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A Review of the Patterns of Clinical Presentation, Histopathological Classes and Outcomes of Lupus Nephritis Patients at Helen Joseph Hospital

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A REVIEW OF THE PATTERNS OF CLINICAL PRESENTATION, HISTOPATHOLOGICAL CLASSES AND OUTCOMES OF LUPUS NEPHRITIS PATIENTS AT HELEN JOSEPH HOSPITAL

SARISHA RAJOO, MBCHB

A research report submitted to the Faculty of health science, University of the Witwatersrand, in fulfilment for the requirements for the degree of Master of Medicine

2023

Declaration

I, Sarisha Rajoo, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature: 

02 Day of September 20 23 in Johannesburg.

Acknowledgments

I would like to thank my supervisors, Dr Malcolm Davies and Dr Zaheera Cassimjee for their guidance and time given, without which this project would not have been possible.

Abstract

Background

Lupus nephritis (LN) is a significant factor in the burden of secondary glomerular disease in South Africa. It can be the presenting feature of SLE, carrying a worse prognosis in people of African descent. Early identification and treatment are required to meaningfully affect patient outcome. This study aimed to evaluate the potential of presenting features in identifying patients at risk for adverse lupus nephritis outcomes.

Methods

A retrospective review of biopsy-proven LN diagnosed over a 10 year period at Helen Joseph Hospital was undertaken. Clinical, histopathology and renal outcomes data was extracted from 48 patient records. The variables were tested with logistic regression and general discriminant analysis. Kaplan-Meier survival curves of renal outcomes were compared using Cox-Mantel F test. Effect of clinical and histological parameters on renal outcomes was determined by multifactorial Cox and multifactorial linear regression.

Results

72.7% of patients were of Black African ancestry with median age at diagnosis of 26.5 years. The majority of lesions were proliferative LN (66%);class III was most common (25.5%). Proliferative lesions were associated with higher creatinine (p=0.007); an eGFR below 90mL/min/1.73m^2 increased the odds of proliferative LN (OR=5.60; CI 1.06-29.59; p=0.043). Proliferative LN was associated with a trend towards poorer renal outcomes (p=0.057); higher baseline eGFR was associated

with better preserved kidney function at follow up (p=0.003). Baseline urine WCC was inversely related to eGFR and directly related with creatinine at follow up (p=0.041 and p=0.001 respectively)

Conclusion

The present study demonstrates a possible role for baseline eGFR and leukocyturia in predicting the presence of proliferative LN. Since proliferative LN is associated with poorer kidney survival, these investigations may identify patients likely to benefit from empiric high-dose immunosuppression when access to biopsy confirmation may be delayed.

Table of Contents

	Page
Declaration	ii
Acknowledgement	iii
Abstract	iv
List of Figures	viii
List of Tables	ix
Abbreviations	1
Chapter 1: Protocol with extended literature review	3
1.1 Background	3
1.1.1Introduction	3
1.1.2Epidemiology	3
1.1.3Classification	4
1.1.4 Pathophysiology	5
1.1.5 Diagnosis	6
1.1.6 Therapy	8
1.1.7 Summary	10
1.2 Methodology	11
1.2.1 Study design	11

1.2.2 Aim **11**

1.2.3 Objectives **11**

1.2.4 Data Collection **12**

1.2.5 Statistical Analysis **15**

1.3 Ethics **18**

1.4 Timing **19**

1.5 Funding **20**

1.6 Limitations **21**

1.7 References **22**

Chapter 2: Article **26**

Chapter 3: Appendix **48**

List of Figures

	Page
Figure 1: Survival of kidney function	**44**

List of tables

Page

Table 1: Presenting clinical parameters and histological patterns of LN in sample population in terms of WHO/ISN classification and proliferative and non-proliferative LN **39**

Table 2: Comparison of demographic and clinical parameters between proliferative and non-proliferative lupus nephritis **40**

Table 3: Stepwise logistic regression for probability of proliferative lesion **41**

Table 4: Cox proportional hazards model, time to remission **42**

Table 5: Association of clinical and histological parameters with residual kidney dysfunction **43**

Abbreviations

ANCA: Antineutrophil Cytoplasmic Antibodies

APLS: Anti Phospholipid Syndrome

APOL1: Apolipoprotein L1

BP: Blood Pressure

CKD: Chronic Kidney Disease

dsDNA: double stranded Deoxyribonucleic Acid

GFR/eGFR: (estimated) Glomerular Filtration Rate

HIV: Human Immunodeficiency Virus

HJH: Helen Joseph Hospital

HREC: Human Research Ethics Committee

IC: Immune Complexes

ISN: International Society of Nephrology

KDIGO: Kidney Disease Improving Global Outcomes

KF: Kidney Failure

LN: Lupus Nephritis

MMF: Mycophenolate Mofetil

NHLS: National Health Laboratory Services

NSAID: Non-Steroidal Anti-inflammatory Drug

ROPD: Renal Outpatient Department

RNP: Ribonucleoproteins

SLE: Systemic Lupus Erythematosus

TMA: Thrombotic Microangiopathy

UPCR: urine Protein: Creatinine Ratio

WHO: World Health Organization

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1. BACKGROUND

1.1.1 Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune-driven multi-systemic inflammatory illness[1]. Although the precise pathophysiology remains uncertain, a genetic predisposition combined with environmental triggers are believed to result in a loss of self-tolerance[2]. This facilitates target organ damage through cellular and auto-antibody mediated immunological injury[3], thus giving rise to the clinical syndrome of SLE.

Targeting of the kidney in SLE arises due to a combination of factors. These include genetic predisposition, pattern of organ involvement, and type of autoantibody generated[4]. Kidney involvement is a common manifestation early in the disease[1]; affecting up to 80% of SLE patients during the course of their illness, and is an important predictor of morbidity and mortality in SLE[5-8]. Additionally, lupus nephritis (LN) is a significant contributor to the burden of secondary glomerular disease in the South African context[9].

The hallmark of kidney disease in SLE is the presence of persistent proteinuria of more than 0.5g per 24 hours or red cell casts[6], although LN may manifest anywhere on the spectrum of “mild asymptomatic proteinuria” to “rapidly progressive glomerulonephritis”. Early diagnosis is vital to meaningfully affect patient outcome[10].

1.1.2 Epidemiology

The incidence of SLE in the general population is approximately 2-5 per 100 000 per annum, with the incidence of SLE and LN being greater in the Black population[11].

The prevalence of SLE is greatest amongst young females, particularly of African ancestry living outside the tropics, in whom the disease carries a poorer prognosis[12]. Higher prevalence of LN has been demonstrated in African-Americans and European-Africans compared to Caucasians[13].

In the local South African context, LN is a prevalent cause of secondary glomerular disease, with one study showing a prevalence of 39%[9]. Females under the age of 30 constitute the majority of LN patients, and LN lesions appear to be more severe in the Black African population[7]. Apolipoprotein L1 (APOL1) risk alleles, which are known to be an important factor in the development of chronic kidney disease (CKD) and kidney failure (KF) in Black African patients, may contribute to the risk of LN progression in this population[2].

1.3 Classification

The histopathological lesions of LN are currently classified in accordance with the International Society of Nephrology (ISN) and Renal Pathology Society systems, originally devised in 2003[6]. The six classes are as follows:

1. Minimal mesangial lupus nephritis
2. Mesangial proliferative
3. Focal lupus nephritis, involving <50% of glomeruli
4. Diffuse segmental or diffuse global lupus nephritis, involving >50% of glomeruli
5. Membranous lupus nephritis
6. Advanced, sclerosing lupus nephritis

Class V may occur in combination with classes III or IV, termed “mixed”, or independently, which carries a more favourable prognosis[14]. The proliferative classes III and IV follow a more aggressive course and tend to occur more frequently than the non-proliferative classes[6,15].

1.1.4 Pathophysiology

The various patterns of glomerular injury arise in response to the nature of immunological injury occurring in the individual patient afflicted with SLE. Immune complexes (IC), which form in-situ within the glomerulus due to the binding of autoantibody with self-antigens, result in complement activation, leading to the recruitment of the cellular arm of the immune response[16]; thus, the glomerulus sustains assault from both direct complement and complement-independent antibody-mediated cytotoxicity, as well as from cell-mediated cytotoxicity. The site of deposition of these IC is critical in determining the site of immunological injury and hence the histological pattern observed in LN; mesangial deposition only favouring mesangial forms of LN (ISN class I or II), sub-endothelial deposition favouring proliferative LN (class III or IV), and sub-epithelial (below the podocyte) favouring a podocytopathy (class V). The pattern of injury observed on light microscopy in turn influences the clinical presentation; thus, class V (podocyte injury) typically presents with nephrotic syndrome, whereas class III and IV (endothelial injury) are more likely to present with nephritic syndrome. Regardless of the original pattern of injury, if left untreated a secondary podocytopathy can occur with progressive development of glomerular sclerosing lesions, manifesting in progressive decline in glomerular filtration rate (GFR) and eventual KF (LN class VI)[2]. The severity of immunological injury, as evidenced by the histological pattern (LN class), is to some degree

predictive of the risk of progression to KF. The treatment strategy prescribed for LN therefore varies depending on the likelihood of progression to KF as determined by the LN class observed.

Although rarely occurring without concomitant glomerular injury, other mechanisms of kidney injury may also be seen in SLE. Thrombotic microangiopathy (TMA), which may be a manifestation of antiphospholipid syndrome (APLS), is frequently found at biopsy in lupus patients. Rarer manifestations of lupus-associated kidney disease include isolated renal vasculitis and isolated interstitial nephritis. Drugs prescribed for the treatment of SLE and its clinical manifestations, such as non-steroidal anti-inflammatories (NSAIDs) and methotrexate, may also result in further kidney assault in patients with SLE[2].

1.1.5 Diagnosis

Percutaneous kidney biopsy remains the gold standard to confirm the diagnosis of LN, and to determine the class of LN and hence the risk of progression to KF, thus facilitating appropriate therapy prescription based on directly observed immunological injury patterns[17]. South Africa is a resource limited nation, and procedures such as native kidney biopsy are relatively restricted, being available only in some facilities[9]. In addition, the accurate interpretation of biopsy histological patterns rests upon the availability of suitably skilled pathologists. Thus, clinical and biochemical features of kidney involvement in SLE which may be predictive of the underlying histopathology are an important area of study in order to optimize the use of the scarce resource of kidney biopsy and facilitate appropriate empiric therapy.

Whereas nephrotic-range proteinuria is the most common indication for kidney biopsy across all kidney disease[9], LN may present with sub-nephrotic-range

proteinuria and microhaematuria; proliferative glomerular lesions (ISN class IV and III) are not uncommon in this setting[16,18,19], highlighting the potential discord between clinical manifestations and severity of histopathological lesion[19].

In view of the lack of correlation between urine findings and histological lesions, resort has been made to the use of other parameters as predictors of the severity of histological injury in LN. Systemic hypertension in SLE, for example, has been associated with proliferative LN lesions and more severe kidney function impairment, and has been shown to carry an increased risk of progression to KF[12,15,20,21].

Reflecting the extent of autoimmune activity, hypocomplementaemia, hypoalbuminaemia and positive anti-dsDNA antibody have also been associated with proliferative LN, with low C3 being associated with poorer renal outcome[12]. ANCA is uncommon in LN, however the presence of this antibody has been associated with the histological presence of necrotising glomerulonephritis with glomerular crescents, resulting in rapidly progressing kidney dysfunction in association with significant haematuria[22]. Of note, anti-Ro, anti-RNP and anti-Smith antibodies are most prevalent in Black African patients diagnosed with LN; a population which is often afflicted with the most severe LN histopathological lesions[11] resulting in an aggressive clinical course and increased likelihood of KF[7]. These observations suggest a correlation between serology and severity of lupus nephritis.

In addition to African race, other factors, such as age greater than 30 years, haematocrit less than 26% and serum creatinine more than 212 μmol/L at baseline have been found in other series to confer a poorer prognosis[17,23].

1.1.6 Therapy

Consensus on the appropriate management of severe LN is lacking[24]. In general, immunosuppressive therapy is prescribed in consideration of the class of the glomerular lesion, with more potent therapy being reserved for use in patients with proliferative injury[6].

In such cases of proliferative LN, therapy is typically divided into induction and maintenance phases. The duration of the induction phase is usually 6 months[6]:

1. Pulsed intravenous methylprednisolone for 3 days followed by oral prednisone, weaned over 6 months
2. Intravenous cyclophosphamide or oral mycophenolate mofetil (MMF)

Following induction, therapy is de-escalated to a maintenance phase, with the most commonly used agents being MMF, azathioprine and steroids. Calcineurin inhibitors may be used in cases of persistent significant proteinuria[6].

Membranous LN (class V), if persistently nephrotic, is treated with corticosteroids in addition to either MMF, cyclophosphamide, calcineurin inhibitors or less commonly azathioprine[6].

In addition to the immunosuppressive mainstay of therapy, adjunctive therapy includes[6]:

1. Angiotensin blocking agents (prescribed for beneficial effects on blood pressure (BP) and proteinuria)
2. Chloroquine: for the pleiotropic effects on dermatological lesions, APLS complications, reduction of cardiovascular disease and improved glycaemic profile[25]. Additionally, patients treated with anti-malarial agents have reduced overall disease activity, and protection from kidney damage[14].

3. HMG-CoA reductase inhibitors (statins) for lipid-lowering effects and anti-proteinuric effects

4. Low dose acetylsalicylic acid (in the case of confirmed secondary APLS)

5. Tuberculosis (with isoniazid) and *Pneumocystis Jiroveci* (with cotrimoxazole) prophylaxis in patients on high potency immunosuppression at risk of these infections

6. Protection against bone side-effects of long-term steroid use, using agents such as Vitamin D and calcium supplementation.

Response to therapy is monitored by serial measurement of kidney function, proteinuria, and through the analysis of urinary sediment for active inflammation. Remission, as defined by KDIGO, is the stabilization or improvement of kidney function, normalization of proteinuria to levels below 300mg per 24 hours, and resolution of active urinary sediment. Failure to achieve remission indicates ongoing tissue damage and is strongly associated with the development of KF[14,21,26]. Thus, inadequate response to therapy should prompt consideration for a switch in immunosuppressive agents or the addition of other drugs, such as rituximab or calcineurin inhibitors; in refractory cases with rapidly deteriorating kidney function, augmented immunosuppression with intravenous immunoglobulin or plasma exchange may be appropriate[6]. Decisions regarding alterations in prescribed immunosuppression regimen may be facilitated by repeat biopsy which allows accurate assessment of disease progression[27]. Features predictive of a good response to therapy include Caucasian race and lower baseline serum creatinine; Black patients and those presenting with nephrotic syndrome tend to experience a poorer response to therapy[11,12].

1.1.7 Summary

In conclusion, LN is a significant contributor to the prevalence of kidney disease in South Africa and is an important determinant of the burden of morbidity and mortality in SLE patients. The ability to identify affected patients at risk of developing aggressive disease early in the course of their illness so as to ameliorate outcomes and prevent the need for chronic renal replacement therapy would be of benefit not only to the individual patient but also to the health care system, particularly since a significant proportion of the South African population has limited access to specialist nephrology services. This study aimed to analyse the patterns of presentation of LN in terms of clinical features, serology and histopathology, and to determine the effects of these parameters on treatment outcomes.

1.2 METHODOLOGY

1.2.1 Study design

This is a retrospective review of all patients diagnosed with biopsy-proven lupus nephritis receiving treatment at the Renal Outpatient Department (ROPD) at Helen Joseph Hospital (HJH) during the period 1 January 2008 – 31 December 2017. The study contains descriptive and inferential elements.

1.2.2 Aim

To describe the clinical presentation, histopathological class, and outcome of a sample population of 48 lupus nephritis patients attending the renal clinic at Helen Joseph Hospital between 1 January 2008 and 31 December 2017.

1.2.3 Objectives

Primary objective

1. To determine the pattern of clinical presentations of the various lupus nephritis histological categories with specific reference to the following parameters:

    i. Age

    ii. Sex

    iii. Race (self reported)

    iv. Cholesterol

    v. Presence or absence of hypertension

    vi. Serum albumin

vii. Creatinine

viii. Glomerular filtration rate

ix. Urine protein:creatinine ratio (UPCR)

x. Presence or absence of active urinary sediment

xi. Autoimmune serology and titre

xii. C3 and C4 level

Secondary objectives

2. To determine the frequency of the various lupus nephritis histopathological categories as described by the WHO (World Health Organization)/ISN classification system, further subcategorizing the lesion into proliferative and non-proliferative types.

3. To assess for any association between the clinical presentation as described by the above parameters (1.2.3) and the histopathological category of LN

4. To determine the effect of clinical presentation parameters and histological lesion on outcomes, including kidney and patient survival, time to first lupus nephritis relapse, and residual kidney dysfunction as measured by most recent creatinine and eGFR

1.2.4 Data collection

Inclusion criteria

All adult patients diagnosed with lupus nephritis by means of native kidney biopsy during the study period were considered for inclusion in the study.

Exclusion criteria:

The following patients were excluded from the study:

1. Patients under the age of 18 years old at time of diagnosis
2. Patients with Human Immunodeficiency Virus (HIV) infection at time of diagnosis of lupus nephritis
3. Patients diagnosed with overlap syndrome
4. Patients with biopsy-proven lupus nephritis where clinical data from the time of diagnosis by means of biopsy was unobtainable
5. Patients in whom the diagnosis of lupus nephritis was made at another institution

Data extraction

Data pertaining to clinical and histological parameters was extracted from all included patients from time of presentation to the renal unit; outcomes data was only extracted for those patients with a minimum period of follow-up at the time of data collection of 12 months.

Data was collected for the following parameters:

1. Demographics (sex, age, race)
2. Total cholesterol
3. Serum creatinine and GFR
4. UPCR
5. Urinalysis

6. Serum albumin

7. Autoimmune serology (antibody type and titre)

8. C3 and C4 level

9. Presence or absence of hypertension and systolic BP reading,

10. WHO / ISN LN histological class

11. Type of immunosuppression regime prescribed

12. Renal outcome:

    - Complete remission with stable kidney function (as defined by KDIGO): the stabilization or improvement of kidney function, normalization of proteinuria to levels below 300mg per 24 hours, and resolution of active urinary sediment

    - Partial remission (as defined by KDIGO): the stabilization or improvement of kidney function, with inactive urinary sediment, and a 50% improvement in proteinuria to below nephrotic range levels

    - Ongoing treatment

    - Loss of kidney function, as defined by the development of an eGFR of less than 15ml/min/1.73m^2 or the documented presence of uraemic syndrome symptoms warranting consideration for the initiation of long-term renal replacement therapies.

13. Time to renal outcome (in months)

14. Time to first relapse (months): as defined by an increase in proteinuria from previously documented complete remission levels to nephrotic range, worsening serum creatinine (eGFR that is below expected level for age/clinical history or declining eGFR, KDIGO) or abnormal urinary sediment, or evidenced by the decision to subject the patient to re-biopsy.

15. most recent creatinine and eGFR and time to this measurement

Patients were identified by retrospective review of ROPD files. Data from patients deemed suitable for inclusion in this study was extracted from patient files and cross-referenced with the National Health Laboratory Services (NHLS) electronic platform and biopsy registers at the department of anatomical pathology in respect of the parameters outlined above and used to populate an Excel spreadsheet. Patient confidentiality was maintained through the deletion of patient names and substitution thereof with study numbers.

1.2.5 Statistical analysis

Statistica v 13.5 (Tibco) was used for statistical analysis. Continuous variables were subjected to interrogation of distribution using the Shapiro Wilk W test and through visual inspection of the histogram plot. Parametric variables were, in subsequent analyses, compared using the Student t-test and non-parametric variables were analysed using the Mann Whitney U test; the central and dispersion measurements were presented as means and standard deviations, or medians and interquartile range, respectively. Categorical data was compared using the Fischer Exact or Pearson's Chi-square tests as appropriate. Survival analysis between proliferative / non-proliferative groups was performed using Kruskall Wallis survival plot; statistical significance of any observed difference was tested using the Grehan F test. The

effect of multiple factors on an outcome over time was modelled using multifactorial Cox regression analysis. The effect of multiple factors on residual kidney dysfunction as measured by most recent creatinine and eGFR was modelled using multifactorial linear regression. For the purposes of determining statistical significance α was be set at 0.05.

Arising from the study aims and objectives the following analyses were undertaken:

1. The clinical picture of lupus nephritis as an entity was described in terms of:

- Demographics of the affected population (age, gender, and race distributions)
- The presentation of lupus nephritis within the affected population (creatinine, eGFR, albumin, UPCR, active / inactive urinary sediment, total serum cholesterol, antibody type and titre, C3 and C4 levels, presence or absence of hypertension and systolic BP reading)

2. The histological patterns of glomerular disease in the affected population was described (both in terms of the WHO / ISN classification, as well as in terms of proliferative vs. non-proliferative lesions)

3. Demographic and clinical parameters were compared between WHO / ISN categories of lupus nephritis as well as between the proliferative / non-proliferative categories using parametric or non-parametric testing as indicated. Any parameter found to be of statistical significance was further tested for association with histological category using logistic regression; for continuous variables general discriminant analysis was used to determine the level of the continuous variable with significant association. The odds ratio was calculated for all variables showing association with a particular histological pattern.

4. Survival analysis curves was fitted for the proliferative and non-proliferative histology groups for the following outcomes:

- Time to remission
- Time to loss of kidney function
- Time to first relapse in cases achieving partial or complete remission

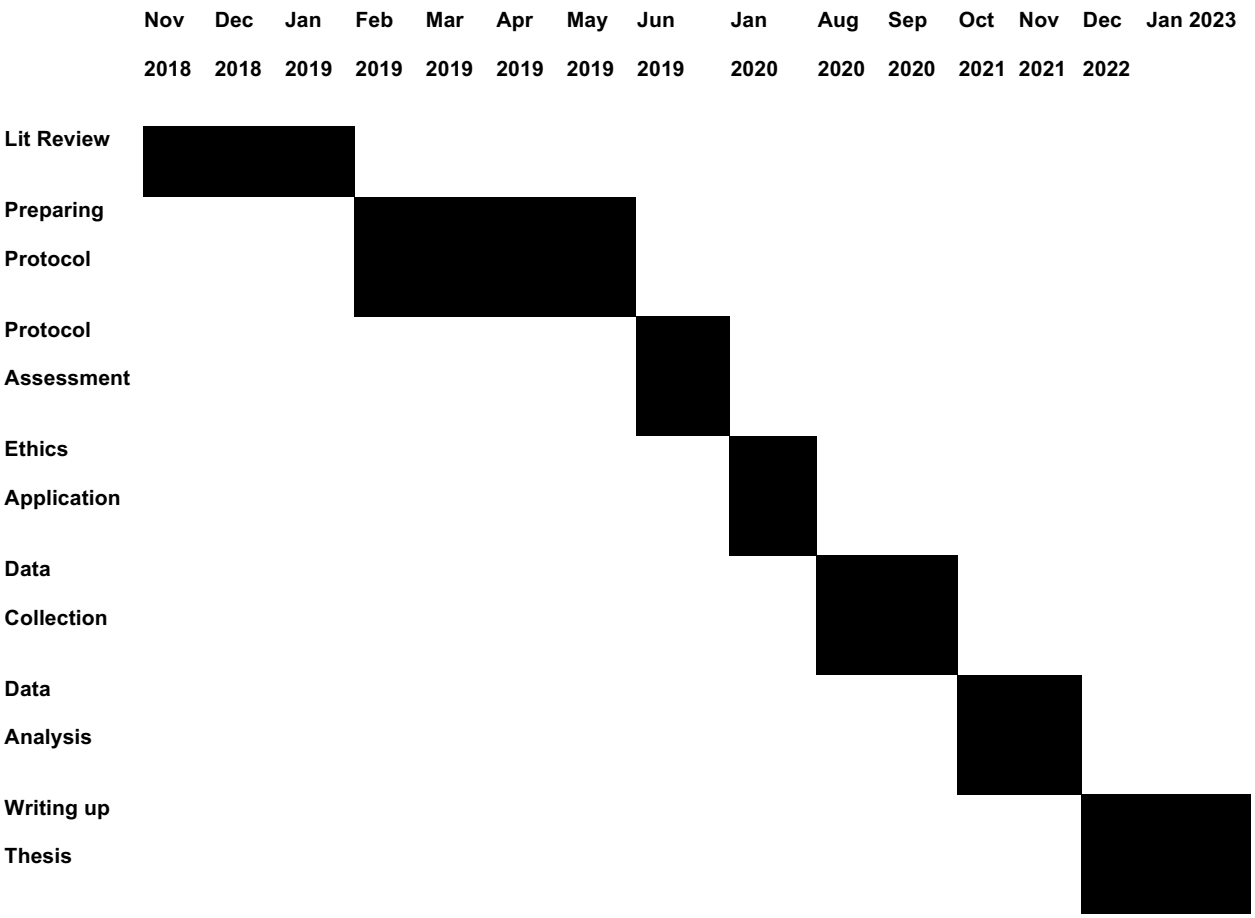
5. To determine the effect of the aforementioned clinical parameters in addition to histological injury on outcomes, multifactorial Cox regression analysis was applied to the above outcome parameters using the extracted clinical and histological parameters. The hazards ratio was calculated for clinical parameters identified as statistically significant in these analyses

6. To determine the effect of clinical and histological parameters on residual kidney dysfunction, a multifactorial linear regression model was fitted for both most recent creatinine as well as eGFR.

1.3 ETHICS

Ethics clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC). Consent for the use of patients' hospital records was obtained from the academic head of the department of internal medicine, as well as the clinical head of the renal unit and CEO of HJH. Due to retrospective data being utilized, individual consent from the patients' whose files were being studied was not required. The study was registered with the National Health Laboratories Services (NHLS) and the Academic Affairs and Research Management System (AARMS).

1.4 TIMING


Nov 2018
Dec 2018
Jan 2019
Feb 2019
Mar 2019
Apr 2019
May 2019
Jun 2019
Jan 2020
Aug 2020
Sep 2020
Oct 2021
Nov 2021
Dec 2022
Jan 2023
Lit Review
Preparing Protocol
Protocol Assessment
Ethics Application
Data Collection
Data Analysis
Writing up Thesis

1.5 FUNDING

Expenses for this project were limited due to the retrospective nature of the study. The costs of photocopying, printing and the statistical programme were covered by the investigator.

1.6 LIMITATIONS

The study was retrospective in nature and thus relied on the quality of the records kept since 2008. The study reviewed histology samples over the last 10 years, and as such, all biopsies were not reviewed by one single pathologist. This introduced a degree of inter-observer variability. Because the study is based on a specific cohort of patients attending a single centre, it was not necessarily representative of the country as a whole.

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CHAPTER 2: SUBMISSIBLE ARTICLE

A Review of the Patterns of Clinical Presentation, Histopathological Classes and Outcomes of Lupus Nephritis Patients at Helen Joseph Hospital

A research report submitted to the Faculty of health science, University of the Witwatersrand, in fulfilment for the requirements for the degree of Master of Medicine

2023

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Conflicts of Interest: None to declare

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Abstract Word Count: 285

Total Word Count: 2229

Declaration

I, Sarisha Rajoo, declare that this research report is my own, unaided work. It is being submitted for the Degree of Master of Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

Signature: 

02 Day of September 20 23 in Johannesburg .

ABSTRACT

Background

Lupus nephritis (LN) is a significant factor in the burden of secondary glomerular disease in South Africa. It can be the presenting feature of SLE, carrying a worse prognosis in people of African descent. Early identification and treatment are required to meaningfully affect patient outcome. This study aimed to evaluate the potential of presenting features in identifying patients at risk for adverse lupus nephritis outcomes.

Methods

A retrospective review of biopsy-proven LN diagnosed over a 10 year period at Helen Joseph Hospital was undertaken. Clinical, histopathology and renal outcomes data was extracted from 48 patient records. The variables were tested with logistic regression and general discriminant analysis. Kaplan-Meier survival curves of renal outcomes were compared using Cox-Mantel F test. Effect of clinical and histological parameters on renal outcomes was determined by multifactorial Cox and multifactorial linear regression.

Results

72.7% of patients were of Black African ancestry with median age at diagnosis of 26.5 years. The majority of lesions were proliferative LN (66%);class III was most common (25.5%). Proliferative lesions were associated with higher creatinine ($p=0.007$); an eGFR below 90mL/min/1.73m^2 increased the odds of proliferative LN (OR=5.60; CI 1.06-29.59; $p=0.043$). Proliferative LN was associated with a trend towards poorer renal outcomes ($p=0.057$); higher baseline eGFR was associated

with better preserved kidney function at follow up (p=0.003). Baseline urine WCC was inversely related to eGFR and directly related with creatinine at follow up (p=0.041 and p=0.001 respectively)

Conclusion

The present study demonstrates a possible role for baseline eGFR and leukocyturia in predicting the presence of proliferative LN. Since proliferative LN is associated with poorer kidney survival, these investigations may identify patients likely to benefit from empiric high-dose immunosuppression when access to biopsy confirmation may be delayed.

Introduction

Lupus nephritis (LN) is a significant contributor to the prevalence of kidney disease in South Africa[1] and an important predictor of morbidity and mortality in SLE[2-5]. Presenting on a spectrum ranging from “mild asymptomatic proteinuria” to “rapidly progressive glomerulonephritis”, early diagnosis of LN is important to meaningfully affect patient and renal outcomes[6].

Percutaneous kidney biopsy remains the gold standard for the diagnosis of LN and determination of risk of progression to KF[7]. Resource limitations in South Africa restrict native kidney biopsy to tertiary facilities with expertise in this procedure[1]. Clinical and biochemical markers may facilitate identification of individuals with aggressive disease. This could facilitate earlier referral for diagnosis and treatment, hence improving outcomes.

Hypertension, hypocomplementaemia, hypoalbuminaemia and anti-double stranded DNA (anti-dsDNA) are among the parameters that have been associated with poorer renal outcomes in LN[8-11]. African ethnicity, age greater than 30 years and elevated baseline serum creatinine levels may also confer a worse prognosis[7,12]. The utility of these parameters in the local context remain untested. Accordingly, this study was undertaken to analyze the patterns of presentation of LN in terms of clinical features, serology, and histopathology. It aimed to determine the effects of these parameters on renal outcomes.

Materials and methods

A retrospective single-centre review of all patients with biopsy-proven lupus nephritis diagnosed during the period 1 January 2008 – 31 December 2017 at the Division of

Nephrology at Helen Joseph Hospital (HJH) was undertaken. Patients were identified by cross referencing renal outpatient department files, biopsy registers both at HJH renal unit and the department of anatomical pathology, and the NHLS electronic platform.

Patients under the age of 18 years at time of diagnosis (n=5), those with concomitant Human Immunodeficiency Virus (HIV) infection at time of diagnosis (n=9), those with overlap syndrome (n=0), those diagnosed at other institutions prior to referral to HJH (n=0), and those with inadequate biopsies (n=3) or missing histopathology data (n=20) were excluded from analysis. A total of 47 patients were included after exclusions.

Demographic data (sex, age, and self-reported race); total cholesterol; serum creatinine; eGFR (as determined by the Modification of Diet in Renal Disease equation); urinalysis and protein: creatinine ratio (UPCR); serum albumin; autoimmune serologies and titres; complement; presence of hypertension; and WHO/ International Society of Nephrology (ISN) LN histological class were anonymously extracted for all included patients. Where data was missing for specific parameters, statistical testing was applied to the remainder of the cohort. Renal outcomes data was extracted for those patients with a minimum period of 12 months follow up. Renal outcomes were categorized (using KDIGO definitions) as complete remission with stable kidney function, partial remission, ongoing treatment, or loss of kidney function. Complete remission was defined by the stabilization or improvement of kidney function, normalization of proteinuria to <300g per 24 hours and resolution of active urinary sediment. Partial remission was defined by 50% improvement in proteinuria to below nephrotic range with inactive urinary sediment and stable kidney

function. Loss of kidney function was defined as an eGFR of <15ml/min/1.73m^2 or initiation of long term RRT. Extracted data was stored using Microsoft Excel (version 16.61.1, Microsoft © 2022) prior to export to Statistica® (version 13.5,TIBCO, Pallo Alto, USA) for analysis.

Distribution of clinical and demographic data was determined using Shapiro Wilk W testing and visual inspection of the histogram plot. Non-parametrically distributed continuous variables were analyzed using the Mann Whitney U test. Categorical data was compared using Fischer Exact or Pearson's Chi-squared tests as appropriate. Statistically significant results were further tested using logistic regression. General discriminant analysis was applied to determine the level of the continuous variable with significant association. Survival analysis curves of proliferative and non-proliferative groups were fitted with respect to time to remission, time to loss of kidney function and time to first relapse using the Kaplan-Meier technique. Survival outcomes were compared using the Cox Mantel F test. Multifactorial Cox regression and multifactorial linear regression were used respectively to determine the effect of clinical and histological parameters on renal outcomes and kidney function at follow-up. Statistical significance was determined by a p-value <0.05.

Ethical approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (protocol number M200152). Consent for the use of patients' hospital records was obtained from the academic head of the Department of Internal Medicine at HJH, the HJH Research Committee and the clinical head of the renal unit. Additionally, access to NHLS data was granted by the NHLS and registered on the AARMS system (reference number #PR20112). Consent to review

biopsy databases was also obtained from the Department of Anatomical Pathology at the University of the Witwatersrand.

Results

Patients of black African ethnicity comprised the largest demographic in the included cohort (32 patients, 72.7%). 73.3% (33 patients) of the cohort was female. The median age at diagnosis in this series was 26.5 years old (IQR 24-36 years). Baseline clinical, biochemical, and autoimmune parameters are shown in *Table 1*. The median creatinine at diagnosis in this series was 74 μmol/L (IQR 64 -126.8 μmol/L), equivalent to a median eGFR of 101.4 ml/min/1.73m2 (IQR 64 -126.8 ml/min/1.73m^2).

Proliferative lesions were more commonly diagnosed in this cohort (n=31; 66%), with WHO/ISN pure class III comprising 12 cases (25.5%), pure class IV comprising 10 cases (21.3%) and mixed class III+V and IV+V comprising 9 cases (19.1%) (Table 1). Males and patients of non-black ethnicity were more frequently diagnosed with proliferative than non-proliferative lesions (p = 0.070 and p = 0.035 respectively, Table 2). Kidney dysfunction was more prevalent in patients subsequently diagnosed with proliferative lesions as evidenced by higher creatinine (p = 0.007) and lower eGFR (p = 0.035). Urine white cell count was also higher in those with proliferative lesions (p = 0.023) (Table 2). General discriminant analysis modeling identified an eGFR of below 90mL/min/1.73m^2 as associated with increased probability of the diagnosis of a proliferative lesion. In subsequent multivariate logistic regression analysis, eGFR below 90mL/min/1.73m^2 was independently associated with increased odds of the diagnosis of proliferative LN (OR=5.6; CI 1.06-29.59; p=0.043). Male sex was associated with a trend towards increased odds of this

diagnosis (OR=8.31; CI 0.89-78.15; p=0.064) (Table 3). Ethnicity was not included in multivariate analysis due to the low numbers of non-black patients with proliferative lesions

Baseline parameters and demographic factors did not appear to affect time to induction of remission (Table 4). 19.95% (n=9) and 21.28% (n=10) achieved partial and complete remission, respectively. Eight patients experienced a relapse of LN after successful induction of remission. The rate of relapse was non-significantly higher in the non-proliferative group (n=3; 23.1%) compared to the proliferative group (n=5; 19.2%; p=0.544). Median time to relapse in cases of non-proliferative LN was 28.9 months (IQR 18.63 – 39.07 months) compared to 59.3 months in proliferative LN (IQR 50.43-69.93 months) (p=0.200).

The diagnosis of a proliferative lesion was associated with a trend towards poorer kidney function survival compared to non-proliferative lesions (p=0.057) (figure 1).

Stepwise multifactorial linear regression analysis found higher eGFR at baseline to be independently associated with preserved eGFR (p=0.003) and creatinine (p=0.009) at follow up. Baseline urine WCC showed an inverse relationship with eGFR (p=0.041) and a positive correlation with creatinine (p=0.001) (Table 5). The presence of a proliferative lesion was negatively associated with eGFR at follow up (p=0.002) (Table 5).

Discussion

This is the first description of the patterns and outcomes of LN at HJH over a 10-year period. Identifying those at risk of having aggressive LN lesions is a novel area of study that may have direct implications on referral and biopsy practices. This may

prove useful in a resource constrained public health sector with limited access to tertiary healthcare. The present study found baseline kidney dysfunction and leukocyturia are among the factors predicting proliferative LN, with proliferative LN associated with poorer kidney function at follow up. Additionally in this cohort, males had higher odds of having proliferative LN, possibly indicating another group at risk of this aggressive lesion.

This study reflects an overall higher prevalence of LN amongst younger females, with African ethnicity being the predominant race affected (Table 2). The median age of diagnosis was 27 years old (for proliferative LN, IQR: 24-37 years) and 25 years old (for non-proliferative LN, IQR: 23-36 years). These findings are in line with current literature[8,13-14]. Within this cohort, proliferative lesions accounted for two-thirds of all biopsy diagnoses; the majority of which were pure class III LN (Table 1). This is consistent with patterns of lesions seen in other similar studies, both locally and internationally[8,15]. As expected, our study found proliferative LN tended toward poorer kidney survival (Figure 1), with low baseline eGFR independently associated with this lesion (Table 3), however, the wide confidence interval observed suggests a relatively weak association which likely arose from the small study sample.

Previous South African reports have noted a trend towards presentation with kidney dysfunction in both proliferative and non-proliferative LN[8]. Kidney dysfunction in the present study was comparatively rare in both groups, which may suggest differences in biopsy practices between units. Briefly, use of proteinuria as a primary indication for biopsy may have selected for the inclusion of patients early in their disease course with relatively preserved kidney function.

Emphasis on proteinuria as a biopsy indication is in part evidenced by the median baseline urine PCR in this series of 0.343. Other studies have similarly reported nephrotic range proteinuria to be a common feature of LN.[13,15-16]. The presence of an active urinary sediment, as evidenced by leukocyturia and haematuria which may be indicative of glomerular inflammation[17], was present in only 33% of this cohort. Similar findings have been reported in a previous local LN study [18], possibly reflecting reliance on proteinuria as a biopsy indication. Although leukocyturia was more significant in cases of proliferative LN in the present study, logistic regression suggested a lack of predictive ability for this marker in identifying such cases. Hypocomplementaemia has long been associated with active lupus, LN, and proliferative lesions[7,19]. In this study, though median C3 was decreased, no association with proliferative LN was shown (p=0.151). Interestingly, previous local reports have also failed to demonstrate significant difference in C3 between membranous LN and proliferative LN[4]. Baseline eGFR <90ml/min/1.73m2 was independently associated with proliferative LN (OR 5.6; CI1.06-29.59; p=0.043), consistent with other series demonstrating a correlation between higher baseline serum creatinine or lower eGFR with aggressive lesions[6,11,16,20]

Males were disproportionately represented in the proliferative group, with males having a higher odd of diagnosis with proliferative lesions (OR=8.31; CI 0.89-78.15; p=0.064). This is consistent with a general trend towards more severe disease in men[8,9,19,20]. Although patients of Black ethnicity constituted the majority of the proliferative LN group, an association between ethnicity and proliferative LN classes was not demonstratable in this series. African ethnicity has been associated with aggressive LN histopathology in many other studies[7,12-13], and it is likely that failure to show similar trends in this study reflects sample bias in the form of a predominant

Black ethnicity cohort. Previous literature has shown a predilection for females, particularly of African descent[13-14]; the findings of this study are broadly consistent with this trend[16,18,20], with females comprising 73.3% (n=33) of the cohort. LN predominantly affects younger patients; in the present study, the median age at diagnosis of LN was 26.5 years old. [21-22].

This study showed lower baseline eGFR, elevated urine WCC, an indicator of an inflammatory response[17], and proliferative lesions were independently associated with kidney dysfunction at most recent follow up. Survival analysis demonstrated a positive association between proliferative LN and poorer kidney survival (p=0.057). This is in keeping with several studies that suggest proliferative LN predicts worse outcome[7,8,13,16]. The possible reasons for unfavourable outcomes in proliferative LN are multifactorial: increased proteinuria, which in itself is tubulotoxic[8]; association with arterial hypertension[10]; increased prevalence of crescents on kidney biopsy[15]; higher baseline serum creatinine indicating early kidney damage[16] and poorer response to induction therapy[11, 16].

Somewhat surprisingly, we did not find a significant difference in the rate of relapse across the different histological classes (0.544). Potentially, the small number of relapses (n=8) could reflect improving outcomes in class III/IV from modern cytotoxic regimens[23]. Similar lack of difference in relapse outcomes between histological lesions have been reported in other series[4,11].

There are, of course, limitations to this study. The study had a restricted sample size. The reasons for this include this being a single-centre study, incomplete patient records, no established biopsy registry at HJH, inability to obtain retrospective pathology records predating 2012 due to changing of electronic data platform, lack of

follow up records, and other exclusion criteria such as HIV. Additionally, histopathology results were not reported by the same pathologist, with some lacking information including activity and chronicity indices, presence of tubulointerstitial disease or vascular involvement. This study is also limited by its tendency to potentially over-represent the African demographic due to the population served by this public health facility.

Conclusion

LN is an important manifestation of SLE, with a higher prevalence in the younger African population, who seem to experience a poorer prognosis. Establishing predictors of severe disease is important in facilitating early diagnosis and intervention. The present study found an association between low baseline eGFR and baseline leukocyturia with kidney dysfunction at follow up. Additionally, males were found to have a higher odd of proliferative LN, with proliferative LN associated with poorer kidney survival. Use of these parameters in the clinical setting may have value in screening and monitoring such patients for aggressive disease.

Conflict of interest statement. None declared.

Tables and Figures

Table 1: Presenting clinical parameters and histological patterns of LN in sample population in terms of WHO/ISN classification and proliferative and non-proliferative LN

	N, %	Median [IQR]	Normal range
Cholesterol	41 (87.2%)	4.57 [3.85 – 6.80]	<5.0 mmol/L
Creatinine	43 (91.5%)	74 [60 – 117]	Male: 62-115 umol/L Female: 53-97 umol/L
eGFR	43 (91.5%)	101.4 [64 – 126.8]	90-120 ml/min/ 1.73m2
UPCR	42 (89.4%)	0.343 [0.161 – 0.580]	<0.015 g/mmol
UWCC	41 (87.2%)	6000 [3000 – 11000]	4500-11000 wbc/ml
URCC	41 (87.2%)	3000 [0 – 36000]	<1000 rbc/ml
Active urine sediment (WCC and RCC > 5000)	39 (83%)	Active: 13, 33.3% Bland: 26, 66.7%	<5000 cells/ml
Albumin	43 (91.5%)	25 [16 – 31]	35-52 g/L
AntidsDNA	36 (76.6%)	0 [0 – 160]	0
ANA	43 (91.5%)	320 [0 – 640]	0-80
AntiSm	35 (74.5%)	0 [0 – 128]	0 U/ml
AntiRNP	35 (74.5%)	50 [0 – 154]	0 U/ml
AntRo	35 (74.5%)	0 [0 – 118]	0 U/ml
AntiLa	35 (74.5%)	0 [0 – 12]	0 U/ml
C3	40 (85.1%)	0.895 [0.550 – 1.300]	0.90-1.80 g/L
C4	40 (85.1%)	0.160 [0.100 – 0.290]	0.10-0.40 g/L
Systolic BP	15 (31.9%)	150 [129 – 179]	<140mmHg
Hypertensive	28 (59.6%)	Hypertensive: 13, 46.4% Normotensive: 15, 53.6%	

Proliferative	31 (66%)
Non-proliferative	16 (34%)
WHO I	1 (2,1%)
WHO II	7 (14.9%)
WHO III	12 (25.5%)
WHO IV	10 (21.3%)
WHO V	8 (17%)
WHO III + V	4 (8.5%)
WHO IV + V	5 (10.6%)

Table 2: Comparison of demographic and clinical parameters between proliferative and non-proliferative lupus nephritis

	Proliferative		Non-proliferative		p
	N, %	Median [IQR]	N, %	Median [IQR]	
Age	30 (63.8%)	27 [24 – 37]	14 (29.8%)	25 [23 – 36]	0.681*
Gender	31 (66.0%)	Female: 20, 64.5% Male: 11, 35.4%	14 (29.8%)	Female: 13, 92.9% Male: 1, 7.1%	0.070**
Ethnicity	29 (61.7%)	Black Afr: 18, 62.1% Mixed: 6, 20.7% Caucasian: 3, 10.3% Indian: 2, 6.9%	15 (31.9%)	Black Afr: 14, 93.3% Mixed: 0, 0% Caucasian: 1, 6.7% Indian: 0, 0%	0.132***
Black / Non-black	29 (61.7%)	Black: 18, 62.1% Non-black: 11, 37.9%	15 (31.9%)	Black: 14, 93.3% Non-black 1, 6.7%	0.035**
Cholesterol	28 (59.6%)	4.56 [3.82 – 6.46]	13 (27.7%)	5.77 [4.10 – 7.05]	0.609*
Creatinine	29 (61.7%)	77 [68 – 145]	14 (29.8%)	61.5 [59 – 70]	0.007*
eGFR	29 (61.7%)	92.9 [43 – 117]	14 (29.8%)	119.45 [100 – 134]	0.035*
UPCR	28 (59.6%)	0.352 [0.170 – 0.640]	14 (29.8%)	0.301 [0.082 – 0.550]	0.348*
UWCC	28 (59.6%)	7500 [5000 – 36500]	13 (27.7%)	2000 [1000 – 9000]	0.023*
URCC	28 (59.6%)	4500 [0 – 32850]	13 (27.7%)	3000 [0 – 83000]	0.668*
Sediment	26 (55.3%)	Active: 10, 38.5% Bland: 16, 61.5%	13 (27.7%)	Active: 3, 23.1% Bland: 10, 76.6%	0.477**
Albumin	29 (61.7%)	25 [17 – 31]	14 (29.8%)	20 [15 – 33]	0.788*
AntiDsDNA	25 (53.1%)	0 [0 – 320]	11 (23.4%)	0 [0 – 0]	0.207*
ANA	29 (61.7%)	320 [0 – 640]	14 (29.8%)	160 [0 – 320]	0.274*
AntiSm	23 (48.9%)	0 [0 – 145]	12 (25.5%)	46 [0 – 127.5]	0.482*
AntiRNP	23 (48.9%)	29 [0 – 148]	12 (25.5%)	131.5 [0 – 181.5]	0.294*
AntiRo	23 (48.9%)	15 [0 – 118]	12 (25.5%)	0 [0 – 109]	0.548*
AntiLa	23 (48.9%)	0 [0 – 7]	12 (25.5%)	0 [0 – 14]	0.851*
C3	27 (57.4%)	0.710 [0.390 – 1.260]	13 (27.7%)	0.940 [0.640 – 1.410]	0.151*
C4	27 (57.4%)	0.150 [0.100 – 0.290]	13 (27.7%)	0.210 [0.100 – 0.230]	0.909*
Systolic BP	11 (23.4%)	150 [129 – 162]	4 (8.5%)	149 [116.5 – 179.5]	0.851*
Hypertensive	18 (38.3%)	HT: 10, 55.6% Normo: 8, 44.4%	10 (21.3%)	HT: 3, 30% Normo: 7, 70%	0.254**

*Mann-Whitney U

**Fischer exact

***Pearson Chi

Table 3: Stepwise logistic regression for probability of proliferative lesion

	Reference	p	OR (95%CI)
Gender: Male	Female	0.128 0.064	 8.31 (0.89 – 78.15]
eGFR: eGFR less than 90	eGFR more than 90	0.058 0.032 0.043	 6.57 (1.17 – 36.88) 5.60 (1.06 – 29.59)*
UWCC: UWCCC more than 50000	UWCC less than 50000	0.998	excluded

*Univariate testing

Table 4: Cox proportional hazards model, time to remission (in years)

	Reference	HR (95% CI)	p
Age	NA	0.974 [0.869 – 1.093]	0.657
Cholesterol	NA	1.387 [0.929 – 2.070]	0.110
eGFR	NA	1.015 [0.992 – 1.038]	0.205
UPCR	NA	5.108 [0.198 – 131.580]	0.325
UWCC	NA	1.000 [1.000 – 1.0001]	0.144
URCC	NA	1.000 [1.000– 1.0000]	0.739
Gender: Male	Female	1.547 [0.096 – 24.901]	0.758
Black / Non-black: Black	Non-black	3.096 [0.329 – 29.173]	0.323
Proliferative / Non-proliferative: Proliferative	Non-proliferative	1.477 [0.174 – 12.524]	0.721

Table 5: Association of clinical and histological parameters on residual kidney dysfunction

For creatinine:

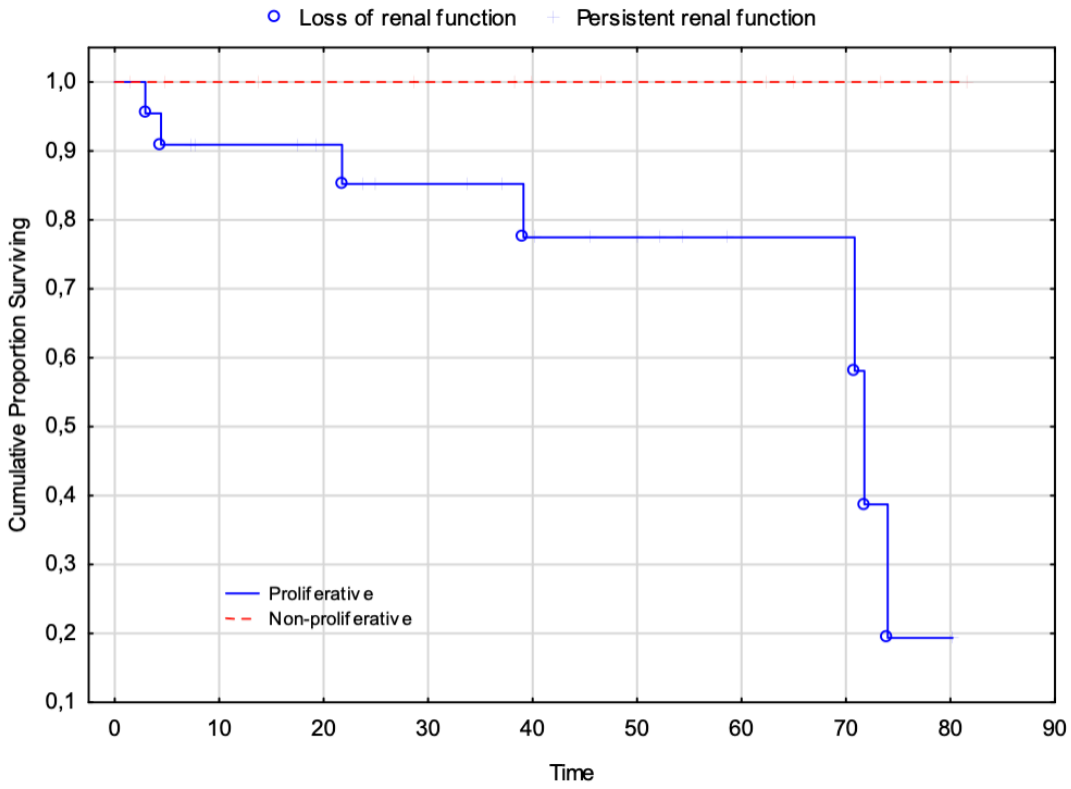
	Age	Cholesterol	eGFR	UPCR	UWCC	URCC	Time to most recent measurement	Gender	Black / Non-Black	Proliferative / Non-proliferative
Ref	NA	NA	NA	NA	NA	NA	NA	Female	Non-B	Non-P
	0.505 excluded	0.123	0.060 -0.370 [-0.643 - -0.098] 0.009*	0.325	0.0001 0.510 [0.218 – 0.803] 0.001*	0.753 excluded	0.709 excluded	0.105	0.973 excluded	0.768 excluded

*Values are: p(multivariate) B (regression coefficient) [95%CI] p

For eGFR:

	Age	Cholesterol	eGFR	UPCR	UWCC	URCC	Time to most recent measurement	Gender	Black / Non-Black	Proliferative / Non-proliferative
Ref	NA	NA	NA	NA	NA	NA	NA	Female	Non-B	Non-P
	0.601 excluded	0.074	0.032 0.415 [0.152 – 0.679] 0.003*	0.229	0.175 -0.264 [-0.516 - -0.012] 0.041*	0.543 excluded	0.972 excluded	0.776 excluded	0.616 excluded	0.032 -0.429 [-0.690 - -0.167] 0.002*

Figure 1: Survival of kidney function



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CHAPTER 3: APPENDIX

Appendix A: Data Collection Sheet

Study number:_____

Demographics:

Sex (F/M)	Age (years)	Race (B/W/A/M)

Presenting parameters:

Total cholesterol	Creatinine	eGFR	Urine PCR	Albumin	Hypertension (Y/N)	Systolic BP	Urinalysis

Immunology:

ANCA (Y/N) (pattern)	Anti DsDNA (Y/N)	ANA (Y/N) (titre/pattern)	AntiSm (Y/N)	AntiRNP (Y/N)	Ro/La (Y/N)	C3	C4	WHO class

Histology:

LN class	[tick box]	NIH activity index	Score [1-3]	NIH chronicity index	Score [1-3]
1		Cellular crescents	X2	Glomerular sclerosis	
2		Leukocyte infiltration		Fibrous crescents	
3		Endocapillary cellularity		Interstitial fibrosis	
4		Wire looping/hyaline deposits		Tubular atrophy	
5		Glomerular fibrinoid necrosis	X2		
6		Interstitial inflammation			

Presence or absence of thrombotic microangiopathy: Y/N_____

SLE duration (in months):

Lupus nephritis duration, at time of data collection (in months):

Therapy prescribed:

Steroids	Cyclophosphamide	MMF	Other (specify)

Outcome:

Renal outcome (remission/ partial remission/ ongoing treatment/ permanent kidney failure)	
Time to renal outcome (months)	
Relapse	
Time to first relapse (months)	
Most recent creatinine (μmol/L)	
Most recent eGFR (ml/min/1.73m^2)	
Time to most recent creatinine/eGFR measurement	

Appendix B: Faculty Protocol Approval Letter

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24 October 2019

To whom it may concern

Subject: HELEN JOSEPH HOSPITAL RESEARCH COMMITTEE APPLICATION

PROTOCOL TITLE: A review of the pattern of clinical presentation histopathological classes and outcomes of lupus Nephritis patients at HJH.

Protocol Ref No: Sarish Rajoo

Ethic Clearance: Pending
Principal investigator: Sarish Rajoo

Department: Internal Medicine

Committee Recommendations
The Committee is giving you Conditional access while awaiting the final ethical clearance certificate from the University of Witwatersrand HREC.

It is the duty of the researcher to collect the data to the relevant department after the Research Committee approved the study.

Dr. M. Mukansi
Chairperson of HJH Ethic and Research Committee

Appendix C: Human Research Ethics Committee Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG	HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Dr S Rajoo
School of Clinical Medicine
Department of Medicine
Division of Internal Medicine
Medical School
University

E-mail: rjxsar001@myuct.ac.za

CC: Supervisor: Drs M Davies and Z Cassimjee <Malcolm.Davies@wits.ac.za>
and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 2020/06/25

REF: *R14/49*

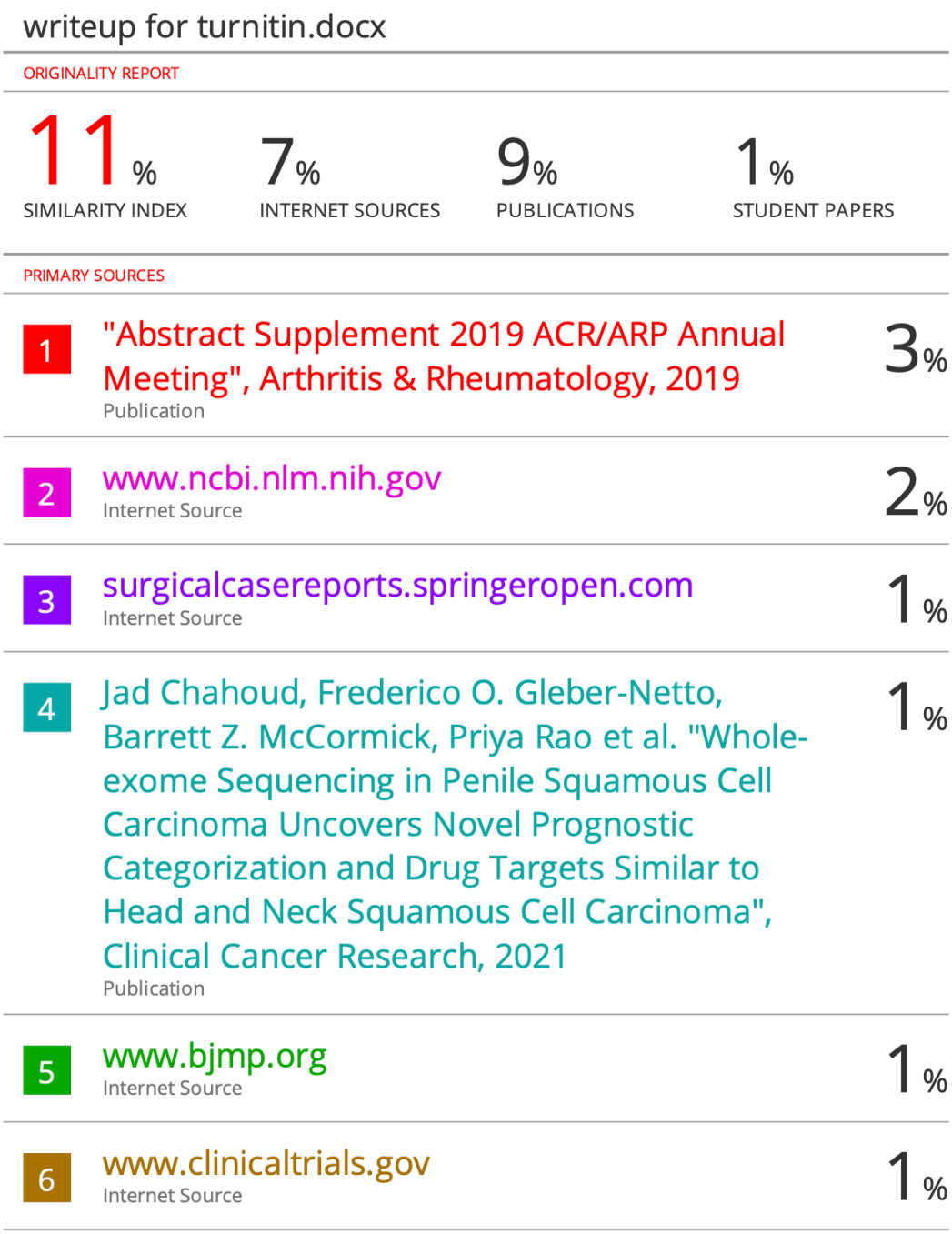
PROTOCOL NO: **M200152** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *A review of the patterns of clinical presentation, histopathological classes and outcomes of Lupus Nephritis patients at Helen Joseph Hospital*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

Appendix D: Turnitin



writeup for turnitin.docx

ORIGINALITY REPORT

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PRIMARY SOURCES

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