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Referral patterns, disease progression and impact of the Kidney Failure Risk Equation (KFRE) in a Queensland chronic kidney disease Registry (CKD.QLD) cohort: a study protocol

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Complete List of Authors:	Mutatiri, Clyson; The University of Queensland Faculty of Medicine, Renal Medicine Ratsch, Angela; Wide Bay Hospital and Health Service McGrail, Matthew R.; The University of Queensland Faculty of Medicine Venuthurupalli, Sree ; West Moreton Hospital and Health Service, Medicine KondalsamyChennakesavan, Srinivas; The University of Queensland Faculty of Medicine, Discipline of Medicine
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Referral patterns, disease progression and impact of the Kidney Failure Risk Equation (KFRE) in a Queensland chronic kidney disease Registry (CKD.QLD) cohort: a study protocol

Clyson Mutatiri[1,2*], Angela Ratsch[3,4], Matthew McGrail[2], Sree Krishna Venuthurupalli[5], and Srinivas Kondalsamy Chennakesavan[2]

ABSTRACT:

Introduction: Chronic kidney disease (CKD) is a rapidly increasing and global phenomenon which carries high morbidity and mortality. Although timely referral from primary care to secondary care confers favourable outcomes, it is not possible for every patient with CKD to be managed at secondary care. With 1 in 10 Australians currently living with markers of CKD against a workforce of about 600 nephrology specialists, a risk stratification strategy is required that will reliably identify individuals whose kidney disease is likely to progress.

Methods and Analysis: This study will undertake a retrospective secondary analysis of the Chronic Kidney Disease Queensland Registry (CKD.QLD) data of consented adults to examine the referral patterns to specialist nephrology services from primary care providers and map the patient trajectory and outcomes to inform the optimal referral timing for disease mitigation. Patient data over a 5-year period will be examined to determine the impact of the kidney failure risk equation (KFRE)-based risk stratification on the referral patterns, disease progression and patient outcomes. The results will inform considerations of a risk stratification strategy that will ensure adequate pre-dialysis management and add to the discussion of the time interval between referral and initiation of kidney replacement therapy or development of cardiovascular events.

Ethics and dissemination: This protocol was approved by the Ethics Committee of the Royal Brisbane and Women's Hospital in January 2021 (LNR/2020/QRBW/69707 14/01/2021). The HREC waived the requirement for patient consent as all patients had consented for the use of their data for the purpose of research on recruitment into CKD.QLD Registry. The results will be presented as a component of a PhD study with The University of Queensland. It is anticipated that the results will be presented at health-related conferences (local, national and possibly international) and via publication in peer-reviewed academic journals.

Keywords: chronic kidney disease; referral pattern; chronic kidney disease progression; eGFR slope; kidney failure risk equation

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Correspondence:

Dr Clyson Mutatiri;

clyson.mutatiri@health.qld.gov.au

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Strengths and limitations of this study

- The study will involve secondary analysis of registry participant data examining CKD progression under specialist nephrology services over a 5-year period and has potential to identify opportunities for improving quality of care for CKD at both state and national level.
- The clinical outcomes will include progression of CKD as well as major adverse cardiac events or mortality, in contrast to previous studies which have focused on outcomes following commencement of kidney replacement therapy.
- An easily applicable risk stratification strategy will enable the coordination of primary care and secondary care providers to optimize value by providing clinically indicated services at the appropriate time and reducing rates of referrals of low-risk participants who could be safely managed in primary care.
- The participants in the CKD.QLD registry represent a fraction of individuals with CKD in QLD as the registry data represents 60% to 70% of the estimated target population and is limited to individuals with CKD referred to renal services in the public hospital system.
- Given the retrospective nature of the study, the availability of information on variables of interest will rely on the completeness of medical records and on whether tests were ever done or measured.

1. Introduction

Most individuals with chronic kidney disease (CKD) can be safely managed in primary care [1]. A successful model of primary care should incorporate early detection of the disease through proactive screening of high-risk individuals, together with timely specialist referral of individuals who are at high risk of progressing to end-stage kidney disease (ESKD) [2]. Nevertheless, whilst the literature suggests that early referral confers favourable outcomes at both individual and system level [3], the benefits can be eroded by the negative impact of high rates of premature referrals on the health care system [4,5].

Optimal timing for referral of individuals with CKD from primary care to specialist nephrology services has been the subject of debate for several decades [6] and there continues to be a lack of consensus on what constitutes a late (or early) referral. This ambiguity impacts the timing of referral to achieve optimum patient outcomes, which continues to pose an ongoing challenge for patients, policymakers and service providers.

The increase in the burden of diabetes and hypertension, considered as the two leading drivers of CKD [7] has led to an increase in individuals diagnosed with CKD in primary care, which in turn has translated into a surge in referrals to specialist nephrology services [8]. Notably, a significant proportion of these are related to individuals who are at low risk of progressing to ESKD or developing cardiovascular (CV) events [9]. Compounding the volume rise is the dearth in nephrology specialists in Australia, creating a mismatch between service demand and service providers. A workforce review committee of the Australian and New Zealand Society of Nephrology (ANZSN) identified 598 practicing nephrologists in Australia in 2017 [10]. Currently there are approximately 1.7 million Australians aged > 18 years with clinical evidence of CKD; specialist referral of all patients with CKD would see an average of > 2800 patients per nephrologist [11]. Although the number of Australian nephrology trainees has been expanding at a faster pace in recent years [12], the shortage of nephrologists persists outside metropolitan areas in regional, rural and remote areas [10]. This maldistribution of nephrology workforce is compounded by a higher prevalence of CKD and other chronic conditions in rural and remote areas, where a larger proportion of Aboriginal and Torres Strait Islander peoples reside [13].

With mounting referrals comes service overload, leading to long wait times and inefficient utilisation of the available nephrologist's time for higher need patients. Moreover, the absense of a precise and easily accessible guide to optimal referral timing escalates the risk that individuals could remain in primary care for too long, resulting in unwanted outcomes for both the affected individual and the health care system. To mitigate this

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situation arising, substantial work has been invested in the development of risk stratification strategies that predict the risk of progression to ESKD as well as CV events, and therefore the likely need for (more urgent) referral to nephrology services. One such prediction strategy is the kidney failure risk equation (KFRE) which was developed in 2011 to quantify the risk of progression to ESKD [14]. Despite its validation in North America and Europe [15,16], the KFRE has not yet been widely adopted in Australian clinical practice.

In this project we will conduct a retrospective analysis of an existing Registry, examining participant data and outcomes from the time of the participant's enrolment into the Registry up to and including the end of the 5th year of their follow-up after enrolment. Referral patterns and disease progression will be described, and the KFRE-based risk stratification tool will be evaluated against the clinical outcomes.

1.1. Chronic Kidney Disease: Epidemiology

The prevalence of diagnosed CKD has increased worldwide since the adoption of the Kidney Disease Outcomes Quality Initiative (KDOQI) classification for CKD, and the implementation of automated reporting of creatinine-based estimated glomerular filtration rate (eGFR) by many laboratories [17]. Currently, there are nearly 700 million people living with diagnosed CKD across the world, representing a global prevalence of 9·1% [18] and it is estimated that by 2040, CKD will catapult from its current ranking of twelfth to fifth as the leading cause of mortality around the world [19]. In Australia, population studies have estimated that every year, at least 16,000 Australian adults will be added to the over 1.7 million Australian adults (1 in 10) currently living with biomedical markers of CKD such as a reduced eGFR or protein in their urine [11].

Given this rise, CKD poses a major challenge to all world health care systems and has motivated investments in research and the development of potential strategies to delay or slow progression [20]. Previous reports by the Australian Institute of Health and Welfare (AIHW) have highlighted that the impact of CKD is not distributed evenly across the population (identifying "CKD Hot Spots"), with people living in remote areas experiencing substantially higher rates than those living in urban areas [21].

1.2. Chronic Kidney Disease: Identification

The timely involvement of specialist nephrology services has been shown to improve health outcomes after commencement of kidney replacement therapy (KRT) and can also reduce overall costs of caring for individuals with CKD [22-24]. In a systematic review of clinical and cost effectiveness modelling for management of individuals with CKD, the data suggested that early referral strategies may have the potential to offer an efficient use of resources [3]. Public health campaigns have therefore focussed on early detection of CKD in high risk individuals and also on strategies to reduce the rates of late referrals to nephrology services [25,26]. Nevertheless, determination of the optimal timing of referral to specialist care is complicated by several factors including: the heterogeneity of CKD, the recognised imprecision of estimates of progression based on eGFR trajectories, and the non-linear nature of eGFR decline due to intercurrent events such as acute kidney injury (AKI) or CV events [23,27].

Knowledge of the trajectory of any disease can form the basis of clinical decision-making by shaping the goals of care and anticipating when interventions might be required [28,29]. The role of kidney disease trajectories was initially used in clinical practice to predict CKD progression by plotting the reciprocal of serial serum creatinine concentration measurements against time [30]. Lately, acknowledgement of the substantial heterogeneity of kidney disease trajectories has prompted studies to examine the clinical implications of eGFR slopes and their links with subsequent outcomes, and whether past decline in eGFR adds information to the assessment of individuals with kidney disease beyond eGFR at a single time point [31-33]. In an international meta-analysis of

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22 diverse cohorts consisting of more than a million participants, lower levels of eGFR and a higher decline in eGFR (described as an eGFR slope of <-5 ml/min per 1.73 m^2 per year) were both found to demonstrate a significant and independent association with higher subsequent risk of ESKD in the CKD cohorts[34]. A less than average negative eGFR slope and a positive eGFR slope have previously been found to be associated with increased risks of death and CV events by some investigators [32,35-37], while a more recent study found no associated risks with eGFR rise or less than average decline in eGFR slopes, suggesting that an improving eGFR might not be associated with adverse outcomes [38].

1.3. Chronic Kidney Disease: Prediction and referral

Risk prediction models of progression of CKD have been developed to aid treatment decisions and prognostication in clinical practice, hence informing the decision on when to refer from primary care, and on when to refer for access planning in preparation for KRT or transplantation [39]. With the use of such models, most individuals with lower risk CKD (e.g., Stage 3) can potentially be treated solely by their primary care provider, whereas those at high risk of progression to ESKD should be referred for specialized care by nephrology services [40].

Many different risk prediction equations have been developed and a few of them, including the KFRE , have been validated in different CKD cohorts[14,41]. The accuracy of these equations for predicting risk of kidney failure was evaluated by Tangri et al. in a meta-analysis involving thirty-one cohorts, including 721,357 participants with CKD stages 3 to 5 in more than 30 countries spanning 4 continents. From the meta-analysis, three ESKD prediction equations were derived and assessed, based on 4, 6, or 8 variables and the performance of the 4-variable KFRE was found to be similar to that of the other 2 equations [42]. In another study which undertook external validation of 11 existing models of kidney failure, the 4- and 8-variable 2-year KFREs were found to be most suitable for short-term prediction of risk of kidney failure. However, for prediction of kidney failure over a longer time frame, the 5-year KFRE overestimated the actual risk of KRT by 10 - 18% due to the competing risk of death [43]. Furthermore, the application of the KFRE was explored more recently by Naranjo et al. Using electronic medical records to estimate the risk of kidney failure, the 4-variable KFRE (with albuminuria) resulted in consistent improvement in risk discrimination when compared to the three-variable KFRE (without albuminuria), even when albumin-creatinine ratio (ACR) was imputed from protein-creatinine ratio (PCR) or urine dipstick protein measurements [44]. These findings were consistent with previous studies that have concluded that ascertainment of albuminuria is central to ESKD prognosis [42,45].

The 4-variable KFRE can be easily implemented in electronic medical records and laboratory information systems and has therefore been recommended as the model for implementation into clinical practice [42]. In its simplest and most common application, the 4-variable KFRE requires the input of age, gender, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based eGFR and urine ACR [46]. In addition to its use for predicting referral from primary care to nephrology services, the KFRE may also be used to improve timing of referral for permanent vascular access creation and kidney transplantation [47]. An examination of data collected at state level and analysed against the KFRE could assist in identifying or mapping the distribution of state-wide CKD and assessing the usefulness of the tool to support health service planning at the state and local level.

1.4. Data source - CKD.QLD Registry

The Chronic Kidney Disease in Queensland (CKD.QLD) Registry is a collaborative of most public sector nephrology practices in Queensland Australia. The main objective of the Registry is to profile all consenting participants with CKD, laying a foundation for CKD surveillance, practice improvement and research. The

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CKD.QLD data collection methods have been described by Venuthurapalli et. al, briefly however, the Registry was designed to use a data linkage framework which centralizes data captured by multiple mechanisms to an individual participant via a unique identifier [48]. Patients already on kidney replacement therapy and those with acute kidney injury (AKI) are excluded unless they subsequently developed and met the diagnostic criteria for CKD.

2. Methods and Design

This is a retrospective study which will undertake a secondary analysis of CKD.QLD Registry data. The aims and hypotheses of this study are:

Aims

1) To describe the referral patterns of participants in the CKD.QLD database with regard to the timing and appropriateness of referral and the associated impact on outcomes.
2) To study the progression of CKD in a subpopulation of participants followed up in specialist nephrology clinics. This includes comparing the association of pre-referral eGFR slope with subsequent adverse outcomes between early referrals and late referrals and examining the consistency of these associations across subgroups.
3) To evaluate the application of the KFRE and its impact on referral patterns.

Hypotheses

1) For participants with CKD, timely referral to specialist care will be associated with slowing down of progression to ESKD, improvement in CV outcomes and efficient utilisation of resources.
2) For participants under the care of nephrology services, past eGFR slope and albuminuria category are associated with the rate of progression of CKD and subsequent clinical outcomes.
3) For participants with CKD, the KFRE will significantly increase identification of those who are at risk of progressing to ESKD, who would benefit from timely referral to specialist nephrology services.

2.1 Sampling framework and study participants

Overall, the Registry includes approximately 7,600 participants $\geqslant$ 18 years who were enrolled between 1st January 2011 and 31st December 2018. The participants were drawn from patients attending public kidney clinics in QLD Health facilities, thus the registry contains a mix of prevalent and incident patients. All such participants will contribute to completing Aim 1, whilst Aim 2 limits participants to those who were enrolled in the CKD.QLD Registry between 1st June 2011 and 30th June 2013 and followed up for at least five years, until 31st December 2018. Approval to access the CKD.QLD data is under the participant's original consent to share their data for research, and access to hospital record(s) has been granted under a waiver of consent by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (LNR/2020/QRBW/69707 14/01/2021).

2.2 Patient and public involvement

The development of the research question or outcome measures was not informed by patients' priorities, experience or preferences. No patients were involved in the design and development of the study protocol. There are no plans to disseminate the results to study participants.

2.3. Research Outcomes

There are a number of outcomes of interest to this study's aims and these are defined below:

2.21. Referral patterns

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- Prevalence of late referrals by eGFR.
- Describe outcomes associated with late referral.
- Proportion of participants who progressed to KRT at 3, 6 and 12 months.
- Proportion of participants who commenced KRT with a temporary vascular access.
- Incident KRT modality (Haemodialysis vs Peritoneal Dialysis vs Pre-emptive transplantation).
- Characteristics of participants who are referred late.

2.22. Progression of CKD under specialist nephrology services

- Association of past eGFR slopes vs eGFR at referral, albuminuria stage, comorbidities, and cause of CKD with subsequent outcomes (ESKD, non-CV death, and major adverse cardiovascular events (MACE).
- Five-year cumulative incidence of KRT, MACE, death without ESKD and KRT-free survival by past eGFR slope, eGFR and albuminuria stage at study entry.
- Correlation of eGFR slope with the time interval between referral and initiation of KRT.
- Outcomes at 3, 6 and 12 months after first visit to nephrology service (MACE, KRT, hospitalization).

2.23. Impact of the KFRE on referral patterns

- The proportion of participants in the database who require redesignation of their referrals to the nephrologist using the KFRE.
- The number of participants in the database who met the QLD Health Clinical prioritisation criteria and Kidney Disease: Improving Global Outcomes (KDIGO) criteria for nephrology referral.
- The proportion of participants who required referral for access creation and the timing of referral as predicted by the KFRE.
- The proportion of participants who progressed to ESKD as predicted by the KFRE and the time it took to progress to ESKD from time of referral.
- The proportion of participants in the database who had a low risk of progression at baseline and could therefore have been managed safely by their primary care providers.
- The effect of the KFRE stratification on number of referrals and wait times.

3. Procedure

The CKD.QLD data custodian will provide the researchers with the CKD.QLD identification number of the eligible population and will provide access to the Registry data set. Each participant's CKD.QLD identification number will be matched with QLD hospital record numbers. The variables to be extracted from CKD.QLD and hospitalisation records are listed in Tables 1-6 and will be entered onto Excel spreadsheets prior to upload in STATA 16.0 [StataCorp LP. Stata Statistical Software: College Station, Texas].

Table 1. Demographic and clinical characteristics of the study participants

Variable	Operational definition	Scale of measurement	Collection interval
Gender	Will be taken as recorded in database	M or F or other	Baseline
Age	Age at the time of enrolment	Years	Baseline and at time of event
Indigenous status	Indigenous vs non-Indigenous	Y or N	Baseline, at 3 and 6 months and 12 monthly

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SES	Low SES will be defined according to the SEIFA scores determined by participant post code	Quintileof disadvantage on a scale of 1-5	Baseline, at 3 and 6 months and 12 monthly
Area of residence	Area of residence by postcode	Rural vs urban	Baseline, at 3 and 6 months and 12 monthly
Wait times	Time from time of referral to first visit to the kidney clinic	Number of months	Baseline
Comorbidities			
T1DM	Clinical label of T1DM or commencing insulin within a year of diagnosis of DM	Y or N	Baseline
T2DM	Clinical label of T2DM or no requirement of insulin within one year of diagnosis of DM	Y or N	Baseline, at 3 and 6 months and 12 monthly
Obesity	BMI $\geqslant$ 30	Y or N	Baseline
Dyslipidemia	Dyslipidemia will be defined as a LDL-C of $\geqslant$ 2.586 without further risk factors and $\geqslant$ 1.81 in patients with CVD or CKD or receipt of lipid lowering drug treatment	Y or N	Baseline
CHD	History of acute myocardial infarction or history of coronary revascularisation	Y or N	Baseline, at 3 and 6 months and 12 monthly
Heart failure	The diagnosis of heart failure will be obtained from participant admission records	Y or N	Baseline, at 3 and 6 months and 12 monthly
Hypertension	Hypertension will be defined as BP levels above 140 mmHg SBP or 90 mmHg DBP or the receipt of antihypertensive drugs	Y or N	Baseline, at 3 and 6 months and 12 monthly
CVD	History of a CVA or a TIA	Y or N	Baseline, at 3 and 6 months and 12 monthly
PVD	PVD will be defined as lower extremity peripheralartery disease or carotid artery stenosis diagnosed using duplex ultrasound scan or CT angiography.	Y or N	Baseline
Smoking	Smoking status.	Former or current or never	Baseline ,
Pulmonary disease	Chronic obstructive pulmonary disease or emphysema	Y or N	Baseline, at 3 and 6 months and 12 monthly
Other diseases	As documented in participant record.	Y or N	Baseline, at 3 and 6 months and 12 monthly

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SES: Socioeconomic status; SEIFA: Socio-Economic Indexes for Areas; *T1DM: Type 1 Diabetes Mellitus; DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; BMI: Body mass index; LDL-C:* Low-density lipoprotein cholesterol; *CVD: Cardiovascular disease; CKD : Chronic kidney disease; CHD: Coronary heart disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PVD: Peripheral vascular disease.*

Table 2. Primary cause of chronic kidney disease at referral

Primary kidney disease	Duration
DKD	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Glomerulonephritis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Obstructive uropathy	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Hypertensive kidney disease	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
ADPKD	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
ANCA vasculitis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Lupus nephritis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Renovascular disease	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Reflux nephropathy	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Other	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Unknown	Date of first diagnosis or if not available, duration prior to entering the CKD Registry

The primary cause of chronic kidney disease will be based on the entry by the treating nephrologist. DKD: Diabetic kidney disease; ACR: Albumin to creatinine ratio; eGFR: Estimated glomerular filtration rate; ADPKD: Autosomal dominant polycystic Kidney disease; ANCA: Antineutrophil cytoplasmic antibodies.

Table 3. Pathology results to be collected

Laboratory Parameter	Units of measurement	Collection interval
Urine albumin to creatinine ratio	mg/mmol or g/mol	Baseline, at 3 and 6 months and 12 monthly
Urine protein to creatinine ratio	mg/mmol or g/mol	Baseline, at 3 and 6 months and 12 monthly
24Hr urine protein excretion	mg/24hrs or g/24hrs	Baseline, at 3 and 6 months and 12 monthly

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Urine dipstick	Negative or positive for protein	Baseline, at 3 and 6 months and 12 monthly
Serum creatinine	micromol/L	Baseline, at 3 and 6 months and 12 monthly
eGFR	mL/min/1.73m^2	Baseline, at 3 and 6 months and 12 monthly
Serum albumin	g/L	Baseline, at 3 and 6 months and 12 monthly
Hb	g/L	Baseline, at 3 and 6 months and 12 monthly
Serum calcium	mmol/L	Baseline, at 3 and 6 months and 12 monthly
Serum phosphate	mmol/L	Baseline, at 3 and 6 months and 12 monthly
Serum PTH	pmol/L	Baseline, at 3 and 6 months and 12 monthly
HbA1C	% or mmol/mol	Baseline

Hb: Hemoglobin; PTH: Parathyroid hormone; HbA1C: Glycated haemoglobin.

Table 4. Parameters of pre-referral management

Parameter	Operational definition	Scale of measurement
Use of RAAS inhibitors	Use of ACE inhibitors or ARBs	Y or N. If yes, details about drug, dosage, duration
Glycemic control	Target HbA1c ⩽ 53mmol/mol (7%)	Optimal vs suboptimal control
Use of vitamin D or calcium supplements	Participants taking vitamin D or calcium supplements at the time of enrolment	Y or N
BP at initial visit (Systolic/diastolic)	BP recorded on first visit to the nephrology clinic with target < 130/80 representing adequate control	Suboptimal vs optimal control
Body mass Index (BMI)	BMI at enrolment, with obesity defined as BMI ⩾ 30	< 30 or ⩾ 30

RAAS: Renin angiotensin aldosterone system; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; HbA1C: Glycated hemoglobin; BP: Blood pressure; BMI: Body mass Index.

Table 5 Participant outcomes under nephrological care

Outcome	Operational definition	Scale of measurement	Collection interval

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Hospitalisation records	Hospitalisation will be defined as an admission to hospital to receive acute clinical care	Y or N Number of hospitalisations, Reason for hospitalisation (ICD-Codes), associated conditions (ICD-Codes)	3, 6 months and 12 monthly
LOS	Average number of days spent in hospital	Date of admission and date of discharge or number of days	3, 6 months and 12 monthly
Progression to ESKD	Defined as sustained reduction in eGFR < 15ml/min or commencement of KRT	Y or N. If yes, the relevant date	
CVD events	CVD will be defined as a composite outcome of fatal and nonfatal events of ischemic heart disease, ischemic stroke, heart failure, and peripheral vascular disease	Y or N. If yes, then the relevant date(s)	3, 6 months and 12 monthly
Death	As entered in patient records	Y or N. If yes, date of death	
Achievement of blood pressure control	Target < 130/80	Y or N	3, 6 months and 12-monthly
Achievement of glycemic control	Target < 53mmol/mol (7%)	Y or N	3, 6 months and 12-monthly
Pharmacy review	Reviewed by pharmacist	Y or N. If yes, date of review	
Dietary education	Received dietary counselling	Y or N. If yes, date of review	
AKI	Frequency/episodes of AKI	Y or N, Single or multiple	

ICD: International Classification of Diseases; LOS: Length of stay; ESKD: End-stage kidney disease; CVD: Cardiovascular disease; AKI: Acute kidney injury.

Table 6. Pharmacological intervention after referral

Medication initiated	Operational definition	Scale of meaasurement
ESA therapy	Initiation of ESA in participants whose Hb is < 100g/L	Y or N. If yes, date of initiation or titration if available
ACE-I or ARB	Initiation of ACE-I or ARB	Y or N. If yes, date of initiation
Other anti-hypertensive medication	Initiation of Other anti-hypertensive medication	Y or N. If yes, date of initiation
Calcium supplements	Calcium supplements	Y or N. If yes, date of initiation
Vitamin D supplements	Vitamin D supplements	Y or N. If yes, date of initiation
Lipid lowering drugs	Lipid lowering drugs	Y or N. If yes, date of initiation

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Loop diuretics	Loop diuretics	Y or N. If yes, date of initiation

ESA: Erythropoiesis stimulating agent; SGLT2-I: Sodium-glucose co-transporter-2 inhibitors; DPP4-I: Dipeptidyl-peptidase 4 inhibitors; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

3.1. Data analysis

This is an observational study and a range of statistical methods will be used to measure the association between data elements and outcomes. Firstly, descriptive statistics and basic inferential statistics will be used to present participant characteristics and explore basic patterns of the data (e.g., describing referral patterns). If the variables are continuous and normally distributed, means and t-tests will be used. For non-normally distributed (skewed) continuous data, medians and equivalent non-parametric tests will be used. For categorical data, proportions and chi-squared tests will be used and reported.

Secondly, where appropriate, multivariate analysis methods will be used to account for measurable covariates, thus better capturing the true effect size. Multiple regression models (linear, multinomial, logistic and Cox proportional hazards or competing risks, where appropriate) will be used to explore the association between participant characteristics and clinical outcomes adjusting for potential confounders based on previous literature and available measures as outlined in Table 2 [49,50]. Variables will be fitted as covariates in the regression models and variables with a $p < .2$ will be accepted for covariate interaction inclusion in the regression model.

The variables broadly categorized as follows will be investigated as any of predictors, covariates or outcomes, as appropriate to the analyses:

1. Demographic variables (age, residential address, gender, ethnicity, socioeconomic status).
2. Lifestyle factors (alcohol and tobacco use).
3. Past and current medical history (cardiac, hypertension, diabetes and type and level of kidney disease, pulmonary disease, obesity).
4. Kidney disease factors (Urine albumin/creatinine ratio, urine protein/creatinine ratio, 24-hr urine protein excretion, serum creatinine, eGFR, HbA1c, serum phosphate, PTH, haemoglobin, serum albumin).
5. Kidney disease outcome variables (transplant, KRT, Dialysis modality, death).
6. Pre-referral parameters (RAAS inhibitors, Lipid lowering drugs, vitamin D or Calcium supplements, Systolic BP, Diastolic BP, BMI, PTH, serum albumin, eGFR, serum calcium, serum phosphate, urine ACR, urine PCR, 24hr protein excretion, urine dipstick, Hb).

Results will be reported with the level of significance at alpha .05 and accompanied by 95% confidence intervals (95% CI). Missing data and outliers will be reported but will be excluded from analysis. Outliers will be identified by the use of boxplots in STATA®. These outliers will be confirmed based on the established procedures from Hoaglin and Iglewicz [51].

4.0. Conclusion

The prevalence of CKD is a burgeoning world-wide issue. The findings from this study are intended to inform clinical practice and policy by:

- Describing the patterns and predicting factors of CKD progression and other end points and the impact of the KFRE on the CKD.QLD examined cohort.
- Correlating the time interval between referral and initiation of KRT or development of CV events to inform the optimal eGFR range for adequate pre-dialysis management.

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- Determining the optimal risk stratification strategy which will accurately predict risk of progression to ESKD.
- Reviewing referral strategies, guidelines, and QLD health service delivery recommendations to improve the health outcomes of CKD and maximize efficiency of its management within the health care system.

Ultimately, the study findings are intended to provide CKD health care providers with a robust decision making tool. This will enable targeted care initiatives to ensure that individuals at high risk of progressing to ESKD are identified early and given an opportunity to benefit from specialized nephrology care.

Author affiliations

[1]Renal Unit, Bundaberg Hospital, Wide Bay Hospital and Health Service, Bundaberg 4670, Australia

[2]Rural Clinical School, Faculty of Medicine, The University of Queensland, Brisbane 4072 Australia; m.mcgrail@uq.edu.au (M.M.); uqskonda@uq.edu.au (S.K.)

[3]Research Education, Development and Support, Wide Bay Hospital and Health Service, Hervey Bay 4655, Australia; angela.ratsch@health.qld.gov.au

[4]School of Nursing, Midwifery and Social Work, The University of Queensland, Brisbane 4072, Australia

[5]Renal Services, West Moreton Hospital and Health Service, Ipswich 4305, Australia; sree.venuthurupalli@health.qld.gov.au

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Referral patterns, disease progression and impact of the Kidney Failure Risk Equation (KFRE) in a Queensland chronic kidney disease Registry (CKD.QLD) cohort: a study protocol

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Referral patterns, disease progression and impact of the Kidney Failure Risk Equation (KFRE) in a Queensland chronic kidney disease Registry (CKD.QLD) cohort: a study protocol

Clyson Mutatiri[1*], Angela Ratsch[2], Matthew McGrail[3], Sree Krishna Venuthurupalli[4], and Srinivas Kondalsamy Chennakesavan[5]

[1]Renal Unit, Bundaberg Base Hospital, Wide Bay Hospital and Health Service, 271 Bourbong St, Bundaberg Central QLD 4670, Australia; Email: clyson.mutatiri@health.qld.gov.au, Ph: +61 7 41502222, Fax: +61 41502449

[2]Wide Bay Hospital and Health Service, Hervey Bay, Australia

[3]The University of Queensland, Rural Clinical School, Rockhampton, Australia

[4]The University of Queensland, Faculty of Medicine, Brisbane, Australia

[5]The University of Queensland Rural Clinical School, Toowoomba, Australia

***Corresponding Author**

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ABSTRACT:

Introduction: Chronic kidney disease (CKD) is a rapidly increasing and global phenomenon which carries high morbidity and mortality. Although timely referral from primary care to secondary care confers favourable outcomes, it is not possible for every patient with CKD to be managed at secondary care. With 1 in 10 Australians currently living with markers of CKD against a workforce of about 600 nephrology specialists, a risk stratification strategy is required that will reliably identify individuals whose kidney disease is likely to progress.

Methods and Analysis: This study will undertake a retrospective secondary analysis of the Chronic Kidney Disease Queensland Registry (CKD.QLD) data of consented adults to examine the referral patterns to specialist nephrology services from primary care providers and map the patient trajectory and outcomes to inform the optimal referral timing for disease mitigation. Patient data over a 5-year period will be examined to determine the impact of the kidney failure risk equation (KFRE)-based risk stratification on the referral patterns, disease progression and patient outcomes. The results will inform considerations of a risk stratification strategy that will ensure adequate pre-dialysis management and add to the discussion of the time interval between referral and initiation of kidney replacement therapy or development of cardiovascular events.

Ethics and dissemination: This protocol was approved by the Ethics Committee of the Royal Brisbane and Women's Hospital in January 2021 (LNR/2020/QRBW/69707 14/01/2021). The HREC waived the requirement for patient consent as all patients had consented for the use of their data for the purpose of research on recruitment into CKD.QLD Registry. The results will be presented as a component of a PhD study with The University of Queensland. It is anticipated that the results will be presented at health-related conferences (local, national and possibly international) and via publication in peer-reviewed academic journals.

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Strength of this study

- The major strength of the current study is the large sample size, derived from one of the largest CKD surveillance cohorts in the world, with longer follow-up, which provides opportunities to study the journey of CKD patients under nephrology care and assess several important clinical outcomes and their predictors, including morbidity, mortality and KRT, and potentially of comprehensive hospitalisations and health service consumption.

Limitations of this study

- Both intertest and interlaboratory variability of serum creatinine values may mean that the index eGFR at first clinic visit might not necessarily represent baseline kidney function.
- The outcome of initiation of KRT as an endpoint excludes those participants who progressed to ESKD but opted to be managed conservatively, which can potentially underestimate the incidence of ESKD in this cohort.
- The participants in the CKD.QLD registry represent a fraction of individuals with CKD in QLD as the registry data represents 60% to 70% of the estimated target population and is limited to individuals with CKD referred to renal services in the public hospital system.
- Given the retrospective and observational nature of the study, it will also be limited by potential confounding, information and selection bias.

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1. Introduction

Most individuals with chronic kidney disease (CKD) can be safely managed in primary care . A successful model of primary care should incorporate early detection of the disease through proactive screening of high-risk individuals, together with timely specialist referral of individuals who are at high risk of progressing to end-stage kidney disease (ESKD) [1]. Nevertheless, whilst the literature suggests that early referral confers favourable outcomes at both individual and system level[2] , the benefits can be eroded by the negative impact of high rates of premature referrals on the health care system [3-5].

Optimal timing for referral of individuals with CKD from primary care to specialist nephrology services has been the subject of debate for several decades and there continues to be a lack of consensus on what constitutes a late (or early) referral. This ambiguity impacts the timing of referral to achieve optimum patient outcomes, which continues to pose an ongoing challenge for patients, policymakers and service providers.

The increase in the burden of diabetes and hypertension, considered as the two leading drivers of CKD [6] has led to an increase in individuals diagnosed with CKD in primary care, which in turn has translated into a surge in referrals to specialist nephrology services [7]. Notably, a significant proportion of these are related to individuals who are at low risk of progressing to ESKD or developing cardiovascular (CV) events [8]. Compounding the volume rise is the dearth in nephrology specialists in Australia, creating a mismatch between service demand and service providers. A workforce review committee of the Australian and New Zealand Society of Nephrology (ANZSN) identified 598 practicing nephrologists in Australia in 2017 [9]. Currently there are approximately 1.7 million Australians aged > 18 years with clinical evidence of CKD; specialist referral of all patients with CKD would see an average of > 2800 patients per nephrologist [10]. Although the number of Australian nephrology trainees has been expanding at a faster pace in recent years[11] , the shortage of nephrologists persists outside metropolitan areas in regional, rural and remote areas [9]. This maldistribution of nephrology workforce is compounded by a higher prevalence of CKD and other chronic conditions in rural and remote areas, where a larger proportion of Aboriginal and Torres Strait Islander peoples reside [12].

With mounting referrals comes service overload, leading to long wait times and inefficient utilisation of the available nephrologist's time for higher need patients. Moreover, the absense of a precise and easily accessible guide to optimal referral timing escalates the risk that individuals could remain in primary care for too long, resulting in unwanted outcomes for both the affected individual and the health care system. To mitigate this situation arising, substantial work has been invested in the development of risk stratification strategies that predict the risk of progression to ESKD as well as CV events, and therefore the likely need for (more urgent) referral to nephrology services. One such prediction strategy is the kidney failure risk equation (KFRE) which was developed in 2011 to quantify the risk of progression to ESKD [13]. Despite its validation in North America and Europe [14,15], the KFRE has not yet been widely adopted in Australian clinical practice.

In this project we will conduct a retrospective analysis of an existing Registry, examining participant data and outcomes from the time of the participant's enrolment into the Registry up to and including the end of the 5th year of their follow-up after enrolment. Referral patterns and disease progression will be described, and the KFRE-based risk stratification tool will be evaluated against the clinical outcomes.

1.1. Chronic Kidney Disease: Epidemiology

The prevalence of diagnosed CKD has increased worldwide since the adoption of the Kidney Disease Outcomes Quality Initiative (KDOQI) classification for CKD, and the implementation of automated reporting of creatinine-based estimated glomerular filtration rate (eGFR) by many laboratories [16]. Currently, there are nearly 700 million people living with diagnosed CKD across the world, representing a global prevalence of 9·1% and it is estimated that by 2040, CKD will catapult from its current ranking of twelfth to fifth as the leading cause of mortality around the world [17]. In Australia, population studies have estimated that every year, at least 16,000 Australian adults will be added to the over 1.7 million Australian adults (1 in 10) currently living with biomedical markers of CKD such as a reduced eGFR or protein in their urine .

Given this rise, CKD poses a major challenge to all world health care systems and has motivated investments in research and the development of potential strategies to delay or slow progression [18]. Previous reports by the Australian Institute of Health and Welfare (AIHW) have highlighted that the impact of CKD is not distributed evenly across the population (identifying "CKD Hot Spots"), with people living in remote areas experiencing substantially higher rates than those living in urban areas.

1.2. Chronic Kidney Disease: Identification

The timely involvement of specialist nephrology services has been shown to improve health outcomes after commencement of kidney replacement therapy (KRT) and can also reduce overall costs of caring for individuals with CKD [19-21]. In a systematic review of clinical and cost effectiveness modelling for management of individuals with CKD, the data suggested that early referral strategies may have the potential to offer an efficient use of resources [2]. Public health campaigns have therefore focussed on early detection of CKD in high risk individuals and also on strategies to reduce the rates of late referrals to nephrology services [22,23]. Nevertheless, determination of the optimal timing of referral to specialist care is complicated by several factors including: the heterogeneity of CKD, the recognised imprecision of estimates of progression based on eGFR trajectories, and the non-linear nature of eGFR decline due to intercurrent events such as acute kidney injury (AKI) or CV events [20,24].

Knowledge of the trajectory of any disease can form the basis of clinical decision-making by shaping the goals of care and anticipating when interventions might be required [25,26]. The role of kidney disease trajectories was initially used in clinical practice to predict CKD progression by plotting the reciprocal of serial serum creatinine

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concentration measurements against time [27]. Lately, acknowledgement of the substantial heterogeneity of kidney disease trajectories has prompted studies to examine the clinical implications of eGFR slopes and their links with subsequent outcomes, and whether past decline in eGFR adds information to the assessment of individuals with kidney disease beyond eGFR at a single time point [28-30]. In an international meta-analysis of 22 diverse cohorts consisting of more than a million participants, lower levels of eGFR and a higher decline in eGFR (described as an eGFR slope of <-5 ml/min per 1.73 m^2 per year) were both found to demonstrate a significant and independent association with higher subsequent risk of ESKD in the CKD cohorts[31]. A less than average negative eGFR slope and a positive eGFR slope have previously been found to be associated with increased risks of death and CV events by some investigators [29,32-34], while a more recent study found no associated risks with eGFR rise or less than average decline in eGFR slopes, suggesting that an improving eGFR might not be associated with adverse outcomes

1.3. Chronic Kidney Disease: Prediction and referral

Risk prediction models of progression of CKD have been developed to aid treatment decisions and prognostication in clinical practice, hence informing the decision on when to refer from primary care, and on when to refer for access planning in preparation for KRT or transplantation [35]. With the use of such models, most individuals with lower risk CKD (e.g., Stage G3) can potentially be treated solely by their primary care provider, whereas those at high risk of progression to ESKD should be referred for specialized care by nephrology services .

Many different risk prediction equations have been developed and a few of them, including the KFRE , have been validated in different CKD cohorts [13,36]. The accuracy of these equations for predicting risk of kidney failure was evaluated by Tangri et al. in a meta-analysis involving thirty-one cohorts, including 721,357 participants with CKD stages G3 to G5 in more than 30 countries spanning 4 continents. From the meta-analysis, three ESKD prediction equations were derived and assessed, based on 4, 6, or 8 variables and the performance of the 4-variable KFRE was found to be similar to that of the other 2 equations [37]. In another study which undertook external validation of 11 existing models of kidney failure, the 4- and 8-variable 2-year KFREs were found to be most suitable for short-term prediction of risk of kidney failure. However, for prediction of kidney failure over a longer time frame, the 5-year KFRE overestimated the actual risk of KRT by 10 - 18% due to the competing risk of death [38]. Furthermore, the application of the KFRE was explored more recently by Naranjo et al. Using electronic medical records to estimate the risk of kidney failure, the 4-variable KFRE (with albuminuria) resulted in consistent improvement in risk discrimination when compared to the three-variable KFRE (without albuminuria), even when albumin-creatinine ratio (ACR) was imputed from protein-creatinine ratio (PCR) or urine dipstick protein measurements [39]. These findings were consistent with previous studies that have concluded that ascertainment of albuminuria is central to ESKD prognosis [37,40].

The 4-variable KFRE can be easily implemented in electronic medical records and laboratory information systems and has therefore been recommended as the model for implementation into clinical practice [37]. In its simplest and most common application, the 4-variable KFRE requires the input of age, gender, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-based eGFR and urine ACR [41]. In addition to its use for predicting referral from primary care to nephrology services, the KFRE may also be used to improve timing of referral for permanent vascular access creation and kidney transplantation [42].

An examination of data collected at state level and analysed against the KFRE could assist in identifying or mapping the distribution of state-wide CKD and assessing the usefulness of the tool to support health service planning at the state and local level.

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1.4. Data source - CKD.QLD Registry

The Chronic Kidney Disease in Queensland (CKD.QLD) Registry is a collaborative of most public sector nephrology practices in Queensland Australia. The main objective of the Registry is to profile all consenting participants with CKD, laying a foundation for CKD surveillance, practice improvement and research. The CKD.QLD data collection methods have been described by Venuthurapalli et. al, briefly however, the Registry was designed to use a data linkage framework which centralizes data captured by multiple mechanisms to an individual participant via a unique identifier [43]. Patients already on kidney replacement therapy and those with acute kidney injury (AKI) are excluded unless they subsequently developed and met the diagnostic criteria for CKD. After commencing in May 2011, recruitment of new participants to the Registry was discontinued in May 2019, on the advice of the CKD.QLD surveillance stream due to funding constraints. However, participating sites who wished to continue enrolling new participants could do so if they had a special reason to. Sites that ceased enrolment could still take up recruitment again, with governance and ethics approvals refreshed, if they later chose to do so, but analyses would be their own responsibilities. Some sites chose to continue, as they found the registry functions useful as an audit tool.

2. Methods and Design

This is a retrospective study which will undertake a secondary analysis of CKD.QLD Registry data. The aims and hypotheses of this study are:

Aims

1) To describe the referral patterns of participants in the CKD.QLD database with regard to the timing and appropriateness of referral and the associated impact on outcomes.
2) To study the progression of CKD in a subpopulation of participants followed up in specialist nephrology clinics. This includes comparing the association of pre-referral eGFR slope with subsequent adverse outcomes between early referrals and late referrals and examining the consistency of these associations across subgroups.
3) To evaluate the application of the KFRE and its impact on referral patterns.

Hypotheses

1) For participants with CKD, timely referral to specialist care will be associated with slowing down of progression to ESKD, improvement in CV outcomes and efficient utilisation of resources.
2) For participants under the care of nephrology services, past eGFR slope and albuminuria category are associated with the rate of progression of CKD and subsequent clinical outcomes.
3) For participants with CKD, the KFRE will significantly increase identification of those who are at risk of progressing to ESKD, who would benefit from timely referral to specialist nephrology services.

2.1 Sampling framework and study participants

Overall, the Registry includes approximately 7,600 participants ⩾ 18 years who were enrolled between 1st January 2011 and 31st December 2018. The participants were drawn from patients attending public kidney clinics in QLD Health facilities, thus the registry contains a mix of prevalent and incident patients. All such participants will contribute to completing Aim 1, whilst Aim 2 limits participants to those who were enrolled in the CKD.QLD

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Registry between 1st June 2011 and 30th June 2013 and followed up for at least five years, until 31st December 2018. Approval to access the CKD.QLD data is under the participant's original consent to share their data for research, and access to hospital record(s) has been granted under a waiver of consent by the Royal Brisbane and Women's Hospital Human Research Ethics Committee (LNR/2020/QRBW/69707 14/01/2021).

2.3. Research Outcomes

There are a number of outcomes of interest to this study's aims and these are defined below:

2.21. Referral patterns

- Prevalence of late referrals by eGFR.
- Describe outcomes associated with late referral.
- Proportion of participants who progressed to KRT at 3, 6 and 12 months.
- Proportion of participants who commenced KRT with a temporary vascular access.
- Incident KRT modality (Haemodialysis vs Peritoneal Dialysis vs Pre-emptive transplantation).
- Characteristics of participants who are referred late.

2.22. Progression of CKD under specialist nephrology services

- Association of past eGFR slopes vs eGFR at referral, albuminuria stage, comorbidities, and cause of CKD with subsequent outcomes (ESKD, non-CV death, and major adverse cardiovascular events (MACE).
- Five-year cumulative incidence of KRT, MACE, death without ESKD and KRT-free survival by past eGFR slope, eGFR and albuminuria stage at study entry.
- Correlation of eGFR slope with the time interval between referral and initiation of KRT.
- Outcomes at 3, 6 and 12 months after first visit to nephrology service (MACE, KRT, hospitalization).

2.23. Impact of the KFRE on referral patterns

- The proportion of participants in the database who require redesignation of their referrals to the nephrologist using the KFRE.
- The number of participants in the database who met the Kidney Health Australia (KHA)'s recommendations for nephrology referral.
- The proportion of participants who required referral for access creation and the timing of referral as predicted by the KFRE.
- The proportion of participants who progressed to ESKD as predicted by the KFRE and the time it took to progress to ESKD from time of referral.
- The proportion of participants in the database who had a low risk of progression at baseline and could therefore have been managed safely by their primary care providers.
- The effect of the KFRE stratification on number of referrals and wait times.

2.3 Definitions related to referral

2.31. Appropriateness of referral:

The appropriateness of referrals will be determined according to the recommendations in Kidney health Australia's The Chronic Kidney Disease Management in Primary Care handbook[44], which are also in tandem with the CARI guidelines[45] (Table 1). Referrals will be deemed as appropriate if any of the indications for referral are met.

Table 1. Indications for referral to a nephrologist

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- eGFR <30 mL/min/1.73m2 (Stage G4 or G5 CKD of any cause).
- Persistent significant albuminuria (urine ACR ≥30 mg/mmol)
- A sustained decrease in eGFR of 25% or more within 12 months OR a sustained decrease in eGFR of 15 mL/min/1.73m2 per year
- CKD with hypertension that is hard to get to target despite at least three antihypertensive agents

2.32. Definition of late referral

KDIGO defines late referral as referral to specialist services less than 1 year before start of KRT[46]. However, many previous studies have applied a cut-off of less than 3-4 months, with others going for less than 6 months. In our analysis we plan to apply the 3 months cut-off as this is the definition that is used in by Kidney Health Australia in their latest edition of their CKD management in primary care handbook [44].

2.4 Kidney Failure Risk Equation

The published KFRE 4-variable non–North American equation will be used at the initial visit to discriminate participants who would develop kidney failure within 5 years from those who would not. The observed kidney failure rate (on the basis of CKD.QLD follow-up data) will be the reference. The variables accessible in the CKD.QLD database will allow for integration into the KFRE to calculate the proportion of patients who would fulfil criteria for referral to the nephrologist based on the calculated risk. eGFR (calculated from serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation), urine ACR (where available), gender and age will be retrieved from the registry to enable the calculation of each patient's risk threshold for progression to ESKD. Where only results of urine protein to creatinine ratio (PCR) or urine dipsticks are available, the equations developed by Sumida et al. in 2020 will be employed to calculate the predicted ACR [47]. Where no ACR, PCR or urine dipsticks are available at the initial visit, we intend to use the earliest interval where the first urine protein examination would have been performed within the first 6 months of the initial visit. We anticipate that most patients seen in the nephrology clinics will be brought back for review within 3-6 months and that most of them will have urine examination for proteinuria/albuminuria ordered by the nephrologist. The date of the proteinuria/albuminuria measurement will automatically become the date for estimating baseline risk using the KFRE and for beginning the follow-up period.

The participants will then be stratified as either high risk or low risk according to the calculated 2-year and 5-year risk of progressing to ESKD. Patients whose 5-year risk for kidney failure is less than 3% and are without any structural abnormalities such as a diagnosis of polycystic kidney disease, would be deemed low risk and hence could be safely managed in primary care, whereas all those with a 5-year risk of >3% would be classified as high risk and therefore would be considered for a nephrology referral. A KFRE threshold of >10% in 2 years would require referral to multidisciplinary team programs, whereas a 2-year threshold of 20-40% would trigger referral for planning a transplant or fistula [48-50].

3. Procedure

The CKD.QLD data custodian will provide the researchers with the CKD.QLD identification number of the eligible population and will provide access to the Registry data set. Each participant's CKD.QLD identification number will be matched with QLD hospital record numbers. The variables to be extracted from CKD.QLD and hospitalisation records are listed in Tables 2-7 and will be entered onto Excel spreadsheets prior to upload in STATA 16.0 [StataCorp LP. Stata Statistical Software: College Station, Texas].

Table 2. Demographic and clinical characteristics of the study participants

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Variable	Operational definition	Scale of measurement	Collection interval
Gender	Will be taken as recorded in database	M or F or other	Baseline
Age	Age at the time of enrolment	Years	Baseline and at time of event
Indigenous status	Indigenous vs non-Indigenous	Y or N	Baseline, at 3 and 6 months and 12 monthly
SES	Low SES will be defined according to the SEIFA scores determined by participant post code	Quintileof disadvantage on a scale of 1-5	Baseline, at 3 and 6 months and 12 monthly
Area of residence	Area of residence by postcode	Rural vs urban	Baseline, at 3 and 6 months and 12 monthly
Wait times	Time from time of referral to first visit to the kidney clinic	Number of months	Baseline
Comorbidities			
T1DM	Clinical label of T1DM or commencing insulin within a year of diagnosis of DM	Y or N	Baseline
T2DM	Clinical label of T2DM or no requirement of insulin within one year of diagnosis of DM	Y or N	Baseline, at 3 and 6 months and 12 monthly
Obesity	BMI $\geqslant$ 30	Y or N	Baseline
Dyslipidemia	Dyslipidemia will be defined as a LDL-C of $\geqslant$ 2.586 without further risk factors and $\geqslant$ 1.81 in patients with CVD or CKD or receipt of lipid lowering drug treatment	Y or N	Baseline
CHD	History of acute myocardial infarction or history of coronary revascularisation	Y or N	Baseline, at 3 and 6 months and 12 monthly
Heart failure	The diagnosis of heart failure will be obtained from participant admission records	Y or N	Baseline, at 3 and 6 months and 12 monthly
Hypertension	Hypertension will be defined as BP levels above 140 mmHg SBP or 90 mmHg DBP or the receipt of antihypertensive drugs	Y or N	Baseline, at 3 and 6 months and 12 monthly
CVD	History of a CVA or a TIA	Y or N	Baseline, at 3 and 6 months and 12 monthly
PVD	PVD will be defined as lower extremity peripheralartery disease or carotid artery stenosis diagnosed using duplex ultrasound scan or CT angiography.	Y or N	Baseline
Smoking	Smoking status.	Former or current or never	Baseline
Pulmonary disease	Chronic obstructive pulmonary disease or emphysema	Y or N	Baseline, at 3 and 6 months and 12 monthly
Other diseases	As documented in participant record.	Y or N	Baseline, at 3 and 6 months and 12 monthly

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SES: Socioeconomic status; SEIFA: Socio-Economic Indexes for Areas; *T1DM: Type 1 Diabetes Mellitus; DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; BMI: Body mass index; LDL-C:* Low-density lipoprotein cholesterol; *CVD: Cardiovascular disease; CKD : Chronic kidney disease; CHD: Coronary heart disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CVA: Cerebrovascular accident; TIA: Transient ischemic attack; PVD: Peripheral vascular disease.*

Table 3. Primary cause of chronic kidney disease at referral

Primary kidney disease	Duration
DKD	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Glomerulonephritis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Obstructive uropathy	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Hypertensive kidney disease	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
ADPKD	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
ANCA vasculitis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Lupus nephritis	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Renovascular disease	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Reflux nephropathy	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Other	Date of first diagnosis or if not available, duration prior to entering the CKD Registry
Unknown	Date of first diagnosis or if not available, duration prior to entering the CKD Registry

The primary cause of chronic kidney disease will be based on the entry by the treating nephrologist. DKD: Diabetic kidney disease; ACR: Albumin to creatinine ratio; eGFR: Estimated glomerular filtration rate; ADPKD: Autosomal dominant polycystic Kidney disease; ANCA: Antineutrophil cytoplasmic antibodies.

Table 4. Pathology results to be collected

Laboratory Parameter	Units of measurement	Collection interval
Urine albumin to creatinine ratio	mg/mmol or g/mol	Baseline, at 3 and 6 months and 12 monthly
Urine protein to creatinine ratio	mg/mmol or g/mol	Baseline, at 3 and 6 months and 12 monthly
24Hr urine protein excretion	mg/24hrs or g/24hrs	Baseline, at 3 and 6 months and 12 monthly
Urine dipstick	Negative or positive for protein	Baseline, at 3 and 6 months and 12 monthly
Serum creatinine	micromol/L	Baseline, at 3 and 6 months and 12 monthly

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eGFR	mL/min/1.73m^2	Baseline, at 3 and 6 months and 12 monthly
Serum albumin	g/L	Baseline, at 3 and 6 months and 12 monthly
Hb	g/L	Baseline, at 3 and 6 months and 12 monthly
Serum calcium	mmol/L	Baseline, at 3 and 6 months and 12 monthly
Serum phosphate	mmol/L	Baseline, at 3 and 6 months and 12 monthly
Serum PTH	pmol/L	Baseline, at 3 and 6 months and 12 monthly
HbA1C	% or mmol/mol	Baseline

Hb: Hemoglobin; PTH: Parathyroid hormone; HbA1C: Glycated haemoglobin.

Table 5. Parameters of pre-referral management

Parameter	Operational definition	Scale of measurement
Use of RAAS inhibitors	Use of ACE inhibitors or ARBs	Y or N. If yes, details about drug, dosage, duration
Glycemic control	Target HbA1c ⩽ 53mmol/mol (7%)	Optimal vs suboptimal control
Use of vitamin D or calcium supplements	Participants taking vitamin D or calcium supplements at the time of enrolment	Y or N
BP at initial visit (Systolic/diastolic)	BP recorded on first visit to the nephrology clinic with target < 130/80 representing adequate control	Suboptimal vs optimal control
Body mass Index (BMI)	BMI at enrolment, with obesity defined as BMI ⩾ 30	< 30 or ⩾ 30

RAAS: Renin angiotensin aldosterone system; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blockers; HbA1C: Glycated hemoglobin; BP: Blood pressure; BMI: Body mass Index.

Table 6. Participant outcomes under nephrological care

Outcome	Operational definition	Scale of measurement	Collection interval
Hospitalisation records	Hospitalisation will be defined as an admission to hospital to receive acute clinical care	Y or N Number of hospitalisations, Reason for hospitalisation (ICD-Codes), associated conditions (ICD-Codes)	3, 6 months and 12 monthly
LOS	Average number of days spent in hospital	Date of admission and date of discharge or number of days	3, 6 months and 12 monthly
Progression to ESKD	Defined as sustained reduction in eGFR < 15ml/min or commencement of KRT	Y or N. If yes, the relevant date	

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CVD events	CVD will be defined as a composite outcome of fatal and nonfatal events of ischemic heart disease, ischemic stroke, heart failure, and peripheral vascular disease	Y or N. If yes, then the relevant date(s)	3, 6 months and 12 monthly
Death	As entered in patient records	Y or N. If yes, date of death	
Achievement of blood pressure control	Target < 130/80	Y or N	3, 6 months and 12-monthly
Achievement of glycemic control	Target < 53mmol/mol (7%)	Y or N	3, 6 months and 12-monthly
Pharmacy review	Reviewed by pharmacist	Y or N. If yes, date of review	
Dietary education	Received dietary counselling	Y or N. If yes, date of review	
AKI	Frequency/episodes of AKI	Y or N, Single or multiple	

ICD: International Classification of Diseases; LOS: Length of stay; ESKD: End-stage kidney disease; CVD: Cardiovascular disease; AKI: Acute kidney injury.

Table 7. Pharmacological intervention after referral

Medication initiated	Operational definition	Scale of meaasurement
ESA therapy	Initiation of ESA in participants whose Hb is < 100g/L	Y or N. If yes, date of initiation or titration if available
ACE-I or ARB	Initiation of ACE-I or ARB	Y or N. If yes, date of initiation
Other anti-hypertensive medication	Initiation of Other anti-hypertensive medication	Y or N. If yes, date of initiation
Calcium supplements	Calcium supplements	Y or N. If yes, date of initiation
Vitamin D supplements	Vitamin D supplements	Y or N. If yes, date of initiation
Lipid lowering drugs	Lipid lowering drugs	Y or N. If yes, date of initiation
Loop diuretics	Loop diuretics	Y or N. If yes, date of initiation

ESA: Erythropoiesis stimulating agent; SGLT2-I: Sodium-glucose co-transporter-2 inhibitors; DPP4-I: Dipeptidyl-peptidase 4 inhibitors; ACE-I: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers.

3.1. Data analysis

This is an observational study and a range of statistical methods will be used to measure the association between data elements and outcomes. Firstly, descriptive statistics and basic inferential statistics will be used to present participant characteristics and explore basic patterns of the data (e.g., describing referral patterns). If the variables are continuous and normally distributed, means and t-tests will be used. For non-normally distributed (skewed) continuous data, medians and equivalent non-parametric tests will be used. For categorical data, proportions and chi-squared tests will be used and reported.

Secondly, where appropriate, multivariate analysis methods will be used to account for measurable covariates, thus better capturing the true effect size. Multiple regression models (linear, multinomial, logistic and Cox proportional hazards or competing risks, where appropriate) will be used to explore the association between participant characteristics and clinical outcomes adjusting for potential confounders based on previous literature and available

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measures as outlined in Table 2 [51,52]. Variables will be fitted as covariates in the regression models and variables with a $p < .2$ will be accepted for covariate interaction inclusion in the regression model.

The variables broadly categorized as follows will be investigated as any of predictors, covariates or outcomes, as appropriate to the analyses:

1. Demographic variables (age, residential address, gender, ethnicity, socioeconomic status).
2. Lifestyle factors (alcohol and tobacco use).
3. Past and current medical history (cardiac, hypertension, diabetes and type and level of kidney disease, pulmonary disease, obesity).
4. Kidney disease factors (Urine albumin/creatinine ratio, urine protein/creatinine ratio, 24-hr urine protein excretion, serum creatinine, eGFR, HbA1c, serum phosphate, PTH, haemoglobin, serum albumin).
5. Kidney disease outcome variables (transplant, KRT, Dialysis modality, death).
6. Pre-referral parameters (RAAS inhibitors, Lipid lowering drugs, vitamin D or Calcium supplements, Systolic BP, Diastolic BP, BMI, PTH, serum albumin, eGFR, serum calcium, serum phosphate, urine ACR, urine PCR, 24hr protein excretion, urine dipstick, Hb).

Results will be reported with the level of significance at alpha .05 and accompanied by 95% confidence intervals (95% CI). Missing data and outliers will be reported but will be excluded from analysis. Outliers will be identified by the use of boxplots in STATA®. These outliers will be confirmed based on the established procedures from Hoaglin and Iglewicz [53].

4.0 Benefits and policy implications

Determination of the optimal risk stratification strategy which will accurately predict risk of progression to ESKD or development of CV events will inform the optimal timing of referral to specialist care. This has several policy implications in the overall care of the CKD patient including:

i) Spurring the need to review referral strategies, guidelines, and QLD health service delivery recommendations to improve the health outcomes of CKD and maximize efficiency of its management within the health care system.

ii) Balancing of quality of care and cost by improving appropriateness of referrals and efficient integration of primary and specialist services.

iii) Enabling the coordination of primary care and secondary care providers to optimize value by providing clinically indicated services at the appropriate time and reducing rates of referrals of low risk participants who could be safely managed in primary care.

iv) Reserving scarce specialist services for individuals at high risk of progressing to ESKD or developing cardiovascular events, where timely intervention is likely to improve outcomes.

v) Helping to inform the need for education of health care providers and implementation of targeted care initiatives, to ensure that individuals at high risk of progressing to ESKD are captured earlier and given an opportunity to benefit from a more specialized care environment.

Ultimately, the study findings are intended to provide CKD health care providers with a robust decision-making tool. This will enable targeted care initiatives to ensure that individuals at high risk of progressing to ESKD are identified early and given an opportunity to benefit from specialized nephrology care.

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5.0 Patient and public involvement

No patients were involved in the development of the research questions, the design and development of the study protocol. However, the conception of the study protocol, the scope of the research questions and outcome measures were informed by identified gaps in the current specialist referral process of individuals with CKD, and the uncertainty of the optimal timing of referral that will enable optimal specialist intervention, all of which were inspired by interaction with patients in the nephrology clinics. Results will be disseminated to patients and the public through social media and through their primary care physicians.

6.0 Ethics and dissemination

6.1 Ethics

The CKD.QLD registry and the hospital record(s) are being examined by the researchers retrospective to the participants' details being entered into CKD.QLD and their hospital admissions. The CKD.QLD data and the hospital record(s) are identifiable data, critical to the data linkage of this research. On enrolment into CKD.QLD, the informed consent for enrolment for the CKD.QLD registry included permission to access and link all relevant clinical material on the participants, including medical history, pathology reports and hospital admissions collected prior to enrolment in the registry for future CKD research. The Participant Information and Consent Form includes the following statement: *"The (CKD.QLD Registry) information is used for improvement of the quality of care for people with kidney disease, to study kidney disease and plan health services"*…and *"The information produced from the database may be used for future research in CKD. However, any research proposal based on the information collected from you will require additional approval from Ethics committees belonging to Queensland Health."*

6.2 Dissemination

The results will be presented as a component of a PhD study with The University of Queensland. It is also anticipated that the results will be presented at health-related conferences (local, national and possibly international) and via publication in peer-reviewed academic journals.

Author affiliations

[1]Renal Unit, Bundaberg Hospital, Wide Bay Hospital and Health Service, Bundaberg 4670, Australia; clyson.mutatiri@health.qld.gov.au (C.M.),

[2]Rural Clinical School, Faculty of Medicine, The University of Queensland, Brisbane 4072 Australia; clyson.mutatiri@uq.edu.au; angela.ratsch@uq.edu.au (A.R.); m.mcgrail@uq.edu.au (M.M.); s.kondalsamychennakes@uq.edu.au (S.K.C); s.venuthurupalli@uq.edu.au (S.K.V).

[3]Research Education, Development and Support, Wide Bay Hospital and Health Service, Hervey Bay 4655, Australia; angela.ratsch@health.qld.gov.au,

[4]Renal Services, West Moreton Hospital and Health Service, Ipswich 4305, Australia; sree.venuthurupalli@health.qld.gov.au.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the Royal Brisbane and Women's Hospital (LNR/2020/QRBW/69707 14/01/2021)

Informed Consent Statement: The HREC waived the requirement for patient consent as all patient's had consented for the use of their data for the purpose of research on recruitment into CKD.QLD Registry.

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