussed above, FSGS 2.2 [0.5-

5.5]mmol/L, MCD 2.6[1.0- 7.4], MN 2.4[0.8-2.5] and IgAN 1.2[0.5-8.2]mmol/L. The Saudi Arabian study mentioned above recorded a mean TG of 3.5 ± 1.1 mmol/L[72].

These studies support this current study in that non-proliferative glomerular disease was associated with more severely aberrant dyslipidaemia than proliferative glomerular disease, consistent with the established pathophysiology of the nephrotic syndrome as discussed above[69].

4.8 Primary Glomerular Disease And Urinary Parameters

The highest UWCC was observed in patients with IgAN 115 500 [38 250 – 321 000] followed by those with MPGN 46 000 [12 000 – 117 000], FSGS 33 000 [7 000 – 77 000], MCD 18 000 [7 500 – 28 000], MN 15 500 [6750 – 56 250] and MesPGN 4 500 [2750 – 6250]. No significant difference in UWCC was noted between histological subtypes (p = 0.234 ANOVA).

An Italian study from 1999-2002, reviewing 100 patients with proliferative and non-proliferative GN reviewed several urinary parameters. They noted that the number of urine leucocytes correlated with intra and extra capillary glomerular proliferation and that patients with leucocytes and red cells in urine, had an odds ratio of 7.85 and 4.33 respectively of having a proliferative GN[73]. This supports this current study, which shows high levels of urinary white cells in IgAN and MPGN.

The highest mean urinary dysmorphic red cell was recorded in patients with IgAN (80%) followed by those with MN (40 ± 39), MCD (34 ± 32), FSGS (33 ± 27) and

MPGN (24 ± 16%). Dysmorphic red cells more than 80% are usually glomerular in origin[74]. It is known that proliferative GN presents with urinary red cells and red cell casts more frequently than non-proliferative GN[75]. In the current study no significant difference in urinary dysmorphic cell percentage was noted between the histological subtypes (p = 0.989). Small sample sizes may have contributed to this

It was noted that 56.8% of patients in this series had no urinary casts present; whilst 15.5% had a combination of Granular and Hyaline, (13.5%) Hyaline, (11.5%) granular, (0.7%) Granular & Waxy, (0.7%) Red Cell Casts and (0.6%) had Cellular casts. Red cell casts are virtually pathognomonic for glomerular disease[74], however there was no significant association between casts and primary glomerular disease in this study. The study in Italy mentioned above, showed the presence of red cell casts in proliferative glomerular disease to be 84.6% vs 39.6% in non-proliferative glomerular disease and patients with red cells in the urine had an odds ratio of 9.91 of having an underlying proliferative GN[73].

A total of 158 values for UPCR were analyzed. The highest mean UPCR value was recorded in patients with FSGS at (0.89 ± 0.66) g/mmol, followed in descending order by MN (0.94 ± 0.74), MPGN (0.66 ± 0.46), IgAN (0.62 ± 0.42) and MCD at (0.60 ± 0.38) g/mmol (p = 0.01). A preponderance of nephrotic range proteinuria was noted, in keeping with the frequency of non-proliferative glomerular disease / podocytopathies in this cohort. The GN PROGRESS trial reported proteinuria as median and interquartile ranges with the highest being MN 0.54 [0.21- 0.81] followed by FSGS 0.34 [0.18-0.6] and IgAN 0.11 [0.05-0.22] [70]. The

Chinese study found the highest levels of proteinuria to be present in MCD 4849 mg /24hr urine, followed by MN 3155mg /24hr, IgAN 1171mg /24hr and lastly FSGS 1095 mg /24hr urine. The lower levels of proteinuria in the Chinese study may be due to the inclusion criteria of patients with CKD stage 1 – IV only. This excluded patients with end stage renal failure and likely contributes to lower levels of proteinuria especially in FSGS compared to the current study[69]. These findings may also support the possibility of a more aggressive type of FSGS in Africa.

Adults with primary FSGS present with nephrotic range proteinuria in more than 70% of cases. It is known that the degree of proteinuria has prognostic significance and patients with non-nephrotic proteinuria have extremely good prognosis[67].

Nephrotic syndrome, including nephrotic-range proteinuria, is classically a manifestation of the non-proliferative glomerular diseases (MCD, FSGS, MN) and is rare in proliferative GN types such as IgAN and MPGN. Possible reasons for the high proteinuria in IgAN and MPGN in this study include a high incidence of renal dysfunction with more proteinuria, more aggressive disease and later presentation. It will be interesting to review the biochemistry in the different histological subtypes amongst FSGS and IgAN as this likely also plays a part in clinical presentation.

4.9 Primary glomerular disease and blood pressure (BP)

It was noted that 39.1% of the patients had hypertension with a BP of > 140/90 mmHg. None of the patients with MCD had hypertension. MCD usually presents

as nephrotic syndrome, and hypertension is more frequent in nephritic syndrome. Hypertension however, may occur in nephrotic syndrome due to fluid overload or renal dysfunction. No significant difference in the presence of hypertension across the histological patterns of glomerular disease was present on Chi-square testing ($p = 0.969$). This could be due to the low numbers of patients that had documented blood pressures.

These results are supported by a study in China in 2013, where most patients were also normotensive and the mean recordings for BP were MCD 125 ± 12 mmHg, IgAN 124 ± 13 mmHg and FSGS at 20 ± 12 mmHg[69]. The GN PROGRESS trial reviewed patients with FSGS, IgAN, and MN and found a total of 34% to be hypertensive (> 140/90 mmHg) with a significant $p < 0.01$ [70]. Even though the patient numbers in my study were low, the frequency of hypertension correlated with the aforementioned studies.

4.10 Primary glomerular disease patterns over time

It was noted that MN had the highest frequency during the periods 2001 to 2002, then FSGS dominated in the period 2003 to 2007. In 2008 MPGN was the most prominent type. In 2009 it was MPGN and MCD and in 2010 the highest frequency was for FSGS and MCD. This highlights the high frequency of FSGS compared to IgAN over the study duration. It was noted that FSGS was amongst the most common subtypes in each year. Although Chi squared testing showed a statistically significant difference in the frequency of histological subtype by year, there was no discernable trend in terms of increasing frequency of subtypes.

5. CONCLUSION

The most frequent primary GN was FSGS (29.8%) followed by MN (19.5%), MPGN (18%), MCD (17%) and IgAN (3%). Nephrotic range proteinuria (60.5%) and unexplained renal dysfunction (24.2%) were the most common indications for biopsy.

There was a 59.4% male predominance. (73.9%) of patients were of African descent. The majority of patients (62.9%) were from the 18-49 year age group. The mean albumin was (26 ± 9.7) g/L, haemoglobin (12.14 ± 2.7) g/dL, cholesterol (8.2 ± 4.4) mmol/L, triglyceride (2.6 ± 1.9) mmol/L and urine PCR (0.8 ± 0.6) g/mmol. The highest median creatinine was found in FSGS 183.5 [101 - 476]. The highest urine leucocytes and dysmorphic red cells were from IgAN. Most patients (56.8%) had no casts observed, and (39.1%) were hypertensive.

Glomerular disease is a highly prevalent complex condition with a wide range of clinical features that present clinicians with a diagnostic dilemma. Renal biopsy has been a crucial innovation in the field of nephrology. This study aimed to review the incidence of different types of glomerular disease and the various demographic and clinical presentations in relation to indication for biopsy. This study was helpful in reviewing mean biochemical and urinary features of primary glomerular disease. It is hoped that this study will spark interest in glomerular disease and will serve as impetus for future studies, including those with genetic variables, as this will be extremely interesting.

6. STUDY LIMITATIONS AND STRENGTHS

6.1 Study Limitations

1. Lack of adequately / sufficiently recorded data pertaining to the clinical presentation parameters discussed in section 2.9 resulted in much smaller numbers for analysis than was predicted.
2. Inability to retrospectively validate contemporary clinical data thus leading to bias.
3. Lack of adequately recorded indications for renal biopsy.
4. A larger than expected prevalence of secondary causes of glomerular disease resulted in decreased numbers for analysis.
5. Disparity in sample size of the frequent and infrequent histological subtypes. Small sample sizes carry inherent risks of bias and inaccuracy but are accounted for in statistical methodology.

The following methods and processes were implemented to try to compensate for the above factors:

1. Only those patients in whom histological diagnosis and sufficient clinical parameters at the time of biopsy were included.
2. In cases where data was incomplete, a review of the electronic records at the head office of the National Health Laboratory Service (NHLS) was made.

6.2 Study Strengths

1. A large number of cases of primary GN were nevertheless included in this analysis (n = 194)
2. The biochemical and patient demographic parameters between the various GN subtypes are objective in nature and not dependent on the subjective opinion of the attending doctor at the time of diagnosis
3. All data included in this study was reviewed by a specialist histopathologist and nephrologist
4. The study duration of 10 years provided a long term analysis of trends.

6.3 Future Studies

1. Further studies of a similar nature with larger sample sizes and at multiple institutions in South Africa are required to substantiate or refute the findings of this study.
2. Given the small group of patients in this case series, many findings were not statistically significant; it would be valuable to determine if observed trends in this study would constitute significant findings in a larger population.
3. A renal biopsy registry, documenting the indication and result would be useful in the South African setting.

7. REFERENCES

1. Hanko JB, Mullan RN, O'Rourke DM, McNamee PT, Maxwell AP, Aisling E, *et al*. The changing pattern of adult primary glomerular disease. Nephrology Dialysis Transplant 2009(24):3050-3054.
2. Hurtado A, Johnson RJ. Hygiene hypothesis and prevalence of glomerulonephritis. Kidney International 2005*(*68)(Suppl.97):S62-S67.
3. Naicker S. Burden of end stage renal disease in Sub- Saharan Africa. Clinical Nephrology 2010;74(suppl 1):S13-S16.
4. Ganong WF. Review of Medical Physiology. 22nd ed. San Francisco: McGraw Hill; 2007, pp 699 – 701.
5. Kriz W, Gretz N, Lemley KV. Progression of glomerular diseases: Is the podocyte the culprit? Kidney International 1998(54):687–697.
6. Fatehi P, Hsu CY. 2015. Evaluation of acute kidney injury (acute renal failure) among hospitalized patients. UpToDate. Topic 102834 Version 1.0. Available: http://0www.uptodate.com.innopac.wits.ac.za/contents/evaluation-of-acute-kidney-injury-acute-renal-failure-among-hospitalized-patients?source=search_result&search=diagnostic+approach+to+the+patient+with+acute+kidney+injury&selectedTitle=2%7E150 [Accessed 01.11.2015]
7. Floege J, Feehally J. Introduction to Glomerular Disease - Clinical Presentation. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 184-197.
8. Floege J, Feehally J. Introduction to Glomerular Disease - Histologic classification. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 198-207.

9. Vinen CS, Oliveira DBG. Acute glomerulonephritis. Postgraduate Medical Journal 2003;79:206–213.

10. Floege J, Feehally J. IgA Nephropathy and Henoch-Schönlein Nephritis. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 266-277.

11. Nair R, Walker PD. Is IgA nephropathy the commonest primary glomerulopathy among young adults in the USA? Kidney International 2006;69:1455–1458.

12. Nachman PH, Jenette JC, Falk RJ. Primary Glomerular Disease. In: Taal MW, Yu ASL, Chertow GM, Brenner BM, Marsden PA, Storecki K, editors. Brenner and Rector's The Kidney. 9th ed. Philadelphia: Saunders; 2011. pp 1100 -1191.

13. Schena FP, Alpers CE. Membranoproliferative Glomerulonephritis and Cryoglobulinemic Glomerulonephritis. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 253-260.

14. Mason PD, Hoyer PF. Minimal Change Nephrotic Syndrome. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 208-217.

15. Couser WG. Basic and Translational Concepts of Immune-Mediated Glomerular Diseases. Journal of the American Society of Nephrology 2012 Mar 1;23:381-399.

16. Grimbert P, Audard V, Remy P, Lang P, Sahali D. Recent approaches to the pathogenesis of minimal-change nephrotic syndrome. Nephrology Dialysis Transplant 2003;18:245–248.

17. Appel GB, D'Agati VD. Primary and Secondary (Non-Genetic) Causes of Focal and Segmental Glomerulosclerosis. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 218-230.

18. D'Agati V. Pathologic classification of focal segmental glomerulosclerosis. Seminars in Nephrology 2003;23:117.

19. Reidy K, Kaskel FJ. Pathophysiology of focal segmental glomerulosclerosis. Pediatric Nephrology 2007;22(3):350-354.

20. Zhang A, Huang S. Progress in Pathogenesis of Proteinuria. International Journal of Nephrology 2012; Article ID 314251: 14 pages.

21. Papeta N, Kiryluk K, Patel A, Sterken R, Kacak N, Snyder HJ, et al. G. APOL1 Variants Increase Risk for FSGS and HIVAN but Not IgA Nephropathy. Journal of the American Society of Nephrology 2011;22(11):1991–1996.

22. Kronenberg F. APOL1 variants and kidney disease. There is no such thing as a free lunch. Nephrology Dialysis Transplant 2011;0:1–4.

23. Salant DJ, Cattran DC. Membranous Nephropathy. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 5th ed. Philadelphia: Elsevier Saunders; 2015. p. 239-252.

24. Naicker S. Patterns of renal disease in South Africa. Nephrology 1998;4(Suppl.2):S21–S24.

25. Naicker S. End stage renal disease in sub Saharan and South Africa. Kidney International Suppl 2003;83:S119-S122.

26. Gold CH, Isaacson C, Levin J. The pathological basis of end stage renal disease in Blacks. South African Medical Journal 1982;61:263-265.

27. Jansen van Rensburg BW, van Staden AN, 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 Transplant 2010;25:820–824.

28. 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 Transplant 2010;1:1-9.

29. Kibukamusoke JW. Kidney disease in the tropics. East Africa Medical Journal 1968;45:632–637.

30. Naicker S. End stage renal disease in Sub Saharan. Ethnicity & Disease 2009;19(Suppl 1):13-1.

31. Nadium WK, Abdelwahab HH, Ibrahim MA, Shigidi MM. Histological pattern of primary glomerular diseases among adult Sudanese patients: A single center experience. Indian Journal of Nephrology 2013; 23(3):176-179.

32. U.S. Renal Data System, USRDS 2010 Annual Data Report: Atlas of chronic kidney disease and end-stage renal disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.

33. Pesce F, Schena FP. Worldwide distribution of glomerular diseases: the role of renal biopsy registries. Nephrology Dialysis Transplant 2010;25:334–336.

34. Polito MG, de Moura LA, Kirsztajn GM. An overview on frequency of renal biopsy diagnosis in Brazil: clinical and pathological patterns based on 9617 native kidney biopsies. Nephrology Dialysis Transplant 2010;2:490-496.

35. Swaminathan S, Leung N, Lager DJ, Melton LJ III, Bergstralh EJ, Rohlinger A, Fervenza FC. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. Clinical Journal of the American Society of Nephrology 2006;1:483–487.

36. Jeganathan J, Kumar S, Khalid M, Maroli C. Pattern of glomerular diseases in a tertiary care center in South India: A prospective study. Saudi Journal of Kidney Diseases and Transplantation 2013;24(1):168-171.

37. Korbet SM. Nephrology and the Percutaneous Renal Biopsy: A procedure in jeopardy of being lost along the way. Clinical Journal of the American Society of Nephrology 2012 October 05;10:1545-1547.

38. Corapi KM, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. American Journal of Kidney Diseases 2012;60(1):62-73.

39. Chung S, Koh ES, Kim SJ, Yoon HE, Park CW, Chang Y, Shin SJ. Safety and tissue yield for percutaneous native kidney biopsy according to practitioner and ultrasound technique. BioMed Central Nephrology 2014;15:96.

40. Whittier WL, Korbet SM. Renal biopsy: update. Current opinion in Nephrology & Hypertension 2004;13(6):661-665.

41. Agarwal SK, Sethi S, Dinda AK. Basics of kidney biopsy: A nephrologist's perspective. Indian Journal of Nephrology 2013 Jul-Aug;23(4):243-252.

42. Topham PS. Renal biopsy. In: Johnson R, Feehally J, Floege J. Comprehensive Clinical Nephrology. 3rd ed. Philadelphia, PA: Mosby Elsevier; 2007, pp. 69–75.

43. Das U, Dakshinamurty KV, Prayaga A. Pattern of biopsy-proven renal disease in a single center of south India: 19 years experience. Indian Journal of Nephrology 2011 Oct-Dec;21(4):250–257.

44. Vermeulen A. A review of patterns of renal disease at Chris Hani Baragwanath Academic Hospital from 1982 to 2011 [dissertation]. Johannesburg: Wits University; 2014. Available at: http://hdl.handle.net/10539/15463

45. Khanna R. Clinical presentation & management of glomerular diseases: Hematuria, nephritic & nephrotic syndrome. Missouri Medicine 2011 Jan-Feb;108(1):33-6.

46. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Annals of Internal Medicine 1999;130:461-470.

47. Dawood AR, Al Shaaili K, Al Bulushi Y, Al Dhahli A, Date A. The spectrum of Glomerular Diseases on Renal Biopsy: Data from a single tertiary center in Oman. Oman Medical Journal 2013;28(3):213-215.

48. Hsiao K, Lian J, Wu S, Hung T, Lin C, Wen M *et al*. Ten year registry of native kidney biopsy from a single centre in Taichung. Acta Nephrologica 2012;26(2):68-73.

49. Wadee S, Tikly M, Hopley M. Causes and predictors of death in South Africans with

systemic lupus erythematosus. Rheumatology 2007;46: 1487-91.

50. Abdou N, Boucar D, Fary KAEH, Mouhamadou M, Abdoulaye L, Mourtala KAM, *et al*. Histopathological profiles of nephropathies in Senegal. Saudi Journal of Kidney Diseases and Transplantation 2003;14(2):212-214.

51. Aatif T, Maoujoud O, Montasser D, Benyahia M, Oualim Z. Glomerular diseases in the Military Hospital of Morocco: Review of a single center renal biopsy database on adults. Indian Journal of Nephrology 2012; 22(4):257-263.

52. Mubarak M, Kazi JI, Naqvi R, Ahmed E, Akhter F, Naqvi SAA *et al*. Pattern of renal diseases observed in native renal biopsies in adults in a single centre in Pakistan. Nephrology 2011;16:87-92.

53. Rivera F, López-Gómez JM, Pérez-García R. Frequency of renal pathology in Spain 1994-1999. Nephrology Dialysis Transplant 2002;17:1594-1602.

54. Barsoum RS, Francis MR. Spectrum of glomerulonephritis in Egypt. Saudi Journal of Kidney Diseases and Transplantation 2000;11:421-429.

55. Mesquita M, Fosso C, Bakoto Sol E, Libertalis M, Corazza F, Vandenhoute K, *et al*. Renal biopsy findings in Belgium. A retrospective single centre analysis. Acta Clinica Belgica 2011;66(2):104-109.

56. Wirta O, Mustonen J, Helin H, Pastermack A. Incidence of biopsy- proven glomerulonephritis. Nephrology Dialysis Transplant 2008;23:193-200.

57. Gesulado L, Palma AMD, Morrone LF, Strippoli GF, Schena FP. The Italian experience of the national registry of renal biopsies. Kidney International 2004;66:890-894.

58. Simon P, Ramee MP, Boulahrouz R, Stanescu C, Charasse C, Ang KS *et al*. Epidemiologic data of primary glomerular diseases in Western France. Kidney International 2004;66:905-908.

59. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S *et al*. Japan Renal Biopsy Registry: the first nationwide, web based and prospective registry system of

renal biopsies in Japan. Clinical and Experimental Nephrology 2011;15:493-503.

60. Arias LF, Henao J, Giraldo RD, Caarvajal N, Rodelo J, Arbelaez M. Glomerular diseases in a Hispanic population: review of a regional renal biopsy database. Sao Paulo Medical Journal 2009;127(3):140-144.

61. Briganti EM, Dowling J, Finlay M, Hill PA, Jones CL, Kincaid-Smith PS, *et al*. The incidence of biopsy proven glomerulonephritis in Australia. Nephrology Dialysis Transplant 2001;16:1364-1367.

62. Chang JH, Kim HW, Park SY, Yoo T, Kim BS, Kang SW *et al*. Changing prevalence of glomerular diseases in Korean adults: a review of 20 years of experience. Nephrology Dialysis Transplant 2009;24:2406-2410.

63. Ossareh S, Asgari M, Abdi E, Nejad- Gashti H, Ataipour Y, Aris S *et al.* Renal biopsy findings in Iran: case series report from a referral kidney centre. International Urology and Nephrology 2010;42:1031-1040.

64. Brenner BM, Garcia DL, Anderson S. Glomeruli and blood pressure. Less of one, more the other? American Journal of Hypertension 1988; 1: 335–347.

65. Statistics South Africa. 2013. South African midyear Statistics 2013 statistical release P0302. Available: www.statssa.gov.za/publications/P0302/P03022013.pdf. [Accessed 2 November 2015]

66. Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, Ping A *et al*. APOL1 Genetic Variants In Focal Segmental Glomerulosclerosis and HIV Associated Nephropathy. Journal of the American Society of Nephrology 2011;11:2129-2137.

67. Korbet S. Treatment of Primary FSGS in Adults. Journal of the American Society of Nephrology 2012;23(11):1769-1776.

68. Waldman M, Crew JR, Valeri A, Busch J, Stokes B, Markowitz G *et al*. Adult Minimal change disease: Clinical characteristics, treatment and outcomes. Clinical Journal of the American Society of Nephrology. 2007;2:445-453.

69. Hao X, Liu X, Wang W, Ren H, Xie J, Shen P *et al*. Distinct Metabolic Profile of

Primary Focal Segmental Glomerulosclerosis Revealed by NMR-Based Metabolomics. PLoS ONE 2013;8(11): e78531.

70. Moranne O, Watier L, Rossert J, Stengel B. Primary glomerulonephritis: an update on renal survival and determinants of progression. The GN-Progress Study Group – QJM 2008;101(3):215-224.

71. Murphy WG. The sex difference in haemoglobin levels in adults — Mechanisms, causes, and consequences. Blood Reviews 2014;28(2):41 – 47.

72. Al Wakeel JS, Mitwalli AH, Tarif N, Alam AA, Hammad D, Abu-Aisha H *et al*. Spectrum and Outcome of Primary Glomerulonephritis. Saudi Journal of Kidney Diseases and Transplantation 2004;15:440-6.

73. Fogazzi GB, Saglimbeni L, Banfi G, Cantu M, Moroni G, Garigali G *et al*. Urinary sediment features in proliferative and non-proliferative glomerular diseases. Journal of Nephrology 2005;18:703-710.

74. Grossfeld GD, Wolf JS Jr, Litwan MS, Hricak H, Shuler CL, Agerter DC *et al*. Asymptomatic Microscopic Hematuria in Adults: Summary of the AUA Best Practice Policy Recommendations. American Family Physician 2001;63:1145-54.

75. Verdesca S, Brambilla C, Garigali G, Croci MD, Messa P, Fofazzi GB. How a skillful and motivated urinary sediment examination can save the kidneys. Nephrology Dialysis Transplant 2007;22:1778–1781.

APPENDICES

Data Collection Sheet - PRIMARY GLOMERULAR DISEASE

Patient reference number ☐

Age ☐ **Blood pressure** ☐

Sex Male ☐ Female ☐

Race White ☐ Coloured ☐ Indian ☐ Black ☐ Asian ☐

Indication for biopsy

Nephrotic range proteinuria ☐

Sub nephrotic range proteinuria ☐

Nephritic features ☐

Nephrotic / nephritic features ☐

Abnormal urinary sediment ☐

Unexplained renal dysfunction ☐

Lupus nephritis ☐

Serum Parameters at biopsy

Creatinine	☐	eGFR	☐	WCC	☐
Cholesterol	☐	Triglyceride	☐	ANA	☐
Albumin	☐	hB	☐		

Urine parameters

White cell count

Dysmorphic red cell

Protein: creatinine ratio

Urine casts

Hyaline casts ☐

White cell casts ☐

Red cell casts ☐

Granular casts ☐

Waxy casts ☐

Other ☐

Other

SLE ☐ DM ☐ HT ☐ HIV ☐ HBV ☐ HCV ☐

Biopsy findings

Ig A Nephropathy ☐

Minimal Change Disease ☐

Focal Segmental Glomerulosclerosis ☐

Membranous Nephropathy ☐

Membranoproliferative GN ☐

Crescentic GN ☐

Idiopathic diffuse proliferative GN ☐

Mesangial proliferative GN ☐

Interstitial nephritis ☐

Acute tubular necrosis ☐

Other ☐

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Yvette Patchapen

CLEARANCE CERTIFICATE	**M121146**
PROJECT	A Retrospective Study Evaluating the Patterns of Primary Glomerular Disease at CM Johannesburg Academic Hospital
INVESTIGATORS	Dr Yvette Patchapen.
DEPARTMENT	Department Internal Medicine/Renal Unit
DATE CONSIDERED	30/12/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 30/11/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr Malcolm Davies

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

FACULTY OF HEALTH SCIENCES
DEPARTMENT OF INTERNAL MEDICINE
Division of Nephrology

7 York Road, Parktown, 2193.Johannesburg, South Africa

Telephone +27 11 4883621
Fax +27 11 4884799

22 October 2012

The Human Research Ethics Committee
University of the Witwatersrand

Re: Dr Yvette Patchapen: Permission to do MMed study "A retrospective study evaluating the patterns of primary glomerular disease at Charlotte Maxeke Johannesburg Academic Hospital"

Dr Yvette Patchapen is hereby given permission to undertake her research at the Division of Nephrology at the Charlotte Maxeke Johannesburg Academic Hospital.

Thank you

Yours sincerely

PROFESSOR S NAICKER

Academic Head, Dept of Internal Medicine
Head, Division of Nephrology
MB ChB (Natal), MRCP (UK), FRCP (London), FCP (SA), PhD (Natal)
Tel/Fax 011 4884799
email: Saraladevi.Naicker@wits.ac.za

NATIONAL HEALTH LABORATORY SERVICE
UNIVERSITY OF THE WITWATERSRAND – JOHANNESBURG

SCHOOL OF PATHOLOGY
Division of Anatomical Pathology

P.O. Box 1038, Johannesburg 2000
Tel : +27-11-489-8477
+27-11- 489-8479
Fax:+27-11-489-8512

Division of Anatomical Pathology
Faculty of Health Sciences
York Road
Parktown e-mail : martin.hale@nhls.ac.za

Professor MJ Hale MBChB (Rhodesia) FCPath (SA). LRCP, LRCS, LRCP&S (Edinburgh & Glasgow)
Professor & Head: Division of Anatomical Pathology.

Human Research Ethics Committee (Medical)
University of the Witwatersrand
Johannesburg
20000

November 26, 2012

Re: Consent for access to NHLS database

This letter serves to confirm that the Department of Anatomical Pathology at the University of the Witwatersrand and NHLS is happy to assist Dr Patchapen with her study entitled "A retrospective study evaluating the patterns of primary glomerular disease at Charlotte Maxeke Johannesburg Academic Hospital".

Notwithstanding the requirement that MMed projects should comprise the researchers work only, it is recognized that publication of such work is encouraged. In the event that the information used co-mprises the diagnosis only then joint authorship from a member of staff in the Department of Anatomical Pathology would not be expected. However should additional information be extracted from the report for purposes of further interpretation such as morphological details and immunohistochemical profiles, it would be expected that this would be done in conjunction with a member of staff in the Department of Anatomical Pathology and that joint authorship would follow in resulting publications. Dr Patchapen will be in contact with the Department of Anatomical Pathology in respect of this.

Assuring you of the Department of Anatomical Pathology's co-operation in this and future research projects.

With best wishes.

Yours sincerely,

Professor MJ Hale
Head: Department of Anatomical Pathology

26th November 2012.
Date

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Office of the CEO
Enquiries:
Ms. L. Mngomezulu
(011): 488-3793
(011) 488-3753
11th December 2012

Dr. Yvette Patchapen
Department of Internal Medicine
University of Witwatersrand

Dear Dr. Patchapen

RE: "a retrospective study evaluating the patterns of primary glomerular disease at Charlotte Maxeke Johannesburg Academic Hospital"

Permission is granted for you to conduct the above research as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic hospital will not in anyway incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall be observed at all times.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the Head of Department and Unit Manager or Sister in Charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Yours sincerely

Dr. T.E. Selebano
Chief Executive Officer