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A 10-year retrospective cohort study on dermatological conditions in renal transplant recipients at the Charlotte Maxeke Johannesburg Academic Hospital, 2008-2018

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A 10-YEAR RETROSPECTIVE COHORT STUDY ON DERMATOLOGICAL CONDITIONS IN RENAL TRANSPLANT RECIPIENTS AT THE CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, 2008-2018.

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment of the requirements for the degree of Master of Medicine in Dermatology.

Johannesburg 2021

1 DECLARATION

I Roseline Chioma Ede declare that this research report is my own work which is being submitted for the degree of Master of Medicine in the department of Dermatology at University of the Witwatersrand, Johannesburg.

This research report has not been submitted previously for any degree or examination at this or any other University.



……

(Signature of candidate)

6th day of October 2021

2 DEDICATION

This project is dedicated to God Almighty for His divine protection and strength to complete this report especially in this pandemic.

To my late parents whose unconditional love in their children has made me a diligent and upright person.

To my husband, Jeffrey, my children, Neme, Kene, and Golibe, for their emotional and physical support to carry on and finish this report. They have sacrificed considerably during the course of this project. Their love and support were the beacon that guided me during the course of this project.

To my supervisor, Professor D. Modi, for his guidance.

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To my colleagues at the department of Dermatology at Charlotte Maxeke Johannesburg Academic Hospital, words alone are not enough to express my gratitude to you.

ABSTRACT

Introduction

Dermatological conditions are common in renal transplant recipients as a consequence of chronic immunosuppression. Awareness of these conditions is important to dermatologists as their presentations may be atypical, and their occurrences affect the overall well-being of renal transplant recipients.

Aim of study

To describe the spectrum of dermatological conditions observed in renal transplant recipients at Charlotte Maxeke Johannesburg Academic hospital between January 2008 and December 2018.

Methods

A retrospective cohort study was performed. All participants aged 18 years and above that received a renal allograft and were followed up at the Renal unit in Charlotte Maxeke Johannesburg Academic Hospital, between January 1, 2008, and December 31, 2018, were recruited. A descriptive analysis of the data was performed. Continuous data were summarised as mean (standard deviation), and median (interquartile range), and categorical data as frequencies and proportions. A test of statistical significance was computed at p less than 0.05. All analyses were performed with Stata Release 15.1.

Results

Of all the renal transplant recipients in the study (n=173), 69% developed dermatological conditions during the study period. Twenty-two percent of the dermatological conditions were viral infections; 17% were fungal infections 6% were bacterial infections; 6 % were cutaneous neoplasms, and 17% were adverse drug reactions.

Twenty-nine participants had more than one condition. There was a statistically significant difference in dermatological conditions for participants who had infection prophylaxis for six months versus greater than six months, p = .025. There was no statistically significance difference in dermatological conditions for gender, age, race, aetiology of end-stage renal disease, organ donor type, and type of immunosuppressant drug. There was a trend to more cases of viral infections in

males, participants less than 50 years, and participants of African descent but a statistical test of significance was not performed because of small sample size. The median time to develop dermatological conditions was two years.

Discussion

The prevalence of dermatological conditions in this study is 69%. The majority of these conditions appear to occur between one year to two years following renal transplantation suggesting this may correspond to peak of immunosuppression.

Conclusion

This study shows that dermatological conditions are common in renal transplant recipients. This study also appears to suggest that majority of these dermatological conditions are cutaneous infections and occur at peak of immunosuppression. Cutaneous adverse drug reactions, mostly acneiform eruptions was also noted to be common during the peak of immunosuppression. It is important that patients are aware of these conditions and follow appropriate preventive strategies. It is even more pertinent that dermatologists collaborate with nephrologists in the surveillance and appropriate management of these conditions.

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ABBREVIATIONS

ADR	Adverse drug reaction
ATG	Anti-thymocyte immunoglobulin
CD	Cluster differentiation
CEO	Chief executive officer
DNA	Deoxyribonucleic acid
EDV	Epidermodysplasia verruciformis
HIV	Human immunodeficiency virus
HIVAN	Human immunodeficiency virus associated nephropathy
HHV8	Human herpes virus 8
IQR	Interquartile range
MMF	Mycophenolate mofetil
mTOR	Mammalian (mechanistic) target of rapamycin
PRA	Percentage panel reactive antibody
RNA	Ribonucleic acid
SD	Standard deviation

1 CHAPTER 1 LITERATURE REVIEW

1.1 Introduction

Renal transplant recipients develop dermatological conditions as a sequela of chronic immunosuppression (Garrido and Borges-Costa, 2017). These dermatological conditions manifest commonly as opportunistic cutaneous infections, cutaneous neoplasms, and adverse cutaneous reactions to the immunosuppressive drugs (Garrido and Borges-Costa, 2017).

1.2 Spectrum of Dermatological conditions

1.2.1 Cutaneous infections

Cutaneous infections in renal transplant recipients are opportunistic and may be caused by viruses, fungi, bacteria, and parasites. There are variations in the spectrum of cutaneous infections across geographical regions and socio-economic strata. In separate studies conducted among Hispanics in Puerto Rico, and another study in India, fungal infections were identified as the predominant cutaneous infection (Lugo-Janer et al, 1991; George et al, 2009).

On the contrary, another study conducted among Caucasians in Portugal showed that viral infections were the commonest cause of cutaneous infections (Garrido and Borges-Costa, 2017). The duration on immunosuppression is another factor that affects the prevalence and spectrum of cutaneous infections in renal transplant recipients. However, age and gender have not been shown to affect the spectrum of dermatological conditions in renal transplant recipients (Sandhu et al., 2003; Alper et al., 2005).

1.2.2 Cutaneous neoplasms

Chronic immunosuppression in renal transplant recipients results in impaired cell-mediated immunity that affects the body's ability to eliminate damaged cells. The accumulation of these damaged cells can result in cell transformation with subsequent development of cutaneous neoplasms. Numerous factors play a role in the initial genetic events that result in cell transformation. Infection by oncogenic viruses like Epstein Barr virus, Kaposi sarcoma herpes virus, Human papilloma virus, Human T-

lymphotropic virus type 1, and Merkel cell polyomavirus can produce genetic mutations (Giampieri and Storey, 2004; Moloney et al., 2005b).

Exposure to ultraviolet rays induces mutation in the tumour suppressor gene, p53 (McGregor et al., 1997; Giampieri and Storey, 2004). Ultraviolet rays also impair the function of antigen-presenting (Langerhans) cells in the epidermis and promote proliferation of regulatory T-cell (Treg) which suppress immune response further (Kelly et al., 2000). Some immunosuppressive drugs like the calcineurin inhibitor, and cyclosporine prevent repair of ultraviolet ray-induced Deoxyribonucleic acid (DNA) damage. Common cutaneous neoplasms that occur in renal transplant recipients are actinic keratosis, seborrheic keratosis, non-melanoma skin cancers and Kaposi sarcoma.

The prevalence of cutaneous neoplasms in renal transplant recipients is influenced by geographic location; older age; male gender; ultraviolet exposure; ethnicity; prior history of cutaneous malignancies and duration of immunosuppression (Lindelöf et al., 2000; Euvrard, Ulrich and Lefrancois, 2004; Ramsey et al., 2007; Kang et al., 2017). A meta-analysis by Matinfar et al., (2018) showed that non-melanoma skin cancer was the most common skin cancer in renal transplant recipients with a pooled incidence of 12.6%, squamous cell cancer was the most prevalent. When geographic location was considered, Australia and New Zealand had the highest incidence of squamous cell cancer in renal transplant recipients. It has been touted that exposure to ultraviolet rays and the people's skin types (Fitzpatrick I to IV) may be responsible for the high incidence of squamous cell cancer in those countries. However, another study from Iran in the Middle East, a geographic region with ultraviolent ray profile similar to Australia and New Zealand and with people of fairly similar skin types showed that Kaposi sarcoma was the most common skin cancer (Einollahi et al., 2012). The author attributed the difference to the ethnic behavioural pattern of wearing protective clothing and sunbathing (Shahidi, Matinfar and Feizi, 2018; Salehiniya, Pakzad and Soltani, 2015). A study in Cape Town showed that Kaposi sarcoma was the most common cancer in South African renal transplant recipients (Moosa, 2005a). In a European study by Ramsey et al., 2007, it was demonstrated that in a cohort of 269 renal transplant recipients, the duration of immunosuppressant therapy was associated with the risk of developing non-melanoma skin cancer. Ramsey et al, showed that the mean incidence per year of

developing non melanoma skin cancer was 3.3% (SD 0.53), if the duration on immunosuppressive therapy was less than five years. This figure increased to 11.1% (SD 1.85) at 10 years of immunosuppressive therapy (Ramsay et al., 2007).

1.2.3 Cutaneous adverse drug reactions (cosmetic/aesthetic side effects)

Each immunosuppressive drug has inherent side effects, some of which are cosmetic or aesthetic in their manifestations. These cosmetic side effects are important to note because they may affect the patients' compliance with therapy with detrimental effects on graft survival. The manifestation of adverse cutaneous drug reactions may require dose adjustment or switching to a newer immunosuppressive drug with less side effect (Ponikvar, Novljan and Ponikvar, 2002).

Lesions of aesthetic interest or cosmetic side effects are more common with Azathioprine, Cyclosporine, and Corticosteroids-based immunosuppressant regimen. Ehsani et al., (2009), showed that in their cohort of 100 renal transplant recipients who were receiving a combination of Azathioprine, Cyclosporine, and prednisolone, cosmetic side effect was the most common dermatological conditions (Ehsani et al., 2009). A study in India by George et al ,2009 on renal transplant recipients documented lesions of aesthetic interest to be the most prevalent dermatological manifestation in their study.

Most of the cutaneous adverse drug reactions are dose dependent, some however persist as long as the patient is on that medication, an example of this type of lesion is skin atrophy and visible telangiectasia.

Sebaceous hyperplasia and epidermal inclusion cysts can be seen in patients who take cyclosporine for more than five years these lesions occur due to hyperplasia of the pilosebaceous unit (Oh et al., 2018).

1.2.4 Immunosuppressive drugs used in renal transplant recipients and associated dermatological conditions

The immunosuppressive regimen used in most transplant centres are categorised into induction therapy and maintenance therapy (Blisard, 2013). The number and type of immunosuppressive agents used have a bearing on the spectrum of dermatological conditions. A retrospective study in the United Kingdom of 262 renal transplant recipients compared the treatment regimen of three-drugs (cyclosporine,

azathioprine, and prednisolone) to two-drugs (azathioprine and prednisolone) and showed that participants on three drugs had more squamous cell cancers compared to those on two drugs (Glover et al., 1997).

1.2.4.1 Induction therapy

Immunosuppressive drugs used as induction therapy prevent acute rejection by suppressing both cellular and humoral immunity (Suthanthiran, Morris and Strom, 1996). They are commenced shortly before organ transplantation and continued post transplantation. Most are monoclonal antibodies like Daclizumab, Basiliximab, and Rituximab that are given in the perioperative period to renal transplant recipients (Vincenti et al., 1998).

Anti-Thymocyte immunoglobulin (ATG) is a horse or rabbit-derived polyclonal gamma immunoglobulin against human thymocytes. It is used in patients who are at risk for acute graft rejections such as patients with HIV infection, and patients with a history of previous solid organ transplant. Anti-Thymocyte globulin induces long term immunosuppression via depletion of T-lymphocytes and other immune cells, thereby predisposing these high-risk patients to opportunistic infections.

Basiliximab (Simulect^{R}) is an Interleukin-2 receptor blocker that inhibits T-cell proliferation, differentiation, and expression (Ghanta et al., 2013).

Rituximab is a monoclonal antibody against cluster differentiation (CD) 20 antigen cells found on naïve B-lymphocytes. Rituximab is used as an induction agent for desensitisation of highly sensitive individuals or in individuals with ABO incompatible kidney transplantation. It has also been reported to be used in treatment of acute and chronic antibody mediated reactions but with minimal efficacy (Sood and Hariharan, 2018; Lee et al., 2021).

The immediate cutaneous side effects of monoclonal antibodies include urticaria and angioedema that result from the cytokine response (Hannon, Wetter and Gibson, 2014). Other rare dermatological conditions include bleeding gums; stomatitis; alopecia; flushing; and peripheral oedema (Ghanta et al., 2013).

The most recent monoclonal antibody is Bortezomib, which is a selective inhibitor of proteasome 26S. It has fewer side effects than its predecessors and it is used as a rescue therapy (Bahena Méndez et al., 2020).

1.2.4.2 Maintenance immunosuppressive therapy

Maintenance therapy in renal transplant recipients is administered following induction therapy as a combination of several immunosuppressive drugs. The goal is to prevent acute graft rejection and achieve to long-term graft survival. Maintenance immunosuppression therapy includes Glucocorticoids, Calcineurin inhibitors (Cyclosporin and Tacrolimus), Azathioprine, Mycophenolate mofetil (MMF), inhibitors of mechanistic target of Rapamycin (mTOR) (Sirolimus and Everolimus), and Belatacept (Melvin et al 2012).

A conventional maintenance cocktail is individualised and transplant centre-driven, but usually includes a glucocorticoid and one or two members of the group (Special Issue: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, 2009).

Glucocorticoids produce a non-specific anti-inflammatory effect by down regulating inflammatory cytokines. This is primarily achieved by inhibiting nuclear factor-kappa-B (NF-kB) and activator protein-1 (AP-1) that play a role in production of inflammatory mediators. Cutaneous side effects seen with corticosteroids are moon face; acneiform eruptions; striae; telangiectasia; purpura and skin atrophy (Stuck, Minder and Frey, 1989; Matas et al., 2001).

The initial Calcineurin inhibitor was Cyclosporine which inhibits interleukin-2 mediated T-cell functions. Cyclosporine produces cutaneous side effects such as gum hypertrophy, hypertrichosis, facial redness, pruritus, and acne. Cyclosporine also increases the susceptibility to fungal infection (Thervet et al., 2003; Khan, El-Charabaty and El-Sayegh, 2015). Tacrolimus is a novel calcineurin inhibitor with fewer adverse effects compared to Cyclosporine.

Azathioprine is an antiproliferative agent derived from 6-mecarptopurine and inhibits T -cell and B-cell function by inhibiting DNA and Ribonucleic acid (RNA) synthesis. Azathioprine causes a non-specific skin rash, aphthous ulcers, stomatitis, and alopecia (Kahan, 2000b).

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase that blocks lymphocyte proliferation. Cutaneous side effects seen with Mycophenolate mofetil are cutaneous candidiasis, peripheral oedema, acne, and alopecia (Carl and Wiesel, 1997).

The inhibitors of the mechanistic target of rapamycin (mTOR) includes Sirolimus and Everolimus. Both drugs bind to the same intracellular protein as tacrolimus called FK506-binding protein-12 (FKBP12) to form a drug-protein complex. This drug-protein complex binds to mTOR and inhibit the kinase-dependent intracellular signalling that results in cell-cycle arrest, thus suppressing the interleukin drive T-cell proliferation. Inhibitors of mTOR can cause acne, rash, oral ulcers, periorbital and peripheral oedema (Kahan, 2000a; Euvrard, Ulrich and Lefrancois, 2004; Moloney et al., 2005a; Ghanta et al., 2013).

Belatacept is a novel drug derived from human cytotoxic T-lymphocyte antigen-4 and portion of human immunoglobulin-1. It binds avidly to CD 80/86 ligands on antigen presenting cells. This binding prevents interaction between co-stimulatory molecules CD 28 and CD 80/86 that play a role in clonal proliferation of cytotoxic T-lymphocytes. In other words, this drug prevents cytotoxic T-cell mediated graft rejection (Melvin, Sandhiya and Subraja, 2012).

1.3 Prevention of dermatological conditions in renal transplant recipients

The prevention of dermatological conditions in renal transplant recipients requires a multi-disciplinary team including a dermatologist, and a nephrologist. Some strategies to prevent dermatological conditions in renal transplant recipients will be described below.

1.3.1 Patient education

Renal transplant recipients should be provided information on risks of skin cancer due to prolonged sun exposure. They should be encouraged to use sun-protective topical agents, and sun-protective clothing during periods of unavoidable sun exposure (Ulrich et al., 2009). In a prospective study of 120 renal transplant recipients, patients that used sunscreen consistently were less likely to develop actinic keratoses and squamous cell carcinoma compared to patients that used sunscreen intermittently (Ulrich et al., 2009).

1.3.2 Substitution of immunosuppressive therapy

Patients with known adverse reaction to specific immunosuppressive drugs should be prescribed alternatives. For example, Tacrolimus in lieu of cyclosporine in patients that develop gum hypertrophy. In addition, some adverse reactions are known to be dose dependent. Hence dose adjustment may eliminate these adverse reactions. Novel immunosuppressant agents such as Sirolimus and Everolimus have not been shown to be associated with development of skin cancers in renal transplant recipients. (Euvrard, Ulrich and Lefrancois, 2004).

1.3.3 Chemoprophylaxis and Immunisation

Chemoprophylaxis entails pharmacologic strategies to reduce the risk of dermatological conditions. The use of antimicrobial drugs in the peri-transplant period as infection prophylaxis is practiced in most transplant centres. Pharmacologic strategies that have shown benefits for preventing squamous cell carcinoma in solid organ transplant recipients include acitretin, capecitabine, and nicotinamide (Otley et al., 2006).

It is advisable that age-appropriate immunization for common viral and bacterial infections be given to renal transplant patients three to six months after transplant. Transplant patients should not be given live or live attenuated vaccine. Likewise, health care workers that attend to transplant patients, and close family members of recipients should be fully vaccinated.

1.3.4 Surveillance following transplantation

It is important that renal transplant recipients perform skin self-examination once every month. This will assist with early detection of skin cancers. Additional information on skin self-examination could be assessed online such as information provided by the American Academy of dermatology (Trinh et al., 2014). However, the frequency of clinic visits should be guided by patient's risk factors and medical history.

1.4 Aims and objectives

Aims

To describe the spectrum of dermatological conditions observed in renal transplant recipients at Charlotte Maxeke Johannesburg Academic hospital between January 1, 2008 and December 31, 2018.

Objectives

Primary:

1. To determine the prevalence of dermatological conditions in renal transplant recipients.
2. To characterize the type of skin conditions found in renal transplant recipients.

Secondary:

1. To describe the demographic characteristics of renal transplant recipients who developed dermatological conditions.
2. To determine time to onset of dermatological conditions post renal transplantation.

1.5 Justification for this study

A number of studies have described dermatological conditions that occur post renal transplantation (Griffiths, 1991; Tan and Goh, 2006). Most of these studies described dermatological conditions that occur post renal transplantations in established economies. The findings from these studies cannot be generalized to emerging economies like South Africa. There is lack of data in emerging economies on dermatological conditions in renal transplant recipients. The only study from South Africa was performed in Cape town where the author considered only cutaneous malignancies (Moosa, 2005a). However, several publications from established economies show that cutaneous infections are more common in renal transplant recipients (Lugo-Janer, Sánchez and Santiago-Delpin, 1991; Hogewoning et al., 2001; Formicone et al., 2005). Hence there is a need to perform another study in South Africa to consider the spectrum of dermatological conditions that may occur following renal transplantations. My study will describe the prevalence and the spectrum of dermatological conditions that may occur following renal transplantation at a public quaternary health institution in South Africa.

2 CHAPTER 2 RESEARCH METHODS

2.1 Study design

A retrospective cohort study was chosen for this study of cutaneous manifestation in renal transplant recipients at the Charlotte Maxeke Johannesburg Academic Hospital between January 1, 2008 and December 31, 2018. This study design essentially involves participants, who have all received renal transplant and are on immunosuppression therapy. This study method evaluates who among these renal transplant recipients developed dermatological conditions. Furthermore, this study is designed to determine other variables. In a retrospective cohort study, the investigator starts with the exposure at the beginning of the study and then measures the outcome during the follow-up of the patient. This can only be done with a retrospective cohort study. Similar studies have been conducted globally (Hogewoning et al., 2001; Formicone et al., 2005; Moosa, 2005a; Bakr et al., 2010; Garrido and Borges-Costa, 2017).

2.2 Study site

The study was conducted at the Renal unit at Charlotte Maxeke Johannesburg Academic hospital. This is a 1088 bedded quaternary health institution affiliated to University of the Witwatersrand. The Renal unit is managed by a team consisting of a nephrologist, physician, fellows, registrars, medical officers and specialized nurses. The unit receives about 20 new patients per month. Among these are up to three renal transplant recipients per month. These patients attended regular visits every two months to three months at the renal clinic after renal transplantation. Renal transplant recipients who develop dermatological conditions were referred to the Dermatology clinic at the same hospital for further assessment. Dermatological evaluation of these patients included a skin biopsy to determine the correct diagnosis. All cutaneous neoplasms were confirmed by histopathology. The hospital records of these patients are stored in a lock-up room at the Renal unit.

2.3 Study participants and inclusion criteria

All participants 18 years and older that received a renal only transplant between January 1, 2008 and December 31, 2018 and were followed-up at the Renal clinic at Charlotte Maxeke Johannesburg Academic hospital, were included in this study.

2.4 Exclusion criteria

I planned to exclude participants that had dermatological conditions at the time of renal transplantation, but none was identified. I planned to exclude participants with incomplete or missing data. Data for the type of induction immunosuppressive drug was missing in 41 patients but the type of maintenance immunosuppressive therapy was documented in all participants. In addition, data on infection prophylaxis was also missing in 36 patients. Considering that the nature of incomplete or missing data will not adversely affect the objective of this study, I made a post-hoc decision to include all participants irrespective of completeness of data.

2.5 Institution's immunosuppression protocol for renal transplant recipients

At Charlotte Maxeke Johannesburg Academic hospital, the preferred induction immunosuppressive therapy for all renal transplant recipients Interleukin-2 receptor antagonist Basiliximab (Simulect^{R} Norvatis, or Anti-thymocyte immunoglobulin (ATG). ATG is often used in high-risk patients: patients with previous transplant, patients who are less than 14 years old, patient diagnosed with Human Immunodeficiency Virus (HIV), and percentage panel reactive antibody (PRA) luminex > 30%. For long term (maintenance) immunosuppression therapy, patients receive a combination of three medications:

- a calcineurin inhibitor- Cyclosporine or Tacrolimus;
- an antiproliferative agent- Azathioprine, Mycophenolate mofetil (MMF), or Sirolimus;
- a glucocorticoid- Prednisolone.

The choice of the maintenance immunosuppression combination therapy depends on patient risk profile, side effects, and drug availability. The preferred regimen is Prednisolone, Tacrolimus, and Mycophenolate mofetil. The administration of Mycophenolate mofetil rather than Azathioprine is preferred. Despite its increased

cost, Mycophenolate mofetil is preferred over Azathioprine because of its superior ability to prevent acute rejection and a more tolerable side effect profile (Special Issue: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, 2009; Einollahi et al., 2012; Coghill et al., 2016). However, Mycophenolate mofetil is teratogenic, and is no**t** used in female recipients of childbearing age unless they are on long term contraception, or have had surgical sterilization procedures, or have absolute infertility (Carl and Wiesel, 1997). In the later patients, azathioprine is the preferred agent (Special Issue: KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients, 2009).

Infection prophylaxis is initiated immediately following transplantation using a cocktail of cotrimoxazole 800/160mg given once a day, or Dapsone 100 mg given once a day for those allergic to sulphur; Isoniazid 200mg once a day if patient less than 50kg and 300mg if more than 50kg; Pyridoxine 25 mg once a day; and Valganciclovir 450mg to 900mg once a day depending on the glomerular filtration rate and organ donor type. Oral Nystatin drops 2 millilitres given as a gargle three times a day. These infection prophylaxes are administered to the patients for a period of six months then stopped. The goal is to prevent nosocomial infections such as Pneumocystis jiroveci pneumonia, Toxoplasmosis, Cytomegalovirus, urinary tract infection, and candidiasis.

2.6 Ethics approval

Institutional approval for this study was obtained from University of the Witwatersrand, Human Research Ethics Committee (HREC) Medical on, 17th August 2020. The ethics registration number for this research is M1911175. Appendix 1 is a copy of the Ethics approval letter.

Additional permission to conduct this research was obtained from the Chief Executive Officer (CEO) of Charlotte Maxeke Johannesburg Academic hospital. Appendix 2 is a copy of letter of permission from the CEO of Charlotte Maxeke Johannesburg Academic hospital.

Finally, an approval letter was obtained from the Head of Renal unit at Charlotte Maxeke Johannesburg Academic hospital. Appendix 3 is a copy of approval letter form the Head of Renal unit at Charlotte Maxeke Johannesburg Academic hospital.

2.7 Data collection

Having obtained study ethics approval, relevant data were extracted from the hospital records of only the patients that fulfilled the requirement for this study. The data extracted were entered into a study approved data collection form. Appendix 4 is a copy of the study data collection form.

The following information was collected from the participants' hospital medical records:

a. Demographic characteristics: age at the time of renal transplantation; age at time of diagnosis of dermatological conditions; age at time of diagnosis of end-stage renal disease, gender and race.

b. Clinical characteristics: comorbidities; aetiology of end-stage renal disease; organ donor type; duration of infection prophylaxis.

c. Immunosuppressant therapy: type of induction and maintenance immunosuppressive therapy; number of immunosuppressive therapies; duration of immunosuppression before diagnosis of dermatological conditions.

I determined the duration of immunosuppression as the difference in the age at renal transplantation and age at which first evaluation for the dermatological condition was made.

d. History of dermatological conditions, documented clinical examinations, specific test performed in appropriate cases including skin/nail scrapings, and biopsy for culture, sensitivity, and histopathology.

2.8 Statistical analysis

For the purpose of data analysis, the participants' information was transcribed onto Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA). Statistical analysis was performed using Stata version software-Release15.1 (StataCorp LP, College Station, Texas, USA). A descriptive analysis was performed. A test of normality of distribution of the variables was performed using Shapiro-Wilk test. The distribution of participants by demographic and clinical characteristics was presented as frequencies and percentages. Mean and standard deviation was computed for age of the participants, and median with interquartile range (IQR) was computed for the time to renal transplant and time to develop dermatological conditions. Overall prevalence of dermatological condition was computed as a proportion of the total

transplant recipients. Prevalence was also computed by demographic and clinical characteristics. Bivariate statistical analysis was carried out and chi-square test was used to assess the association between development of a dermatological condition and demographic and clinical characteristics. Statistical significance is accepted as $p<0.05$.

CHAPTER 3 RESULTS

3.1 Demographic and clinical characteristics of renal transplant recipients

There was a total of 173 renal transplant recipients that attended the renal transplant clinic at Charlotte Maxeke Johannesburg Academic hospital from January 1st 2008, to December 31st 2018. Sixty-three percent of the participants were males and 37% were females. The mean age at time of transplant was 45 years. When the age distribution was categorised, 40% participants were 50 years and above, and 60% were less than 50 years. Africans represented most of the participants 73%, Whites 13%, Indians 8%, and Coloured 5% participants.

All participants received renal allotransplantation as a consequence of end-stage renal disease. When the aetiology of end-stage renal disease was considered, 83% of the participants had essential hypertension while 17% did not have hypertension. The aetiology of end stage renal disease in the non-hypertensive group were: diabetes mellitus, glomerulonephritis, nephrotic syndrome, obstructive uropathy, congenital anomalies, lupus nephritis, and HIV-associated nephropathy (HIVAN).

The median time to renal transplantation was three years; 75% of the organs were from deceased donors, and 25% were from living-related donors. Our institution's protocol of infection prophylaxis was implemented in 79% transplant recipients as 21% participants were transferred from other institutions. Sixty-five percent participants had their infection prophylaxis for six months, while 14% participants had their prophylaxis extended beyond six months. The polyclonal gamma globulin, Anti-Thymocyte immunoglobulin, was used as an induction agent in 36% of the participants, while Basiliximab (Simulect^{R}) was used in 40% of the participants. In 24% participants the induction agent was not documented. A combination of Prednisolone, Tacrolimus, and Mycophenolate mofetil was used in 81% participants as maintenance therapy, while 19% of the participants had other combinations. The type of immunosuppression regime used by participants in this study was based on the participants immunologic risks and co-morbidities.

The demographic and clinical characteristics of the study population is shown in Table 1

Table 1: Demographics and clinical characteristics of renal transplant recipients

Characteristic	**Subgroups**	N=173	Percent
Gender	Male	109	63.0
	Female	64	37.0
Age group at transplant (years)			
Mean age (SD)		44.7 (11.9)	
Age groups (years)	<30	22	12.7
	30-39	34	19.7
	40-49	47	27.2
	50+	70	40.5
Race			
	African	127	73.4
	Coloured	9	5.2
	Indian	14	8.1
	White	23	13.3
Aetiology of end-stage renal disease			
	Hypertension	144	83.2
	Non-hypertension	29	16.8
Time to transplant (Years)			
Median (IQR)		3 (2-5)	
Time range	2	55	34.4
	3-4	57	35.6
	5+	48	30.0
Donor type	Cadaveric donor	130	75.1
	Living-related donor	43	24.9
Duration of infection prophylaxis			
	6 months	112	64.7
	>6 months	25	14.5
	Not documented	36	20.8
Types of induction therapy			
	Anti-Thymocyte Globulin	62	35.8

	Basiliximab	70	40.5
	Not documented	41	23.7
Types of maintenance therapy			
	Cyclosporine/ /Prednisone/Azathioprine	3	1.7
	Cyclosporine/Prednisone/MMF	20	11. 6
	Tacrolimus/ Prednisone/Azathioprine	8	4.6
	Tacrolimus/Prednisone/MMF	140	80.9
	Azathioprine/Prednisone/MMF	2	1.2

3.2 Prevalence of dermatological conditions in renal transplant recipients.

Of the 173 renal transplant recipients, 119 (69%) participants developed dermatological conditions during the study period. There were 76 males and 43 females. There is no significant difference between males and females that developed dermatological conditions, $p = 0.73$.

When the age categories of participants that developed dermatological conditions were considered, 11 participants who were less than 30 years of age, followed by 26 participants who were between 30 years and 39 years, 33 participants who were between 40 years and 49 years, and 49 participants who were 50 years and above developed dermatological conditions. There was no significant difference between the age categories that developed dermatological conditions, $p = 0.11$.

When considering the race of the population group who developed dermatological conditions, 88 participants were Africans, 6 participants were Coloured, 10 participants were Indians, and 15 participants were White. There was no significant difference within each racial group when the participants that developed dermatological conditions were compared to participants without dermatological conditions, $p = 0.87$.

A total of 102 renal transplant recipients who developed dermatological conditions had hypertension as the aetiology of their end-stage renal disease, while 17 participants had non-hypertensive aetiologies as the cause of their end-stage renal disease. There was no significant difference in dermatological conditions between

hypertension versus non-hypertension, p = 0.19.

Of the organ donor procurement types, 88 participants who received cadaver allografts developed dermatological conditions, while 31 participants that received living-related allografts developed dermatological conditions. There was no significant difference in dermatological conditions in cadaver versus living-related donor, p = 0.59.

Seventy-three participants that received their infection prophylaxis for six months developed dermatological conditions, while 22 participants that continued infection prophylaxis beyond six months developed dermatological conditions. There was a significant difference in dermatological conditions between duration of infection prophylaxis at six months versus greater than 6 months, p = 0.025.

When the type of induction therapy was considered, 39 participants that received ATG developed dermatological conditions. Likewise, 50 participants that received Basiliximab (Simulect^{R}) developed dermatological conditions. There was no significant difference in dermatological conditions between participants that received ATG versus Basiliximab, p = 0.29.

A total of 94 participants that received the triple combination maintenance immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil), developed dermatological conditions. Twenty-five participants that received other combinations developed dermatological conditions. There was no significant difference between type of maintenance immunosuppressive drug and dermatological conditions, p = 0.45.

The prevalence of dermatological conditions by demographic and clinical characteristics is shown in Table 2. The prevalence of dermatological conditions in renal transplant recipients is shown in figure 1.

Table 2: Prevalence of dermatological conditions by demographic and clinical characteristics

Characteristics	**Dermatological conditions**				p-value
	No		**Yes**		
	N=54	**%**	**N=119**	**%**	
Overall prevalence	54	31.2	119	68.8	
Types of conditions					
Viral infections	NA		38	22.0	
Fungal infections	NA		30	17.3	
Bacterial infections	NA		11	6.4	
Cutaneous neoplasms	NA		11	6.4	
Adverse drug reactions	NA		29	16.8	
Gender					
Male	33	30.3	76	63.9	.728
Female	21	32.8	43	39.1	
Age group (years)					
<30	11	50.0	11	50.0	.106
30-39	8	23.5	26	76.5	
40-49	14	29.8	33	70.2	
50+	21	30.0	49	70.0	

Race					
African	39	30.7	88	69.3	.870
Coloured	3	33.3	6	66.7	
Indian	4	28.6	10	71.4	
White	8	34.8	15	65.2	
Aetiology of end-stage renal disease					
Hypertension	42	29.2	102	70.8.	.195
Non-hypertension	12	41.4	17	58.6	
Donor type					
Cadaveric donor	42	32.3	88	67.7	.590
Living-related donor	12	27.9	31	72.1	
Duration of infection prophylaxis					
6 months	39	34.8	73	65.2	.025
>6 months	3	12.0	22	88.0	
Not documented	12	33.3	24	66.7	
Type of induction therapy					
ATG	23	37.1	39	62.9	.299
Basiliximab(Simulect^{R})	20	28.6	50	71.4	
Type of maintenance therapy					
Tacrolimus/ Prednisone/MMF	46	32.9	94	67.1	.452
others	8	24.2	25	75.8	
Time to skin diseases (years)					
Median (IQR)			2 (1-4)		
<1	NA		6	5.0	
1-2	NA		53	44.5	
3-4	NA		23	19.3	
5+	NA		37	31.1	

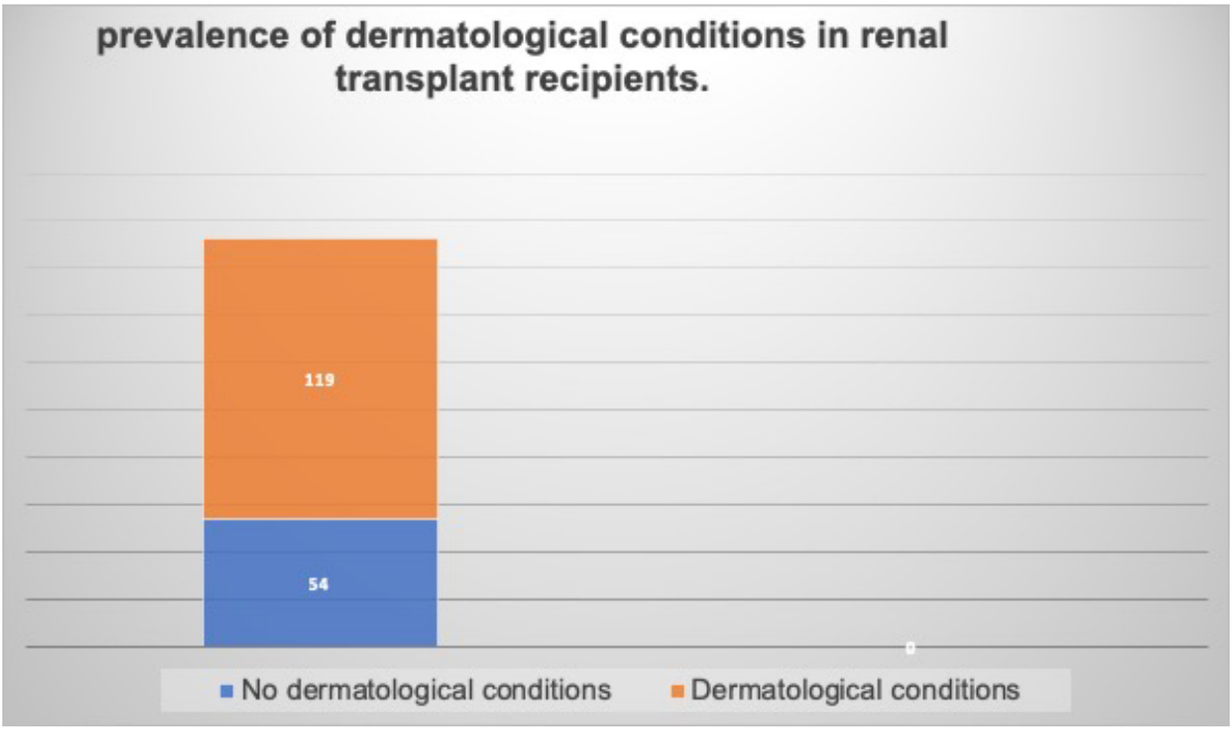

Figure 1: Prevalence of dermatological conditions in renal transplant recipients

3.3 Types of dermatological conditions in renal transplant recipients

The classification of dermatological conditions observed in this study cohorts were cutaneous infections in 46% participants, cutaneous neoplasms in 6% participants, and adverse cutaneous drug reactions in 17% participants. Of the cutaneous infections, viral infections occurred in 22% participants; followed by fungal infection in 17% participants; and the least was bacterial infections in 6% participants. Table 5 shows the types of dermatological conditions in renal transplant recipients.

When the subgrouping of the types of dermatological conditions was considered, there were a total of 148 dermatological conditions as 29 participants had more than one type of dermatological conditions. Herpes simplex infection occurred in 17% of cases, warts in 8%, and varicella in 5%.

The distribution of fungal infections was superficial dermatophyte infections (T. capitis, T. corporis, T. cruris, T. faciei, and T. unguium) in 9% cases, muco-cutaneous candidiasis in 8% cases, pityriasis versicolor in 3% cases, and onychomycosis in 1% of the cases.

For bacterial infections, there were cutaneous abscess in 5% cases; cellulitis in 1% cases; and other bacterial infections in 1%.

The most common neoplasms were benign and included: actinic keratosis in 4% cases; and others (seborrheic keratosis, sinus histiocytosis, and pyogenic granuloma). There were only two cases of Kaposi sarcoma in this study.

The most common adverse cutaneous reaction was acneiform eruptions, in 9% cases. This was attributed to prednisolone. Other adverse cutaneous reactions observed were stasis dermatitis in 6% cases, gum hypertrophy in 5% cases, peripheral oedema in 3% cases, moon face in 1% cases, drug rash in 1% cases, and others.

Table 3 shows the types of dermatological conditions observed.

Table 4 shows the subtypes of dermatological conditions. Figure 2 shows a cluster chart depicting the subtypes of dermatological conditions.

Table 3: Types of dermatological conditions

Conditions	Number of patients	%
None	54	31.2
Viral cutaneous infection	38	22.0
Fungal cutaneous infection	30	17.3
Bacterial cutaneous infection	11	6.4
Cutaneous neoplasms	11	6.4
Adverse drug reactions	29	16.8
Total	173	100

.

Table 4: Subtypes of dermatological conditions

Dermatological conditions	Subgroups	N	%
Viral infection		**44 (29.7%**	
	Herpes	25	16.9
	Warts	12	8.1
	Varicella	7	4.7
Fungal infection		**33 (22.2%)**	
	Dermatophyte infection	14	9.5
	Pityriasis versicolor	5	3.4
	Candidiasis	12	8.1
	Onychomycosis	2	1.3
Bacterial infection		**12 (8.1%)**	
	Abscess	7	4.7
	Cellulitis	2	1.3
	Folliculitis	1	0.7
	Cutaneous tuberculosis	1	0.7
	Syphilis	1	0.7
Cutaneous neoplasm		**13 (8.7%)**	
	Pyogenic granuloma	1	0.7
	Seborrheic Keratosis	3	2.0
	Sinus histiocytosis	1	0.7
	Actinic keratosis	6	4.0
	Kaposi sarcoma	2	1.3
Adverse drug reaction		**46 (31%)**	
	Chronic pruritus	1	0.7
	Moon face	2	1.3
	Gum hypertrophy	8	5.4

	hirsutism	1	0.7
	purpura	1	0.7
	Seborrheic dermatitis	1	0.7
	Stasis dermatitis	9	6.1
	striae	1	0.7
	urticaria	1	0.7
	acne	14	9.5
	Skin rash	2	1.3
	Peripheral oedema	5	3.4
Total		**148**	100

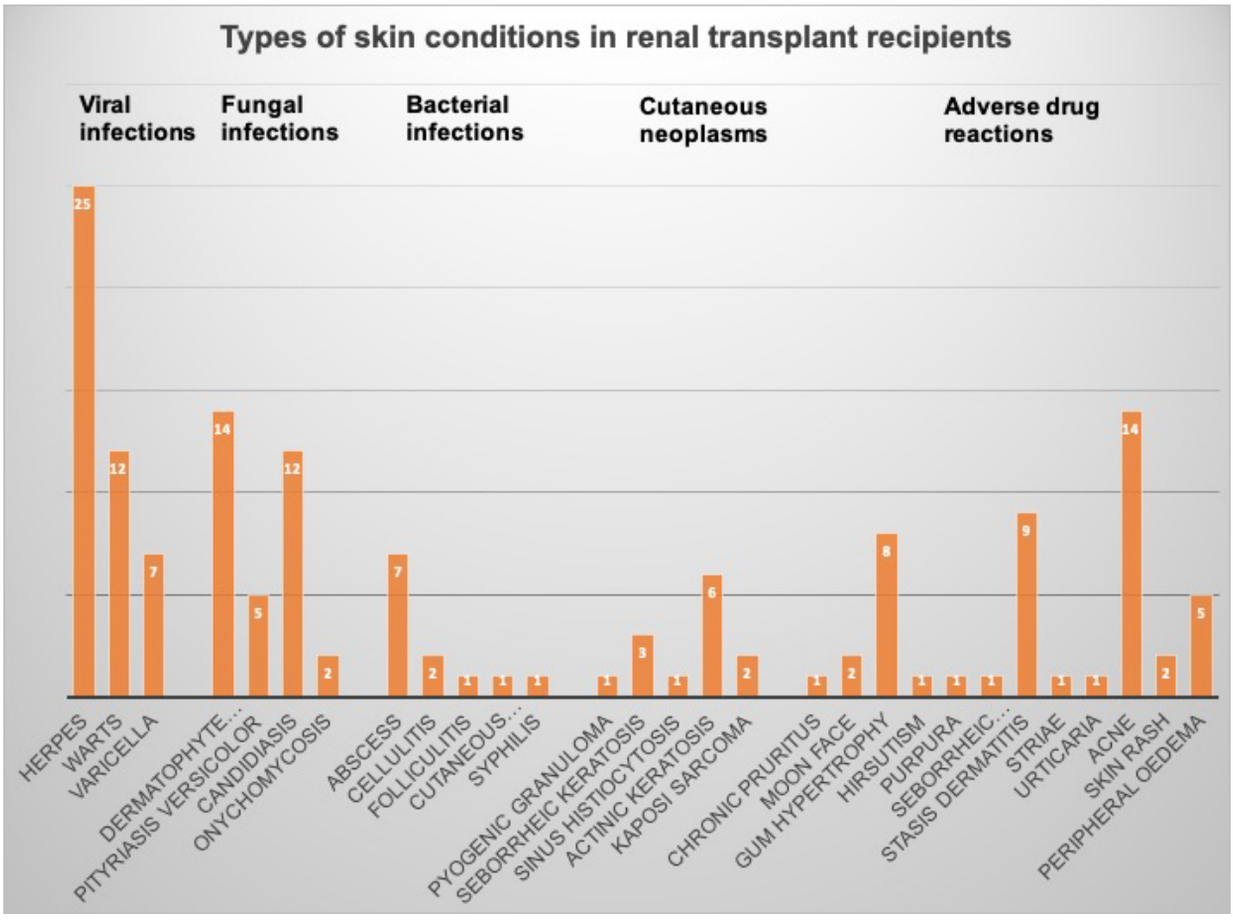

Figure 2: Cluster chart depicting the subtypes of dermatological conditions

3.4 Comparison of types of dermatological conditions with demographic and clinical characteristics

Viral cutaneous infections were the most common dermatological condition in 30% male participants, and 35% female participants.

In all age groups, viral infections remained the most common dermatological infection, except in participants 50 years and above, where 83% participants developed cutaneous neoplasms.

Viral infections were more common in 36% of people of African descent compared to Coloureds (10%), Indian (17%); and Whites (27%).

Fifty percent of Indians developed cutaneous adverse drug reactions, compared to Africans (19%); Coloureds (33%); and Whites (33%).

Thirty-three percent of Whites developed cutaneous neoplasms compared to Africans (4%); Coloureds (33%). Indians in this study did not develop cutaneous neoplasm.

Irrespective of the type of induction immunosuppressant therapy, viral infections remained the most common dermatological condition and occurred in 36% participants that received ATG, and 28% participants that received Basiliximab.

A statistical test of association could not be computed because of the small number of participants.

Table 6 shows the comparison of types of dermatological conditions by demographic and clinical characteristics.

Table 5: Comparison of types of dermatological conditions by demographic and clinical characteristics

		Viral	Fungal	Bacterial	Neoplasm	ADR
Gender		N(%)	N(%)	N(%)	N(%)	N(%)
	male	23(30.3)	20(26.3)	5(6.6)	9(11.8)	19(25.0)
	Female	15(34.9)	10(23.3)	6(14.0)	2(4.7)	10(23.3)
Age group						
	<30	12(33.3)	9(25.0)	1(2.8)	3(8.3)	11(30.6)
	30-39	11(29.7)	10(27.0)	6(16.2)	2(5.4)	8(21.6)
	40-49	12(37.5)	9(28.1)	2(6.3)	5(15.6)	4(12.5)
	50+	0(0.0)	0(0.0)	1(16.7)	0(0.0)	5(83.3)
Race						
	African	32(36.4)	24(27.3)	11(12.5)	4(4.5)	17(19.3)
	Coloured	1(16.7)	1(16.7)	0(0.0)	2(33.3)	2(33.3)
	Indian	1(10.0)	4(40.0)	0(0.0)	0(0.0)	5(50.0)
	White	4(26.7)	1(6.7)	0(0.0)	5(33.3)	5(33.3)
Induction agent						
	ATG	14(35.9)	10(25.6)	4(10.3)	3(7.7)	8(20.5)
	Basiliximab	14(28.0)	14(28.0)	6(12.0)	4(8.0)	12(24.0)
	Not documented	10(33.3)	6(20.0)	1(3.3)	4(13.3)	9(30.0)
Immunosuppression duration						
	<1	3(50.0)	2(33.3)	0(0.0)	0(0.0)	1(16.7)
	1-2	11(20.8)	18(34.0)	5(9.4)	4(7.5)	15(28.3)
	3-4	10(43.5)	3(13.0)	4(17.4)	3(13.0)	3(13.0)
	5+	14(37.8)	7(18.9)	2(5.4)	4(10.8)	10(27.0)

3.5 Time to development of dermatological condition post renal transplantation

The time to develop dermatological conditions was grouped. Five percent of participants developed dermatological condition in less than one year post transplantation. Forty-five percent of participants for one year to two years, 19%

participants for three years to four years, and 31% participants for five years and above. The median time to develop dermatological conditions was two years. All the participants were on immunosuppressant at the time of development of dermatological conditions.

Table 7 shows time to development of dermatological conditions.

The occurrence of viral cutaneous infections appears to peak one year following renal transplantation and prevalence remain high after five years.

Fungal infection appears to peak at one year following transplantation but prevalence drops sharply by three years.

Bacterial infection appears to peak at one year and prevalence wanes over the years.

On the other hand, cutaneous neoplasm did not appear until after one year on immunosuppressant. The prevalence of cutaneous neoplasms appears to remain the same over the study period.

For adverse cutaneous reactions, there were two peaks in prevalence at one to two years and after five years.

The prevalence of dermatological conditions based on duration on immunosuppressant therapy is shown in figure 3.

Table 6: Time to development of dermatological conditions in renal transplant recipients

Time	Classifications of dermatological conditions				
(years)	Viral N(%)	Fungal	Bacterial	Neoplasms	Adverse drug reactions
<1	3(50.0)	2(33.3)	0(0.0)	0(0.0)	1(16.7)
1-2	11(20.8)	18(34.0)	5(9.4)	4(7.5)	15(28.3)
3-4	10(43.5)	3(13.0)	4(17.4)	3(13.0)	3(13.0)
5+	14(37.8)	7(18.9)	2(5.4)	4(10.8)	10(27.0)

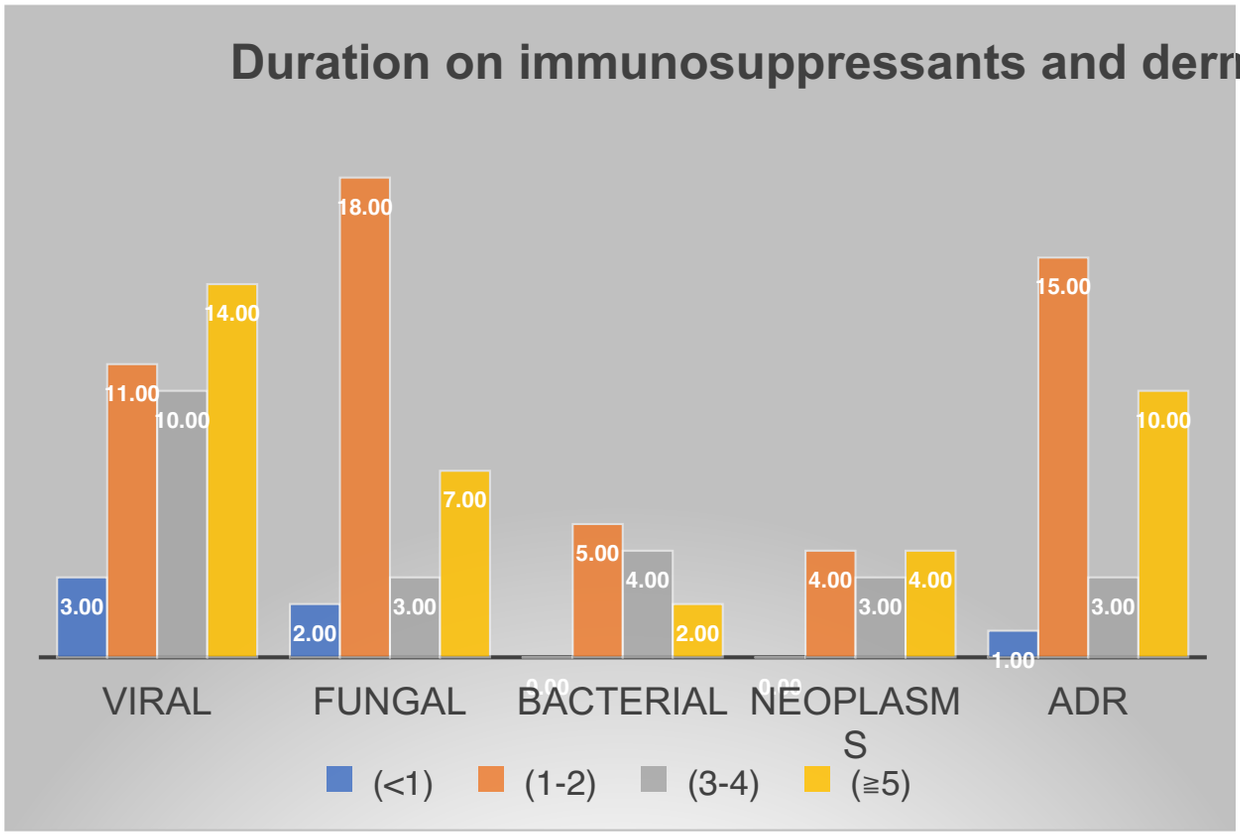

Figure 3: The prevalence of dermatological conditions based on duration on immunosuppressant therapy

CHAPTER 4 DISCUSSION

Renal transplant recipients require chronic immunosuppression to prevent graft loss and prolong survival. This is achieved using various types of immunosuppressants. Often, the immunosuppressive drugs are administered in various combinations at the lowest effective doses to mitigate adverse events. Chronic immunosuppression has been shown to predispose patients to opportunistic infections and malignancies, not only in transplant recipients but also in other disease conditions like HIV infection (Hamilton et al., 1981; Wisgerhof et al., 2010; Garrido and Borges-Costa, 2017; Das, Sharma and Karn, 2021). In addition, there is a layer of complications related to side effects of the immunosuppressive drugs that may occur.

This study shows that in a population of renal transplant recipients from a university-affiliated transplant centre in South Africa, dermatological conditions are common with a prevalence rate of 69%. This figure is supported by recent publications from other countries (George et al., 2009; Wisgerhof et al., 2010; Garrido and Borges-Costa, 2017; Das, Sharma and Karn, 2021).

Cutaneous viral infections, specifically Herpes simplex infection is the most prevalent dermatological condition in renal transplant recipients. This study supports that notion.

Herpes simplex infection tend to present within the first year following renal transplantation. It is characterised by cluster of vesicles in an erythematous base or punched out superficial erosions of infection that occurs in the genital area. Knowledge of herpetic infections in renal transplant recipients will enable appropriate surveillance and effective treatment. My finding agrees with a study from Portugal by Garrido and Borges-Costa in 2017, that showed that viral infection was the most common dermatological conditions among renal transplant recipients, but contrasts with a study from India by George et al., 2009. This later study showed that fungal infection was the most common dermatological conditions seen in renal transplant recipients (George et al., 2009). It is possible that the hot and humid climate in India favoured the occurrence of fungal infection.

The prevalence of cutaneous neoplasms is low from this study. This could be explained by the majority of the participants being of African descent who are known to have lower risk of skin cancers. Another factor in support of the low prevalence of cutaneous neoplasms can be attributed to the immunosuppression maintenance regime of Tacrolimus, Prednisone and Mycophenolate mofetil. Data from two observational studies documented a low cancer prevalence in participants with this regime when compared to patients on Azathioprine based regime (Einollahi et al., 2012; Coghill et al., 2016).

In addition, the short duration of the study period could explain this as one study from Australia showed an association between the incidence of skin cancers and duration of immunosuppression. This Australian study showed that incidence of non-melanoma skin cancers approach 50% after 20 years of immunosuppression (Carrol et al 2003).

The influence of race on dermatological conditions in renal transplant recipients is explored in this study. People of African descent were observed to develop more viral infections compared to other races. People of White race had more cutaneous neoplasms. Apart from the effect of ultraviolet light exposure, an association between skin type and cutaneous neoplasms have been demonstrated. A meta-analysis by Shahidi et al, 2018 showed that, people with Fitzpatrick skin types I to IV are more likely to develop cutaneous neoplasms.

Overall, the prevalence of cutaneous adverse drug reaction of 17% in my study is much lower than from the study by George et al, of 62% (George et al., 2009). This

observation may be explained by under-reporting in my hospital setting. The most common adverse drug reaction shown in the study by George et al, were moon facies and acneiform eruptions. In my study, the most common cutaneous adverse drug reactions were acneiform eruptions, gum hypertrophy and stasis dermatitis. The addition of high doses of glucocorticoid in the immunosuppressive regimen within the first-year post-transplant may explain the high prevalence of acneiform eruptions in my study. However, the low prevalence of moon facies in my study may be explained by poor reporting as these cushingoid features are often missed by non-dermatologist. Hence, the importance of early referral to a dermatologist. Most acneiform eruptions and moon face often resolve with glucocorticoid dose adjustments (Bencini et al., 1983). When this initial measure fails, treatment with either topical or systemic antibiotics and topical retinoids are introduced. In patients that develop gum hypertrophy to cyclosporine, switching to Tacrolimus will resolve this problem (Chugh et al., 1994;Greenberg, Armitage and Shiboski, 2008)

Most studies show that age does not affect spectrum of dermatological conditions (Sandhu et al., 2003; Alper et al., 2005). My study shows a trend towards more viral infections in patients less than 50 years of age. The relevance of this finding needs to be explored further in future studies.

Our institution administers a cocktail of anti-microbial drugs to prevent nosocomial infections following renal transplantation. Systemic infection in the post-transplant period is attended by a significant mortality. My study showed that transplant recipients that continued infection prophylaxis beyond six months are more likely to develop dermatological conditions than those that stopped at six months. This finding supports the practice of stopping infection prophylaxis at six months as there is no benefit to continuing infection prophylaxis beyond six months.

The median duration of immunosuppression before diagnosis of dermatological conditions was two years. This period is usually the peak of maximum immunosuppression when patients are at higher risk of developing opportunistic as well as community acquired infections (Ponikvar, Novljan and Ponikvar, 2002; Moloney et al., 2005b; van Delden et al., 2020). Another reason for the high prevalence of cutaneous infection can be the prolonged duration on infection prophylaxis in some patients which can further dampen the immune response of patients. Furthermore, prolonged infection prophylaxis can cause emergence of

resistant micro- organisms, thus increasing their risk to developing cutaneous infection (van Delden et al., 2020).

My study showed that patient characteristics like gender, age, race, type of donor, aetiology of end-stage renal disease, and type of immunosuppression induction or maintenance drugs did not appear to affect the prevalence of dermatological conditions in renal transplant recipients. However, there was a trend towards more cases of cutaneous viral infections in males' participants less than 50 years, and participants of African descent, but a statistical test of significance was not performed because of small numbers of participants.

4.1 Strength of this study

This study was conducted at an academic hospital that receives referrals from almost a third of the population of South Africa. Hence the findings of this study are generalizable to the rest of the country. As South Africa is a multi-racial society, this study created the opportunity to explore the influence of race on dermatological conditions in renal transplant recipients.

4.2 Limitations of this study

As this is a retrospective study, it is prone to selection bias. This could have affected the result of this study as only patients referred to a public-funded hospital have been studied, while patients from private-funded hospitals were not studied. The spectrum of dermatological conditions reflects what had been documented in the participant's hospital records such that lesions not considered as relevant by the assessing clinician may have been under-reported.

4.3Recommendations for future studies

Future study should be multicentre and prospective. It should have a structured format (a structured data collection form) to ensure all study relevant variables are captured. Patient follow up period should be structured to accommodate the natural history of some dermatological conditions. This will allow adequate accrual of participants for a meaningful statistical analysis.

4.4Conclusion

As chronic immunosuppression is required to promote allograft survival, renal transplant recipients are at risk of dermatological conditions that could be challenging to treat. This study has demonstrated that these dermatological conditions are common and has further characterised the type of conditions observed in an emerging economy. The patients should be made aware of these conditions and should be encouraged to follow preventive strategies highlighted in this study. It is important that dermatologists be aware of these conditions. It is also important that they work closely with nephrologists in the surveillance and appropriate management of these conditions.

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4 Appendix 1: Ethics clearance certificate

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

R14/49 Dr Roseline Chioma Ede

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1911175

NAME: (Principal Investigator)	Dr Roseline Chioma Ede
DEPARTMENT:	Dermatology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A 10-year retrospective cohort study of Dermatology conditions in Renal Transplant Recipients (RTR) at the Charlotte Maxeke Johannesburg Academic Hospital in 2008-2018
DATE CONSIDERED:	29/11/2019
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Deepak Modi
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/08/2020

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

DECLARATION OF INVESTIGATORS

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

Principal Investigator Signature _____ Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

5 Appendix 2

GAUTENG PROVINCE
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Ms. N. Mzila
Office of the Clinical Director
Email: Nolwazi.Mzila@gauteng.gov.za
Tell: (011): 488-4812
15th October 2019

Dear Dr. RC Ede

STUDY TITLE: A 10 Year Retrospective Cohort Study of Dermatological Conditions in Renal Transplant Recipients (RTR) at the Charlotte Maxeke Johannesburg Academic Hospital

Permission to review patient file for conduction of the above mentioned study is provisional approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your Ethics Clearance Certificate as soon as the study is approved by the Ethics Committee for the CEO's office to give you the final approval to conduct the study.

Supported / not supported

Dr. M.I. Mofokeng
Clinical Director
DATE: 17/10/2019

Approved / not approved

Ms. G. Bogoshi
Chief Executive Officer
DATE: 21.10.2019

6 Appendix 3

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF INTERNAL MEDICINE

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Division of Nephrology, Charlotte Maxeke
Johannesburg Academic Hospital

02/10/2019

Dear colleagues

Re: Dr R. Ede

Regarding the study entitled " A 10 year retrospective cohort study of Dermatological conditions in Renal transplant Recipients(RTR) at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) , 2008-2018".

I hereby give my permission to conduct the study from the Division of Nephrology. She may access patient records in the renal transplant unit at CMJAH.

Yours sincerely

Prof Graham Paget MBBCh (Wits) FCP (SA) Cert. Neph (SA) MMed (Wits) FRCP (UK)

Head-Division of Nephrology at the University of the Witwatersrand

7 Appendix 4: Data collection sheet

Unique id					
BIODATA					
Age (years)					
sex					
race					
weight					
CLINICAL COMORDITIES					
HYPERTENSION					
DIABETES					
COPD					
RVD		ARV Yes/ No	ONSET	TYPE OF ARVS	CD4/VL
TB					
OTHERS					
CHRONIC KIDNEY DZ(CKD)					
Cause					
Age at Diagnosis of CKD					
Time to Transplant					
Age at time of transplant					
DONOR TYPE		CADAVER= 1		LIIVING	

IMMUNOSUPPRESSANTS				
Names		I	2	3
Time of commencement				
Class of immunosuppression				
Duration on immunosuppression				

(years)				
Immune stopped due to skin lesion		YES	NO	
TYPE OF INDUCTION		SIMULECT -A	ATG-B	
DERMATOLOGICAL CONDITION				
Type of skin dx				
Time to onset of skin dx (from date of TX)				
duration on immunosuppressant at time of skin dx				
How was diagnosis made		CLINICAL	HISTOLOGY	OTHERS
Treatment received				
Treatment response		RESOLVED	NOT RESOLVED	OTHER TRT