PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Mutatiri, Clyson; Ratsch, Angela; McGrail, Matthew R.; Venuthurupalli, Sree; KondalsamyChennakesavan, Srinivas

VERSION 1 – REVIEW

REVIEWER	Park, Ken Kaiser Permanente Northwest
REVIEW RETURNED	27-Jun-2021

GENERAL COMMENTS	The authors plan to undertake a comprehensive study of a large CKD registry to try to answer several important including the impact of early vs. late referral to nephrology on several outcomes include ESKD and death as well as examining how use of KRFE would change referrals (hopefully for the better). I look forward to the author's findings and hopefully this will spur interest in prospective studies looking at impact of applying KRFE in improving important outcomes including earlier referral of patients at high risk for KRT, timely referral for modality education, as well as timely referral for AVF placement. I have several comments for the author: 1. Would recommending using terminology G3, G4, G5 in keeping with KDIGO recommendations. 2. Appropriateness for referral is very subjective and may be important to define what an appropriate referral is. The authors mention KDIGO and QLD criteria and may be helpful to define these criteria for the reader. 3. Would consider defining early vs. late referral for the reader. 4. I assume that the authors will be looking at hypothetical application of KRFE and that KRFE is not routinely used by primary care or nephrology. 5. I would recommend defining what is high risk based on KRFE as well as KRFE criteria for access referral 6. Will the KRFE be calculated at initial visit and at regular time intervals (i.e. 3 months) or at initial visit only? How will the authors treat patients with incalculable KRFE as several studies show that many CKD patients are missing ACR measurements? The authors mention looking at proportion of patients that progressed to ESKD as predicted by KRFE but at what time point? At initial visit nephrology? Similar to eGFR, KRFE will likely fluctuate from visit to visit. 7. 12 months time period for outcome of KRT may be too short as KRFE calculates KRT risk at 2 and 5 years.

REVIEWER	Thomas, Nicola London South Bank University, School of Health and Social Care
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	Thank you for submitting this interesting protocol. I have some queries and also suggestions that might help strengthen the paper: 1. The abstract is clear but I would like to have more detail of the mechanism for patient opt-out and consent written in the main body of the paper. "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" and " access to hospital record(s) has been granted under a waiver of consent." 2. Strengths and limitations: it is not entirely clear which are strengths and which are limitations. Please write clearly. Also please explain in the body of the paper exactly how the study "has potential to identify opportunities for improving quality of care for CKD at both state and national level." 3. References 4 and 5 are a little outdated and might not reflect the current situation with regards negative impact of high rates of premature referrals. Please update or review and change wording. 4. Section 2.2. Please justify why there will no PPI. If one of the aims is 'appropriateness of the referral' see my comment below, then there might be patient-centred outcomes to be considered. Also why would you not provide results to patients as you are involving their data? The UK Renal Registry has a patient council so wonder if the CKD.QLD Registry has one too? https://renal.org/patients/patient-council 5. Methods. One of the aims is stated as "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. I could not see how appropriateness is to be measured and linked with the stated outcomes. For example referral might result in improved BP control that would manifest in a positive way in terms of eGFR. Please explain. 6. It is not clear why Registry data is only available until 2018. Please explain. Overall an interesting protocol. Thank you for asking me to review it

VERSION 1 – AUTHOR RESPONSE

Reviewers' Comments	
Reviewer: 1 Dr. Ken Park	Authors' responses
1. Would recommending using terminology G3, G4, G5 in keeping with KDIGO recommendations	The suggested terminology has been adopted and used throughout the manuscript (e.g. Page 4, Paragraph 2, Line 4; Page 4, Paragraph 3, Line 4; etc)

2. Appropriateness for referral is very subjective and may be important to define what an appropriate referral is. The authors mention KDIGO and QLD criteria and may be helpful to define these criteria for the reader.	Our definition of appropriateness for referral used in this study has been added in a new section 2.31 on page 6.
3. Would consider defining early vs. late referral for the reader	The general practitioners in Australia are usually guided by recommendations from Kidney Health Australia and the CARI guidelines in their management of their patients with CKD, including the criteria for specialist referral. The definition for late referral has been added in a new section 2.32 on page 7 in line with Australian GP practice recommendations.
4. I assume that the authors will be looking at hypothetical application of KRFE and that KRFE is not routinely used by primary care or nephrology.	It is noted in the second last paragraph of the introduction that "despite its validation in North America and Europe, the KFRE has not yet been widely adopted in Australian clinical practice". The equation will therefore be applied hypothetically in this retrospective analysis, consistent with this suggestion.
5. I would recommend defining what is high risk based on KRFE as well as KRFE criteria for access referral	A new section (2.4), "Kidney Failure Risk Equation" on Page 7 has been created to incorporate this suggestion.
6. Will the KRFE be calculated at initial visit and at regular time intervals (i.e. 3 months) or at initial visit only? How will the authors treat patients with incalculable KRFE as several studies show that many CKD patients are missing ACR measurements? The authors mention looking at proportion of patients that progressed to ESKD as predicted by KRFE but at what time point? At initial visit nephrology? Similar to eGFR, KRFE will likely fluctuate from visit to visit	The KFRE will be calculated to estimate baseline risk at the initial visit where ACR is available. Where only results of PCR or Urine dipsticks are available, the equations developed by Sumida et al in 2020 will be employed to calculate the predicted ACR. 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 measurement will automatically become the date for estimating baseline risk using the KFRE and for beginning the follow-up period. The KFRE will be applied to our analysis to determine the proportion of participants who progressed to ESKD after 2 years and 5 years of follow up from the initial visit. Regarding the fluctuation of eGFR from visit to visit, we will adopt a similar approach to that

	employed by Tangri et al in their development cohort during the development of the equation. The eGFR at the initial visit will be used as index. All the patients who are consented to registry are acknowledged CKD patients as they would have multiple pathology reports prior to referral and would therefore fulfill the definition of CKD G3-G5. However, the limitation of using an absolute single time eGFR with the associated inter- test variability will be acknowledged in the limitations section of the manuscript.
7. 12 months time period for outcome of KRT may be too short as KRFE calculates KRT risk at 2 and 5 years.	We agree. As noted above (response 6), participants will be followed up to five years. However, we also intend to conduct a study that will follow the progression of CKD under specialist nephrology services. Outcomes including KRT initiation, 40-57% eGFR decline or doubling of serum creatinine, MACE and non-cardiovascular mortality at different time intervals will be explored to determine the association of past eGFR slopes vs eGFR at referral, albuminuria stage, comorbidities, and cause of CKD with these outcomes.
Reviewer: 2 Dr. Nicola Thomas	
1. The abstract is clear but I would like to have more detail of the mechanism for patient opt-out and consent written in the main body of the paper. "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" and " access to hospital record(s) has been granted under a waiver of consent."	Section 2.1 on “Sampling framework and study participants” has been expanded to include the following statements; On enrolment into CKD.QLD the informed consent for enrolment 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. 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 Heath*.”

2. Strengths and limitations: it is not entirely clear which are strengths and which are limitations. Please write clearly. Also please explain in the body of the paper exactly how the study "has potential to identify opportunities for improving quality of care for CKD at both state and national level."	The section on strengths and limitations has been revised in response to this comment, with new subheadings now separating these parts. A paragraph has been added in the main body of the manuscript (see section 4.0 on page 12) addressing the benefits and policy implications of the study.
3. References 4 and 5 are a little outdated and might not reflect the current situation with regards negative impact of high rates of premature referrals. Please update or review and change wording.	References 4 and 5 have been updated and replaced with more recent papers.
4. Please justify why there will no PPI. If one of the aims is 'appropriateness of the referral' see my comment below, then there might be patient-centred outcomes to be considered. Also why would you not provide results to patients as you are involving their data? The UK Renal Registry has a patient council so wonder if the CKD.QLD Registry has one too? https://renal.org/patients/patient-council	The PPI statement has been modified (Page 13).
5. Methods. One of the aims is stated as "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. I could not see how appropriateness is to be measured and linked with the stated outcomes. For example referral might result in improved BP control that would manifest in a positive way in terms of eGFR. Please explain.	By describing the referral patterns of participants in the registry, we are aiming to gain information on both appropriateness of referrals and the timing of referrals. However, appropriateness of referrals although not spelt out on the list of outcomes, will enable us to gain information on the level of adherence to national guidelines. This is important to improve the quality of referrals and can form the basis for the strengthening of GP education initiatives. On the other hand, the timing of referrals will enable us to describe outcomes associated with late referrals. We are hypothesising that timely referral to specialist care will be associated with slowing down of progression to ESKD, improvement in clinical outcomes and efficient utilisation of resources. This will be investigated by comparing outcomes of participants referred early to those referred late, including the level of BP control, time taken to correction of anaemia and CKD bone mineral disease, amongst other outcomes.

6. It is not clear why Registry data is only available until 2018. Please explain.	The CKD.QLD registry was established as a core component of CKD surveillance in Queensland, funded by various grants between 2008 and 2019 (with first participants enrolling in May 2011). Recruitment of new participants was discontinued in 2019 due to funding constraints. After 2019, the long-term success of the Registry was left to largely depend on the ability to recognize and incorporate registry activities into public health system as an important core component of healthcare delivery. For our study, we decided to include participants enrolled from 2011 and 2013 and follow them up until 2018. This would allow us at least 5 years of follow up for participants recruited between 2011 and 2013.

VERSION 2 – REVIEW

REVIEWER	Park, Ken Kaiser Permanente Northwest
REVIEW RETURNED	12-Nov-2021

GENERAL COMMENTS	All of my comments have been addressed. Manuscript is written clearly and goals of the study is well defined.

REVIEWER	Thomas, Nicola London South Bank University, School of Health and Social Care
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	Thank you for all your changes and edits. The paper has been strengthened and I am happy to recommend for publication