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Comparison of quality of life in patients with advanced chronic kidney disease undergoing haemodialysis, peritoneal dialysis and conservative management

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Title of Research: Comparison of Quality of Life in patients with Advanced Chronic Kidney Disease undergoing Haemodialysis, Peritoneal Dialysis and Conservative Management

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

DECLARATION

I, Neelu Susan Mathew, declare that this research report is my own work. It is submitted in the submittable format with my protocol and extended literature review 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:  (21/10//2022)

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ABSTRACT

Introduction: Quality of life is an under-appreciated clinical target which affects patient and modality survival. Lack of dialysis slots in the state sector result in assignment to treatment modalities without regard to effects on these parameters. We assessed the effect of dialysis modality, demographic, and laboratory parameters on mental health and quality of life measurements.

Methods: Size-matched voluntary cohorts were recruited from patients on haemodialysis (HD), peritoneal dialysis (PD), and patients on conservative management (CM). Responses to self-administered Hospital Anxiety and Depression Scale (HADS) and Kidney Disease Quality of Life Short Form 36 (KDQOL-SF36) questionnaires and demographic and baseline laboratory parameters were compared between treatment modalities using the Student t-test and Pearson Chi-square test. Linear regression was used to test for independent effect where significant difference was observed.

Results: HADS anxiety score was highest ($p < 0.001$) and KDQOL-SF36 emotional wellbeing was poorer in HD ($p < 0.001$). Social functioning ($p = 0.011$) and physical limitation due to pain ($p = 0.03$) were poorer in PD. Unemployment ($p = 0.044$) was more frequent in HD; fewer PD patients required social support grants ($p = 0.008$). Significant independent effect was found for age ($p = 0.009$), employment ($p = 0.007$), and Haemoglobin (Hb) ($p = 0.025$) on anxiety; HD worsened ($p = 0.037$) and PD improved ($p = 0.007$) anxiety. Unemployment ($p < 0.001$) and low Hb ($p = 0.018$) worsened depression. PD improved ($p = 0.002$) and HD worsened ($p < 0.001$) emotional well-being. PD worsened social functioning ($p = 0.0018$). PD ($p = 0.007$) and higher phosphate ($p = 0.022$) worsened and HD ($p = 0.01$) and higher Hb ($p = 0.02$) improved physical discomfort / pain.

Conclusion: Advanced CKD increases anxiety and depression and limits quality of life. PD improves mental health and emotional wellbeing and preserves ability to undertake economic activity but limits social functioning and causes greater physical discomfort. Targeting Hb and phosphate may ameliorate modality effects on mental health and quality of life.

Keywords: Quality of Life; chronic kidney disease.

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LIST OF ABBREVIATIONS

Alb	Albumin
ANOVA	Analysis of Variance
CAPD	Continuous Ambulatory Peritoneal Dialysis
CKD	Chronic Kidney Disease
CM	Conservative Management
eGFR	Estimated Glomerular Filtration Rate
HADS	Hospital Anxiety And Depression Scale
Hb	Haemoglobin
HD	Haemodialysis
HR-QOL	Health Related Quality Of Life
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcome
KDOQI	Kidney Disease Outcome Quality Initiative
KDQOL-SF	Kidney Disease Quality Of Life- Short Form
KF	Kidney Failure
LTRRT	Long Term Renal Replacement Therapy
MWUT	Mann Whitney u Test
PD	Peritoneal Dialysis
Pmp	Per Million Population
PO4	Phosphate
PTH	Parathyroid Hormone
ROPD	Renal Out Patient Department
RRT	Renal Replacement Therapy
SD	Standard Deviation
SF-36	Short Form-36
QOL	Quality Of Life
WHO	World Health Organisation
X^2	Chi Squared

CHAPTER 1 – PROTOCOL WITH EXTENDED LITERATURE REVIEW

1. LITERATURE REVIEW

1.1 INTRODUCTION

Quality of life (QOL) is an underappreciated and under-researched component of the management of kidney failure (KF). Increased survival rates of patients with KF on dialysis, combined with declining rates of transplantation, result in patients being confined for many years, if not permanently, to these therapies. Although life-preserving, a host of disease and treatment-related factors may reduce the quality of life of patients on dialysis, which may lead to non-compliance with therapy or requests to discontinue with treatment. Thus, the provision of appropriate and adequate dialysis should aim to return patients to near normal social functioning (1–3). There are few studies in South Africa comparing the QOL of patients with Chronic Kidney Disease (CKD) undergoing haemodialysis, peritoneal dialysis and conservative management. This study evaluated the quality of life of patients with advanced chronic kidney disease (CKD) with and eGFR <20 ml/min/1.73m^2, not yet on dialysis with those on haemodialysis (HD) and peritoneal dialysis (PD).

1.2 BACKGROUND

A significant burden of communicable and non-communicable diseases such as diabetes, hypertension, and HIV infection, combined with poor access to specialist nephrology services combine to render CKD and KF not uncommon in the developing world. Genetic risks such as the APOL1 mutation exacerbate this pattern in the African context (4,5). Improving socio-economic conditions in the developing world may paradoxically contribute to this trend through increasing the prevalence of hypertension and diabetes and lengthening life expectancy, in turn increasing the effect of age-related kidney disease (6). As a result, it is predicted that by the year 2030, 70% of patients with KF will live in the developing world (1). At present, 15.8% of the adult population of Africa are believed to have CKD (stages 1-5), with 4.6% of this population having clinically significant (stage 3

– 5) CKD (7). The South African Renal Society Registry has reported that there are 10774 patients with KF receiving dialysis therapy in the country, giving a prevalence of 190 per million population (pmp) (8).

A significant proportion of these patients access dialysis in the private sector which services a comparatively small portion of the general South African population; the prevalence of patients receiving dialysis in the private sector is 855 pmp compared to 66 pmp in the state sector (2). Historical inequalities in health care provision have resulted in the majority of patients requiring dialysis therapy being dependent on the state sector for treatment; the lower prevalence of patients on dialysis in this sector is reflective of the shortages in the availability of this therapy in state facilities. As a result of these limitations together with the declining transplant rates(8), patients with KF in the state sector may not be able to access dialysis but may instead be offered conservative therapy, and those patients fortunate enough to receive dialysis in the state sector are not usually given the opportunity to choose the dialysis modality which is most acceptable to them.

Although palliative care guidelines exist, which includes symptom management and interdisciplinary care(9), state units have been slow to implement dedicated programmes for the care of patients living with KF who are not able to access dialysis. The development of an appropriate palliative care programme requires an understanding of the uraemic symptoms which most compromise the quality of life (QOL) of such patients. Patients fortunate enough to be able to receive dialysis do not necessarily experience a significant improvement in individual QOL, due to multiple contributing factors such as depression, anxiety, comorbidities and vascular issues to name a few(10). Dialysis treatments carry the potential for significant morbidity which may offset the amelioration of uraemic symptoms (11). Such physical discomfort may exacerbate the psychosocial distress of diagnosis and treatment. Assignment to a dialysis modality not acceptable to the patient or not accommodating to their individual circumstance may exacerbate the psychosocial stress attendant upon living with a chronic life-limiting disease such as KF and may result in non-compliance with prescribed dialysis. Examining factors which

limit QOL in dialysed patients would thus facilitate the delivery of optimised dialysis and improve individual patient survival on this therapy.

Despite the utility of QOL assays in facilitating patient-centric care, assessment of this parameter is rarely undertaken in state facilities. The present study was undertaken in patients on active, dialysis-based therapies and on conservative treatment for advanced CKD, in order to characterise factors affecting the quality of life of patients undergoing management for this condition. Sub-analysis was undertaken evaluating the effect of comorbidities and of KF-related complications on quality of life scores. Comparison of quality of life scores was made between those patients on active therapy and those on conservative treatment, as well as between dialysis modalities (peritoneal and haemodialysis). This study contributes to literature on KF patient quality of life in the South African context and may assist in service provision at Helen Joseph Hospital in the future.

1.3 QUALITY OF LIFE IN CHRONIC KIDNEY DISEASE

Chronic kidney disease manifests with a variety of non-specific symptoms, including fatigueability, cognitive slowing, altered taste sensation, gastrointestinal disturbance, pruritus, peripheral oedema, and peripheral neuropathy (12,13), the cumulative effect of which may result in significant impairment of quality of life. Significant clinical symptomatology characteristically onsets in CKD stage 3 and worsens as renal function progressively declines (14). The presence of symptoms which limit quality of life to a significant degree are considered indications to initiate dialysis in patients with stage 5 CKD (estimated glomerular filtration rate, eGFR, less than 15ml/min/1.73m^2) (15); impaired quality of life is therefore a recognised feature of advanced CKD and is considered to be an independent indicator for dialysis initiation.

Adequate dialysis prescribed to target recommended KDOQI clearance levels has the potential in the short term to dramatically improve quality of life through control of uraemic toxins. Both haemodialysis

(HD) and peritoneal dialysis (PD) are efficacious in this regard. Nevertheless, patients on dialysis may continue to experience significant psychological disturbance which may impair QOL. Depression has been found to be an independent factor for prolonged stay and mortality and morbidity for patients with KF (14). It has been reported that 6 – 18% of patients on long-term dialytic support experience depression (15), with a further 12 – 52% of these patients experiencing generalised anxiety (14); the prevalence of depression and anxiety in patients with CKD increases with CKD stage (16). Whilst it is likely that persistent depression and anxiety in dialyzed patients partly results from the psychological burden of living with the life-limiting diagnosis of KF, additional disease related factors may also be important contributors. For example, depression has been linked to the presence of a pro-inflammatory cytokine milieu in KF (16)(. Of note, this cytokine milieu has additionally been identified as a causative factor in the increased incidence of cardiovascular disease in patients with KF (16), a finding which may partially account for the association between depression and anxiety and an increased risk for mortality as well as morbidity in KF and CKD (16–18).

It has traditionally been held that PD may provide for a better overall QOL due to improved independence of patients assigned to this treatment modality: whereas patients on HD are required to attend a dialysis centre three times per week for four hours to receive treatment, patients on PD are usually seen once a month in an outpatient setting and at all other times conduct their dialysis at home or in their place of employment. However, the application of either form of dialysis may result in impaired QOL due to modality-related factors. For example, patients on HD must contend with frequent painful access cannulation, a higher prevalence of anaemia-related symptoms due to blood loss in the dialysis circuit, cardiovascular disease symptoms due to haemodynamic strain during dialysis, intradialytic hypotension arising as an effect of time-concentrated ultrafiltration, and physical restriction during the prolonged dialysis session (11). In comparison, patients on PD may experience gastrointestinal discomfort during dialysate dwell, frequent peripheral overload due to the non-

volumetric nature of ultrafiltration in this modality, and isolation from support systems due to the outpatient nature of this therapy (11).

It is known that the success of a dialysis modality is enhanced by the acceptability of the prescribed therapy to the individual patient (19). Planned initiation of dialysis has been proven to have better clinical outcomes than unplanned start (20) A systemic review of pre-dialysis decision making showed that decisions on modality are influenced by personal and family values, demonstrating the need for discussions with the patient and family in planning dialysis initiation (21). Numerous factors may influence a patient's acceptance of a dialysis modality, including the effect of access type on body image, the suitability of home circumstances to prescribed therapy (for example, sufficient space to store PD dialysate), the ability of the patient to attend scheduled dialysis appointments (for example, access to transport to attend 3 haemodialysis sessions per week at the dialysis unit), and confidence on the part of the patient to be able to perform prescribed dialysis (for example, to undertake the correct sterilization technique required to perform the PD dialysate indwell) (19). Failure to adequately consider such factors in the prescription of a dialysis therapy may contribute to patient psychological stress which may negatively impact on quality of life and in some cases lead to non-compliance with dialysis which in turn may worsen quality of life due to the recurrence of uraemic symptoms. In the state sector, patients are rarely involved in decisions regarding which dialysis modality is prescribed, mainly because of the limited number of available dialysis slots.

This limited number of dialysis slots restricts the provision of treatment in the state sector to patients medically fit to undergo transplantation, as a result, dialysis patients receiving therapy in public units tend to be younger with fewer comorbidities than the dialysis population in the private sector (8,11). It is generally agreed that the quality of life of transplant recipients is better than that of patients remaining on dialysis (11,14), which can to some degree be validated by the observation that transplantation improves the morbidity of KF patients as measured by hospital admissions (22). However, the reducing

number of transplants undertaken in the state sector and the lack of suitable living donors result in patients waiting for many years on dialysis until a graft becomes available (8). As a result, KF patients receiving dialysis may accrue aging and dialysis vintage-associated pathologies which may compromise quality of life, including progressive cardiovascular disease, CKD-bone mineral disease sequalae, and access failures with deteriorating clearances. Thus, quality of life in patients with CKD progressing to KF is restricted by the disease process itself as well as dialysis treatment modality.

1.4 CURRENT EVIDENCE

Quantification of health-related quality of life (HR-QOL) in patients with CKD / KF is complex due to the number of potential compounding factors operating in the individual setting. The Kidney Disease Quality of Life Short Form (KDQOL-SF 36) is a frequently used tool which measures eight domains of functioning and wellbeing including: physical function, role limitations due to physical problems, role limitations due to emotional problems, pain, general health perceptions, social function, emotional well-being and energy or fatigue (23,24). Depression or anxiety in these patients may be assessed using the Hospital Anxiety and Depression scale (HADS). A depression score of eight or above suggests possible depression (25,26) and correlates well with the diagnosis for mood disorders by the Structural Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (25). The effect of CKD / KF on quality of life has been assessed by a number of studies in both the developing and developed world. A large population-based study of 46 676 patients from Korea by *Park JI et.al.* showed a graded association between the CKD stages and quality of life (27). The effect of socioeconomic factors and clinical comorbidities on HR-QOL in CKD patients was investigated amongst more than 3800 people in North America by *Jhamb M et.al* (28), which showed lower scores associated with female gender, lower education and lower income. *Modi GK et.al* have described a negative effect of socioeconomic variables such as female gender, lower income and lower education on QOL in India (29). Similar findings were shown in an Ethiopian study by *Kefale B et.al*, who in addition demonstrated a decreased QOL in the early stages of the CKD (30).

There is limited research comparing quality of life in patients on conservative management with that in patients receiving dialysis. A recent study by *Iyasere O et.al.* in the United Kingdom found mildly improved quality of life with in-patients receiving dialysis by either HD or PD as compared to those on conservative management for KF; however, the median age of patients in this study was 82 years, resulting in significant comorbidities in both cohorts (31). *Da Silva-Gane M et al.* have reported that KF patients on conservative management maintain their quality of life with appropriate symptomatic care, although in this study age groups were not matched and there was a discrepancy in the number of patients in each of the study groups, with only 30 patients included in the conservative group (32). *Brown MA et al*. have reported from Australia in an elderly study group that compared individuals who chose to undergo conservative management including renal palliative care with individuals who undergo dialysis that those receiving conservative care have reduced life expectancy but acceptable quality of life with appropriate palliative care interventions (33)

In a further study, *Iyasere OU et al.* reported no difference in the quality of life and physical function in older patients between HD and PD modalities, although treatment satisfaction rates were higher in PD patients (25). Similarly, a systematic review of studies published from January 1990 to May 2016 by *Ho YF et. al.* failed to find an overall significant difference in HR-QOL between HD and PD, although a higher percentage of PD patients were reported to have a better HR-QOL in relation to physiological, psychological, social parameters and disease symptoms (34). Factors which have been identified as contributing to the poorer HR-QOL observed in HD patients include the time consumed by each HD session and the imposition thereof on work study and regular life plans (35). *Atapour A et al.* have reported from Saudi Arabia that PD patients in that country had a significantly better KDQOL-SF 36 score compared to HD patients, similar findings were reported from a Greek cohort by *Theofilou* (36,37). In comparison, a study undertaken by *Goncalves FA et al*. demonstrated better QOL in patients

undergoing HD; this study has however been criticised for having unequal numbers of patients in the HD and PD groups (38).

In South Africa, a cross-sectional study undertaken at the Groote Schuur Hospital in Cape Town by *Okpechi IG et al*. did not show any significant difference in HR-QOL between HD and PD (39). Another study by *Clark* that involved both public and private sectors in two provinces (Gauteng and Limpopo), showed no difference in HR-QOL by dialysis modality; however, HD patients had a better vitality and physical component score (40)(38). A study from Tygerburg Hospital by *Tannor EK et al* also showed no difference between PD and HD in KDQOL-SF 36 score, but PD patients were shown to have a greater symptom burden and greater social functioning limitation (3). Available literature on the quality of life of patients with CKD / ESRD is therefore contradictory and subject to limitations arising from poor quality data.

The present study sought to investigate factors affecting the quality of life of patients with advanced CKD / ESRD and the effect of dialysis on ameliorating or exacerbating health-related limitations on quality of life in these patients through analysis of the KDQOL-SF 36 responses from size-matched PD, HD, and conservative management patient cohorts.

2. AIM AND OBJECTIVES

2.1 AIMS

The aim of this study was to investigate and describe factors limiting the quality of life in patients with advanced CKD / ESRD across management strategies.

2.2 STUDYOBJECTIVES

2.2.1 *PRIMARY OBECTIVES*

The primary objective of this study was to characterise factors affecting the quality of life experienced by patients with advanced CKD / ESRD.

2.2.2 *SECONDARY OBJECTIVES*

Secondary objectives of this study were:

- To compare quality of life scores and factors affecting HR-QOL between management strategies (conservative, peritoneal dialysis, and haemodialysis)
- To investigate the effect of clinical and demographic parameters on quality of life scores, specifically:
    - i patient age
    - ii patient gender
    - iii marital status
    - iv education level
    - v employment and income status
    - vi distance of residence from dialysis centre
    - vii dialysis vintage (time spent on dialysis)
    - viii haemoglobin level
    - ix serum ferritin concentration
    - x serum albumin concentration
    - xi serum calcium concentration
    - xii serum phosphate concentration
    - xiii serum PTH concentration
    - xiv serum urea concentration (in lieu of Kt/V, the measurement of which in PD patients is too complex for this study) – for HD patients pre dialysis urea concentration was used
    - xv comorbidity (diabetes mellitus, confirmed cardiovascular disease, HIV infection)

xvi number of admissions over the antecedent 1 year

xvii time since most recent admission

xviii number of access complications over the antecedent 1 year

xix number of peritonitis episodes over the antecedent 1 year (PD patients only)

3. METHODS

3.1 STUDY DESIGN

The study was a comparative cross-sectional study, containing descriptive and comparative elements.

3.2 STUDY SETTING

The study was a single centre study undertaken at Helen Joseph Hospital Renal Unit and General Nephrology Outpatient Clinic.

3.3 STUDY POPULATION

a. Inclusion Criteria

The following patients were considered for participation in the present study:

i Age > 18 years

ii Patients under the care of the Helen Joseph Division of Nephrology for at least 3 months

iii Patients with an eGFR documented to be below 20ml/min/1.73m^2 on at least 2 measurements. This upper limit of eGFR for inclusion in the advanced CKD group was chosen in view of the probability of CKD-related symptoms at GFR levels below 25mL/min/1.73m^2, and the improbability of prolonged survival at more advanced levels of renal dysfunction which might have compromised representation of patients not on dialysis in final analysis.

iv Patients who gave voluntary informed consent to participate in the study

b. Exclusion Criteria

The following patients were not considered as eligible to participate in the present study:

i Patients transferred to dialysis at Helen Joseph from other dialysis centres

ii Patients with known psychiatric illness, or cognitive or neurosensory impairment, or other conditions preventing the patient from giving informed consent to participate in the study

iii Patients admitted to the hospital within the past 1 month

3.4 SAMPLING METHOD, SIZE AND SELECTION

Patients were recruited from the chronic haemo- and peritoneal dialysis units and from the Renal Outpatient Department (ROPD) at Helen Joseph Hospital in consideration of the inclusion and exclusion criteria outlined previously using convenience sampling. Fifty patients were recruited from each unit; a total of 150 patients was therefore included in the study. The sample size of 50 patients for each group was chosen in consideration of the minimum number of patients receiving peritoneal or haemodialysis at the hospital over the year preceding this study. Patients were counselled and invited to participate in the study during scheduled dialysis or ROPD appointments; participation was on a voluntary basis. Patients who were unable to understand the English questionnaires and assessment forms were assisted with translation by a single nurse from the Renal Unit in order to standardise the responses.

3.5 MEASUREMENT INSTRUMENTS/TOOLS

• Patients who agreed to participate in the study were requested to complete the following:

1. The Kidney Disease and Quality of Life- Short Form Questionnaire, which is made up of 12 questions measuring physical and mental functioning, and 24 specific questions related to the disease itself (see Annexure A). The KDOQL-SF provides information on quality of life across 4 subdomains, namely:

i Combined physical and mental functioning (questions 1 – 12)

ii Burden of kidney disease (questions 13 – 16)

iii Symptoms and problems of kidney disease (questions 17 – 28)

iv Effects of kidney disease on daily life (questions 29 – 36)

In addition, the KDOQL-SF provides an overall score for quality of life. Subdomain and overall scores were derived using on-line calculators in which patient responses were entered anonymously providing scores as continuous variables facilitating statistical analysis. In general, a higher score is indicative of a better quality of life.

2. The Hospital Anxiety and Depression Scale questionnaire, which uses a score from 0-21 for either depression or anxiety (see Annexure B). A score of eight or above suggests possible depression or anxiety.

3. The datasheet (Annexure C), with respect to socioeconomic parameters.

3.6 DATA COLLECTION

Patients were counselled with the aid of a participant information sheet and informed consent (Annexure D) was obtained from each participating patient. The data collection sheet (Annexure C) was used to collect demographic and dialysis related data as described under the measurement tools. The HR-QOL was assessed using the KDQOL-SF (Annexure A), which is explained under the measurement tools. Depression and anxiety screening was undertaken using the Hospital Anxiety and Depression Scale.

Questionnaires completed by study participants were collected at the end of each dialysis session or clinic and immediately sealed in an envelope and forwarded to the primary investigator. Relevant laboratory parameters as outlined previously were collected from the patient records by the primary investigator recorded on the individual patient data collection sheet (Annexure C).

During the process of data collection, all completed data collection sheets were collated and securely maintained offsite by the primary investigator; only the primary investigator had access to the completed data collection sheets. Following the completion of collection, data was uploaded onto an electronic Excel database in an anonymous fashion and individual data collection sheets were destroyed in order to ensure the anonymity of participating patients.

Safety measures were practiced during collection of all data to prevent Covid transmission. Adequate Personal Protective Equipment (PPE) was worn, and social distancing was maintained while collecting data.

4. DATA ANALYSIS

Once completed, the Excel database was exported to Statistica in order to undertake the following analyses:

a) Descriptive analysis of the sample population as a whole and within the treatment subgroups (PD, HD, and conservative management), including analysis of demographic and socioeconomic parameters, laboratory values, and KDQOL-SF 36 and the HAD scale scores. During this process continuous variables were assessed for normality of distribution using the Shapiro Wilk W test and visual inspection of the histogram plot in order to inform subsequent inferential testing. The outcomes of these analyses were tabulated; the distributive frequency of categorical parameters was presented as N and % of total N, and the distribution of continuous parameters was presented as dictated by the outcome of the assessment of Gaussian distribution with the central tendency being represented by the mean or median and the dispersion of data represented by 95% standard deviation or interquartile range for parametric and non-parametric parameters, respectively.

b) Quality of life scores as determined by the KDQOL-SF and HAD scale was compared between treatment groups using either the ANOVA technique or the Kruskall Wallis test as dictated by the distribution of the relevant data. Analysis was made of both the overall KDOQL-SF score and subdomain scores.

c) The contribution of demographic, socio-economic, laboratory parameters and treatment modality on KDOQL-SF overall and subdomain scores and on HAD scale was analysed by means of linear regression.

5. ETHICAL CONSIDERATIONS

a) The protocol was submitted for ethics approval to the Helen Joseph Hospital Ethics Committee and to the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (Clearance Certificate no: M200635). Consent for recruitment of patients and

access to the relevant laboratory data from clinical records was obtained from the Division of Nephrology at Helen Joseph Hospital.

b) Patient participation in the study was on a voluntary basis and informed consent was obtained prior to answering the questionnaires. Counselling for participation in the study was undertaken by the primary investigator; all patients thus counselled were be provided with a participant information sheet (see Annexure D).

c) Individual responses of the participating patients remained anonymous and confidential in final reporting. Individual responses as recorded in the data collection sheet were accessible to the primary researcher; the data collection sheet was destroyed upon completion of data collection and variables uploaded anonymously to a database which was used for statistical analysis.

6. STUDY STRENGTHS

a) Data was collected by the primary researcher using the same data collection sheet formats and standardized questionnaires. This ensured that the data was standardized and reliable.

b) There are no other South African studies that compare QOL of patients with CKD on HD, PD and conservative management. This will be valuable in the overall management of patients with CKD

7. STUDY LIMITATIONS

a) Possible selection bias due to the convenience sampling method.

b) The study population involves the patients in Helen Joseph Hospital only, which might not be the true reflection of the entire population.

c) The sample size was limited to 50 by the number of patients on haemodialyis and peritoneal dialysis in the unit.

8. FINANCIAL IMPLICATIONS

The study was self-funded by the primary researcher collecting the data. There will be no additional costs to the hospital or the patient.

9. TIMELINE

The study commenced following protocol approval by the HREC.

The following Gantt chart in Table 1 shows the timeline of the study.

Table 1: Gantt chart

	Mar - 2020	Apr - 2020	May - 2020	Jun - 2020	Jul - 2020	Aug - 2020	Sep - 2020	Oct - 2020	Nov - 2020	Dec - 2020	Jan - 2021	Feb - 2021	Mar - 2021	
Literature review														
Protocol preparation														
Protocol Assessment														
Ethics application														
Data Collection														
Data Analysis														
Writing up paper														

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CHAPTER 2 – SUBMISSIBLE ARTICLE

Title of the article: Comparison of Quality of Life in patients with Advanced Chronic Kidney Disease undergoing Haemodialysis, Peritoneal Dialysis and Conservative Management

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Article type: Original article

Running title: Comparison of Quality of Life in Patients with CKD.

ABSTRACT

Introduction: Quality of life is an under-appreciated clinical target which affects patient and modality survival. Lack of dialysis slots in the state sector result in assignment to treatment modalities without regard to effects on these parameters. We assessed the effect of dialysis modality, demographic, and laboratory parameters on mental health and quality of life measurements.

Methods: Size-matched voluntary cohorts were recruited from patients on haemodialysis (HD), peritoneal dialysis (PD), and patients on conservative management (CM). Responses to self-administered Hospital Anxiety and Depression Scale (HADS) and Kidney Disease Quality of Life Short Form 36 (KDQOL-SF36) questionnaires and demographic and baseline laboratory parameters were compared between treatment modalities using the Student t-test and Pearson Chi-square test. Linear regression was used to test for independent effect where significant difference was observed.

Results: HADS anxiety score was highest ($p < 0.001$) and KDQOL-SF36 emotional wellbeing was poorer in HD ($p < 0.001$). Social functioning ($p = 0.011$) and physical limitation due to pain ($p = 0.03$) were poorer in PD. Unemployment ($p = 0.044$) was more frequent in HD; fewer PD patients required social support grants ($p = 0.008$). Significant independent effect was found for age ($p = 0.009$), employment ($p = 0.007$), and Haemoglobin (Hb) ($p = 0.025$) on anxiety; HD worsened ($p = 0.037$) and PD improved ($p = 0.007$) anxiety. Unemployment ($p < 0.001$) and low Hb ($p = 0.018$) worsened depression. PD improved ($p = 0.002$) and HD worsened ($p < 0.001$) emotional well-being. PD worsened social functioning ($p = 0.0018$). PD ($p = 0.007$) and higher phosphate ($p = 0.022$) worsened and HD ($p = 0.01$) and higher Hb ($p = 0.02$) improved physical discomfort / pain.

Conclusion: Advanced CKD increases anxiety and depression and limits quality of life. PD improves mental health and emotional wellbeing and preserves ability to undertake economic activity but limits social functioning and causes greater physical discomfort.
Targeting Hb and phosphate may ameliorate modality effects on mental health and quality of life.

Keywords: Quality of Life; chronic kidney disease.

INTRODUCTION:

A significant burden of communicable and non-communicable diseases, combined with poor access to nephrology services, render chronic kidney disease (CKD) not uncommon in low-to-middle income countries (LMIC); in Africa genetic risks exacerbate this pattern(1,2). Improving socio-economic conditions in LMIC may paradoxically exacerbate this trend through higher prevalence of hypertension, diabetes and increased life expectancy(3). As a result, it is predicted that by the year 2030, 70% of patients with kidney failure (KF) will live in LMIC (4). At present, 15.8% of the adult population of Africa are believed to have some degree of CKD, with 4.6% of this population having clinically significant (stage 3 – 5) CKD(5). CKD manifests with a myriad of nonspecific physical and psychological symptoms and significant symptomatology usually manifests in CKD stage 3, which worsens with graded decline in renal function(6–8). Symptoms which limit quality of life to a significant degree are considered indications to initiate dialysis in patients with stage 5 CKD (Estimated Glomerular Filtration Rate (eGFR) less than 15ml/min/1.73m^2) (9).

At present, 10774 patients with KF receive dialysis therapy in South Africa. Although the majority of South Africans are reliant on the state sector for management of CKD, long-term under-resourcing of state dialysis units has resulted in disparities in access to treatment, with the prevalence of patients on dialysis in the private sector being 855 per million population (pmp) as compared to 66 pmp in the state sector(10). Patients with KF in the state sector may therefore not be able to access dialysis but may instead be offered conservative therapy; those patients fortunate enough to receive dialysis do not have the luxury of choosing their preferred dialysis modality. Assignment to treatment modalities that are not tailored to the patient's individual circumstances may exacerbate the psychosocial stress of dialysis (14). Increased survival rates of patients with KF on dialysis, combined with declining rates of transplantation result in prolonged waitlisting of patients on dialysis (10). As a result, KF patients receiving dialysis may accrue aging and dialysis vintage-associated pathologies which may compromise quality of life (QOL). Dialysis treatments carry the potential for significant morbidity which may offset the

amelioration of uraemic symptoms (11,12). These factors lead to depression and anxiety being prevalent in patients receiving dialysis (13,14); the presence of which results in higher morbidity and hospital admissions(15) and which may lead to noncompliance with therapy (14).

Despite its clinical significance, Quality of life (QOL) is an underappreciated and under-researched component of the management of KF. It has been traditionally held that peritoneal dialysis (PD) offers better health-related quality of life (HRQOL) as compared to haemodialysis (HD) (11). There are few studies in the African context comparing the QOL of patients with advanced CKD between patients undergoing haemodialysis (HD), peritoneal dialysis(PD) and those on conservative management (CM)(16–18). This study evaluates the quality of life of patients with advanced CKD not on dialysis with those on HD and PD, and considers the effect of comorbidities and of KF-related complications on quality-of-life scores.

METHODS [328]

Approval for this study was obtained from the Human Research Ethics Committee (HREC) of the University of the Witwatersrand (protocol number M200635). Size-matched cohorts were voluntarily recruited from the outpatient haemodialysis, peritoneal dialysis, and renal outpatients department at Helen Joseph Hospital using convenience sampling. Non-dialyzed patients were only considered for inclusion if baseline eGFR was consistently below 20mL/min/1.73m^2. This upper limit of eGFR for inclusion in the advanced CKD group was chosen in view of the probability of CKD-related symptoms at GFR levels below 25mL/min/1.73m^2, and the improbability of prolonged survival at more advanced levels of renal dysfunction which might have compromised representation of patients not on dialysis in final analysis. eGFR of <20mL/min/1.73m^2 was chosen instead of <15mL/min/1.73m^2, as the latter group usually do not cope well without and this could affect the results as the group sizes would not be comparable. Patients with a history of hospitalization within the antecedent month were excluded. Participants self-administered the Hospital Anxiety and Depression Scale (HADS) and the Kidney Disease Quality of Life Short-Form 36 (KDQOL- SF36) questionnaires during routine clinical

appointments. KDQOL-SF36 responses were transformed using the online RAND health group KDQOL-SF^{TM} 1.3 calculator to domain scores. Respondent demographics, HADS and transformed KDQOL-SF36 domain scores were entered with most recent laboratory results in an anonymized database which was used for statistical analysis.

Both the HADS and the KDQOL-SF36 surveys are validated for use in patients with advanced CKD (19,20). The KDQOL-SF36 consists of 36 questions which provide information on quality of life across a number of subdomains, namely physical functioning, role-physical, pain, emotional well-being, role-emotional, and social functioning. The HADS scale questionnaire produces a score of 0 – 21 for both anxiety and depression symptoms, a score of more than 8 correlates with overt clinical disorder, whilst a score of 4 – 8 is indicative of borderline symptomatology.

Baseline laboratory and demographic characteristic were compared between treatment groups using the ANOVA or Student t-test and Pearson Chi-square test respectively, in order to determine baseline differences between these groups. The Mann Whitney U-test was used to analyse dialysis vintage where visual inspection of the histogram plot and the Shapiro-Wilk W test indicated non-parametric distribution. HADS and KDQOL-SF36 scores were then compared between treatment groups using the ANOVA or Student t-test as indicated. Where statistically significant difference was observed for quality of life measurement, subsequent analysis using multivariate stepwise sigma restricted linear regression modelling was undertaken to test the independence of treatment modality from confounding effect caused by differences in baseline parameters.

RESULTS [1257]

One hundred and fifty patient participants were recruited to this study, comprising 50 patients on HD and PD each, and 50 patients with advanced kidney dysfunction (eGFR less than 20mL/ min/1.73m^2) undergoing conservative outpatient management (CM). Amongst CM participants, 31 (62%) were in stage 5 of CKD (eGFR consistently below 15mL/min/1.73m^2). Baseline characteristics and the HADS and KDQOL-SF36 responses of participants are shown in Table 1 below.

Table 1. Baseline characteristics and questionnaire responses of participants.

	HD (n = 50)	**PD** (n = 50)	**CM eGFR<20** (n = 50)	**CM stage 5 eGFR<15** (n = 31)
Age (years)	45.5 ± 12.3	44.1 ± 11.6	59.0 ± 13.5	59.9 ± 14.1
Gender	Male: 23 (46%) Female: 27 (54%)	Male: 25 (50%) Female: 25 (50%)	Male: 27 (54%) Female: 23 (46%)	Male: 14 (45.2%) Female: 17 (54.8%)
Highest level of education	None: 2 (4%) Primary: 6 (12%) Secondary: 31 (62%) Tertiary: 11 (22%)	None: 1 (2%) Primary: 5 (10%) Secondary: 33 (66%) Tertiary: 11 (22%)	None: 2 (4%) Primary: 10 (20%) Secondary: 30 (60%) Tertiary: 8 (16%)	None: 1 (3.3%) Primary: 5 (16.1%) Secondary: 20 (64.5%) Tertiary:3 (16.1%)
Relationship status	None: 23 (46%) Partner: 9 (18%) Married: 14 (28%) Widowed: 4 (8%)	None: 22 (44%) Partner: 5 (10%) Married: 19 (38%) Widowed: 4 (8%)	None: 19 (38%) Partner: 3 (6%) Married: 21 (42%) Widowed: 3 (6%)	None: 13 (41.9%) Partner: 2 (6.4%) Married: 10 (32.3%) Widowed: 6 (19.4%)
Source of income	Unemployed: 47 (94%) Social grant: 37 (74%)	Unemployed: 42 (84%) Social grant: 21 (42%)	Unemployed: 38 (76%) Social grant: 29 (58%)	Unemployed: 25 (80.6%) Social grant: 17 (54.8%)
Dialysis vintage (months)	47 (15 – 82)	24 (13 – 40)	N/A	NA
Comorbidities	Diabetic: 11 (22%) HIV positive: 11 (22%) CVS disease: 48 (96%)	Diabetic: 8 (16%) HIV positive: 10 (20%) CVS disease: 43 (86%)	Diabetic: 25 (50%) HIV positive: 11 (22%) CVS disease: 47 (94%)	Diabetic: 14 (45.2%) HIV positive: 7 (22.6%) CVS disease: 31 (100%)
Hb (g/dL)	9.6 ± 1.6	11.1 ± 2.3	11.3 ± 2.4	10.9 ± 2.4
Urea (mmol/L)	18.8 ± 8.8	22.2 ± 9.7	21.7 ± 8.0	24.2 ± 8.2
Ca (mmol/L)	2.24 ± 0.28	2.18 ± 0.23	2.23 ± 0.24	2.19 ± 0.26
PO_4 (mmol/L)	1.89 ± 0.81	1.84 ± 0.90	1.43 ± 0.56	1.54 ± 0.60
Albumin (g/L)	38.1 ± 6.1	33.6 ± 6.8	40.2 ± 4.6	40.0 ± 4.7
PTH (ng/mL)	46.6 ± 44.6	58.26 ± 40.26	15.83 ± 8.82	17.99 ± 9.16

HD: Haemodialysis; PD: Peritoneal Dialysis; CM: Conservative management; HIV: Human Immunodeficiency Virus; CVS: Cardiovascular; Hb: Haemoglobin; Ca: Calcium; PO4: Phosphate; PTH: Parathyroid Hormone.

Patients on CM were older than those on dialytic therapies ($p < 0.000001$), there was no significant difference in age between patients on PD or HD. Haemoglobin (Hb) levels were lower in patients on HD compared to those on PD ($p = 0.0003$) and those on CM ($p = 0.00004$), Hb levels were similar for those on PD and CM ($p = 0.556$). Phosphate levels were higher in patients on dialysis therapies compared to those on CM ($p = 0.001$), levels were not significantly different between dialysis modalities ($p = 0.776$). PTH levels were higher in those patients on dialysis ($p = 0.000009$); although PTH levels were numerically higher in PD there was no significant difference in PTH level between dialysis modalities ($p = 0.184$). Observed differences in phosphate and PTH levels between dialysis and CM groups persisted when analysis was restricted to only include stage 5 CKD CM patients ($p = 0.046$ and $p = 0.001$ respectively). Albumin levels were lower in patients on PD than in those on HD ($p = 0.0007$) and lower than those on CM ($p < 0.000001$); albumin levels in patients on HD trended towards being

significantly higher than those on CM (p = 0.055). Dialysis vintage was longer in those patients on HD compared to those on PD (p = 0.017). Diabetics were over-represented in the CM group (p = 0.0004). There was no significant difference observed for gender (p = 0.726), highest level of education (p = 0.790), relationship status (p = 0.803), HIV infection status (p = 0.962), history of cardiovascular disease (p = 0.149), urea (p = 0.116) or calcium (p = 0.472) between treatment groups.

Significant socio-economic effects of kidney disease were observed in this cohort. The majority of patients in all treatment groups were unemployed; however, unemployment was significantly more frequent in the HD treatment group (p = 0.044). Patients on PD were less frequently supported by a social grant than other treatment groups (p = 0.008); patients on HD were more frequent recipients of a social grant than other groups (p = 0.005).

HADS and KDOQL scores are show in Table 2. HADS anxiety score was highest in patients on HD (p = 0.0008), a finding which persisted even when restricting analysis only to those patients with CKD stage 5 (p = 0.003). Patients meeting HADS criteria for the presence of anxiety symptoms of significance (score > 4) were significantly more frequent in the HD group (22, 44%) than in the PD (8, 16%) or CM (11, 22%) groups (p = 0.004). Depression score was numerically higher in patients on HD compared to other treatment groups, a finding which trended towards significance (p = 0.083). Symptoms of depression (HADS score > 4) were numerically more frequent in the HD group (17, 34%) than the PD (12, 24%) or CM (11, 22%) groups (p = 0.348). Composite physical score was better in patients on HD compared to those on PD (p = 0.005) but was similar in this group to patients on CM (p = 0.095); composite mental score was higher in patients on HD compared to those on PD (p = 0.002) and similar to that of patients on CM (p = 0.095).

Analysis of the subdomains which constitute the KDQOL-SF36 composite scores detected significant differences for all parameters between treatment groups apart from the physical functioning domain. Subjective assessment of the ability to meet physical activity expectations (role – physical domain) was better in patients on CM compared to those on dialysis modalities (p = 0.00003) but similar between those on PD and HD (p = 0.574), significance persisted when analysis was restricted to the CM CKD

stage 5 group (p = 0.003). Patients on PD reported greater physical limitation due to pain than either those on HD (p = 0.030) or those on CM (p = 0.036). Emotional well-being was poorer in HD compared to either the PD (p < 0.000001) or CM treatment groups (p < 0.000001). Subjective assessment of limitations imposed on meeting emotional roles (role – emotional) appeared to be better in patients on HD compared to those on CM (p = 0.017), however, this positive effect for HD was lost when HD was compared to those patients on CM with stage 5 CKD (p = 0.153); there was no significant difference in role-emotional domain scores between HD and PD groups (p = 0.066). Finally, patients on HD reported being better able to meet their social functioning expectations compared to patients on PD (p = 0.011) but showed no difference in comparison to the CM group (p = 0.288); social functioning domain score differences did not reach statistical significance between the PD and CM groups (p = 0.082).

Table 2. HADS/KDQOL Scores comparing HD, PD and CM study groups.

	HD (n=50)	**PD** (n=50)	**CM eGFR < 20** (n=50)	**CM stage 5 eGFR<15** (n=31)
HADS anxiety score	7.16 ± 3.95	4.56 ± 3.66	4.56 ± 3.98	5.38 ± 3.78
HADS depression score	6.12 ± 4.24	4.70 ± 3.43	4.38 ± 4.60	4.77 ± 4.31
Composite physical score	63.24 ± 9.64	57.26 ± 10.98	66.19 ± 7.73	64.95 ± 8.37
Physical functioning	48.70 ± 11.59	50.0 ± 9.04	51.50 ± 10.31	51.45 ± 10.10
Role-physical	60.0 ± 35.36	56.0 ± 35.56	82.50 ± 26.85	79.03 ± 29.65
Pain	86.05 ± 16.69	76.90 ± 24.26	85.80 ± 17.03	84.03 ± 17.23
Composite mental score	53.56 ± 9.27	48.56 ± 6.55	50.70 ± 7.59	51.15 ± 7.49
Emotional well-being	40.40 ± 10.04	55.0 ± 9.85	54.60 ± 7.48	55.32 ± 7.85
Role-emotional	46.67 ± 32.30	34.67 ± 32.27	32.0 ± 27.73	36.56 ± 27.70
Social functioning	59.25 ± 17.8	49.75 ± 18.98	55.75 ± 14.77	53.63 ± 15.54

HD: Haemodialysis; PD: Peritoneal Dialysis; CM: Conservative Management; HADS: Hospital Anxiety and Depression Score

In summary, treatment with HD appeared to increase anxiety and to reduce emotional well-being. In comparison, patients on PD reported greater limitation in physical activity due to pain, and had poorer levels of social functioning than patients on HD.

Since significant differences in baseline characteristics were detected between treatment groups, the possibility that these observed differences in mental health and quality of life could be attributable to

confounding factors was tested using stepwise sigma restricted multivariate linear regression modelling, the outcomes of which are depicted in tables 3 - 5 below.

Table 3. Regression analysis, HADS anxiety and depression scores.

		HADS anxiety			HADS depression		
Parameter	**Ref**	**p**	**β**	**(95% CI β)**	**p**	**β**	**(95% CI β)**
Age	-	0.009	-0.238	(-0.416 - -0.060)	0.128		
Employment	*Unemployed*	0.072	-0.145	(-0.303 – 0.013)	0.0009	-0.269	(-0.425 - -0.112)
Social grant	*Yes*	0.423			0.691		
Diabetes	*Diabetic*	0.987			0.375		
Treatment modality	*CM*	0.037 0.007	HD: 0.205 PD: -0.273	(0.013 – 0.397) (-0.475 - -0.070)	0.593		
Hb	-	0.025	-0.191	(-0.358 - -0.24)	0.018	-0.189	(-0.345 - -0.033)
Phosphate		0.974			0.586		
PTH		0.423			0.828		
Albumin		0.193			0.457		

HADS: Hospital Anxiety and Depression Score; Hb: Haemoglobin; PTH: Parathyroid Hormone.

Younger age and prescription of HD were independently associated with an increased anxiety score, whereas being employed, prescription of PD, and improving Hb levels reduced anxiety. Dialysis vintage was not found to be an independent factor in anxiety score in univariate regression modelling (p = 0.510). Treatment modality did not exert an effect on depression, but employment and improving Hb independently reduced depression levels in respondents in this study.

Table 4. Regression analysis, KDQOL-SF36 mental health scores.

		Emotional well-being			Social functioning		
Parameter	**Ref**	**p**	**β**	**(95% CI β)**	**p**	**β**	**(95% CI β)**
Age	-	0.844			0.058	-0.200	(-0.408 – 0.007)
Employment	*Unemployed*	0.294			0.082	-0.158	(-0.336 – 0.020)
Social grant	*Yes*	0.362			0.283		
Diabetes	*Diabetic*	0.981			0.116		
Treatment modality	*CM*	<0.00001 0.002	HD: -0.712 PD: 0.270	(-0.872 - -0.552) (0.104 – 0.436)	0.086 0.0018	0.175 -0.338	(-0.025 – 0.375) (-0.547 - -0.128)
Hb	-	0.285			0.573		
Phosphate		0.800			0.505		
PTH		0.781			0.770		
Albumin		0.006	-0.210	(-0.359 - -0.061)	0.325		

Hb: Haemoglobin; PTH: Parathyroid hormone; HD: Haemodialysis; PD: Peritoneal Dialysis.

Prescription of haemodialysis reduced emotional wellbeing, and prescription of PD improved emotional well-being when compared to CM. An inverse effect for serum albumin on emotional well-being was also demonstrated. Dialysis vintage appeared to show in univariate analysis a trend towards significant effect ($p = 0.098$). When combined in multivariate analysis with dialysis modality and serum albumin, no independent effect was demonstrable for dialysis vintage ($p = 0.764$), whilst that of modality ($p < 0.000001$) and albumin ($p = 0.020$) were preserved. Significant independent effect for dialysis modality only was shown for the social functioning domain, with HD improving social function and PD reducing social function relative to CM; univariate testing did not find a significant effect for dialysis vintage on this domain ($p = 0.672$).

Table 5. Regression analysis, KDQOL-SF36 pain score.

36 pain score.	Ref	p	β	(95% CI β)
Age		0.621		
Employment	*Unemployed*	0.290		
Social grant	*Yes*	0.528		
Diabetes	*Diabetic*	0.656		
Treatment modality	*CM*	0.010 0.007	HD: 0.256 PD: -0.252	(0.063 – 0.449) (-0.433 - -0.072)
Hb		0.023	0.192	(0.027 – 0.357)
Phosphate		0.022	-0.188	(0.063 – 0.449)
PTH		0.284		
Albumin		0.227		

CM: Conservative Management; HD: Haemodialysis; PD: Peritoneal Dialysis; Hb: Haemoglobin; PTH: Parathyroid Hormone.

Improving Hb level, control of phosphate levels, and prescription of HD were found to be independent factors in improving pain score, while prescription of PD resulted in a worsening of pain score relative to CM. No independent effect was shown for dialysis vintage on this domain.

Together, this data shows significant effects for prescribed dialysis modality on patient anxiety and emotional well-being. Prescription of PD, although having salutatory effects on anxiety and emotional well-being, also results in higher pain scores and reduced social functioning. Improving Hb levels can decrease anxiety and depression and improve pain score. Younger patients are likely to experience higher levels of anxiety. The ability to find employment significantly reduces anxiety and depression in patients living with advanced CKD.

DISCUSSION [1448]

This study emphasises the significant psychosocial challenges faced by patients living with advanced chronic kidney disease. Depression and anxiety disorders appear to be prevalent in these patients with attendant low emotional well-being. Underpinning this disordered psychological health, patients with advanced chronic kidney disease experience significant physical limitation, resulting in concerns regarding their ability to meet socially expected levels of physical function. Younger patients may be more prone to experiencing depression and anxiety symptoms. Whilst disease-dependent physiological factors such as anaemia may contribute to these symptoms, choice of dialysis modality may play an important role in the severity of depression and anxiety and in individual emotional well-being.

Population studies estimate the prevalence of depression amongst South Africans to be 9.8% and that of anxiety disorder to be 15.8%(21) ; prevalence of symptoms of these disorders as evidenced by HADS scoring was higher in this cohort of patients living with advanced CKD. Prevalence rates of depression and anxiety disorders have been reported to be higher in patients living with CKD than in the general population(22–24) and to increase with progression of chronic kidney disease stage (25). Diagnosis of these disorders is more frequent in CKD than in other chronic illnesses, suggesting the contribution of CKD-specific factors to their prevalence in patients living with kidney disease (23).

HRQOL scores deteriorate with advancing CKD as uraemic symptoms mount (26,27). Physical function is prominently affected by CKD due to the limitations imposed on activity by ensuing anaemia, fluid retention, and acidosis (27). Reflecting this, physical functioning was reduced in all treatment groups in this study. Consistent with the high prevalence of mood and anxiety disorders amongst patients in this study, emotional well-being was generally poor in all treatment groups, and patient subjective assessment of ability to meet expected emotional function (role – emotion) was uniformly poor in all respondents.

Proponents of PD cite improved patient satisfaction with the modality arising from reduced impact of dialysis treatments on quality of life (28). Actual evidence for a difference in mental health and quality of life between HD and PD modalities depends on few studies with contradictory findings (23,29,30).

Metanalysis has suggested small but significant improvements in emotional distress and psychological well-being measures for patients on PD compared to those on in-centre HD (31). In the present study, PD patients demonstrated lower HADS anxiety scores, manifested anxiety symptoms less frequently, and had better emotional well-being scores than other treatment groups. Despite these salutatory effects of PD, overall composite mental score was lower in this group than in patients on HD in this study, reflecting the contribution of lower-scoring domains such as social functioning and the related subjective assessment of emotional role fulfilment (role – emotional) in this group.

Apparent differences in quality of life and mental health measurements between treatment groups may reflect the confounding effect of therapy-dependent factors such as patient selection, effect on socio-economic activity, and biochemical effects of dialysis modality. For example, comorbidities such as diabetes may increase the risk of depression (26,27,29,32), as may advancing age (32). In the present study, patients on CM were older and more likely to be diabetic than patients receiving dialysis, reflecting local transplant eligibility-based criteria for entrance to dialysis programmes. Since assignment to PD requires the ability to perform dialysis in the home environment, patients receiving this modality may have better social circumstances than other groups which may affect quality of life scores (33). In this study patients on PD were less frequently unemployed than those on HD and were less frequent recipients of social grants than other treatment groups, indirect evidence perhaps of better socio-economic circumstances in this group.

Albumin has been shown to correlate with several physical and emotional KD-QOL domains (26,34,35), an association believed to derive from the effect of underlying nutritional and inflammation-related pathologies on overall health, but which may in patients on PD reflect increased membrane transport (35). Anaemia is known to reduce both physical (16,26) and mental (26,27) quality of life scores; correction of Hb with erythropoiesis stimulating therapy (ESA) improves quality of life scores (36). In this study, haemoglobin levels were lower amongst patients on HD, a discrepancy which may have arisen from a host of modality-related factors including blood loss in the extracorporeal circuit, vascular

access procedures, and compliance with scheduled dialysis sessions during which erythropoiesis stimulating agent (ESA) therapy is administered.

Parathyroid hormone (PTH) and phosphate have been linked to reduced physical function quality of life scores (16,37); in the present study, phosphate and PTH levels were higher in those patients on dialysis therapy compared to the CM group, possibly reflecting progressive loss of residual renal function in patients on dialysis or self-liberalised diet in this group. Dialysis vintage may result in progressive accumulation of psychological distress (36,38) Dialysis vintage in this study was significantly greater in patients on HD compared to those on PD, raising the possibility of confounding effect for this parameter on mental health and quality of life scores in HD patients.

To exclude the possibility of confounding factor effect, stepwise sigma-restricted multivariate linear regression was undertaken for those mental health and quality of life measurements which appeared to significant difference between treatment groups. In these analyses, PD reduced anxiety and improved emotional well-being. Perhaps reflecting the continuous nature of this therapy in comparison to the intermittent nature of HD, PD was associated with higher pain score. PD was also linked to poorer social functioning, an association which may be due to the need to perform regular exchanges. HD was associated with a higher anxiety score and poorer emotional well-being, although limitations imposed by physical discomfort / pain were reduced in these patients.

The ability to undertake meaningful employment were identified as a significant contributor to anxiety and depression in this cohort. The direct effect of PD on reducing anxiety and improving emotional well-being may be enhanced through the ability of patients on this modality to maintain economic activity.

The inverse association between albumin and emotional well-being score was an unexpected finding. In this young population, we speculate that improving albumin levels may result in improved general fitness, which in turn may result in frustration with persistent inability to meet physical and socio-economic expectations, in turn reducing emotional well-being. Limited exploratory analysis validates this hypothesis to some extent; in univariate testing a significant effect for albumin on the energy /

fatigue domain was observed (β 0.282, 95% CI β 0.125 – 0.438, p = 0.0005). In bivariate testing for the effect of albumin and the energy / fatigue domain on emotional well-being, significance for albumin was lost (p = 0.082), whilst energy / fatigue showed significant negative effect on this domain (β -0.388, 95% CI β -0.540 to -0.235, p = 0.000001), suggesting that at least some of the effect of albumin on emotional well-being may have been mediated as hypothesized. It should be noted that the role of albumin as a marker of nutritional status is subject to significant criticism (39) and that multiple other factors may affect serum concentration. A detailed evaluation of these factors, which is not possible in the present study, would be required to fully elucidate the mechanisms underlying the reported association.

As expected, haemoglobin showed significant correlation with anxiety, depression, and pain score. In patients on HD, improvement in Hb may ameliorate the prevalence on anxiety in this group. Similarly, the effect of PTH on pain score may offer a target for improving this parameter in patients on PD to offset the limitation imposed by the modality.

There are limitations to the present study. In particular, treatment groups were not well matched for age, dialysis vintage, and comorbidities, and had significant differences in a number of measured laboratory parameters, most notably Hb, phosphate, PTH, and albumin. Although not measured, there is also likely to have been significant variation in GFR between treatment groups. The systematics of provision of dialytic therapy in the state sector, and the effect of different treatments on lab parameters, make these differences unavoidable, and their distribution in this study is reflective of clinical reality. Related to this, differences in laboratory sampling between PD (i.e., intradialytic) and HD (i.e., predialytic) may also contribute to differences in these parameters between treatment groups. Such effects are, however, inherent, and were compensated for by the statistical methodology as discussed. Limitations imposed by the cross-sectional nature of this study should also be acknowledged. Although the exclusion of recently admitted patients and the administration of the questionnaires on routine appointment days were employed to limit the effects of recent perturbations on responses, it may be that long-term pooled data would be better reflective of the burden of mental health disorders in these patients.

CONCLUSIONS [154]

Mental health and quality of life of patients on dialysis are under-appreciated clinical targets for patients living with advanced chronic kidney disease which have real impact on patient and modality survival. In the South African context, the epidemiology of CKD and the limited treatment options available consign a young population to dialysis without the option of modality choice and with scant regard to the impact thereof on quality of life. The present study confirms the significant prevalence of anxiety, depression, and reduced quality of life in patients living with advanced CKD, but also offers hope. In particular, the direct effect of PD on reducing anxiety and improving emotional well-being, and the potential indirect effect of PD on anxiety and depression through facilitation of employment, provides reassurance on the "PD-first" programmes adopted by many state units. Finally, direct deleterious effects of modality on quality of life may be ameliorated through attention to haemoglobin and PTH targets.

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CHAPTER 3: APPENDICES

ANNEXURE A

Your Health
– and –
Well-Being

Kidney Disease and Quality of Life (KDQOL™-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.



Thank you for completing these questions!

Kidney Disease and Quality of Life™ (KDQOL™-36)
English Version 1.
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Study of Quality of Life
For Patients on Dialysis

What is the purpose of the study?

This study is being carried out in cooperation with physicians and their patients. The purpose is to assess the quality of life of patients with kidney disease.

What will I be asked to do?

For this study, we want you to complete a survey today about your health, how you feel and your background.

Confidentiality of information?

We do not ask for your name. Your answers will be combined with those of other participants in reporting the findings of the study. Any information that would permit identification of you will be regarded as strictly confidential. In addition, all information collected will be used only for purposes of the study, and will not be disclosed or released for any other purpose without your prior consent.

How will participation benefit me?

The information you provide will tell us how you feel about your care and further understanding about the effects of medical care on the health of patients. This information will help to evaluate the care delivered.

Do I have to take part?

You do not have to fill out the survey and you can refuse to answer any question. Your decision to participate will not affect your opportunity to receive care.

Your Health

This survey includes a wide variety of questions about your health and your life. We are interested in how you feel about each of these issues.

1. In general, would you say your health is: [Mark an ☒ in the one box that best describes your answer.]

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

The following items are about activities you might do during a typical day. <u>Does your health now limit</u> you in these activities? If so, how much? [Mark an ☒ in a box on each line.]

	Yes, limited a lot	Yes, limited a little	No, not limited at all
2. <u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
3. Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
4. Accomplished less than you would like.....	☐ 1	☐ 2
5. Were limited in the kind of work or other activities.....	☐ 1	☐ 2

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
6. Accomplished less than you would like.....	☐ 1	☐ 2
7. Didn't do work or other activities as carefully as usual.....	☐ 1	☐ 2

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks…

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
9. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
10. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
11. Have you felt downhearted and blue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

12. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Your Kidney Disease

How true or false is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
13. My kidney disease interferes too much with my life	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
14. Too much of my time is spent dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
15. I feel frustrated dealing with my kidney disease	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
16. I feel like a burden on my family	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

During the <u>past 4 weeks</u>, to what extent were you bothered by each of the following?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
		▼	▼	▼	▼	▼
17.	Soreness in your muscles?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
18.	Chest pain?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
19.	Cramps?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
20.	Itchy skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
21.	Dry skin?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
22.	Shortness of breath?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
23.	Faintness or dizziness?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
24.	Lack of appetite?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
25.	Washed out or drained?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
26.	Numbness in hands or feet?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
27.	Nausea or upset stomach?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[a].	(Hemodialysis patient only) Problems with your access site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
28[b].	(Peritoneal dialysis patient only) Problems with your catheter site?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Effects of Kidney Disease on Your Daily Life

Some people are bothered by the effects of kidney disease on their daily life, while others are not. How much does kidney disease <u>bother</u> you in each of the following areas?

		Not at all bothered	Somewhat bothered	Moderately bothered	Very much bothered	Extremely bothered
		▼	▼	▼	▼	▼
29.	Fluid restriction?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
30.	Dietary restriction?.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
31.	Your ability to work around the house?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
32.	Your ability to travel?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
33.	Being dependent on doctors and other medical staff?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
34.	Stress or worries caused by kidney disease?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
35.	Your sex life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
36.	Your personal appearance?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

ANNEXURE B

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

ANNEXURE C

DATA COLLECTION SHEET

1. DEMOGRAPHICS:

Age: _____
Gender: M ☐ / F ☐

Educational Status: No Schooling ☐ / Primary ☐ / High School ☐ / College or University ☐

Place of residence (suburb): _____

Distance from Hospital: Less than 10 km ☐ / 10 - 30 km ☐ Greater than 30km ☐

Marital Status: Single ☐ /Married ☐ /Widowed ☐ / Relationship ☐

Social Support: Grant ☐ / No Grant ☐

Employment Status: Employed ☐ /Unemployed ☐

Comorbidities: Diabetes ☐ / HIV ☐ / / Cardiovascular Disease ☐

_____

2. DIALYSIS AND ACCESS (FOR THOSE ON DIALYSIS):

Modality: Haemodialysis ☐ /Peritoneal Dialysis ☐

Duration on dialysis: _____

a. Patients on Peritoneal Dialysis

No.of access problems over the past year:_____

No.of peritonitis episodes: _____

b. Patients on Haemodialysis

Current access: _____

No. of access problems over the past year:_____

No. of Line sepsis: _____

c. Number of admissions over the antecedent 1 year: _____

d. Time since most recent admission:_____

3. RESULTS:

HB	
FERRITIN/SAT%	
UREA	
CALCIUM	
PHOSPHATE	
ALBUMIN	
PTH	

ANNEXURE D

WITS UNIVERSITY

PARTICIPANT INFORMATION SHEET

Comparison of Quality of Life in patients with Chronic Kidney Disease (Stage 3-5) undergoing Haemodialysis, Peritoneal Dialysis and Conservative Management

Greetings

Primary Investigator: Dr N S Mathew 078 322 4270 (moo.neelu@yahoo.com)
Supervisors: Dr M Davies (Malcolm.davies@wits.ac.za)
Dr Z Cassimjee (zaheeracassimjee@gmail.com)
Ms F Kaldine (fmkpsych123@gmail.com)

We are performing a research study on comparison of Quality of Life in patients with Chronic Kidney Disease (Stage 3-5) undergoing Haemodialysis, Peritoneal Dialysis and Conservative Management. Research is a process to seek new knowledge. In this study, we will be using different questionnaires to assess your quality of life as a patient living with chronic kidney disease. This is not part of routine care; however, this study may assist us in improving the care of patients living with chronic kidney disease.

We are kindly asking you to participate in this research study.

The study includes the following:

1. This will be a questionnaire-based study, where you will be asked questions from two different questionnaires, that includes questions about quality of life. A data collection form will be used to collect your demographic data and renal management history (including dialysis). This will only be done after obtaining your consent.
2. The study will take place when you attend the clinic appointments or dialysis sessions and will not be asked to travel to the hospital for the completion of the study.
3. The questionnaires and data collection will approximately take ten minutes of your time. We might ask the nursing staff to help as a translator if we have difficulty understanding each other.
4. The researcher will administer the questionnaires and will assist you to complete the forms. The necessary safety measures will be taken when conducting the study, with the aid of Personal Protective Equipment (PPE) and safe social distancing to prevent Covid transmission.

There are no risks involved in being part of this study and the necessary safety measures will be taken to prevent Covid transmission, with the aid of appropriate PPE and social distancing.

There are no direct benefits for the participants involved in this study, however this study will help us understand the factors that affect quality of life in patients living with Chronic Kidney Disease. These results may assist us in improving the management of patients with CKD in the future.

Participation is voluntary, and the refusal to participate will not involve any changes to your current management, penalty, or loss of benefits that you are currently entitled to.

There will be no costs or payment attached to the participation of this study.

All personal information will be kept confidential and will only be made available to the personal investigator and the Supervisor. Participants' names will not be recorded, and all the data recorded will be securely retained. Participant anonymity can be guaranteed.

The outputs of this study can also be shared with you, on your request.

The contact information of the primary investigator and supervisors is provided above, should you have any further questions of the study.

If you have any concern over the way the study is being conducted, please contact the Chairperson of the Human Research Ethics Committee (HREC) of the University of Witwatersrand who is Professor Clement Penny, who may be contacted on telephone number 011 717 2301, or by e-mail on Clement.Penny@wits.ac.za. The telephone numbers for the Committee secretariat are 011 717 2700/1234 and the e-mail addresses are Zanele.Ndlovu@wits.ac.za and Rhulani.Mukansi@wits.ac.za

Thank you for reading this Study Information Sheet.

July 2020.

ANNEXURE E



PARTICIPANT CONSENT SHEET

Comparison of Quality of Life in patients with Chronic Kidney Disease (Stage 3-5) undergoing Haemodialysis, Peritoneal Dialysis and Conservative Management

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

Principal Investigator: Dr Neelu S Mathew
Telephone no: 078 322 4270 E-mail: moo.neelu@yahoo.com

Supervisor: Dr Malcolm Davies
Telephone no: 0780990487 E-mail: malcolm.davies@wits.ac.za

i. Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za. Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za ii.

iii. Name of Participant: _____

Date: _____
Place: _____
Signature or mark _____
Witnessed by:

Name of Witness: _____
Signature: _____
Date: _____

ANNEXURE F

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr NS Mathew

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200635

NAME: (Principal Investigator)	Dr NS Mathew
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	Comparison of quality of life in patients with advanced chronic kidney disease undergoing haemodialysis, peritoneal dialysis and conservative management
DATE CONSIDERED:	2020/06/26
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr M Davies
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/08/07

This clearance certificate is valid for 5 years from the 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 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore reports and re-certification will be due early in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____