CLINICO-PATHOLOGICAL CHARACTERISTICS AND OUTCOMES OF NEPHROLOGY ADOLESCENTS AND YOUNG ADULTS IN CAPE TOWN: A SINGLE CENTRE STUDY.

By

ZIBYA BARDAY

STUDENT NUMBER: BRDZIB001

MPHIL DISSERTATION

SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

MASTER OF PHILOSOPHY (MPhil dissertation) in Nephrology

Faculty of Health Sciences

University of Cape Town

Date: 31 August 2022

Supervisor: Dr. Bianca Davidson

Co-supervisors: Prof. Nicola Wearne, Prof. Erika Jones, Prof. Mignon McCulloch.

E13 Renal Unit, Division of Nephrology & Hypertension, Groote Schuur Hospital Observatory, Cape Town, South Africa

TABLE OF CONTENTS

DECLARATION OF ORIGINALITY

I, Zibya Barday, hereby declare that the work, on which this dissertation is based upon, is my original and independent work (except where acknowledgements indicate otherwise). The complete work or any part of it, has not been or is to be submitted at this or any other university. This manuscript has not been published prior to the registration for the above-mentioned degree. I empower the university to reproduce this work for the purpose of furthering research, either in its entirety or in any specific portion selected out of the contents.

SIGNATURE:

Signed by candidate

Dr. Zibya Barday

DATE: 31 August 2022

ACKNOWLEDGMENTS

- Dr. Bianca Jane Davidson, Professor Nicola Wearne, Professor Erika Jones and Professor Mignon McCullouch: It has been an honour to have the supervision and guidance of these experienced adult and paediatric nephrologists, throughout the MPhil process. Their encouragement, guidance and mentorship have helped shape my understanding of research.

- Ms. Kathryn Manning: Thank you for your expertise in the statistical analysis of this research.

- My husband, Dr. Riyaad Salie: Thank you for your belief in me and unwavering support in my quest for knowledge.

- To dearest Aidan and Pumpkin, I look forward to sharing this world with you.

- My parents Mrs. Zainab Chikte-Barday and Mr. Hanief Barday: Thank you for supporting my love for nephrology and encouraging me to pursue my dreams.

- My brother Mikhail and my sisters Mish-Al and Sozarn: Thank you for your constant support of my work.

DEFINITIONS

(i) Adolescents

Young individuals aged between 10 and 19 years of age. (1)

(ii) Young Adults

Young individuals aged between 10 and 25 years of age.(2)

(iii) Hypertension

In young adults, aged between 19 and 25 years old, hypertension is defined as a persistent elevation of blood pressure with a systolic blood pressure [SBP] ≥140mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg; or if a patient is on treatment with anti-hypertensive medication.(3)

In adolescents, aged between 13 and 18 years old, hypertension is defined as a persistent elevation of blood pressure with a systolic blood pressure [SBP] ≥130mmHg and/or diastolic blood pressure [DBP] ≥ 80 mmHg; or if a patient is on treatment with anti-hypertensive medication.(3,4)

In children, aged between 1 to 13 years old, hypertension is defined as an average blood pressure ≥ 95^{th} percentile for their age, sex and height; or if blood pressure ≤ 95^{th} percentile with 12mmHg elevation; or if the blood pressure is ≥130/80mmHg.(3,4)

(iv) Acute Kidney Injury

Sudden loss of kidney function, determined by an increased serum creatinine level (a marker of kidney excretory function) and reduced urinary output (a quantitative marker of urine production) and is limited to 7 days.(5)

(v) Chronic Kidney Disease

Renal damage due to structural or functional abnormalities of the kidney for ≥3 months, with markers of a reduced eGFR < 60mL/min/1.73m^2 and/or markers of kidney injury according to albuminuria criteria (Cause, Glomerular Filtration Rate and Albuminuria Classification).(6,7)

(vi) End-Stage Kidney Disease

Advanced irreversible chronic kidney disease (CKD) with a eGFR of less than 15mL/ min/1.73m^2, which requires the initiation of kidney replacement therapy.(8,9)

(vii) Composite End-Point:

The composite end-point for this study will include:

(a) Persistent doubling of serum creatinine over the baseline creatinine value.

(b) Reduction in eGFR >40%

(c) Development of end-stage kidney disease (ESKD)

(e) Death

For patients who have reached this end-point, the period of follow up is the interval between the first diagnosis and the 31st of May 2020.

(viii) Kidney Survival

Kidney survival is the period of event-free status from composite outcome; calculated from the time of diagnosis until the 31st May 2020, or until the composite end-point is reached or if loss to follow up has occurred.

(ix) Adherence

Adherence is the extent to which the patient follows medical instructions, with good communication, in addition to patients being active partners together with health professionals in the care of their own health.(10,11)

(x) Lost to Follow Up (LTFU)

LTFU is a term used to describe patients who are followed up at a sentinel site, and have not had contact with the health facility for a certain specified time period since their last clinic visit.(12,13)

REFERENCES

1. Singh PK. Adolescent Health at aglance in South-East Asia Region: fact sheet. World Health Organisation: Regional Office for South-East Asia. 2007; 53.
2. Moreno M, Thompson L. What Is Adolescent and Young Adult Medicine? JAMA Pediatr. 2020 May 1;174(5):512–512.
3. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents: The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Journal of the American Academy of Pediatrics. 2004; 114 (Suppl 4):555-76.
4. Flynn JT, Kaelber DC, Baker-Smith CM. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. Pediatrics. 2017; 140.
5. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nat Rev Dis Prim. 2021;7(1).
6. Kasiske B. Kidney Disease: Improving Global Outcomes Guideline on CKD [Internet]. Mandaluyong City; 2014 [cited 2020 Feb 10]. Available from: www.kdigo.org.
7. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516–26.
8. Davids R, Jardine T, Marais N, Jacobs J. South African Renal Registry Annual Report 2016. African J Nephrol. 2018;21:61–72.
9. Hall YN, Chertow GM. End stage renal disease. BMJ clinical evidence. StatPearls Publishing. 2007.
10. Adherence to Long-Term Therapies: Evidence for action Report. World Health Organization. 2003:1-209.
11. Sabate E. Adherence to long-term therapies: policy for action: meeting report [Internet]. 2001 Jun [cited 2022 Aug 24]. Available from: https://apps.who.int.pdf.
12. Naome Mberi M. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004–2012: a cohort study. BMC Health Serv Res. 2015; 4(15):259.
13. Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C. Universal Definition of Loss to Follow-Up in HIV Treatment Programs: A Statistical Analysis of 111 Facilities in Africa, Asia, and Latin America. PloS medicine. 2011; 8(10).

LIST OF COMMON ABBREVIATIONS

AKI	Acute Kidney Injury
AYA clinic	Adolescent and Young Adult Clinic
BP	Blood Pressure
CKD	Chronic Kidney Disease
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
ESKD	End-Stage Kidney Disease
GN	Glomerulonephritis
GSH	Groote Schuur Hospital
HD	Haemodialysis
HPT	Hypertension
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
KRT	Kidney Replacement Therapy
Non-AYA Clinic	Non-Adolescent and Young Adult Clinic
PD	Peritoneal Dialysis
SA	South Africa
SSA	Sub-Saharan Africa
RCWMCH	Red Cross War Memorial Children's Hospital
SBP	Systolic Blood Pressure
UCT	University of Cape Town
UPCR	Urine protein:creatinine ratio

PUBLICATION-FORMAT MANUSCRIPT

CHAPTER1: BACKGROUND

1.1 CONTEXT/LITERATURE REVIEW

1.1.1. Introduction

Adolescents and young adults [AYA] are a unique population, who frequently access the nephrology health care service and are challenging to manage. During this period there are rapid changes in physical, cognitive and psychosocial developments. The WHO defines adolescence as a phase of life between the age of 10-19 years(1) and young adults as individuals between the age of 15 and 25 years.(2) In recent years, there has been a keen interest in AYA medicine as a distinct paediatric sub-specialty.(2) A dedicated nephrology AYA transition clinic could provide the opportunity to provide a holistic health care that would encourage better patient engagement and improved health-related outcomes. The health and well being of AYA is of utmost importance as they represent the future of society and potential key contributors of productive economy.

1.1.2. Epidemiology: Spectrum of Kidney Diseases

Worldwide AYA is estimated to constitute almost a quarter of the global population.(1,3) Approximately 35% of the global burden of disease has its roots in adolescence.(1) There is a global rise in cardio-metabolic risk factors, such as obesity, hypertension, diabetes and dyslipidaemia.(4) Unhealthy eating habits, lack of physical exercise, smoking and obesity have it's roots in adolescence, and may result in the development in these non-communicable

diseases [NCDs], contributing to future chronic kidney disease [CKD]. The rise in cardio-metabolic risk profile is reflected in the South African setting with 40.2% of young South Africans reported to be overweight or obese, and the metabolic syndrome described in 3.1% of females and 6.0% of males.(5) However, large studies have not clearly shown a link reflecting this NCD epidemiological change to result in an increased risk of kidney disease amongst adolescence. It does however show a relationship between individual cardio-metabolic risk factors and microalbuminuria.(6,7) High-risk social activities in AYA such as unprotected sex, alcohol and illicit drug use may result in increased risk of communicable diseases [CD] such as sexually transmitted diseases [STIs], including HIV, hepatitis B and C infection; which could contribute to kidney disease.

Internationally, there is a significant concern of the number of people living with end-stage kidney disease [ESKD] dramatically increasing, with the USRDS reporting more than a double increase in ESKD prevalence between 2000-2019.(8) The combination of children, adolescents and young adults constitute less than 5% of the ESKD population.(9,10) In general this group has increased 10-year survival rates compared to older adult counterparts, with survival rates ranging from 70 to 85%.(4,5) The spectrum of kidney diseases and the causes of ESKD vary across the different age groups. According to the USRDS paediatric registry the top three aetiologies of ESKD are glomerulonephritis [GN], congenital anomalies of the kidney and urinary tract [CAKUT], and cystic or hereditary disorders.(11) Limited international adolescent registry data report the leading causes of ESKD to be due to GNs and reflux nephropathy.(12,13) Large adult registry databases report diabetes and hypertension to be the most significant causes of ESKD, with GNs only contributing to 7.2% of the causes.(11)

In Africa, there is a paucity of published data on the prevalence and aetiology of adolescent kidney disease, including ESKD. The shortfall of adolescent renal registries limits our understanding of the extent of the problem.(11) The current aetiology of adolescent ESKD is suspected and extrapolated from data describing the burden of disease seen in paediatric and adult populations. Published data in Africa report a higher prevalence of GNs in adults compared to well-resourced countries.(14,15)

In South Africa [SA], adolescents aged 10-19 contribute to a significant proportion of the population at 17.4%.(16) There is limited data on the spectrum of adolescent kidney disease. It is uncertain whether this sub-group has a unique aetiological profile of CKD, compared to paediatric and adult counterparts **(Figure 1).** In SA, the leading cause for paediatric CKD is glomerular disease, with **Figure 2** showing the contrasting aetiological profiles of primary GN's in the paediatric and adult populations. In adults, hypertension and diabetic nephropathy have been reported as the main causes of ESKD.(17)

Figure 1: Graph illustrating the different aetiologies of ESKD in the paediatric and adult populations in South Africa. (14,17)

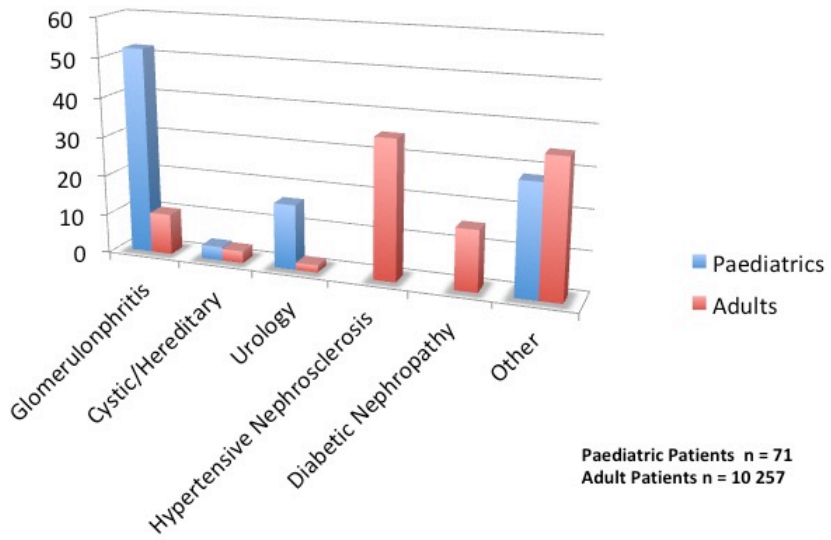
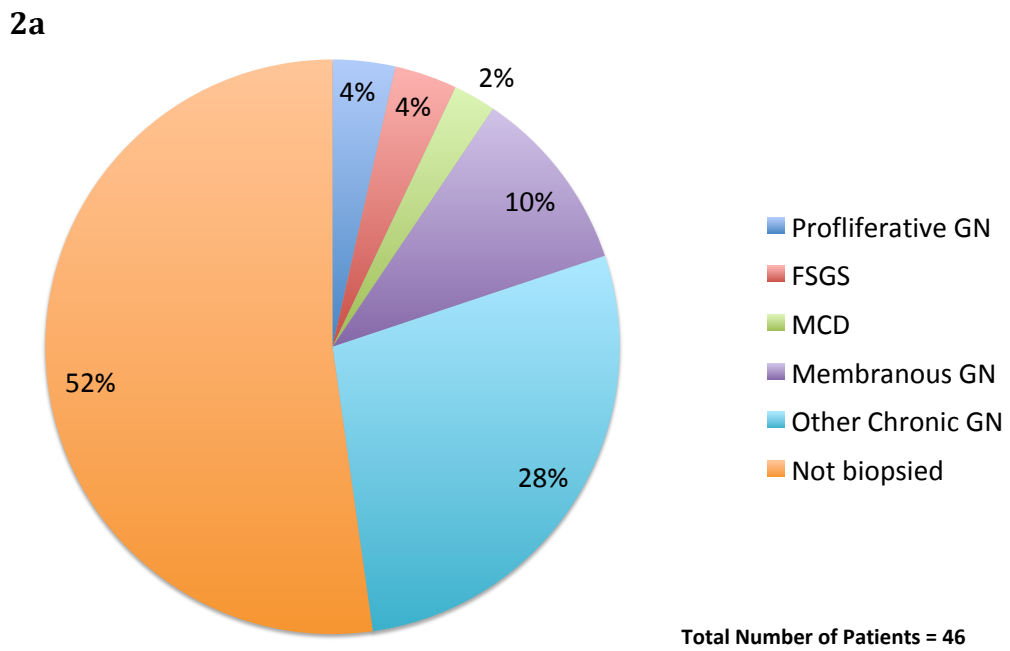
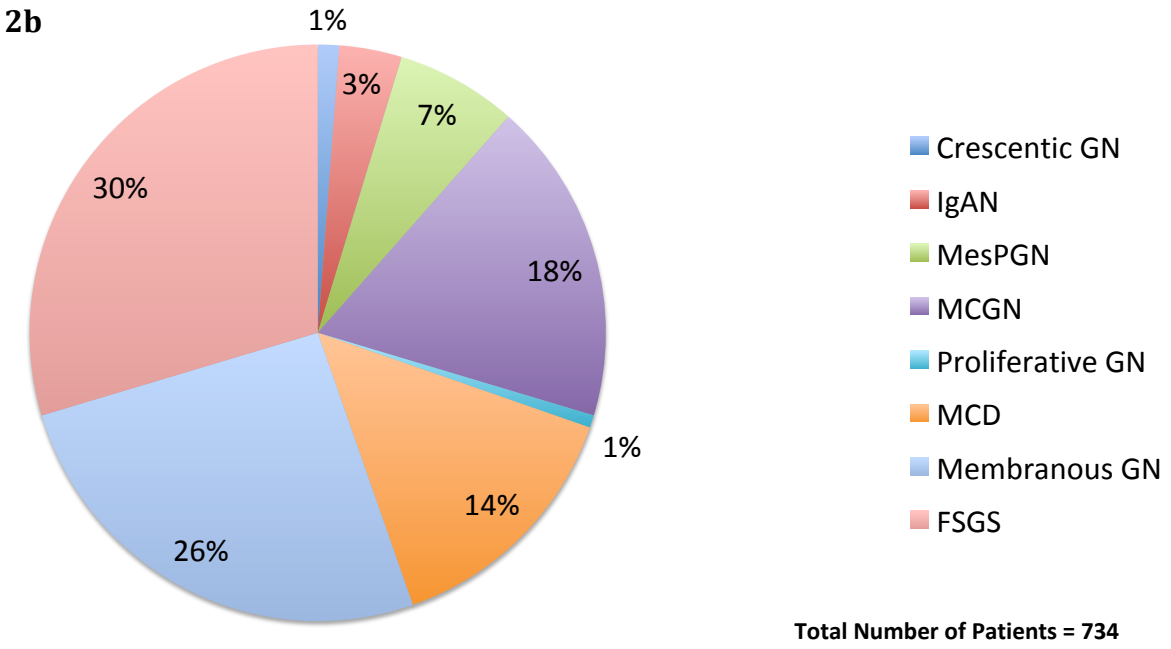


Figure 2: Diagram showing primary glomerulonephritis aetiologies, in the paediatric population, aged 0-16 years **(2a)**,(14) and adult population, aged greater than 18 **(2b),**(18) in South Africa.



GN, glomerulonephritis; IgAN, Immunoglobulin A Nephropathy, MesPGN, mesangioproliferative glomerulonephritis; MCGN, mesangiocapillary glomerulonephritis; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis.

2b



Total Number of Patients = 734

GN, glomerulonephritis; IgAN, Immunoglobulin A Nephropathy, MesPGN, mesangioproliferative glomerulonephritis; MCGN, mesangiocapillary glomerulonephritis; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis.

1.1.3. Adolescent Brain Development

Adolescence is a phase of development where there are dynamic anatomical and physiological maturation processes. During this period there is reorganization of cortical circuits, which is reflected in cognitive functioning and regulation. The completion of brain development in a healthy adolescent brain occurs in mid to late adolescence.(19) This could be aggravated by the impact of CKD on neurocognitive function.

During adolescence, there are important structural neurobiological changes which are supported by neuroimaging studies.(20) The pre-frontal cortex, which controls higher cognitive functions such as executive planning, behavioral regulation and assessment of risk, matures later than other cortical regions and sub-cortical regions.(21) Imaging studies also show increased activity in the limbic regions.(22) There appears to be more activity in the

nucleus accumbens, which may explain the short-term reward-seeking behaviour and risk-taking tendencies.(23) Adolescents are able to make rational decisions but in certain situations the probability of rewards and emotions affect behaviour more strongly than rational decision-making processes.(22–24) In adolescence, brain development is not static and a highly dynamic process with the capacity of the nervous system to adapt to constant internal and external stimuli.

The maturation of the reproductive system during adolescence has given rise to proposed models where puberty and associated gonadal steroid hormones influence cerebral pathways.(26) The hypothalamic-hypophyseal-gonadal axis is responsible for the production of eostrogens, progrestrogens and androgens. The brain has a high density of steroid receptors and these hormones contribute to the organizational phenomena, where there is re-structuring of the shape of certain brain circuits.(27) It may constitute a period in life where there is unique neural plasticity, and the hormonal influence on the encephalon determines some of the behavioural patterns seen in individuals later in adulthood.(27)

From an evolutionary perspective, adolescence is a developmental period where growth and acquisition of autonomy takes place. This could be viewed as a period of biological disequilibrium, which results in risk-taking behavior in search for new experiences and diversion from normal routine. This potentially enables adolescents to become independent and break away from the security of close family, in order to explore the world or seek a partner.(28) An immature pre-frontal cortex seems to favour certain types of learning and flexibility characteristics.(29) The sensitivity to socio-affective stimuli may assist adaptation in social development.

In children and adolescents with CKD, cognitive impairment is more common compared to the general population.(30–32) In CKD pathophysiological changes can contribute to neurocognitive dysfunction. The neuro-biololgical model suggests that neurotoxic exposure to the brain, contribute to changes in neuronal myelination and synaptic development. Advanced uraemia and anaemia have also been reported to alter brain metabolism. The clinical effects correspond to neuroimaging and electrophysiological studies showing periventricular white matter lesions, cortical atrophy and delayed myelination of somatosensory cortex.(33) In general, CKD patients have low-average cognition compared to the age-matched controls with mild deficits in academic skills, executive function, visual and verbal memory.(34) The relationship between kidney function and cognitive abilities is not linear but there does appear to be an increased risk in advanced CKD. The extent and patterns of neurocognitive dysfunction can vary with CKD stage, with lower IQ scores reported in those with ESKD and on haemodialysis [HD];(30–32,34) but improved IQ, attention and mental processing speeds after kidney transplantation.(35)

1.1.4. Kidney Disease Outcomes in Adolescent and Young Adults

Worldwide there is limited data evaluating the outcomes of kidney disease and kidney replacement therapy [KRT] in the AYA population. Chronic dialysis in the South African state sector is a scarce resource, and is rationed in the Western Cape with assistance of ethical guidelines. The overarching principle for eligibility to the KRT programme has been the assessment for patients to be good future kidney transplantation candidates. This is challenging in the adolescent population, who have high rates of non-adherence and high-risk social behaviour, which could impact their eligibility for future KRT opportunities and potentially result in poor kidney outcomes.

Kidney transplantation in the AYA population has been of keen research interest in recent years. Kidney allograft failure rates are reported to increase at age 13 and peak during age 17-24, regardless of age of transplantation .(36) Risk factors that affect long-term outcomes of adolescent kidney transplants are multi-factorial, including recipient-specific factors such as age and timing of transition between centres; as well as allograft-specific factors such as history of graft rejection. Adherence to immunosuppressive agents is key to kidney allograft survival. Non-adherence has been reported in up to 43% of adolescents and it has been suggested to be a main contributor to poor kidney graft outcome.(37,38)

The mortality rates in the AYA population vary across the world. The United Nations Child Mortality Report has assessed the highest mortality age group to be between 10-24 years of age, especially in Sub-Saharan Africa [SSA].(39) In SA, kidney disease is the 9th leading cause of natural death amongst AYA.(40,41) However, there is a striking lack of data on the kidney disease related death in this population.

HIV is the second leading cause of natural death in in AYA. SA has a high prevalence of HIV infection (19.5%) in AYA.(41,42) In SSA, gender disparity is highly prevalent with women aged 15-24, having the highest incidence of HIV infection.(43) The prevention and management of HIV is a critical part of nephrology adolescent care. Unnatural causes are also highly prevalent in this age group, especially in male adolescents. A comprehensive approach to AYA health is key to reducing the rates of mortality and morbidity.

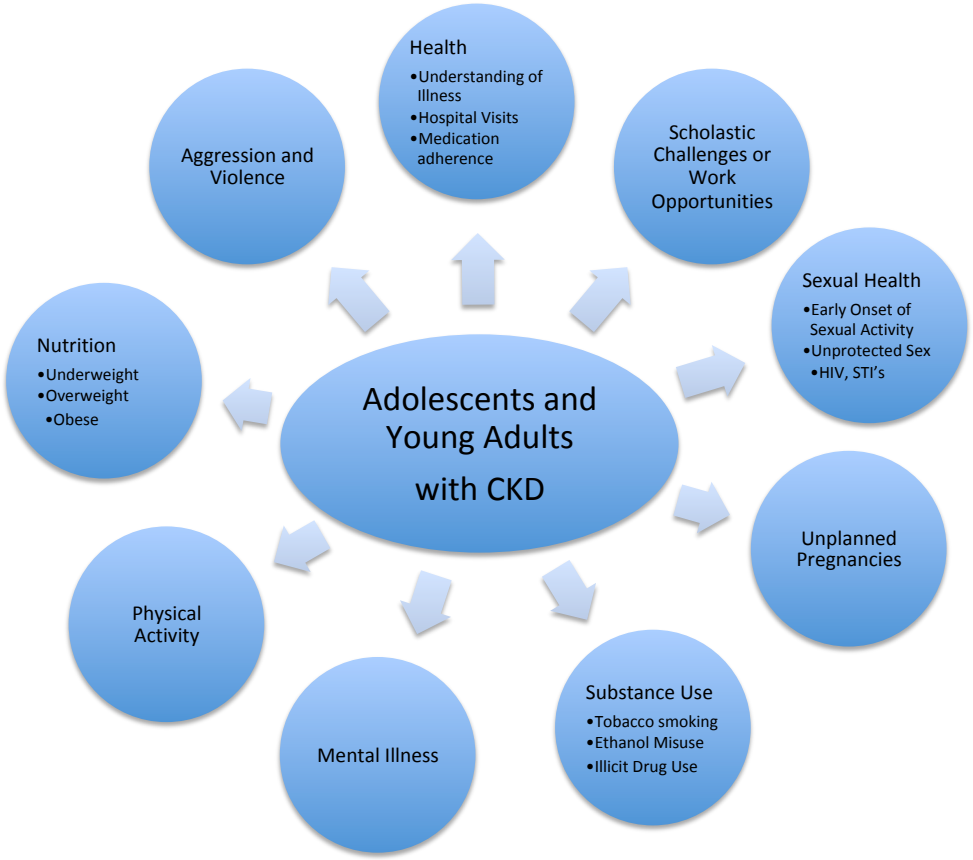
Lost to follow up (LTFU) has a significant impact on outcomes in AYA. The LTFU term has not been standardized internationally, making it challenging to compare studies. LTFU has been defined in one study as non-attendance to a health clinic for >1 year.(44) There are limited studies evaluating LTFU in adolescence with kidney disease, except in kidney transplantation. The Organ Procurement and Transplantation Network [OPTN] reported 32.9% of LTFU in paediatric kidney transplant recipients within 10 years of transplantation.(45) Institutional transfer with transition from a paediatric to an adult service was found to be a significant risk factor for LTFU with an OR 3.36 (95% CI 3.1-3.6).(44) The outcome from LTFU could result in an increased risk of death, with one study showing the LTFU cohort to have a 26.1% increased chance of death.(44) Graft failure rates were not shown to be elevated in LTFU, but this could be attributed to graft failure rates not being recorded if there was clinic non-attendance. Thus the true-scope of LTFU and implications for graft loss and graft rejection is not well understood. Transplant organs are scarce and a valuable resource. It is important in young kidney transplant recipients that we maximise the utility and gain from each organ, minimiszing the need for future KRT and re-transplantation. In light of the strong association with institutional transfer, the utility of adolescent transition clinic for AYA kidney transplants and improving LTFU and kidney outcomes need further exploration in studies.

1.1.5. Challenges encountered by Adolescents and Young Adults

AYA is a unique population sub-set and are vulnerable during this phase of life due to key neurocognitive developmental changes. This vulnerability could lead to high-risk behaviour, which may critically impact the management of chronic kidney conditions, as well as adherence to therapy.

AYA have a higher prevalence of unsafe sex practices, substance use, mental illness, adherence challenges and are more prone to trauma compared to the older adult population. This is compounded by the socio-economic challenges in South Africa. All these factors, could impact the management of CKD conditions **(Figure 3).**

Figure 3: Challenges encountered by AYA population.



CKD, chronic kidney disease.

Adolescents account for 13% of the global burden of mental disorders, with 1 in 7 between the ages of 10 – 19 years suffering from a mental illness.(46) In children with CKD, high rates of depression are recognized with an estimated prevalence ranging from 10-35%.(47) Major depressive disorder is one of the leading causes of mental illness.(48) Depression is associated with lower achievement, lower IQ and lower health-related quality of life scores.(47)

Worldwide, suicide is the third leading cause of death amongst this population sub-set.(48) The peak age of onset for most mental health disorders is during adolescence.(48,49) If it is not addressed early or left untreated it could result in adverse life trajectories.(50) Adolescents who have mental illnesses and who do not access health care have an increased risk of physical health co-morbidities and injury,(51) as well as more advanced psychopathology later in adulthood. (52,53) AYA have a high risk of mental illness, which is very important to be aware of and recognize.(48)

Non-adherence is complex and very common amongst adolescents with chronic diseases, including kidney disease. It is important to understand the background reasons adolescents may not engage with health services. STATS SA Global Household Survey report 2022 showed numerous reasons for non-consultation to health care services among adolescents when they were ill. The top three reasons given include preference for self-medication, perception that consultation was not necessary and long queues at health care services**.**(41) Self-medication could also be a risk factor for possible kidney injury.

It is important to consider the adolescent stage of development in addressing adherence challenges.(56) Goal directed, future-orientated and complex abstract thinking, which assist management of chronic conditions, develop late adolescence and early adulthood. Thus, it is essential to tailor adherence interventions to the individual. The factors which influence adherence, globally and in the context of Sub-Saharan Africa, can be viewed in **Table 1**.

Table 1: Adherence and challenges in an international and Sub-Saharan African setting.(57)

WHO – 5 categories linked to adherence	WHO factors influencing adherence	Challenges faced in the Sub-Saharan and South African context
Socio-economic status (SES) and demographic factors	• Low SES, poverty • Cultural and lay beliefs about illness • Illiteracy and poor education • Unemployment • Lack of social networks • Instability and family dysfunction • Financial burden of health care • Extreme anxiety and overprotection of child by parent • Single parent family	**Poor SES circumstances** • Poverty • Substance abuse • Violence • High unemployment rates
Condition – related factors	• Severity of symptoms • Level of disability • Rate of progression availability of effective treatment	**Unhealthy adolescent population in South Africa [SA]** • Rising overweight and obesity rates for adolescents.[20] • 38.2% of adolescents have pre-hypertensive systolic BP with hypertension incidence at 5.3%.[35] • SA least physically active adolescents on the continent.[36] • In LMICs 40% have two cardiovascular risk factors and one in 10 had three.[37]
Patient related factors	• Psychiatric illness (PTSD, anxiety, depression) • Poor coping mechanisms • Knowledge & beliefs of illness • Low self-esteem of body image • History of child abuse • Forgetfulness	• Prevalence of child abuse in Africa 64%[38] • SA has highest sexual abuse in Africa[38] • SA teen pregnancy 21.3% in 2011[39] • Drugs used in the <20 years. age group were methamphetamines, cannabis and inhalants.[40]
Treatment related factors	• Complexity of medications • Duration of treatment • Previous treatment failure • Side-effects – cosmetic or other	• Limited medications available • Lack of alternative drugs if side effects occur • Lack of access to combination tablets
Healthcare related factors	• Poorly developed health services • Poor medication distribution • Short consultation • Inability to establish community support • Poor patient education • Lack of continuity of care	• Lack of adolescent friendly services • No transitional units • Overburdened healthcare system • Staff shortages

Permission received from WHO to adapt text to table.

***Permission to use table in thesis granted by the author.**

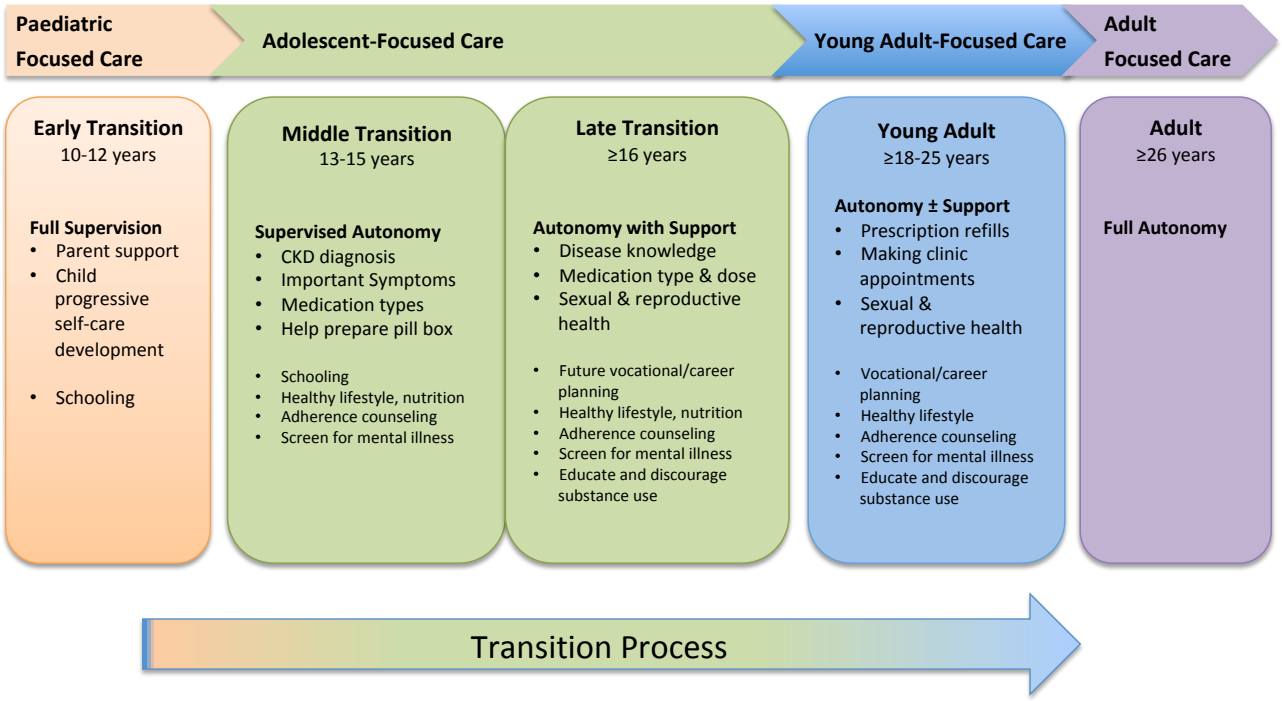
1.1.6. Adolescent Renal Transition clinics

Transitioning of care in adolescence is a complex process. Adolescent transition clinics have developed to support the transfer of young patients from paediatric to adult health care systems limiting interruption to care. Transition care should be a period of celebration. In paediatric nephrology, this period could represent the success of management of kidney disorders, which some previously regarded as fatal. In adult nephrology this could provide an opportunity for early intervention in the course of kidney disease and has the potential to

alleviate long-term morbidity and mortality.

There is a growing body of evidence on the benefits of transitioning adolescent patients with chronic conditions, but a paucity of literature in nephrology.(1-3) The concept of transition should be introduced pre-emptively, granting enough time to the patients and family to adjust to the change **(Figure 4).** Transition clinics have the ability to manage health care needs, assist with adolescent challenges as well as navigation of the new adult health care system.

Figure 4: Nephrology Transition Clinic Model. *Adapted from Bell et al. CJASN. 2022.(58-60)



In SA, the first state sector nephrology AYA service was established, at Groote Schuur Hospital, in June 2015. The design of this innovative clinic was preceded by a patient-centred needs assessment **(Supplementary Table 1)**. This service was designed to include patients aged 13-24 years. The service begins with an hour-long group session, facilitated by the social worker and co-facilitated by a patient mentor. The clinic runs directly afterwards and consists of a

multidisciplinary team, which includes an adult and paediatric nephrologist, a senior renal fellow, a professional nurse, a dedicated social worker and clinical psychologist. The aim of the clinic is to provide a non-judgmental medical care, focusing on nephrology condition and treatment education; in addition to addressing high-risk aspects of adolescent care. This service serves as a platform to train South African and African nephrology fellows, as well as the potential to form the basis of an AYA kidney disease registry. This pioneering innovation is the first service of its kind in SSA.

1.1.7. Rationale for Current Study

There is a paucity of data on AYA kidney disease in Africa. This study aimed to explore the complexities of adolescent care nephrology, which includes the description of the spectrum of kidney disease, assessment of kidney outcomes and prognostic predictors; as well as evaluating the impact of a dedicated intensive AYA nephrology service in the SA Setting. It is important for nephrologists to be aware and trained in the principles of adolescent care.

REFERENCES

1. Singh PK. Adolescent health. World Health Organisation: Regional Office for South-East Asia. 2017; 53.
2. Moreno M, Thompson L. What Is Adolescent and Young Adult Medicine? JAMA Pediatr. 2020;174(5):512–512.
3. Schichor A. Adolescent Health. NMS Pediatr 5th Ed. 2012;83–108.
4. Group NRFC-AW. Treands in Obesity and Diabetes across Africa from 1980 to 2014: An analysis of pooled population-based studies. Int J Epidemiol. 2017;10:1421–32.
5. Sekokotla AS, Goswami N, Rufaro C, Rusike A, Iputo JE, Ngwenchi B CN. Prevalence of metabolic syndrome in adolescents living in Mthatha, South Africa. Ther Clin Risk Manag. 2017;13:131–7.
6. Cho H, Kim JH. Prevalence of microalbuminuria and its associated cardiometabolic risk factors in Korean youth: Data from the Korea National Health and Nutrition Examination Survey. PLos One. 2017;12.
7. Li L, Pérez A, Wu LT, Ranjit N, Brown HS, Kelder SH. Cardiometabolic Risk Factors among Severely Obese Children and Adolescents in the United States, 1999–2012. https://home.liebertpub.com/chi. 2016;12(1):12–9.
8. Kuehn BM. End-stage Kidney Disease Doubles. JAMA. 2022 Apr 26;327(16):1540–1540.
9. Ferris ME, Cuttance JR, Javalkar K, Cohen SE, Phillips A, Bickford K, et al. Self-Management and Transition Among Adolescents/Young Adults with Chronic or End-Stage Kidney Disease. Blood Purif. 2015; 39:99-104.
10. Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2015;66(1):A7.
11. USRDS. United States Renal Data System Annual Data Report Volume 2: ESRD in the United States. 2015.
12. De Ferris MEDG. Adolescents and emerging adults with chronic kidney disease: Their unique morbidities and adherence issues. Blood Purif. 2011;31(1–3):203–8.
13. SAHMRI. ANZDATA: Dialysis and Transplant Registry Annual Report [Internet]. 2021 [cited 2020 Feb 10]. Available from: https://www.anzdata.org.au/anzdata/publications/reports.
14. Bhimma R, Adhikari M, Asharam K, Connolly C. The spectrum of chronic kidney disease (stages 2-5) in KwaZulu-Natal, South Africa. Pediatr Nephrol. 2008 Oct [cited 2020 Feb 10];23(10):1841–6.
15. Anochie I, Eke F. Chronic renal failure in children: A report from Port Harcourt, Nigeria (1985-2000). Pediatric Nephrology. Springer-Verlag; 2003;18:692–5.
16. Department of Statistics South Africa R of SA. The Young and the Restless – Adolescent Health in SA | Statistics South Africa [Internet]. Stats SA. 2022 [cited 2022 Aug 5]. Available from: https://www.statssa.gov.za.
17. Davids R, Jardine T, Marais N, Sebastian S, Davids T JJ. South African Renal Registry Annual Report 2019. African Journal of Nephrology. 2019: 95–106.
18. Vermeulen A, Menezes CN, Mashabane M, Butler OK, Mosiane P, Goetsch S, et al. Patterns of renal disease: A 30-year renal biopsy study at Chris Hani Baragwanath Academic Hospital, Soweto, Johannesburg, South Africa. South African Med J. 2019;109(7):486–92.
19. Ferris ME, Miles JA, Seamon ML. Adolescents and Young Adults with Chronic or End-Stage Kidney Disease.

Blood Purif. 2016;41:205–10.

20. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006;30(6):718–29.
21. Konrad K, Firk C UP. Brain development during adolescence. Dtsch Arztebl Int. 2013;425–31.
22. Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, et al. Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. J Neurosci. 2006 Jun 21;26(25):6885–92.
23. Galvan A, Hare T, Voss H, Glover G, Casey BJ. Risk-taking and the adolescent brain: who is at risk? Dev Sci. 2007 Mar 1;10(2):F8–14.
24. Chein JM, Albert D, O'Brien L, Uckert K, Steinberg L. Peers increase adolescent risk taking by enhancing activity in the brain's reward circuitry. Dev Sci. 2011;14(2):F1.
25. Dumontheil I. Adolescent brain development. Curr Opin Behav Sci. 2016 Aug 1;10:39–44.
26. Sisk CL, Foster DL. The neural basis of puberty and adolescence. Nat Neurosci. 2004 27;7(10):1040–7.
27. Vigil P, Pablo J, Río D, Carrera BB, Ara´nguizara´nguiz FC, Rioseco H, et al. Article Influence of sex steroid hormones on the adolescent brain and behavior: An update. Linacre Q. 2016;83(3):308–29.
28. Steinberg L. Risk Taking in Adolescence: What Changes, and Why? Ann N Y Acad Sci. 2004;1021(1):51–8.
29. Crone EA, Dahl RE. Understanding adolescence as a period of social–affective engagement and goal flexibility. Nat Rev Neurosci 2012 139. 2012 Aug 20 [cited 2022 May 24];13(9):636–50.
30. Hooper SR, Gerson AC, Butler RW, Gipson DS, Mendley SR, Lande MB, et al. Neurocognitive Functioning of Children and Adolescents with Mild-to-Moderate Chronic Kidney Disease. Clin J Am Soc Nephrol. 2011;6:1824–30.
31. Krb M, Brouhard BH, Donaldson LA, Lawry KW, B McGowan KR, Drotar D, et al. Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplant. 2000;4:261–7.
32. Icard P, Hooper SR, Gipson DS FM. Cognitive improvement in children with CKD after transplant. Paediatr Transpl. 2010;14:887–90.
33. Gipson DS, Duquette PJ, Icard PF, Hooper SR. The central nervous system in childhood chronic kidney disease. Padiatr Nephrol. 2007; 22(10)L1702-1710.
34. Chen K, Didsbury M, van Zwieten A, Howell M, Kim S, Tong A, et al. Neurocognitive and educational outcomes in children and adolescents with CKD: A systematic review and meta-analysis. Clin J Am Soc Nephrol. 2018;13(3):387–97.
35. Mendley SR, Zelko FA. Improvement in specific aspects of neurocognitive performance in children after renal transplantation. Kidney Int. 1999;56(1):318–23.
36. Foster BJ, Dahhou M, Zhang X, Platt RW, Samuel SM, Hanley JA. Association between age and graft failure rates in young kidney transplant recipients. Transplantation. 2011;92(11):1237–43.
37. Foster BJ. Heightened graft failure risk during emerging adulthood and transition to adult care. Pediatr Nephrol 2014 304. 2014.
38. Hart A, Smith JM, Skeans MA, Gustafson SK, Stewart DE, Cherikh WS, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 2017;17:21–116.

39. Kantorova V, Kariuki S, Kunju S, Lay KK, Li N, Riffe T, et al. Levels & Trends in Child Mortality 2021 UNICEF. 2021.
40. STATS SA. Mortality and causes of death in South Africa, 2017: Findings from death notification STATISTICAL RELEASE Mortality and causes of death in South Africa: Findings from death notification 2017 [Internet]. 2017 [cited 2022 May 19]. Available from: www.statssa.gov.za.
41. Maluleke R. Profiling health challenges faced by adolescents (10-19 years) in South Africa Statistics South Africa Risenga Maluleke Statistician General [Internet]. 2022. 1–92 p. Available from: www.statssa.gov.za.
42. Africa SS. Statistical release Mid-year population estimates. 2014 [cited 2017 Mar 12]; Available from: https://www.statssa.gov.za/publications/P0302/P03022014.pdf.
43. Women and HIV — A spotlight on adolescent girls and young women | UNAIDS [Internet]. [cited 2022 May 16]. Available from: https://www.unaids.org/en/resources/documents/2019/women-and-hiv.
44. Melanson TA, Mersha K, Patzer RE, George RP. Loss to Follow-up in Adolescent and Young Adult Renal Transplant Recipients. Transplantation. 2021 Jun 1;105(6):1326–36.
45. OPTN, Unos. Public Comment Proposal Guidance on Pediatric Transplant Recipient Transition and Transfer OPTN/UNOS Pediatric Transplantation Committee. [cited 2022 Aug 6]; Available from: https://optn.transplant.hrsa.gov/media/1200/optn_policies.
46. World Health Organisation. Adolescent mental health [Internet]. WHO fact sheet. 2021 [cited 2022 Aug 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health.
47. Hernandez EG, Reyner L, Vargas H JM. Depressive Symptomatology in Children and Adolescence.pdf. Int J Nephrol. 2011.
48. World Health Organisation. Adolescent and Young Adult Health WHO [Internet]. WHO fact sheet. 2022 [cited 2022 May 16]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescents-health-risks-and-solutions.
49. Sorsdahl K, van der Westhuizen C, Neuman M, Weiss HA, Myers B. Addressing the mental health needs of adolescents in South African communities: a protocol for a feasibility randomized controlled trial. Pilot Feasibility Stud. 2021;7(1):1–14.
50. Kessler R C, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S UT. Age of onset of mental disorders: A review of recent literature. Curr Opin Psychiatry. 2007;20(4):359–64.
51. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. 859 Glob Ment Heal. 2007; 8.
52. Kessler RC, Berglund P, Demler O, Ma R, Jin MA, Merikangas KR, et al. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
53. Eyre O, Thapar A. Common adolescent mental disorders: transition to adulthood. Lancet. 2014;383:1366–8.
54. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant. 2005 Jun 1;9(3):381–90.
55. Andreoni KA, Forbes R, Andreoni RM, Phillips G, Stewart H, Ferris M. Age-related kidney transplant

outcomes health disparities amplified in adolescence. JAMA Intern Med. 2013 Sep 9;173(16):1524–32.

56. Beier UH, Green C, Meyers KE. Caring for adolescent renal patients. Kidney Int. 2010;77(4):285–91.
57. Davidson B, Okpechi I, McCulloch M, Wearne N. Adolescent nephrology: An emerging frontier for kidney care in sub-Saharan Africa. Nephrology. 2017;22(12):933–9.
58. Bell LE. The Transition of a Pediatric Kidney Transplant Recipient from Childhood to Adult Care. Clin J Am Soc Nephrol. 2022;17(5):736–8.
59. Fernandez HE, Foster BJ. Long term care of pediatric kidney transplant recipient. CJASN. 2022; 17(2):296-304.
60. Matsuda-Abedini M, Marks SD, Foster BJ. Transition of young adult kidney transplant recipients. Pediatric Nephrology. 2022.

1.2 ETHICAL CONSIDERATIONS

There is benefit in understanding the spectrum of kidney disease and kidney outcomes of the adolescent and young adult [AYA] population in South Africa [SA]. Ethical considerations were taken into account. This was a retrospective observational study, which utilized the review of hospital medical records, laboratory, histology and imaging data. The risk to the patients enrolled in this study was minimal. All patient data captured was stored on a password-encrypted computer, in the Division of Hypertension and Nephrology, at Groote Schuur Hospital (GSH). Only the primary investigator and the supervisor had access to this data. Patient details entered on the computer were collected under a study number. All the kidney conditions assessed in the study were treated as per KDIGO guidelines. No additional risks, procedures or treatment to patients occurred as a result of this study. This study was approved by the Human Research Ethics Committee at the University of Cape Town (HREC REF 646/2020) **(Appendix 1a and 1b)**.

1.3 AUTHOR GUIDELINES: KIDNEY INTERNATIONAL JOURNAL

This MPhil dissertation has been structured in a publication-ready format for **Kidney International (KI) Journal**. This is a world-renowned, well-respected international nephrology journal. It is the official journal of the International Society of Nephrology and have a high impact factor. KI publishes a vast range of dedicated kidney-related research. The KI Guide for Authors can be viewed in **Appendix 2**.

CHAPTER2: PUBLICATION-READY MANUSCRIPT

Clinico-Pathological Characteristics and Outcomes of Nephrology Adolescents and Young Adults in Cape Town: a Single Centre Study

Zibya Barday[1], Nicola Wearne[1], Erika S.W. Jones[1], Mignon McCulloch[2], Bianca J. Davidson[1]

[1]Adult Nephrologist, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; [2] Paediatric Nephrologist, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa.

Corresponding Author:

Dr. Zibya Barday, Division of Nephrology and Hypertension, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Observatory 7925, Western Cape, South Africa.

Email: zibs.barday@gmail.com

Tel: +27-21-404 3318

Reference: Vancouver Reference Style

Manuscript Word Count: 4019 words

AUTHOR AND CO-AUTHOR CONTRIBUTIONS

Zibya Barday[1], Nicola Wearne[1], Erika S.W. Jones[1], Mignon McCulloch[2], Bianca J. Davidson[1]

[1]Adult Nephrologist, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa; [2] Paediatric Nephrologist, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa.

Contributions

1. **Dr. Zibya Barday** [1]

   Principle Investigator, manuscript author, creator of tables, figures and supplementary tables.

2. **Professor Nicola Wearne** [1]

   Manuscript co-author and reviewer.

3. **Professor Erika Jones** [1]

   Manuscript co-author and reviewer, statistical analysis.

4. **Professor Mignon McCulloch** [2]

   Manuscript reviewer.

5. **Dr. Bianca Davidson** [1]

   Primary Supervisor, manuscript author and reviewer.

ABSTRACT

Background

Adolescents and young adults [AYA] are important users of the nephrology health care services. Worldwide, there is a paucity of data on AYA kidney disease and outcomes. This study evaluates kidney outcomes, survival and challenges faced by AYA in a South African setting.

Methods

This 5-year retrospective study included AYA [aged 10-24] with chronic kidney disease, at a tertiary nephrology service in South Africa. Descriptive analysis characterised the aetiology of kidney disease. A comparative analysis of baseline characteristics, outcomes and social challenges were performed between patients attending a dedicated AYA clinic and those attending the standard adult clinics [non-AYA clinics]. Primary composite outcome assessed included doubling of creatinine, reduction of eGFR >40%, end-stage kidney disease and death. Logistic regression evaluated associations between relevant variables, death and lost to follow up [LTFU].

Results

The total AYA cohort consisted of 292 patients, 111 (38.0%) attended the AYA clinic and 181 (62.0%) the non-AYA clinics. The main aetiologies of disease were glomerular 212 (72.6%), congenital anomalies of the urinary tract 31 (10.6%), and hereditary conditions 24 (8.2%). There was a significantly lower mortality (p=0.007) and reduction in LTFU (p=0.012) in the cohort attending the AYA clinic. A statistically significant composite outcome (p=0.018), with improved

kidney survival was found in the AYA clinic group. High proportions of non-adherence (33.9%) and substance use (25.0%) was demonstrated in both cohorts.

Conclusion

This study adds to the dearth of literature on AYA kidney disease. A dedicated nephrology AYA clinic is shown to have lower mortality, less LTFU and improved kidney outcomes, which is essential in a resource-limited setting where access to kidney replacement therapy is restricted.

Key Words: Adolescent and Young Adults – Chronic kidney disease – Transition Clinic –South Africa

INTRODUCTION

Adolescents comprise almost a quarter of the world's population(1) and are important users of the nephrology health care services. The WHO defines adolescence as a phase of life between the age of 10-19(1) and young adults as individuals between the age of 15 and 25.(2) A paediatric sub-specialty has evolved to manage both adolescent and young adult [AYA] groups.(2) Although the combination of children, adolescents and young adults constitute less than 5% of the end-stage kidney disease [ESKD] population, they utilize a significant proportion of health care resources.(3,4)

The spectrum of kidney disease and causes of ESKD vary throughout different age groups. Internationally, the USRDS paediatric registry have recorded the top three aetiologies of ESKD to be glomerulonephritis [GN], congenital anomalies of the kidney and urinary tract [CAKUT], and cystic or hereditary disorders.(5) This contrasts to large adults registry databases which report diabetes and hypertension to be the leading causes of ESKD.(5) There are limited adolescent kidney registries. However, published literature on adolescents report the main cause of ESKD to be GN and reflux nephropathy.(6,7) In Africa, especially in South Africa [SA], there is a paucity of data on the spectrum of kidney disease in adolescence, despite kidney disease being the 9th top cause of death in this age group.(8) The lack of data limits our understanding of the extent of the problem and the creation of sustainable solutions.

Adolescence is a period of rapid physical, cognitive and psychosocial development. During this period there are dynamic developmental processes involving neuroplasticity, which are influenced by gonadal hormones.(9,10) This is particularly relevant in the pre-frontal cortex, which matures later than other cortical and subcortical regions. It controls executive planning,

risk assessment and behavioural regulation.(9–11) There also appears to be more activity in the limbic system, which could explain the short-term reward-seeking behavior and risk-taking tendencies over long term gain.(12,13) In the setting of chronic kidney disease [CKD], cognitive impairment is more common in adolescents.(14,15) Advanced CKD patients have low-average cognition compared to age-matched controls with mild deficits in academic skills, executive function, visual and verbal memory.(16) All these factors contribute towards an increase in high-risk behaviour, poor adherence and health-seeking tendencies, which may critically impact the management of CKD.

In addition to the neurodevelopmental changes in this population, there are significant socio-economic challenges facing AYA. Adolescents have a higher use of tobacco, alcohol and illicit drugs.(17) They are more likely to participate in unsafe sexual practices(18–20) and are also more prone to trauma.(8) Furthermore, there are high rates of mental illness in this population, with most psychiatric disorders having their roots in adolescence.(21,22) This makes it essential to recognize and efficiently manage mental illness.(23–25)

Non-adherence is very common and is complex to manage amongst adolescents. This could be expressed in the delay or omission of medication doses, sub-therapeutic drug levels, poor appointment attendance, as well as difficulty following through with medical advice. In the SA state sector, chronic kidney replacement therapy [KRT] is a limited resource and is rationed in the Western Cape Province. Kidney transplantability is the overarching principle for acceptance to the KRT programme. Adherence is essential in being considered good transplant candidates.

Considering the challenges and outcomes in this high-risk cohort, in 2015 we set out to improve adolescent kidney care at Groote Schuur Hospital [GSH], SA. This commenced with a needs assessment of all AYA patients in the nephrology service and identified 6 central themes, which needed to be addressed to improve the service **(Supplementary Table 1)**. (26) This led to the creation of an innovative state-sector dedicated nephrology AYA clinic, co-designed with the patients to improve their care. In the SA state sector, patients requiring tertiary care, with an index presentation of 13 years or older are referred to the adult health care service. The new GSH nephrology AYA clinic included patients aged between 13-24 years or transitioning from the paediatric referral center. It incorporated all new patients (CKD, HPT or general nephrology) in this age group, and existing patients receiving KRT. The clinic was designed to incorporate a large spectrum of kidney disease, at all stages of CKD, including those on KRT. The clinic consists of a multidisciplinary team, which includes an adult and paediatric nephrologist, nephrology fellows, professional nurse, dedicated social worker and clinical psychologist. The aim of the clinic was to provide adolescent-friendly nephrology care to AYA, focusing on best clinical practice and education. It also aimed to foster a supportive environment while actively addressing high-risk aspects of adolescent care.

The primary aim of this study was firstly, to characterise the spectrum of kidney disease in AYA, especially in view of the lack of adolescent registry data in Sub-Saharan Africa [SSA] and secondly to compare the outcomes of patients attending a dedicated AYA kidney clinic to those who attended the mainstream adult kidney clinics [non-AYA clinics]. The outcomes assessed included kidney survival and mortality. The secondary aim was, to identify specific challenges that impact these outcomes, including social challenges, adherence and loss to follow up.

METHODS

This retrospective study assessed all patients aged between 10 – 24 years at the tertiary nephrology hospital in Cape Town, SA, between the period 01 June 2015 to 31 May 2020. This was assessed using data from the online hospital booking system [Clinicom]. Criteria for inclusion eligibility were patients within the pre-specified age range during the study period, who followed up at our nephrology service with either (1) a diagnosis of CKD, defined as per KDIGO definition,(27,28) or (2) on KRT, which included peritoneal dialysis, haemodialysis, and (3) post-kidney transplantation. Exclusion criteria utilized were (1) patients not followed-up at this institution, or (2) patients with acute kidney injury [AKI], defined as a sudden loss of kidney function, determined by an increased serum creatinine level and reduced urinary output limited to 7 days, with complete recovery.(29) Patients who were eligible for the study were stratified into to two groups, those recorded to have attended the nephrology AYA clinic and those that attended the nephrology "standard of care" adult service, referred to as the non-AYA clinic. As the AYA clinic was a new service it incorporated all new patients (CKD, HPT, transitioning adolescents or general nephrology) in this age group, existing patients receiving KRT and young patients needing extra support in adult services (non-AYA clinics). Not all patients during this period were referred to the AYA clinic, thus still attended the non-AYA clinics. This study was approved by the Human Research Ethics Committee at the University of Cape Town [HREC REF 646/2020].

Relevant data was collected from clinical, laboratory and radiological records. These included demographic, clinical, biochemical, histological and radiological information. This was recorded at baseline, annually over a 5-year period and at last follow-up. Baseline data was defined as the data collected at first clinic visit, during the pre-specified study time period. Demographic and

clinical data included: age, sex, blood pressure [mmHg], weight [kg], BMI [kg/m^2], primary aetiology of the kidney disease and co-morbidities (including HIV status). The primary diagnosis for CKD was categorised as glomerular disease, urological abnormalities, hereditary conditions, tubulointerstitial disease [TID] or CKD with unknown aetiology. Urological conditions, were divided into congenital anomalies of the kidney and urinary tract (CAKUT) and non-CAKUT (i.e. reflux, recurrent pyelonephritis, stones, obstruction)

Biochemical data recorded included serum creatinine [µmol/L], estimated glomerular filtration rate [eGFR; ml/min/1.73m^2] using the Swartz formula for patients younger than 18 years,(30) and CKD-EPI 2021 for patients older than 18 years.(31) Additional variables collected were haemoglobin [g/dL], total cholesterol [mmol/L] and albumin [g/dL]; as well as urine protein-to-creatinine ratio [UPCR; g/mmol creatinine]. The CKD stage and KRT status was documented at baseline, annually and at last follow up. Histological and radiological data were used to record the primary diagnosis.

A comparative analysis was performed between patients attending the AYA clinic and those who attended the non-AYA clinics. The primary outcomes of interest assessed were the spectrum of primary aetiology of CKD, as well as the proportion of patients reaching a pre-specified composite outcome; which included doubling of serum creatinine, reduction in eGFR greater than 40%, reaching ESKD or death. KRT patients on dialysis were censored in the primary composite outcome analysis, but included in the independent death analysis. Death and LTFU were analysed separately. A sub-set analysis of AYA kidney transplant outcomes was reviewed. The pre-specified composite outcome of kidney transplantation was assessed, in addition to kidney allograft rejection, allograft failure, adherence and LTFU.

Social challenges analysed included unplanned pregnancies, sexually transmitted diseases [STIs], engaging in substance use, mental illness and non-adherence. Substance use was self-reported and included documentation of tobacco smoking, alcohol or marijuana misuse and illicit drug use. Mental illness was screened for in the clinic and a diagnosis was confirmed by the tertiary centre psychiatry service. Non-adherence was defined as missing two or more clinic visits within a year, self-reported medication omission on two or more occasions per month or having sub-therapeutic drug levels on two or more occasions per year. In this study, LTFU was defined as non-attendance to the clinic for more than one year.

Data was analyzed using STATA software (StataCorp. 2021. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC)]. Categorical variables were analysed using X^2 test and are presented as frequencies and percentages. Continuous variables were reported as median with interquartile ranges [IQR], and were compared using Mann-Whitney U test. Bivariate analysis and univariable logistic regression was used to evaluate associations between clinical and biochemical relevant variables with death and LTFU. The low number of deaths (n=26) particularly in the AYA group precluded multivariable analysis. Kaplan-Meier analysis was used to estimate differences in composite survival probability and patient survival between AYA and non-AYA patients and with varying aetiology. The log-rank test and survival curves were used to illustrate differences between groups. Data was censored for LTFU and for study completion. A p-value of $p < 0.05$ was considered statistically significant.

RESULTS

The total of 351 nephrology AYA patients over the 5-year-period were identified. Of these, 59 patients were excluded due to either having a diagnosis of AKI, not being followed up at this tertiary hospital or having missing or incomplete medical records. Thus, 292 patients were eligible for inclusion into the study. Out of the total cohort, 111 (38.0%) attended the AYA clinic and 181 (61.9%) attended the non-AYA clinic **(Figure 1).**

The baseline characteristics of the two groups are shown in **Table 1**. There was a slight predominance of females (55.1%) and the majority of patients had hypertension (65.8%) and CKD stage 1 (45.9%). Those attending the AYA clinic were younger (19 versus [vs] 21 years respectively; p=0.013), predominantly CKD stage 1 (49 vs 44%; p=0.042), had a longer duration of follow up (37 vs 18 months; p <0.001), a higher prevalence of diabetes mellitus (7 vs 1%; p=0.001) and a higher proportion were on KRT (23 vs 12%; p=0.007). There was no significant difference between the two groups in terms of hypertension, creatinine or eGFR. However, a higher UPCR was found in the non-AYA group (0.13 vs 0.04g/mmol creatinine; p=0.035).

In terms of the spectrum of AYA kidney disease, glomerular disease was the most common aetiology detected (72.6%), followed by CAKUT (10.6%), hereditary conditions (8.2%), CKD with unknown aetiology (4.1%) and lastly TID (2.3%) **(Table 2).** The GN cohort comprised of 66.5% primary GN and 33.5% secondary GN. The top three primary GNs were mesangioproliferative glomerulonephritis [MPGN] (19.3%), mesangiocapillary glomerulonephritis [MCGN] (16.0%) and IgA Nephropathy [IgAN] (11.7%). Secondary GN was commonly due to lupus nephritis [LN] (90.0%) with a LN class IV predominance. CAKUT comprised of vesicoureteral reflux [VUR], posterior urethral valve [PUV] and neuropathic bladder with recurrent urinary tract infections

[UTIs] occurring in 21.6%, 18.9% and 16.2%, respectively. The most common hereditary condition was autosomal dominant polycystic kidney disease [ADPKD] (58.3%). A similar pattern of disease was seen across both patient cohorts in primary GNs and CAKUT, but hereditary conditions were more commonly followed up in the AYA clinic.

The kidney outcomes in the two groups can be viewed in **Table 3**. There was a lower mortality (2 vs 12%; p=0.007) and less LTFU (21 vs 37%; p=0.012) in the patients attending the AYA clinic. The Kaplan Meier demonstrated a statistically significant composite outcome, with improved kidney preservation and survival in patients attending the AYA clinic (p= 0.018) **(Figure 2a). Figure 2b** stratifies event-free survival according to the underlying aetiology in the two cohorts.

The sub-group analysis of death in nephrology AYA is demonstrated in the **Supplementary Table 2.** The Kaplan Meier **(Figure 3)** demonstrates better event free survival from death in those attending the AYA clinic (p<0.001). Death was associated with hypertension (Odds Ratio [OR] 4.5; 95% CI 1.33-15.50; p=0.016) and nephrotic range proteinuria (OR 3.56; 95% CI 1.78-7.12; p <0.0001) **(Supplementary Table 3)**. The leading causes of death in AYA with kidney disease was infection (42.3%), progression to ESKD without KRT (30.8%), cardiovascular events (15.4%), and to a lesser extent malignancy (7.7%) (**Figure 4).** The most common cause of infection on presentation included pneumonia, intra-abdominal sepsis, UTI's and access related bacterial sepsis. The leading cause of cardiovascular-related death included heart failure and arrhythmias**.**

Approximately one third of the cohort was LTFU (30.8%). However, fewer patients attending the AYA clinic were LTFU (21 vs 37%; p=0.012) **(Table 3).** The sub-group analysis comparing

demographic and clinical characteristics of LTFU patients can be viewed in **Supplementary Table 4.** Those LTFU were less likely to have hypertension (54 vs 70%; p=0.015), had less proteinuria (UPCR 0.04 vs 0.11; p=0.013), and had a lower serum creatinine (75 vs 101mmol/L; p=0.004), with a preserved eGFR (97 vs 77ml/min/1.73m^2; p=0.008). An eGFR >60ml/min/1.73m^2 (OR 2.28; 95% CI 1.282-4.055; p=0.005) at baseline was strongly associated with being LTFU, while attendance to the AYA clinic was protective (OR 0.38; 95% CI 0.211-0.689; p=0.001) **(Supplementary Table 5).**

Secondary analysis assessed engagement in certain high-risk behaviours. The total study cohort demonstrated high rates of substance abuse (25.0%), unplanned pregnancies (16.8%) and STIs (5.8%) **(Table 4).** Illicit substance use was self-reported in 7.5% of patients, with the most frequently used substances being marijuana, methamphetamines and mandrax. There was no significant difference between the two comparative groups, except in the prevalence of mental illness, which was found to be higher in those attending the AYA clinic. Depression was the leading cause of mental illness, followed by anxiety disorders. Non-adherence was noted in 33.9% of the total cohort, with better attendance and fewer missed appointments or dialysis sessions (10 vs 18%; p=0.054) in those attending the AYA clinic. **Supplementary Table 6** illustrates a sub-group analysis of non-adherent patients. This group was found to be younger (mean age 19 vs 21years; p=0.023), and more likely to have social challenges such as unplanned pregnancies (14 vs 7%; p=0.040), STI's (11 vs 3%; p=0.005), substance use (42 vs 16 %; p <0.001) and mental illness (14 vs 6%; p=0.024).

The sub-group analysis of the kidney transplant patients in the cohort can be viewed in **Supplementary Table 7**. There were 32 kidney transplant patients out of the total cohort

(32/292; 11%). Fifty-six percent attending the AYA clinic and 43.7% attended the non-AYA transplant clinic. Over the 5-year period, 28.1% had allograft rejection and 18.7% had allograft failure, with no significant difference between the two groups. Death occurred in 9.3% of the kidney transplant recipients and the aetiology was predominantly attributed to bacterial sepsis and the progression of ESKD from kidney graft failure. LTFU was identified in 12.5% and occurred predominantly in those attending the non-AYA clinic.

DISCUSSION

Globally, there is a paucity of data on the spectrum of adolescent kidney disease and outcomes, particularly in resource-limited regions. This paper adds to the dearth of existing literature in the following ways: firstly, we report on the spectrum of kidney disease in our AYA population. Secondly, our dedicated nephrology AYA service demonstrated lower mortality and less LTFU, as well as improved kidney survival. Lastly, it highlights the high-risk nature of this challenging population, which impacts clinical management.

The spectrum of CKD in AYA is heterogeneous and encompasses a wide variety of aetiologies, differing from those found in paediatric and adult nephrology patients. A worldwide comparison on the spectrum of CKD aetiologies between paediatrics, adolescents and adult cohorts can be seen in **Table 5**. When comparing the paediatric and adolescent data, in less-resourced regions, GNs were the leading cause of CKD. This differed from well-resourced countries where CAKUT was the leading cause of CKD in paediatrics, with a high prevalence of both CAKUT and GN found in adolescent populations. When compared to adult cohorts, adolescents tended to have a much higher prevalence of GNs (7.2 vs 61.3%), less hypertensive nephrosclerosis (29.3 vs

4.4%) and less diabetic nephropathy (47.7 vs 0.7%).(32,33) This highlights the need for specialised training for the care of adolescents as a distinct sub-group in Nephrology.

This higher prevalence of GNs seen in our cohort vs the USRDS data (61.3 vs 36.6%),(32) corresponds to several studies which have demonstrated a higher proportion of GNs reported in Africa.(34,35) In Africa, GNs are an important contributor to ESKD.(35) Worldwide, IgAN is the most common form of primary GN(34,36,37) but is reported less frequently in Africa, and rare in Black Africans.(34) In this AYA cohort, the most common primary GNs were MPGN and MCGN, which is similar to a retrospective review of adult GNs, performed in the same region.(38) This contrasts with a large meta-analysis of biopsy proven GNs in Africa, which included paediatric, adolescent and adult cohorts, and found Minimal Change Disease [MCD], Focal Segmental Glomerulosclerosis [FSGS] and MCGN to be the most frequent primary GNs.(34) The diverse spectrum of GNs could be attributed to different genetic and environmental exposures, which needs to be explored further. The higher proportion of hypertensive nephrosclerosis, HIVAN and TIN found in the non-AYA clinic cohort could have contributed to the poorer outcomes seen in this group. There is a high burden of hypertension in SA and is there is a need for increased awareness, earlier detection and better treatment strategies in hypertension in our setting; including a focus on adherence. (39,40) Screening for HIV is important in AYA, due to high rates of high-risk sexual practices in this population. The lower proportion of CAKUT seen in this cohort compared to international data may be attributed to a lack of diagnosis detection or the referral system from the paediatric services to predominantly adult urology services.

There is a lack of international data evaluating the outcomes in AYA with kidney disease. The progression of kidney disease is important to recognize in these age groups, especially in

resource-limited settings where access to KRT is scarce. There was a significant reduction seen in the composite outcome, with improved kidney survival, in those attending the AYA clinic. To note at baseline the cohort attending the AYA clinic were younger (less than 18 years vs greater than 18 years; p=0.013) with predominantly CKD stage 1 (49% vs 44%; p=0.042). In addition, the adult service [non-AYA] had a higher UPCR (0.13 vs 0.04 g/mmol creatinine; p=0.035), and although not statistically significant hypertension occurred more frequently. The median blood pressures were controlled in both cohorts assessed. These differences could impact the comparative kidney outcomes seen in this study, especially as a raised UPCR is a well-known risk factor for progression of kidney disease. Additionally, the heterogeneous spectrum of kidney disease in the two cohorts makes the outcome trajectories complex to analyse. Although the proportion of patients with hereditary CKD occurred in less than 10% of the total cohort, these patients predominantly attended the AYA clinic and this could have impacted the outcomes assessed. Kidney hereditary conditions usually have slow progression to ESKD and thus reflect better short-term kidney outcomes. When different aetiologies were analysed [GN vs non-GN], attending the AYA clinic resulted in better kidney survival irrespective of underling aetiology **(Figure 2b)**. The improved composite outcome could be attributed to more frequent follow up, intense focus on preservation on residual kidney function, education and targeted adherence interventions.

The mortality was lower in the cohort attending the AYA clinic (2 vs 12%; p=0.007). The poor prognostic predictors at baseline of the non-AYA clinic cohort correlate with well-known indicators for mortality in the setting of CKD.(47–49) This could also be attributed to the non-AYA clinic patients having more severe kidney disease, or having less regular follow up with multi-disciplinary interventions, compared to the AYA clinic patients. The leading cause of death

in this study is related to infection (42.3%) which could be attributed to high burden of infectious diseases in SA, coupled with multi-factorial reasons for late presentation.(50) This was followed by progression to ESKD (30.8%), which may reflect the restricted access to chronic dialysis in our setting. Eligibility to KRT in the SA state sector is closely linked to adherence, and the significant proportion of non-adherence seen in the total AYA cohort (34%) may impact acceptance onto KRT in provinces where it is rationed. The causes of death in our cohort differs from a large Canadian study that reported cardiovascular death as the leading cause (43.5%), with only a small proportion of mortality attributed to infection (5.2%).(51) This may reflect the difference in disease profiles and late presentations often seen in less-resourced countries compared to well-resourced countries.

LTFU is common in children and adolescents with complex chronic conditions.(52) In a SSA review, the rate of LTFU amongst adolescents in other chronic illnesses ranged from 15-54%.(53) Lack of regular medical follow up visits is associated with poorer long-term health outcomes.(54) There are limited studies on LTFU in CKD. In kidney transplantation, rates of LTFU have been reported as high as 32%,(55,56) and have the potential to impact mortality with one study showing an increased risk of death of 26.1%.(55) In our total cohort, we found LTFU in almost a third of patients (30.8%) over the 5-year period, with lower rates in the AYA clinic group. Reported predictors of LTFU in adolescents, include younger age (15-20 years), male gender, institutional transfer and more severe illness.(55,57,58) These predictors contrast to our cohort where age and gender were not found to be statistically significant. In addition, those patients with less disease severity were less likely to follow up in the service. Retention in a follow-up service is vital for kidney preservation and survival. The lower LTFU rates in the AYA clinic cohort could be attributed to the strategic, multi-disciplinary approach aimed to improve

adherence and attendance to this clinic. The peer-led support group provides a sense of belonging and unity. The AYA clinic also has as a dedicated social worker with better access to social support. Social services include provision of child dependency or disability grants; as well as career counseling and learnership programs, which could have contributed to less LTFU seen in this group. The identification of those at risk for LTFU is important for targeted interventions and for optimizing long-term kidney prognosis.(59–61)

This study highlights the significant rates of high-risk behaviour in the AYA population, all of which impact adherence and progression of kidney disease. Sexual intercourse in adolescents has been associated with increased prevalence of unprotected sex, multiple partners, and increased risk of unplanned pregnancies, STIs and HIV infection.(62–65) Adolescent pregnancy is a significant challenge in SA, with nearly 20% of women having reported a pregnancy between the age 10-19 years.(66–69) In this study, 16.7% of the total cohort had unplanned pregnancies, with STI's occurring in 6% of patients. Pregnancies in this age group have increased risk of medical complications for mother (pre-eclampsia and progression of kidney disease) and poor fetal outcomes; as well as socio-economic and mental health consequences.(70–75)

Internationally, early age onset experimentation with substances has been well-described.(76) In SSA substance use is a major public health concern with an estimated prevalence of 42%.(77,78) A quarter of this study cohort used substances, with the most frequently self-reported substances were tobacco and ethanol, which correlates to SA data.(78) Those using substances were more likely to be non-adherent, as seen in this study (42 vs 16 %; $p < 0.001$). In the setting of CKD, tobacco use has been associated with higher all cause mortality and illicit drug use with a higher risk of CKD progression.(79) Although the adult data on ethanol use and

the relationship with CKD is conflicting,(79) it has been conclusively shown that ethanol exposure to the brain in adolescents, especially binge drinking, can be detrimental and potentially exacerbate cognitive impairment in CKD.(80,81)

Adolescents account for 13% of the global burden of mental disorders, with 1 in 7 between the ages of 10 – 19 years, suffering from a mental illness.(82) The patients attending the AYA clinic were more likely to have a mental illness identified (p= 0.010) and managed. This is likely due to vigilance and screening for mental health conditions, in addition to supportive multidisciplinary team involvement in the clinic, which included a psychologist. If not recognized and managed, mental illness leads to an increased risk of physical health co-morbidities, injury and more advanced psychopathology later in adulthood.(24,25,83)

High-risk behaviour, can play an integral role in a young patient's health seeking behaviour and adherence. Most of the adherence literature in adolescent kidney disease is rooted in kidney transplantation, which report alarmingly high rates of non-adherence (43%). (84) Current transplant literature suggests non-adherence to be a main contributor to poor kidney allograft outcomes.(84–90) This corresponds to the high non-adherence rate noted in our study cohort (34.0%). Those patients that attended the AYA clinic missed fewer clinic appointments. The improvement seen in the AYA clinic likely reflects early identification of non-adherence and implementation of targeted interventions in a supportive environment. This includes a social support group prior to clinic, consistent multi-disciplinary staff, afternoon appointments and pre-ordered medication.

LIMITATIONS

The strength of this study is that it addresses a world-wide gap in clinical research. It assesses important aspects of a highly vulnerable group, who are often overlooked in adult nephrology. It adds to the understanding of the spectrum of adolescent kidney disease in SSA and enables the provision targeted management strategies to key conditions. It also highlights the positive impact an AYA clinic could have on kidney outcomes, death and LTFU. Limitations include the retrospective design of the study with its known shortcomings. The AYA clinic had more detailed pre-formatted clinical notes, than the non-AYA clinic, for clinicians to utilize in assessment of patients. This could have resulted in the underestimation of secondary outcomes in the non-AYA cohort. Selection bias could have occurred in terms of the method eligible patients were included in this study. The majority of patients referred to the AYA clinic are from the nephrology paediatric service. Their referral to the AYA clinic occurred when schooling was completed or if patient maturity suitable, which usually occurred once patients were older than 18 years of age. he relatively small sample size and heterogeneous nature of the underlying kidney disease, as well as the slightly different baseline kidney function variables could limit the statistical analysis of sub-groups and influence outcomes. The impact of duration of follow up from index diagnosis of CKD and the referral source to clinics were not evaluated. The kidney transplant sub-set was relatively small for meaningful analysis. Those LTFU in the cohort did not re-enter the healthcare system, therefore limiting the evaluation of this group's contribution towards CKD progression and mortality. Future research could evaluate AYA kidney outcomes in a larger multi-centred study, over a longer time period. Additionally, there is a need to better characterize the complexities of adherence and evaluate factors that could limit LTFU.

CONCLUSION

This study has added to the dearth of literature on the AYA spectrum of kidney disease in our setting. Adolescent nephrology is a growing field and it is important for all nephrologists to be trained and aware of the principles of adolescent care. A dedicated nephrology AYA clinic has the potential significantly improve kidney survival, reduce mortality and decrease the frequency of LTFU. This is essential in a resource-limited setting like SA, where restricted access to KRT can result in death due to ESKD in our youth.

DISCLOSURE STATEMENT

The authors have no competing interests or disclosures to declare.

REFERENCES

1. Singh PK. Adolescent health. Vol. 53, World Health Organisation: Regional Office for South-East Asia. 2017.
2. Moreno M, Thompson L. What Is Adolescent and Young Adult Medicine? JAMA Pediatr. 2020 May 1;174(5):512–512.
3. Ferris ME, Cuttance JR, Javalkar K, Cohen SE, Phillips A, Bickford K, et al. Self-Management and Transition Among Adolescents/Young Adults with Chronic or End-Stage Kidney Disease. Blood Purif. 2015;39(1–3):99–104.
4. Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. US Renal Data System 2014 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2015;66(1):A7.
5. USRDS. United States Renal Data System Annual Data Report Volume 2: ESRD in the United States. 2015.
6. De Ferris MEDG. Adolescents and emerging adults with chronic kidney disease: Their unique morbidities and adherence issues. Blood Purif. 2011;31(1–3):203–8.
7. SAHMRI. ANZDATA: Dialysis and Transplant Registry Annual Report [Internet]. 2021 [cited 2020 Feb 10]. Available from: https://www.anzdata.org.au/anzdata/publications/reports.
8. Department of Statistics South Africa R of SA. The Young and the Restless – Adolescent Health in SA | Statistics South Africa [Internet]. Stats SA. 2022 [cited 2022 Aug 5]. Available from: https://www.statssa.gov.za.
9. Sisk CL, Foster DL. The neural basis of puberty and adolescence. Nat Neurosci 2004;7(10):1040–7.
10. Vigil P, Pablo J, Río D, Carrera BB, Ara´nguizara´nguiz FC, Rioseco H, et al. Article Influence of sex steroid hormones on the adolescent brain and behavior: An update. Linacre Q. 2016;83(3):308–29.
11. Konrad K, Firk C UP. Brain development during adolescence. Dtsch Arztebl Int [Internet]. 2013 [cited 2022 May 24];425–31. Available from: https://psycnet.apa.org/record/2013-24648-002.
12. Galvan A, Hare T, Voss H, Glover G, Casey BJ. Risk-taking and the adolescent brain: who is at risk? Dev Sci. 2007;10(2):F8–14.
13. Galvan A, Hare TA, Parra CE, Penn J, Voss H, Glover G, et al. Earlier Development of the Accumbens Relative to Orbitofrontal Cortex Might Underlie Risk-Taking Behavior in Adolescents. J Neurosci. 2006; 26(25):6885–92.
14. Krb M, Brouhard BH, Donaldson LA, Lawry KW, B McGowan KR, Drotar D, et al. Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplantation. 2000; 4:261-267.
15. Icard P, Hooper SR, Gipson DS FM. Cognitive improvement in children with CKD after transplant. Paediatr Transpl. 2010;14:887–90.
16. Chen K, Didsbury M, van Zwieten A, Howell M, Kim S, Tong A, et al. Neurocognitive and educational outcomes in children and adolescents with CKD: A systematic review and meta-analysis. Clin J Am Soc Nephrol. 2018;13(3):387–97.
17. Tapert SF. Recent binge drinking predicts smaller cerebellar volumes in adolescents. Psychiatry Res. 2014;211(1):17–23.
18. Thepthien B, Celyn. Risky sexual behavior and associated factors among sexually-experienced adolescents in Bangkok, Thailand: findings from a school web-based survey. Reprod Health. 2022;19(1):1–11.
19. Ngom P, Magadi MA, Owuor T. Parental presence and adolescent reproductive health among the Nairobi urban poor. J Adolesc Heal. 2003;33(5):369–77.
20. Fetene N, Mekonnen W. The prevalence of risky sexual behaviors among youth center reproductive health clinics users and non-users in Addis Ababa, Ethiopia: A comparative cross-sectional study. PLoS One. 2018;2:1–15.
21. Sorsdahl K, van der Westhuizen C, Neuman M, Weiss HA, Myers B. Addressing the mental health needs of adolescents in South African communities: a protocol for a feasibility randomized controlled trial. Pilot Feasibility Stud. 2021;7(1):1–14.
22. World Health Organisation. Adolescent and Young Adult Health WHO [Internet]. WHO fact sheet. 2022 [cited 2022 May 16]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescents-health-risks-and-solutions.
23. Kessler R C, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S UT. Age of onset of mental disorders: A review of recent literature. Curr Opin Psychiatry. 2007;20(4):359–64.
24. Kessler RC, Berglund P, Demler O, Ma R, Jin MA, Merikangas KR, et al. Lifetime Prevalence and Age-of-Onset

Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593–602.
25. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. 859 Glob Ment Heal [Internet]. 2007;8. Available from: www.thelancet.com.
26. Davidson B, Okpechi I, McCulloch M, Wearne N. Adolescent nephrology: An emerging frontier for kidney care in sub-Saharan Africa. Nephrology. 2017;22(12):933–9.
27. Kasiske B. Kidney Disease: Improving Global Outcomes Guideline on CKD [Internet]. Mandaluyong City; 2014 [cited 2020 Feb 10]. Available from: www.kdigo.org.
28. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516–26.
29. Kellum JA, Romagnani P, Ashuntantang G, Ronco C, Zarbock A, Anders HJ. Acute kidney injury. Nat Rev Dis Prim. 2021;7(1).
30. Schwartz GJ, Muñ A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New Equations to Estimate GFR in Children with CKD. J Am Soc Nephrol. 2009;20:629–37.
31. Inker LA, Coresh HT, Sang DC, Crews A, Estrella M, Froissart EM, Grams T, Greene A, Grubb V, Gudnason OM, Gutierrez R, Karger AB, Mauer M, Navis G, Nelson RG, Poggio ED, Rodby R, Rossing P, Rule AD, Selvin E, Seegmiller JC, Slipak MG, Torres VE, Yang W, B LA. New Creatinine-and Cystatin C-Based Equations to estimate GFR without Race. N Engl J Med. 2021;385(19).
32. Saran R, Robinson B, Abbott KC, Bragg-Gresham J, Chen X, Gipson D, et al. US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2020;75(1):A6–7.
33. USRDS. Annual Data Report | United States Renal Data System: ESRD among Children and Adolescents. 2020.
34. Okpechi IG, Ameh OI, Bello AK, Ronco P, Swanepoel CR, Kengne AP. Epidemiology of Histologically Proven Glomerulonephritis in Africa: A Systematic Review and Meta-Analysis. Remuzzi G, editor. PLoS One. 2016 Mar 24;11(3).
35. Maoujoud O, Aatif T, Bahadi A, Zajjari Y, Benyahya M, Ahid S, et al. Regional disparities in etiology of end-stage renal disease in Africa. Saudi J Kidney Dis Transpl. 2013;24(3):594–5.
36. Maisonneuve P, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, et al. Distribution of primary renal diseases leading to end-stage renal failure in the United States, Europe, and Australia/New Zealand: results from an international comparative study. Am J Kidney Dis. 2000 Jan;35(1):157–65.
37. Nair R, Walker PD. Is IgA nephropathy the commonest primary glomerulopathy among young adults in the USA? Kidney Int. 2006 Apr;69(8):1455–8.
38. Okpechi I, Swanepoel C, Duffield M, Mahala B, Wearne N, Alagbe S, et al. Patterns of renal disease in Cape Town South Africa: A 10-year review of a single-centre renal biopsy database. Nephrol Dial Transplant. 2011;26:1853–61.
39. Jones ESW, Esack I, Mangena P, Rayner BL. Hypertension in adolescents and young adults referred to a tertiary hypertension clinic in Cape Town, South Africa. Medicine (Baltimore). 2020;99(48):1–5.
40. Day C, Groenewald P, Laubscher R, Chaudhry S, van Shaik N BD. Monitoring of non-communicable diseases such as hypertension in South Africa: Challenges for the post-2015 global development agenda. South African Med J. 2014;104.
41. Hattori M, Sako M, Kaneko T, Ashida A, Matsunaga A, Igarashi T, et al. End-stage renal disease in Japanese children: a nationwide survey during 2006–2011. Clin Exp Nephrol. 2015 Oct 1;19(5):933–8.
42. ANZDATA Annual Report. Paediatric Patients with End-Stage Kidney Disease Requiring Renal Replacement Therapy [Internet]. 2019 [cited 2022 Aug 23]. Available from: http://www.anzdata.org.au.
43. Asinobi AO, Ademola AD, Ogunkunle OO, Mott SA. Paediatric end-stage renal disease in a tertiary hospital in South West Nigeria. BMC Nephrol. 2014;15(25):1–9.
44. Australian Government: Institute of Health and Welfare. Chronic kidney disease: Australian facts, Summary - Australian Institute of Health and Welfare [Internet]. 2022 [cited 2022 Aug 23]. Available from: https://www.aihw.gov.au/reports/chronic-kidney-disease/chronic-kidney-disease.
45. Alebiosu CO, Ayodele OO, Abbas A, Olutoyin IA. Chronic renal failure at the Olabisi Onabanjo university teaching hospital, Sagamu, Nigeria. Afr Health Sci [Internet]. 2006;6(3):132.
46. Davids R, Jardine T, Marais N, Jacobs J. South African Renal Registry Annual Report 2016. African J Nephrol. 2018;21(November):61–72.
47. Hansrivijit P, Chen Y-J, Lnu K, Trongtorsak A, Puthenpura MM, Thongprayoon C, et al. World Journal of Nephrology Prediction of mortality among patients with chronic kidney disease: A systematic review Conflict-of-interest statement: PRISMA. World J Nephrol. 2021;10(4):59–75.

48. Wang J, Wang F, Saran R, He Z, Zhao MH, Li Y, et al. Mortality risk of chronic kidney disease: A comparison between the adult populations in urban China and the United States. PLoS One. 2018 Mar 1;13(3).
49. O'Seaghdha CM, Perkovic V, Lam TH, McGinn S, Barzi F, Gu DF, et al. Blood pressure is a major risk factor for renal death: An analysis of 560 352 participants from the asia-pacific region. Hypertension. 2009 Sep 1;54(3):509–15.
50. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Rhodes Kievlan D, et al. Global, regional, and national sepsis incidence and mortality, 1990â€"2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395:200–11.
51. Thompson S, James M, Wiebe N, Hemmelgarn B, Manns B, Klarenbach S, et al. Clinical Epidemiology Cause of Death in Patients with Reduced Kidney Function. J Am Soc Nephrol. 2015;26:2504–11.
52. Skogby S, Bratt E-L, Johansson B, Moons P, Goossens E. Discontinuation of follow-up care for young people with complex chronic conditions: conceptual definitions and operational components. Health Serv Res. 2021;21:1343.
53. Farirai JT, Cooper D. Predictors of Lost-To-Follow-Up Amongst Adolescents on Antiretroviral therapy in an urban setting in Botswana. University of the Western Cape; 2018.
54. Blackwell CK, Elliott AJ, Ganiban J, Herbstman J, Hunt K, Forrest CB, et al. General health and life satisfaction in children with chronic illness. Pediatrics. 2019;143(6).
55. Melanson TA, Mersha K, Patzer RE, George RP. Loss to Follow-up in Adolescent and Young Adult Renal Transplant Recipients. Transplantation. 2021 Jun 1;105(6):1326–36.
56. Hung YC, Williams JE, Bababekov Y, Rickert AG, Chang DC YH. Surgeon crossover between pediatric and adult centers is associated with decreased rate of loss to follow-up among adolescent renal transplantation recipients Ya-Ching. Pediatr Transplant. 2019;23:1347.
57. Geng EH, Glidden D V, Emenyonu N, Musinguzi N, Bosco Bwana M, Neilands TB, et al. Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa. Trop Med Int Heal. 2004;15(Suppl 1):63–9.
58. Id ET, Kishimba R, Njau P, Revocutus B. Predictors of loss to follow up from antiretroviral therapy among adolescents with HIV / AIDS in Tanzania. PLoS One. 2022;Open Acces:1–14.
59. Graves MM, Roberts MC, Abpp P, Rapoff M, Boyer A. The Efficacy of Adherence Interventions for Chronically Ill Children: A Meta-Analytic Review. J Pediatr Psychol. 2010;35(4):368–82.
60. Kyngäs HA, Kroll T, Duffy ME. Compliance in adolescents with chronic diseases: A review. J Adolesc Heal. 2000 Jun 1;26(6):379–88.
61. Atger-Lallier L, Guilmin-Crepon S, Boizeau P, Zenaty D, Simon D, Paulsen A, et al. Factors Affecting Loss to Follow-Up in Children and Adolescents with Chronic Endocrine Conditions: Horm Res Paediatr. 2006;92(4):254–61.
62. Shrestha R, Karki P, Copenhaver • Michael. Early Sexual Debut: A Risk Factor for STIs/HIV Acquisition Among a Nationally Representative Sample of Adults in Nepal. J Community Health. 2016;41:70–7.
63. Ma Q, Ono-Kihara M, Cong L, Xu G, Pan X, Zamani S, et al. Early initiation of sexual activity: a risk factor for sexually transmitted diseases, HIV infection, and unwanted pregnancy among university students in China. BMC Public Health. 2009;9(111).
64. Magnusson BM, Masho SW, Lapane KL. Early Age at First Intercourse and Subsequent Gaps in Contraceptive Use. J Women's Heal. 2012 Jan 1;21(1):73.
65. State of the World's Children 2021 | UNICEF [Internet]. UNICEF. 2021 [cited 2022 Aug 25]. Available from: https://www.unicef.org/reports/state-worlds-children-2021.
66. Baumgarter JN, Geary CW, Tucker H WM. The Influence of Early Sexual Debut and Sexual Violence On Adolescent Pregnancy: A Matched Case-Control Study In Jamaica | Guttmacher Institute. Int Perspect Sex Reprod Health. 2009;35(1):21–8.
67. Mchunu G, Peltzer K, Tutshana B, Seutlwadi L. Adolescent pregnancy and associated factors in South African youth. Afr Health Sci. 2012;12(4):426.
68. Barron P, Subedar H, Letsoko M, Makua M, Pillay Y. Teenage births and pregnancies in South Africa, 2017 - 2021 - a reflection of a troubled country: Analysis of public sector data. South African Med J. 2022;112(4):252–8.
69. May J WC. South African Child Gauge 2020: Food and nutrition security [Internet]. Child Gauge. 2020 [cited 2022 Aug 25]. Available from: http://www.ci.uct.ac.za/sites/Child_Gauge/South_African_Child_Gauge_2020.pdf
70. Fraser AM, Brockert MPH WR. Association of Young Maternal Age with Adverse Reproductive Outcomes. N Engl J Med. 1995;332(17):1113–20.
71. Lewis LN, Hickey M, Doherty DA, Skinner SR. How do pregnancy outcomes differ in teenage mothers? A

Western Australian study. Med J Aust. 2009 May 1;190(10):537–41.
72. Chen X-K, Wen SW, Fleming N, Demissie K, Rhoads GG, Walker M. Teenage pregnancy and adverse birth outcomes: a large population based retrospective cohort study. Int J Epidemiol. 2007;36:368–73.
73. Moore DR, Florsheim P, Butner J. Journal of Clinical Child and Adolescent Psychology Interpersonal Behavior, Psychopathology, and Relationship Outcomes Among Adolescent Mothers and Their Partners. J Clin Child Adolesc Psychol. 2007;36(4):541–56.
74. Dvořák J, Koucký M, Jančová E, Mysliveček M, Tesař V PA. Chronic kidney disease and pregnancy outcomes. Sci Reports 2021 111. 2021 Oct 29;11(1):1–6.
75. Maule SP, Ashworth DC, Blakey H, Osafo C, Moturi M, Chappell LC, et al. CKD and Pregnancy Outcomes in Africa: A Narrative Review. Kidney Int Reports. 2020;5(8):1342.
76. CDC. Teen Substance Use & Risks | CDC [Internet]. Centre for Disease Control and Prevention. 2020 [cited 2022 Aug 24]. Available from: https://www.cdc.gov/ncbddd/fasd/features/teen-substance-use.html.
77. Hassan A, Csemy L, Rappo MA, Knight JR. Adolescent substance abuse around the world: an international perspective. Adolesc Med State Art Rev. 2009;20(3):915–29.
78. Morojele NK, Ramoomar L, Dumbili EW KS. Adolescent Health Series-Alcohol, tobacco, and other drug use among adolescents in sub-Saharan Africa: A narrative review. Trop Med Int Heal. 2021;26:1528–38.
79. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, Brabec BA, O'corragain OA, Edmonds PJ, et al. High alcohol consumption and the risk of renal damage: a systematic review and meta-analysis. Q J Med. 2015;108:539–48.
80. Carbia C, Cadaveira F, Caamaño-Isorna F, Rodríguez-Holguín S, Corral M. Binge drinking during adolescence and young adulthood is associated with deficits in verbal episodic memory. PLoS One. 2017;1–17.
81. Ruebner RL, Laney N, Young Kim J, Hartung EA, Hooper SR, Radcliffe J, et al. Original Investigation Neurocognitive Dysfunction in Children, Adolescents, and Young Adults With CKD. Am J Kidney Dis. 2016;67(4):567–75.
82. World Health Organisation. Adolescent mental health [Internet]. WHO fact sheet. 2021 [cited 2022 Aug 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/adolescent-mental-health.
83. Eyre O, Thapar A. Common adolescent mental disorders: transition to adulthood. Lancet. 2014;383:1366–8.
84. Dobbels F, Ruppar T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: A systematic review. Pediatr Transplant. 2010 Aug;14(5):603–13.
85. Meyers KEC, Weiland H, Thomson PD. Paediatric renal transplantation non-compliance. Pediatr Nephrol 1995 92. 1995 Apr;9(2):189–92.
86. Blowey DL, Hébert D, Arbus GS, Pool R, Korus M, Koren G. Compliance with cyclosporine in adolescent renal transplant recipients. Pediatr Nephrol. 1997 Oct;11(5):547–51.
87. Rianthavorn P, Ettenger RB, Malekzadeh M, Marik JL, Struber M. Noncompliance with immunosuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. Transplantation. 2004 Mar 15;77(5):778–82.
88. Cochat P, De Geest S, Ritz E. Drug holiday: a challenging child–adult interface in kidney transplantation. Nephrol Dial Transplant. 2000 Dec 1;15(12):1924–7.
89. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: Non-adherence with the immunosuppressive regimen in adolescent transplant recipients. Pediatr Transplant. 2005 Jun 1;9(3):381–90.
90. Annunziato RA, Emre S, Shneider BL, Barton C, Dugan CA SE. Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult services. Pediatr Transplant. 2017;11:608–14.

List of Tables, Figures and Supplementary Material

A. Tables

B. Figures

C. Supplementary Material

Supplementary Table 1: Qualitative needs assessment of adolescent nephrology patients attending Groote Schuur Hospital, South Africa.(92)

Supplementary Table 2: Characteristics of the AYA patients attending the nephrology service with death as an outcome.

Supplementary Table 3: Association between death and clinically relevant variables in AYA with kidney disease.

Supplementary Table 4: Characteristics of AYA patients with lost to follow up at the nephrology service.

Supplementary Table 5: Association between LTFU in AYA kidney disease with demographic and clinical variables.

Supplementary Table 6: Characteristics of AYA patients with non-adherence attending the nephrology service.

Supplementary Table 7: Outcomes of kidney transplantation patients attending the AYA clinic and the non-AYA clinic.

A. Tables

Table 1: Baseline Characteristics - clinical and biochemical features of nephrology patients attending the AYA clinic and the non-AYA clinic.

Parameters	All *n* = 292	Nephrology AYA Clinic *n* = 111	Nephrology non-AYA Clinic *n*=181	P-value
Age at first visit, years (median, IQR)	20 (18-23)	19 (17-21)	21 (18-23)	0.003
Age <18 years (*n*, %)	81 (28)	40 (36)	41 (23)	-
Age >18 years (*n*, %)	211 (72)	71 (64)	140 (77)	0.013
Sex: Male (*n*, %)	131 (45)	47 (42)	84 (46)	0.500
Duration of follow up, months (median, IQR)	24 (8-54)	37 (19-60)	18 (3-45)	<0.001
BMI, kg/m^2 (median, IQR)	22 (20-26)	22 (20-27)	22 (20-24)	0.280
Co-morbidities				
Hypertension (*n*, %)	192 (66)	71 (64)	121 (67)	0.610
Systolic BP, mmHg (median, IQR)	130 (120-144)	128 (119-139)	133 (120-146)	0.085
Diastolic BP, mmHg (median, IQR)	80 (70-88)	78 (68-86)	80 (70-90)	0.200
Diabetes Mellitus (*n*, %)	9 (3)	8 (7)	1 (1)	0.001
HIV infection (*n*, %)	12 (4)	2 (2)	10 (6)	0.120
Laboratory Data				
Serum Creatinine, μmol/L (median, IQR)	91 (60-254)	76 (56-284)	96 (61-250)	0.200
eGFR, ml/min/1.73m^2) (median, IQR)	84 (26-126)	94 (25-129)	79 (27-120)	0.280
Serum Albumin, g/L (median, IQR)	39 (30-43)	40 (34-44)	38 (28-42)	0.009
Serum Total Cholesterol, mmol/L (median, IQR)	4 (4-6)	4 (4-5)	4 (4-6)	0.410
Serum Haemoglobin, g/dL (median, IQR)	11.5 (9-13)	12.1 (10-13)	11.1 (9-13)	0.310
UPCR, g/mmol creatinine (median, IQR)	0.07 (0.02-0.31)	0.04 (0.02-0.21)	0.13 (0.02-0.34)	0.035
Stage of CKD				
Stage 1 (*n*, %)	134 (46)	55 (49)	79 (44)	0.042
Stage 2 (*n*, %)	54 (22)	16 (18)	38 (24)	0.320
Stage 3 (*n*, %)	9 (4)	1 (1)	8 (5)	0.170
Stage 4 (*n*, %)	19 (8)	7 (8)	12 (8)	0.890
Stage 5, not on KRT (*n*, %)	28 (10)	6 (5)	22 (12)	0.700
Kidney Replacement Therapy (*n*, %)	48 (16)	26 (23)	22 (12)	0.007
Haemodialysis (*n*, %)	17/48 (35)	6/26 (23)	11/22 (50)	-
Peritoneal dialysis (*n*, %)	19/48 (40)	14/26 (53)	5/22 (23)	-
Kidney Transplant (*n*, %)	12/48 (25)	6/26 (23)	6/22 (27)	-

AYA clinic, adolescent and young adult clinic; non-AYA clinic, non- adolescent and young adult clinic; BMI, body mass index; BP, blood pressure; HIV, human immunodeficiency virus; eGFR, estimate glomerular filtration rate; UPCR, Urine protein: creatinine ratio; CKD, chronic kidney disease; *n*, number; *IQR*, interquartile range.

Table 2: Chronic Kidney Disease Primary Diagnosis Aetiology –the spectrum of kidney disease in patients attending the AYA clinic and the non-AYA clinic.

Parameters	All *n* = 292	Nephrology AYA Clinic *n* = 111	Nephrology non-AYA Clinic *n* = 181	P-value
1. Glomerular Disease (*n*, %)	212/292 (73)	70 /111 (63)	142/181 (78)	0.110
Primary Glomerulonephritis (*n*, %)	119/292 (41)	43/111 (39)	76/181 (42)	0.580
MPGN	23/119 (19)	13/43 (30)	10/76 (13)	-
MCGN	19/119 (16)	4/43 (4)	15/76 (20)	-
IgAN	14/119 (12)	2/43 (5)	12/76 (16)	-
MCD	13/119 (11)	6/43 (14)	7/76 (9)	-
FSGS	11/119 (9)	4/43 (9)	7/76 (9)	-
PIGN	11/119 (9)	2/43 (5)	9/76 (12)	-
RPGN	6/119 (5)	2/43 (5)	4/76 (5)	-
Membranous GN	3/119 (3)	2/43 (5)	1/76 (1)	-
Chronic suspected GN	18/119 (15)	8/43 (19)	10/76 (13)	-
Other	1/119 (1)	4/43 (9)	4/76 (5)	-
Secondary Glomerular Disease *(n*, %)	93/292 (32)	27/111 (24)	66/181 (36)	0.031
Secondary Glomerulonephritis	60/292 (21)	19/111 (17)	41/181 (23)	
Lupus Nephritis	54/60 (90)	18/19 (95)	36/41 (88)	0.470
Class II	14/54 (26)	7/18 (39)	7/36 (19)	-
Class III	8/54 (15)	3/18 (17)	5/36 (14)	-
Class IV	26/54 (48)	6/18 (33)	20/36 (56)	-
Class V	6/54 (11)	2/18 (11)	4/36 (11)	-
ANCA GN	3/60 (5)	1/19 (5)	2/41 (5)	-
HUS (TMA)	2/60 (3)	0/19 (0)	2/41 (5)	-
LCDD GN	1/60 (2)	0/19 (0)	1/41 (2)	-
Other Glomerular Disease	33/93 (35)	8/27 (30)	25/66 (38)	
Hypertensive Nephrosclerosis	13/33 (39)	2/8 (3)	11/25 (44)	-
HIVAN	6/33 (18)	0/8 (0)	6/25 (24)	-
Diabetic Nephropathy	2/33 (6)	1/8 (13)	1/25 (4)	-
Other	12/33 (36)	5/8 (6)	7/25 (28)	-
2. Urological Conditions	37/292 (13)	17/111 (15)	20/181 (11)	0.230
CAKUT *(n*, %)				
Vesicoureteral Reflux	8/37 (22)	3/17 (18)	5/20 (25)	-
Posterior Urethral Valve	7/37 (19)	5/17 (29)	2/20 (10)	-
Neuropathic Bladder	6/37 (16)	3/17 (18)	3/20 (15)	-
Single Kidney Agenesis	3/37 (38)	1/17 (6)	2/20 (10)	
Pelvic-Ureteric Junction Pathology	2/37 (8)	2/17 (12)	0/20 (0)	-
Single Kidney (other aetiology)	2/37 (8)	0/17 (0)	2/20 (10)	-
Bilateral Kidney Dysplasia	1/37 (3)	0/17 (0)	1/20 (5)	-
Sacral Agenesis with Neuropathic Bladder	1/37 (3)	1/17 (6)	0/20 (0)	-
VATER syndrome	1/37 (3)	1/17 (6)	0/20 (0)	-
Other Urological Conditions (*n, %)*	6/37 (16)	1/17 (6)	5/20 (25)	-
3. Hereditary Conditions *(n*, %)	24/292 (8)	15/111 (14)	9 /181(5)	0.010

ADPKD	14/24 (58)	7/15 (47)	7/9 (8)	-
Tuberous Sclerosis	3/24 (13)	2/15 (13)	1/9 (11)	-
Hereditary RTA	3/24 (13)	2/15 (13)	1/9 (11)	-
Cystinosis	2/24 (8)	2/15 (13)	0/9 (0)	-
Congenital Diabetes Insipidus	1/24 (4)	1/15 (7)	0/9 (0)	-
Other	1/24 (4)	1/15 (7)	0/9 (0)	-
4. Tubulointerstitial Disease (*n*, %)	7/292 (2)	0/111 (0)	7/181 (4)	0.047
5. CKD unknown aetiology (*n*, %)	12/292 (4)	8/111 (7)	4 /181 (2)	0.037

AYA clinic, adolescent and young adult clinic; non-AYA clinic, non- adolescent and young adult clinic; MPGN, mesangioproliferative glomerulonephritis; MCGN, mesangiocapillary glomerulonephritis; IgAN, Immunoglobulin A Nephropathy; MCD, minimal change disease; FSGS, focal segmental glomerulosclerosis; PIGN, post-infectious glomerulonephritis; GN, glomerulonephritis ; ANCA GN; antineutrophil cytoplasmic antibody associated glomerulonephritis; HUS, haemolytic uraemic syndrome; TMA, thrombotic microangiopathy; LCDD, light chain deposition disease; HIVAN, HIV-1 associated nephropathy; CAKUT, congenital anomalies of the kidney and urinary tract; ADPKD, autosomal dominant polycystic kidney disease; RTA, renal tubular acidosis.

Table 3: Outcomes of nephrology patients attending the AYA clinic and the non-AYA clinic.

Parameters	**All** *n* = 256	**Nephrology AYA Clinic** *n* = 91	**Nephrology Non-AYA clinic** *n* = 165	**P-value**
Change in CKD stage				0.390
No change (*n*, %)	176/256 (69)	62/91 (69)	113/165 (68)	
Improvement (*n*, %)	31/256 (12)	8/91 (9)	23/165 (14)	
Deterioration (*n*, %)	49/256 (19)	20/91 (22)	29/165 (18)	
Kidney Outcome				
Doubling of Creatinine (*n*, %)	35/256 (14)	13/91 (14)	22/165 (13)	0.830
Reduction in eGFR >40% (*n*, %)	44/256 (17)	14/91 (15)	30/165 (18)	0.570
ESKD at last visit (*n*, %)	43/256 (17)	10/91 (11)	33/165 (20)	0.065
KRT at last visit (*n*, %)	34/256 (13)	16/91 (18)	18/165 (11)	0.150
Peritoneal dialysis (*n*, %)	10/34 (29)	3/16 (19)	7/18 (39)	
Haemodialysis (*n*, %)	4//34 (12)	1/16 (6)	3/18 (17)	
Kidney Transplant (*n*, %)	20/34 (59)	12/16 (75)	8/18 (44)	
Graft Failure (*n*, %)	4/20 (20)	1/12 (8)	3/8 (4)	0.730
Death (n, %)	22/253 (9)	2/89 (2)	20/164 (12)	0.007
Lost to Follow Up (n, %)	79/256 (31)	19/91 (21)	60/164 (37)	0.012

AYA clinic, adolescent and young adult clinic; non-AYA clinic, non- adolescent and young adult clinic; CKD, chronic kidney disease; eGFR, estimate glomerular filtration rate; ESKD, end-stage kidney disease; KRT, renal replacement therapy;

Table 4: Social challenges experience by nephrology patients attending the AYA clinic and the non-AYA clinic.

Parameters	**All** *n* = 292	**Nephrology AYA Clinic** *n* = 111	**Nephrology Adult Service Attended** *n* = 181	**P-value**
Unplanned pregnancies (*n*,%)	27/161 (17)	9/64 (14)	18/97 (19)	0.590
Sexually Transmitted Diseases (*n*,%)	17/291 (6)	6/111 (5)	11/180 (6)	0.800
Substance Abuse (*n*,%)	73/292 (25)	32/111 (29)	41/181 (23)	0.240
Cigarette smoker (*n*,%)	64/292 (22)	25/111 (23)	39/181 (22)	0.840
Ethanol misuse (*n*,%)	28/292(10)	12/111 (11)	16/181 (9)	0.580
Illicit substance use (*n*,%)	22/292 (8)	7/111 (6)	15/181 (8)	0.530
Marijuana	15	6	9	
Methamphetaine	7	2	5	
Mandrax	6	4	2	
Heroin	2	0	2	
Other	1	0	1	
Mental Illness (*n*,%)	26/292 (9)	16/111 (14)	10/181(6)	0.010
Non-adherence (*n*, %)	99/292 (34)	43/111 (39)	56/181 (31)	0.170
Missed appointments (*n*,%)	44/292 (15)	11/111 (10)	33/181 (18)	0.054
Sub-therapeutic drug level (*n*=23, %)	13/23 (57)	6/14 (43)	7/9 (78)	0.099

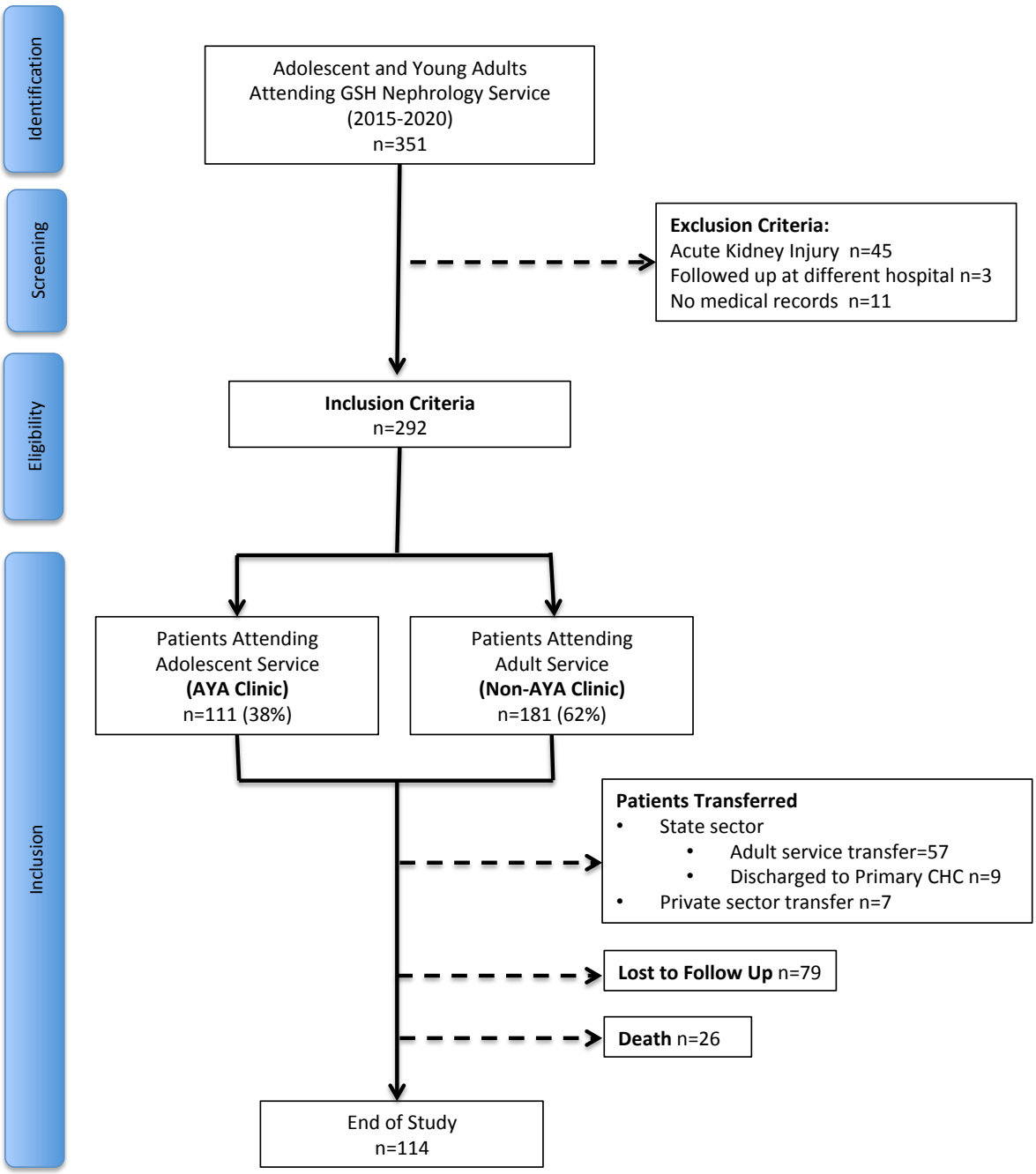
Table 5: Variations in the aetiology of chronic kidney disease between different age groups; and between well-resourced countries and less-resourced countries.

		Paediatrics					Adolescents				Adults			
		WRC			LRC		WRC			LRC	WRC		LRC	
Country **Date of Study Publication**		**USRDS**(33) **2020**	**Japan**(41) **2015**	**ANZ**(42) **2019**	**Nigeria**(43) **2014**	**SA**(43) **2008**	**USRDS** (33) **2020**	**ANZ**(42) **2019**	**Japan**(41) **2015**	**SA** (this study) **2022**	**USRDS**(32) **2019**	**Australia**(44) **2020**	**Nigeria**(45) **2006**	**SA**(46) **2017**
Age Represented (years)		0-12	0-14	0-14	0-16	5-16	13-17	15-17	15-19	13-19	>21	>18	14-72	>18
Year of Data Collection		2015-2018	2006-2011	2013-2018	2005-2012	1994-2006	2015-2018	2013-2018	2006-2011	2015-2020	2017	2020	1992-2002	2017
Patient Number in Cohort		2 728	540	267	53	71	2 682	77	118	292	119 577	1 244	153	10 257
AETIOLOGY	**Glomerulonephritis** (%)	21.2	14.9	16.9	77.4	52.1	36.6	32.0	29.6	61.3	7.2	17.6	41.2	10.3
	Primary GN	16.0	-	-		-	25.9	-	-	40.7	-			
	Secondary GN	5.2	-	-		-	10.7	-	-	20.5	-			
	CAKUT (%)	39.8	42.2	33.3	21.2	9.5	21.8	16.0	30.5	12.7	-	-	-	-
	Cystic/hereditary (%)	13.6	23.7	12.3	-	3.4	11.3	7.0	18.6	8.2	2.9	5.4	6.5	6.5
	Urological (non-CAKUT) (%)	4.4	-	-	-	14.1	-	-	-	-	-	1.6	9.1	9.1
	TID (%)	-	-	0	-	-	-	1.0	-	2.4	-	-	-	-
	Hypertension (%)	-	-	-	-	-	-	-	-	-	29.3	11.6	26.1	26.1
	Diabetic Kidney Disease (%)	-	-	0	-	-	-	3.0	-	-	47.7	30.2	13.1	13.1
	Other Causes (%)	25.3	18.9	23.4	1.8	1.8	30.3	41	21.1	4.1	1.3	33.6	4.0	4.0

WRC, well-resourced country; LRC, less-resourced country; USRDS, United States Renal Data System; ANZ, Australia and New Zealand; SA, South Africa; CAKUT, congenital anomalies of the kidney and urinary tract, TID, tubulointerstitial disease.

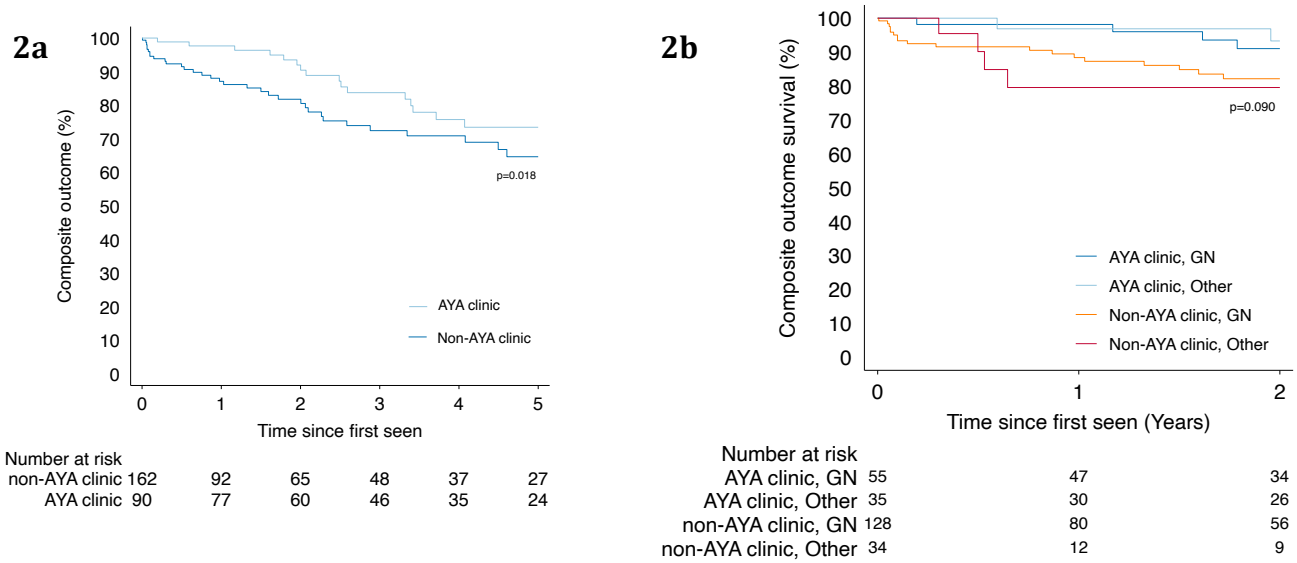
B. Figures

Figure 1: Flow diagram demonstrating patient selection for the study population.



GSH, Groote Schuur Hospital; AYA clinic, adolescent young adult clinic; Non-AYA clinic, non-adolescent young adult clinic; CHC, community health care.

Figure 2: Kaplan-Meier Curve composite outcome* of nephrology patients attending the AYA clinic and the non-AYA clinic **(2a)**, and stratified by attendance and underlying aetiology **(2b)**.



*Composite End Point, doubling of creatinine + reduction in eGFR >40% + ESKD + death.

Figure 3: Kaplan-Meier Curve of survival in nephrology patients attending the AYA clinic and the non-AYA clinic.

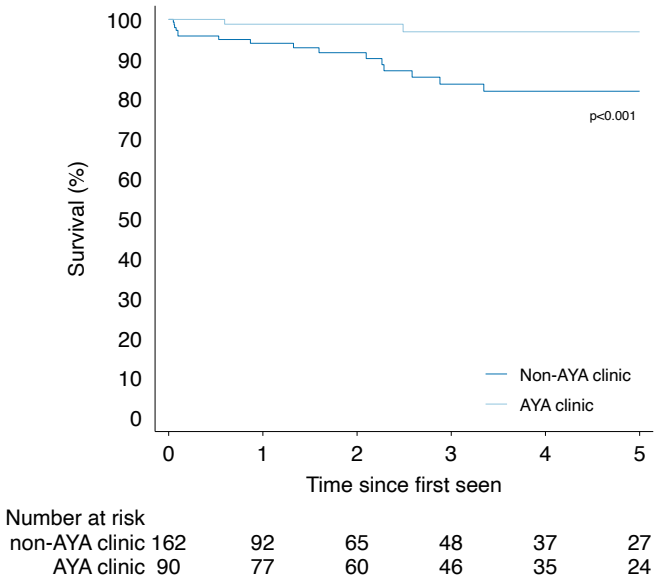
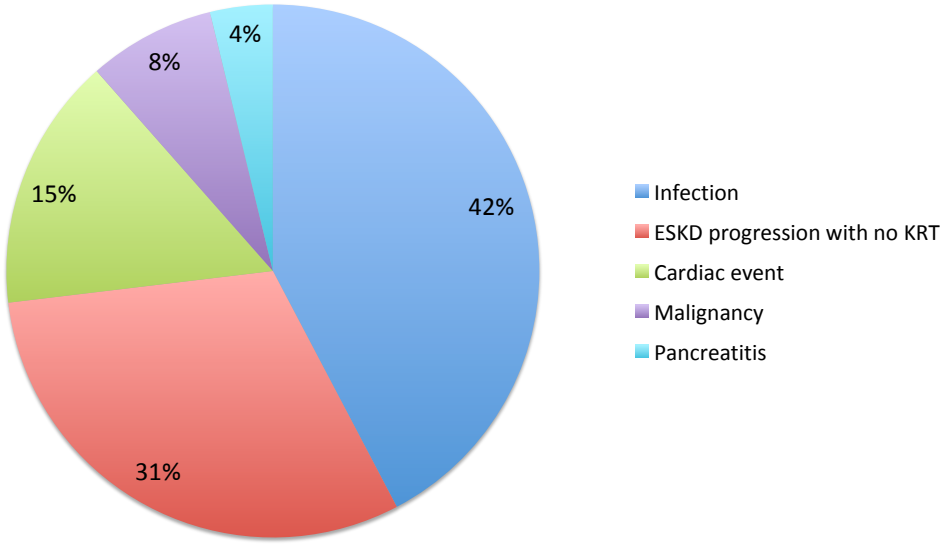


Figure 4: The aetiology of death in CKD patients attending the nephrology service.



ESKD, end-stage kidney disease

C. Supplementary Material

Supplementary Table 1: Qualitative needs assessment of adolescent nephrology patients attending Groote Schuur Hospital, South Africa. (26)

NEEDS ASSESSMENT CENTRAL THEMES
1. Feelings of isolation and loneliness
2. Anxiety regarding their medical illness
3. Dissatisfaction of physical appearance
4. Difficulty communicating with staff
5. Perception of staff not appreciating the challenge related to lifestyle changes
6. Difficulty in remembering and taking chronic medication

Supplementary Table 2: Characteristics of the AYA patients attending the nephrology service with death as an outcome.

Parameters	All *n* = 287	Alive *n* = 261	Death *n* = 26	P-value
Age, years (median, IQR)	20 (18-23)	20 (18-23)	20 (18-23)	0.610
Sex: Male (n, %)	128/287 (45)	114/261 (44)	14/26 (54)	0.320
Duration of follow up, months (median, IQR)	24 (8-54)	24 (8-55)	18 (6-35)	0.160
Attended Adolescent Service (n, %)	107/287 (37)	102/261 (39)	5/26 (19)	0.046
Primary Diagnosis (n, %)				
Glomerular Disease	209/287 (73)	188/261 (72)	21/26 (81)	0.340
CAKUT	35/287 (12)	33/261 (13)	2/26 (8)	0.460
Hereditary	19/287 (7)	24/261 (9)	0/26 (0)	0.110
Tubulointerstitial disease	19/287 (7)	16/261 (6)	3/26 (12)	0.290
Hypertension (n, %)	187/287 (65)	164/261 (63)	23/26 (88)	0.009
UPCR, g/mmol creatinine (median, IQR)	0.07 (0.02-0.31)	0.06 (0.02-0.28)	0.31 (0.15-1.13)	<0.001
Serum Creatinine, μmol/L (median, IQR)	90 (60-250)	80 (57-198)	359 (155-736)	<0.001
eGFR, ml/min/1.73m^2 (median, IQR)	85 (27-127)	92 (38-128)	14 (6-49)	<0.001
Stage of CKD				
Stage 1 (n, %)	140/242 (57)	137/221 (62)	3/21 (15)	<0.001
Stage 2 (n, %)	53/242 (22)	50/221 (23)	3/21 (14)	0.380
Stage 3 (n, %)	9/242 (4)	7/221 (3)	2/21 (10)	0.140
Stage 4(n, %)	18/242 (7)	15/221 (7)	3/21 (14)	0.210
Stage 5, not on KRT (n, %)	22/242 (21)	12/221 (5)	10/21 (48)	<0.001
Kidney Replacement Therapy (n, %)	46/286 (16)	41/260 (16)	5/26 (19)	0.550
Haemodialysis (n, %)	16/286 (6)	13/260 (5)	3/26 (12)	-
Peritoneal dialysis (n, %)	18/286 (6)	17/260 (7)	1/26 (4)	-
Kidney Transplant (n, %)	12/286 (4)	11/260 (4)	1/26 (4)	-
Social Challenges				
Pregnancy (unplanned) (n, %)	27/159 (17)	24/147 (16)	12/26 (46)	0.070
Sexually Transmitted Diseases (n, %)	17/286 (6)	14/260 (5)	3/26 (12)	0.210
Substance Abuse (n, %)	73/287 (25)	63/261 (24)	10/26 (8)	0.110
Non-adherence (n, %)	99/287 (34)	92/261 (35)	7/26 (27)	0.390
Mental Illness (n, %)	26/287 (9)	24/261 (9)	2/26 (8)	0.800

CAKUT, congenital anomalies of kidney and urinary tract; UPCR, Urine protein: creatinine ratio; eGFR, estimate glomerular filtration rate; CKD, chronic kidney disease; *n*, number; *IQR*, interquartile range.

Supplementary Table 3: Association between death and clinically relevant variables in AYA with kidney disease.

FACTORS	OR	95% Confidence Interval (CI)	P-value
Male	1.50	0.669-3.378	0.320
Hypertension	4.50	1.327-15.499	0.016
UPCR (g/mmol creatinine)	3.56	1.784-7.122	<0.0001
Serum Creatinine (mmol/L)	1.00	1.000-1.001	0.004
eGFR (ml/min/1.73m^2)	0.97	0.967-0.987	<0.0001
AYA clinic attendance	0.40	0.136-1.015	0.054

UPCR, Urine protein: creatinine ratio; eGFR, estimate glomerular filtration rate; AYA, adolescent and young adult; OR, odds ratio.

Supplementary Table 4: Characteristics of AYA patients with lost to follow up at the nephrology service.

Parameters	All *n* = 290	LTFU *n* = 79	Not LTFU *n* = 211	P-value
Age, years (median, IQR)	20 (18-23)	21 (18-23)	20 (17-23)	0.340
Age >18 years (median, IQR)	209/290 (72)	63/79 (80)	146/211 (69)	0.075
Sex: Male (n, %)	130/290 (45)	39/79 (49)	91/211 (43)	0.340
Duration of follow up, months (median, IQR)	24 (8-54)	9 (2-25)	31 (14-60)	<0.001
Attended Adolescent Service (n, %)	110/290 (38)	18/79 (23)	92/211 (44)	0.001
Hypertension (n, %)	190/290 (66)	43/79 (54)	147/211 (70)	0.015
UPCR, g/mmol creatinine (median, IQR)	0.08 (0.02-0.31)	0.04 (0.01-0.26)	0.11 (0.02-0.34)	0.013
Serum Creatinine, μmol/L (median, IQR)	91 (60-251)	75 (57-122)	101 (62-350)	0.004
eGFR, ml/min/1.73m^2 (median, IQR)	84 (27-127)	97 (60-128)	77 (17-126)	0.008
Stage of CKD				
Stage 1 (n, %)	139/245 (56)	48/73 (66)	91/172 (53)	0.130
Stage 2 (n, %)	54/245 (22)	17/73 (23)	37/172 (22)	0.760
Stage 3 (n, %)	9/245 (4)	4/73 (5)	5/172 (3)	0.330
Stage 4(n, %)	19/245 (8)	3/73 (4)	16/172 (9)	0.160
Stage 5, not on KRT (n, %)	24/245 (10)	4	57	0.004
Kidney Replacement Therapy (n, %)	67/290 (23)	6/79 (8)	61/211(29)	<0.007
Social Challenges				
Pregnancy (unplanned) (n, %)	27/289 (9)	8/79 (10)	19/210 (9)	0.780
Sexually Transmitted Diseases (n, %)	17/289 (6)	5/78 (6)	12/211 (6)	0.820
Substance Abuse (n, %)	71/290 (24)	24/79 (30)	47/211 (22)	0.150
Mental Illness (n, %)	26/290 (9)	5/79 (6)	21/211 (10)	0.340

UPCR, Urine protein: creatinine ratio; eGFR, estimate glomerular filtration rate; CKD, chronic kidney disease; KRT, kidney replacement therapy; *n*, number; *IQR*, interquartile range.

Supplementary Table 5: Association between lost to follow up in AYA kidney disease with demographic and clinical variables.

FACTORS	OR	95% Confidence Interval (CI)	P-value
Age	1.03	0.979-1.092	0.220
Age greater than 18 years (reference: age < 18years)	1.75	0.941-3.264	0.077
Male	1.28	0.765-2.159	0.340
AYA Clinic Attendance	0.38	0.211-0.689	0.001
eGFR (ml/min/1.73m^2)	1.00	1.002-1.013	0.004
eGFR >60ml/min/1.73 m^2 (reference: eGFR <60ml/min/1.73m^2)	2.28	1.282-4.055	0.005
UPCR (g/mmol)	0.47	0.216-1.025	0.058
Substance use	1.52	0.853-2.716	0.155
Mental Illness	0.61	0.222-1.681	0.340
Non-adherence	1.61	0.944-2.749	0.080

AYA, adolescent and young adult.; eGFR, estimate glomerular filtration rate; UPCR, urine protein: creatinine ratio; OR: unadjusted odds ratio.

Supplementary Table 6: Characteristics of AYA patients with non-adherence attending the nephrology service.

Parameters	All *n* = 292	Non-Adherence *n* = 99	Adherence *n* = 193	P-value
Age, years (median, IQR)	20 (18-23)	19 (17-22)	21 (18-23)	0.023
Age >18 years (median, IQR)	211/292 (72)	68/99 (69)	143/193 (74)	0.330
Sex: Male (n, %)	131/292 (45)	50/99 (51)	81/193 (42)	0.170
Duration of follow up, months (median, IQR)	24 (8-54)	28 (10-58)	23 (6-49)	0.230
Attended Adolescent Service (n, %)	111/292 (38)	43/99 (43)	68/193 (35)	0.170
Social Challenges				
Pregnancy (unplanned) (n, %)	27/291 (9)	14/99 (14)	13/192 (7)	0.040
Sexually Transmitted Diseases (n, %)	17/291 (6)	11/98 (3)	11/98 (11)	0.005
Substance Abuse (n, %)	73/292 (25)	42/99 (42)	31/193 (16)	<0.001
Mental Illness (n, %)	26/292 (9)	14/99 (14)	12/193 (6)	0.024

n, number; *IQR*, interquartile range.

Supplementary Table 7: Outcomes of kidney transplantation patients attending the AYA clinic and the non-AYA clinic.

Parameters	All *n* = 32	Nephrology AYA Clinic *n* = 18	Nephrology Non-AYA clinic *n* = 14	P-value
Kidney Outcome				
Allograft Rejection (*n*, %)	9/32 (28)	5/18 (28)	3/14 (21)	-
Allograft Failure (*n, %)*	6/32 (19)	3/18 (17)	3/14 (21)	-
Death (*n, %)*	3/32 (9)	1/18 (6)	2/14 (14)	-
Composite End Point Outcome	7/18 (39)	4/18 (22)	3/14 (21)	-
Adherence (*n, %*)	10/32 (31)	7/18 (39)	3/14 (21)	-
Knows Medication (*n*,%)	4/32 (13)	1/18 (6)	3/14 (21)	
Missed appointments (*n*,%)	1/32 (3)	0/18 (0)	1/14 (7)	-
Sub-therapeutic drug level (*n*= %)	10/32 (31)	7/18 (39)	3/14 (21)	-
Lost to Follow Up (*n, %*)	4/32 (13)	1/18 6)	3/18 (21)	-

AYA clinic, adolescent and young adult clinic; non-AYA clinic, non- adolescent and young adult clinic; Composite End Point Outcome, doubling of creatinine + reduction in eGFR >40% + ESKD + death; *n*, number; *IQR*, interquartile range.

APPENDIX 1 (a): HREC Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

27 October 2020

HREC REF: 646/2020

Dr Bianca Davidson
Division of Nephrology & Hypertension
Groote Schuur Hospital
Observatory
7925

Email: bianca.davidson@uct.ac.za
Student email: zibs.barday@gmail.com

Dear Dr Davidson

PROJECT TITLE: CLINICO-PATHOLOGICAL CHARACTERISTICS AND OUTCOME OF NEPHROLOGY ADOLESCENT YOUTH IN CAPE TOWN: A SINGLE CENTRE STUDY-MASTERS CANDIDATE-DR ZIBYA BARDAY SUB-STUDY LINKED TO 323/2020

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 and 06 July 2020, found on the following website link:
http://www.health.uct.ac.za/fhs/research/humanethics/about

Approval is granted for one year until the 30 October 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Zibya Barday will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

HREC 646/2020 le

APPENDIX 1(b): HREC Ethics Approval

HUMAN RESEARCH ETHICS COMMITTEE
25 MAR 2022
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.3.23
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	26/3/2022

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you for the deviation document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	24 March 2022		
HREC REF Number	646/2020	Current Ethics Approval was granted until	30 October 2021
Protocol title	**Clinico-Pathological Characteristics and Outcome of Nephrology Adolescent Youth in Cape Town: A Single Centre Study.**		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?		X Yes	☐ No
If yes, could you please provide the HREC Reference number for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.		This *is* a sub-study of the main study HREC REF:323/2020	
Principal Investigator	Dr. Zibya Barday		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

APPENDIX 2: Kidney International Guide for Authors

KIDNEY INTERNATIONAL

Official Journal of the International Society of Nephrology

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

ISSN: 0085-2538

DESCRIPTION

Kidney International (***KI***) is the official journal of the International Society of Nephrology. Under the editorial leadership of Dr. Pierre Ronco (Paris, France), ***KI*** is one of the most cited journals in nephrology and widely regarded as the world's premier journal on the development and consequences of kidney disease.

KI offers features with premier benefits for both readers and authors. Here you will find some of the most highly cited original articles in nephrology, sharply focused reviews, latest imaging techniques, controversial discussions and much more.

KI is devoted to kidney research. It aims to inform the researcher, the clinical investigator, and the practicing nephrologist on all aspects of kidney research. These include:

The latest **clinical studies** on emerging developments in nephrology The highest level of **original research studies** in clinical and basic kidney research **Brief Reports** of exceptional findings that induce a change in basic concept or in standard of care **Nephrology Digest** comments on and puts into perspective several areas of new developments in basic and clinical research in nephrology at large, as reported in the recent literature and at scientific meetings **Editorials** that highlight important issues in international nephrology **Nephrology sans Frontieres** are occasional short articles that discuss matters of local interest to nephrologists around the world, but which we feel need to be known by nephrologists world-wide **In-depth reviews** about major issues in kidney research **Controversies** on hot topics or debated issues written by two opposing authorities with a summary by the editors **Nephrology Images** which are presentations of interesting images in kidney pathology, radiology chosen for their illustrative nature or simply for their esthetic qualities **Policy Forum** that features issues of importance to the international renal community including the politics of funding, of organ transplantation, of adequacy of dialysis, of world-wide affordability of end stage patient care and many other topical issues **Journal Club** are synopses that bring you the latest research highlights from across a wide spectrum of journals in fields relevant to renal research

Your subscription to Kidney International also includes the companion journal, Kidney International Supplements.

IMPACT FACTOR

2020: 10.612 © Clarivate Analytics Journal Citation Reports 2021

ABSTRACTING AND INDEXING

PubMed/Medline
Science Citation Index
Current Contents - Life Sciences and Clinical Medicine
Web of Science
BIOSIS Citation Index
Chemical Abstracts
Embase
Reference Update
CAB Health
Biological Abstracts
Scopus

EDITORIAL BOARD

Areas of Expertise - Kidney Organogenesis and Congenital Defects, Kidney Injury and Regeneration, Kidney Genetic Model Systems
Yun Xia, Lee Kong Chian School of Medicine, Singapore, Singapore
Areas of Expertise - Kidney Organoid, Pluripotent Stem Cell, Differentiation, Disease Modelling

Statisticians

Vernon Chinchilli, Penn State College of Medicine, Hershey, Pennsylvania, United States of America
Monique M. Elseviers, University of Antwerp, Antwerp, Belgium
Vic Hasselblad, Duke University, Jacksonville, Florida North Carolina, United States of America
Georg Heinze, Medical University of Vienna, Vienna, Austria
Susan L. Hogan, The University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, North Carolina, United States of America
Zhezhen Jin, Columbia University, New York, New York, United States of America
Eiichiro Kanda, Kawasaki Medical School, Kurashiki, Japan
Joseph Kim, Toronto General Hospital, Toronto, Ontario, Canada
Lan Kong, Penn State College of Medicine, Hershey, Pennsylvania, United States of America
Yi-Ju Li, Duke University Hospital, Durham, North Carolina, United States of America
Jennie Ma, University of Virginia, Charlottesville, Virginia, United States of America
Rajasekhar Ramakrishnan, Columbia University, New York, New York, United States of America
Jesse Schold, Cleveland Clinic Department of Quantitative Health Sciences, Cleveland, Ohio, United States of America
Peter X.K. Song, University of Michigan, Ann Arbor, Michigan, United States of America
Elani Streja, Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, California, United States of America
Natasha Wiebe, University of Alberta, Edmonton, Alberta, Canada

KI Editorial Fellows

Amelie Bernier-Jean, Université de Montréal, Beaupré, Quebec, Canada
Letizia De Chiara, University of Florence Department of Experimental and Clinical Biomedical Sciences "Mario Serio", Florence, Italy
Sho Hasegawa, The University of Tokyo Division of Nephrology and Endocrinology, Bunkyo-Ku, Japan

Editorial Office Staff

Patricia Morrissey, Executive Managing Editor, St. Louis, Missouri, United States of America
Susan Small, Managing Editor, St. Louis, Missouri, United States of America
Christine Burgos Clavel, Assistant Managing Editor, Paris, France

Editorial Board

Anupam Agarwal, The University of Alabama at Birmingham, Birmingham, Alabama, United States of America
Evren Azeloglu, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America
Sean Barbour, The University of British Columbia, Vancouver, British Columbia, Canada
Jonathan Barratt, University of Leicester, Leicester, United Kingdom
David Basile, Indiana University School of Medicine, Indianapolis, Indiana, United States of America
John Bertram, Monash University, Clayton, Victoria, Australia
Peter Boor, University Hospital Aachen, Aachen, Germany
Frank Bridoux, University Hospital Centre Poitiers, Poitiers, France
Kirk Campbell, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America
Daniel Cattran, Toronto General Hospital, Toronto, Ontario, Canada
Christos Chatziantoniou, National Institute of Health and Medical Research, Paris, France
Yi-pu Chen, Beijing An Zhen Hospital, Beijing, China
Philip Clayton, Royal Adelaide Hospital, Adelaide, South Australia, Australia
Steven Coca, The Mount Sinai Hospital, New York, New York, United States of America
Terence Cook, Imperial College London, London, United Kingdom
Vivette D'Agati, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, United States of America
Farhad Danesh, Baylor College of Medicine, Chicago, Illinois, Texas, United States of America
John Daugirdas, University of Illinois Chicago College of Medicine, Chicago, Illinois, United States of America
Andrew Davenport, University College London School of Life and Medical Sciences, London, United Kingdom
Marc De Broe, University of Antwerp, Antwerp, Belgium
Vikas Dharnidharka, Washington University in St Louis Department of Pediatrics, Saint Louis, Missouri, United States of America
Kent Doi, The University of Tokyo, Tokyo, Japan
Jie Dong, Peking University First Hospital, Renal Division and Institute of Nephrology, Beijing, China
Zheng Dong, Augusta University, Augusta, Georgia, United States of America
Kai-Uwe Eckardt, Charite University Hospital Berlin, Berlin, Germany
Somchai Eiam-ong, Chulalongkorn University, Bangkok, Thailand
Michael Emmett, Baylor University Medical Center at Dallas, Dallas, Texas, United States of America

Roger Evans, Monash University, Clayton, Victoria, Australia
Pieter Evenepoel, KU Leuven University Hospitals Leuven, Leuven, Belgium
Robert Fairchild, Cleveland Clinic, Cleveland, Ohio, United States of America
Sarah Faubel, University of Colorado Denver Division of Renal Diseases and Hypertension, Aurora, Colorado, United States of America
Christian Faul, The University of Alabama at Birmingham, Birmingham, Alabama, United States of America
Fernando Fervenza, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America
Steven Fishbane, Northwell Health, Mineola, New York, United States of America
Danilo Fliser, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany
Josephine Forbes, Mater Research, South Brisbane, Australia
Alessia Fornoni, University of Miami Katz Family Division of Nephrology and Hypertension, Miami, Florida, United States of America
Anna Francis, Children's Health Queensland Hospital and Health Service, Brisbane, Queensland, Australia
Barry Freedman, Wake Forest University School of Medicine, Winston-Salem, North Carolina, United States of America
Masafumi Fukagawa, Tokai University School of Medicine, Isehara, Japan
Amit X. Garg, Western University, London, Ontario, Canada
Vesna D. Garovic, Mayo Clinic Rochester, Rochester, Minnesota, United States of America
Richard Glassock, University of California Los Angeles David Geffen School of Medicine, Los Angeles, California, United States of America
David Goldfarb, New York University Grossman School of Medicine, New York, New York, United States of America
Mark Haas, Cedars-Sinai Medical Center, Los Angeles, California, United States of America
Volker Haase, Vanderbilt University, Nashville, Tennessee, United States of America
Jan Halbritter, Leipzig University, Leipzig, Germany
Peter C. Harris, Mayo Clinic Rochester, Rochester, Minnesota, United States of America
John C. He, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America
Michelle Hladunewich, University of Toronto, Toronto, Ontario, Canada
Fan Fan Hou, Southern Medical University, Guangzhou, Guangdong, China
Pascal Houillier, University of Paris, Paris, France
Chi-yuan Hsu, University of California San Francisco, San Francisco, California, United States of America
Tobias B. Huber, Medical Center-University of Freiburg, Freiburg, Germany
Benjamin Humphreys, Washington University in St Louis School of Medicine, Saint Louis, Missouri, United States of America
Reiko Inagi, The University of Tokyo, Tokyo, Japan
Kenar Jhaveri, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, United States of America
Jaap Joles, University Medical Centre Utrecht, Utrecht, Netherlands
Kamyar Kalantar-Zadeh, University of California Irvine, Irvine, California, United States of America
Roberto Kalil, The University of Iowa, Iowa City, Iowa, United States of America
Frederick J. Kaskel, Children's Hospital at Montefiore, Bronx, New York, United States of America
A. Richard Kitching, Monash University, Clayton, Victoria, Australia
Jeffrey Kopp, National Institutes of Health, Bethesda, Maryland, United States of America
Anna Köttgen, Medical Center-University of Freiburg, Freiburg, Germany
Matthias Kretzler, University of Michigan, Ann Arbor, Michigan, United States of America
Christian Kurts, University of Bonn Institute of Molecular Medicine and Experimental Immunology, Bonn, Germany
David Leaf, Brigham and Women's Hospital, Boston, Massachusetts, United States of America
Christophe Legendre, University of Paris, Paris, France
Kevin Lemley, Children's Hospital of Los Angeles, Los Angeles, California, United States of America
Emmanuel Letavernier, Hospital Tenon, Paris, France
Adeera Levin, The University of British Columbia, Vancouver, British Columbia, Canada
Philip K.T. Li, Prince of Wales Hospital, Shatin, Hong Kong
Christoph Licht, The Hospital for Sick Children, Toronto, Ontario, Canada
John Lieske, Mayo Foundation for Medical Education and Research, Rochester, Minnesota, United States of America
Adrian Liew, Tan Tock Seng Hospital, Singapore, Singapore
Wai Lim, Sir Charles Gairdner Hospital, Nedlands, Australia
Melissa Little, The Royal Children's Hospital Melbourne, Brisbane, Queensland, Australia
Kathleen Liu, University of California San Francisco, San Francisco, California, United States of America
Youhua Liu, University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America
Alexandre Loupy, National Institute of Health and Medical Research, Paris, France
Christopher Y. Lu, The University of Texas Southwestern Medical Center, Dallas, Texas, United States of America
Friedrich Luft, Charite University Hospital Berlin, Berlin, Germany
Sethu Madhavan, The Ohio State University, Columbus, Ohio, United States of America

Johannes Mann, KfH Dialysis Centre Munich Schwabing, Munchen, Bavaria, Germany
Peter Margetts, McMaster University, Hamilton, Ontario, Canada
Glen Markowitz, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, United States of America
Ziad Massy, Ambroise-Pare Hospital Department of Nephrology and Dialysis, Boulogne Billancourt, France
Kunihiro Matsushita, Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland, United States of America
Mignon McCulloch, Red Cross War Memorial Children's Hospital, Rondebosch, South Africa
Timothy Meyer, Stanford University, Stanford, California, United States of America
Imari Mimura, The University of Tokyo Graduate School of Medicine Faculty of Medicine, Bunkyo-Ku, Japan
Jeffrey Miner, Washington University in St Louis, Saint Louis, Missouri, United States of America
Marcus Moeller, RWTH Aachen University, Aachen, Germany
Jeremiah Morrissey, Washington University in St Louis School of Medicine, Saint Louis, Missouri, United States of America
Rosa Moysés, University of Sao Paulo, São Paulo, Brazil
David Nikolic-Paterson, Monash University Department of Medicine, Clayton, Victoria, Australia
Marina Noris, Mario Negri Institute for Pharmacological Research Aldo and Cele Daccò Center, Ranica, Italy
Ikechi Okpechi, University of Cape Town, Cape Town, South Africa
Mark Okusa, University of Virginia School of Medicine, Charlottesville, Virginia, United States of America
Juan Oliver, Columbia University, New York, New York, United States of America
Cristian Pattaro, European Academy, Bolzano, Italy
Aldo Peixoto, Yale University, New Haven, Connecticut, United States of America
Mark A. Perazella, Yale School of Medicine, New Haven, Connecticut, United States of America
Janos Peti-Peterdi, University of Southern California, Los Angeles, California, United States of America
Martin R. Pollak, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America
Ambra Pozzi, Vanderbilt University, Nashville, Tennessee, United States of America
Susan Quaggin, Samuel Lunenfeld Research Institute, Chicago, Illinois, United States of America
William B. Reeves, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America
Heather Reich, University of Toronto, Toronto, Ontario, Canada
Giuseppe Remuzzi, Negri Bergamo Laboratories, Bergamo, Italy
Connie Rhee, University of California Irvine, Irvine, California, United States of America
Mariano Rodriguez, Reina Sofia University Hospital, Cordoba, Spain
Paola Romagnani, University of Florence, Florence, Italy
Avi Rosenberg, National Institutes of Health, Bethesda, Maryland, United States of America
Michael J. Ross, Albert Einstein College of Medicine, Bronx, New York, United States of America
Robert Safirstein, Yale University, New Haven, Connecticut, United States of America
Frank van der Sande, Maastricht University Medical Centre+ Internal Medicine, Maastricht, Netherlands
Simone Sanna-Cherchi, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, United States of America
Mario Schiffer, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany
Johannes Schlondorff, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America
Kai Schmidt-Ott, Charite University Hospital Department of Nephrology and Internal Intensive Care Medicine, Berlin, New York, New York, USA
Stephan Segerer, Cantonal Hospital Aarau, Aarau, Switzerland
Kumar Sharma, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States of America
Natalie Staplin, University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom
Katalin Susztak, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, United States of America
Tetsuhiro Tanaka, The University of Tokyo Graduate School of Medicine Faculty of Medicine, Bunkyo-Ku, Japan
Sydney C. W. Tang, The University of Hong Kong, Pok Fu Lam, Hong Kong
Yoshio Terada, Kochi Medical School, Nankoku, Japan
Ravi Thadhani, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, United States of America
Pierre-Louis Tharaux, University of Paris, Paris, France
Joshua Thurman, University of Colorado, Denver, Colorado, United States of America
Jens Titze, Duke-NUS Medical School, Singapore, Singapore
Marcello Tonelli, University of Calgary, Edmonton, Alberta, Canada
Hernan Trimarchi, British Hospital of Buenos Aires, Buenos Aires, Argentina
Marc Vervloet, Amsterdam UMC VUMC Site, Amsterdam, Netherlands
Marina Vivarelli, Bambino Gesu Pediatric Hospital, Rome, Italy
Carsten Wagner, University of Zurich, Zurich, Switzerland
Angela Yee-Moon Wang, The University of Hong Kong, Department of Medicine, Hong Kong SAR, China
Donald E. Wesson, Baylor Scott & White Health, Dallas, Texas, United States of America
Jack Wetzels, Radboudumc, Nijmegen, Netherlands
Adam T. Whaley-Connell, University of Missouri, Columbia, Missouri, United States of America
Keng-Thye Woo, Singapore General Hospital, Singapore, Singapore

Motoko Yanagita, Kyoto University, Kyoto, Japan
Xueqing Yu, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangdong, China
Suzuki Yusuke, Juntendo University, Tokyo, Japan

GUIDE FOR AUTHORS

ABOUT THE JOURNAL

Informed consent and patient details

Studies on patients or volunteers require ethics committee approval and informed consent, which should be documented in the paper. Appropriate consents, permissions and releases must be obtained where an author wishes to include case details or other personal information or images of patients and any other individuals in an Elsevier publication. Written consents must be retained by the author but copies should not be provided to the journal. Only if specifically requested by the journal in exceptional circumstances (for example if a legal issue arises) the author must provide copies of the consents or evidence that such consents have been obtained. For more information, please review the Elsevier Policy on the Use of Images or Personal Information of Patients or other Individuals. Unless you have written permission from the patient (or, where applicable, the next of kin), the personal details of any patient included in any part of the article and in any supplementary materials (including all illustrations and videos) must be removed before submission.

Note: Manuscripts should be organized under the following 11 headings, **with the Methods appearing BEFORE the Results**: Graphical Abstract, Title page, Abstract, Translational Statement (only for Basic Research articles), Introduction, **Methods,** Results, Discussion, Disclosure statement, References, and Acknowledgements.

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Content should make no assumptions about the beliefs or commitments of any reader; contain nothing which might imply that one individual is superior to another on the grounds of age, gender, race, ethnicity, culture, sexual orientation, disability or health condition; and use inclusive language throughout. Authors should ensure that writing is free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions. We advise to seek gender neutrality by using plural nouns ("clinicians, patients/clients") as default/wherever possible to avoid using "he, she," or "he/she." We recommend avoiding the use of descriptors that refer to personal attributes such as age, gender, race, ethnicity, culture, sexual orientation, disability or health condition unless they are relevant and valid. When coding terminology is used, we recommend to avoid offensive or exclusionary terms such as "master", "slave", "blacklist" and "whitelist". We suggest using alternatives that are more appropriate and (self-) explanatory such as "primary", "secondary", "blocklist" and "allowlist". These guidelines are meant as a point of reference to help identify appropriate language but are by no means exhaustive or definitive.

Please add your Twitter Handle ("@+twitter user name") and ORCID (Open Researcher and Contributor ID) to your user account in manuscript central. If you don't have an ORCID, you can sign up for free at https://orcid.org/.

Frequency

Published monthly.

Impact factor

2019 Impact Factor: 8.945
6 of 85 journals in Urology & Nephrology

ISSN

ISSN: 0085-2538
EISSN: 1523-1755

Abstracted/indexed in

Index Medicus/Medline, Science Citation Index, Current Contents/Life Sciences, Current Contents/Clinical Medicine, SciSearch, BIOSIS, Chemical Abstracts, EMBASE, Reference Update, CABS, Biological Abstracts, Global Health, Adonis, PASCAL, Scopus

Publication charges

Page charges cover a proportion of the costs of processing and producing the article for publication. After final layout for publication, each page of basic research, landmark communication, technical notes, clinical investigation, and clinical trial articles will incur a fixed charge of US$165 per page.

Page charges do not apply to invited articles (commentaries, controversies in nephrology, editorials, mini reviews, nephrologists sans frontiers, next generation clinicopathological conference, policy forums, practice guidelines, research letters, reviews, and xyz of statistics).

Scope

Kidney International devotes itself to renal research. It aims to inform the renal researcher and the practicing nephrologist on all aspects of renal research. These include the latest clinical studies on emerging developments in renal medicine and the highest level of original research studies in clinical and basic renal research. In each issue some of these articles will be highlighted by **commentaries** that aim to put these studies in the appropriate context. These will form a research tool for clinical and basic investigators. **Nephrology Digest** comments and puts in perspective several areas of new developments in basic and clinical research in nephrology at large, as reported in the recent literature and at scientific meetings. **Editorials** highlight important issues in international nephrology. **Nephrology sans Frontières** are occasional short articles that discuss matters of local interest to nephrologists around the world, but which we feel need to be known by nephrologists worldwide. **In-depth reviews** are about major issues in renal research and controversial discussions on renal therapeutics or diagnosis written by two opposing authorities. **Nephrology Images** are presentations of interesting images in renal pathology; radiology chosen for their illustrative nature or simply for their esthetic qualities; issues of importance to the international renal community, including the politics of funding, of organ transplantation, of adequacy of dialysis, of worldwide affordability of end-stage renal care, and many other topical issues. **Journal Club** is a synopses that brings you the latest research highlights from across a wide spectrum of journals in fields relevant to renal research.

Reporting Guidelines

KI requires authors to completely, accurately, and transparently report their findings. Authors submitting articles to *KI* should refer to the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network website (http://www.equator-network.org/), which provides a central repository of reporting guidelines and other resources to assist authors.
Authors of the following study types are required to upload a copy of the corresponding checklist with their manuscript: CONSORT checklist and flow diagram for Randomized clinical trials STROBE checklist for Observational Studies (see modified STROBE Statement) PRISMA checklist and flow diagram for Systematic reviews and meta-analyses—interventional studies MOOSE checklist and flow diagram for Systematic reviews and meta-analyses—observational studies STARD checklist and flow diagram for Diagnostic accuracy studies COREQ for Qualitative research TRIPOD for Development and updating of predictive models CHEERS for Economic evaluation STARI statement and checklist for Implementation studies STREGA Checklist for studies that investigate Associations between genetic factors and clinical measurements or disease outcomes. These checklists help improve the quality and consistency of data reporting and assist reviewers in assessing the manuscript. Missing items or deviations should be explained by the authors.

KI encourages the use of PENELOPE for help with identification of the appropriate checklist for data reporting. This tool can be found at http://www.peneloperesearch.com/equatorwizard.

Peer Review

This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for *Kidney International*. Papers deemed suitable are then sent to at least two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. For more information on the types of peer review, please visit our peer-review site (https://www.elsevier.com/reviewers/peer-review).

Editor Disclosures

Kidney International follows the ICMJE Guidelines for Disclosures and Conflicts of Interest. Editors and editorial staff must not use information gained through working with manuscripts for private gain. Editor disclosure forms about potential conflicts of interests related to their own commitments are collected annually and kept on file in the editorial office. Authors and reviewers who require this information should contact the editorial office staff.

PREPARATION OF MANUSCRIPTS

Note: Manuscripts should be organized under the following 11 headings, **with the Methods appearing BEFORE the Results**: Graphical Abstract, Title page, Abstract, Translational Statement (only for Basic Research articles), Introduction, Methods, Results, Discussion, Disclosure statement, References, and Acknowledgements.

The *American Medical Association Manual of Style* (10th edition) should be used as a style guideline.

Manuscripts that do not adhere to the following instructions will be returned to the corresponding author for technical revision before undergoing peer review.

Types of articles

Review

Word limit: Reviews should be between 3,000 and 5,000 words, and on average 4,000 words, including abstract but excluding references, tables, and figures. Abstract: 250 words maximum.Keywords: 3–6References: 150 maximum.Figures/tables: 1–3 images or figures required.Disclosure statement required.Reviews are comprehensive analyses of specific topics in nephrology that are solicited by the Editors. Proposals for reviews should be submitted to the editorial office by email: pmorriss@wustl.edu. Authors should only send an outline of the proposed paper for initial consideration. Unsolicited reviews submitted directly to Manuscript Central will not be considered. All invited review articles will undergo peer review prior to decision, and there is no absolute guarantee of acceptance.

Original Article

Subcategories: Basic Research, Clinical Investigation.Word limit: 4,000 words (22,400 characters) maximum including spaces and abstract but excluding references, tables, and figures. Abstract: 250 words (1,500 characters) maximum including spaces.Keywords: 3–6.Results: Include headings about what is being tested in each individual experiment.References: no limit.Figures/tables: no limit. However, additional figures and tables may be considered as supplements for web-only publication.Disclosure statement required. Full-length reports of current research in either basic or clinical science. Data Sharing Statement—Large biological datasets Graphical Abstract required. See Graphical Abstract section for more details. Systematic Reviews: submit as an Original Article. Include PRISMA checklist and PRISMA flow diagram with submission.

Landmark Communication

The purpose of the *Landmark Communication* format is to publish concise but complete reports that present **high-quality findings of exceptional interest, novelty, transformative value, and broad significance for the readers of *Kidney International*.** This category can include manuscripts dealing with clinical, translational, or basic research.
Case Reports and Case series will not be reviewed unless they provide groundbreaking insights, for instance, identification of a new gene.
The accepted manuscripts will be highlighted in all *Kidney International* channels including social media, web page, and front matters.

A manuscript considered as a potential *Landmark Communication* by the Editors will be sent to referees with a request of rapid review. If the manuscript is deemed interesting but not of sufficiently transformative potential, authors may be asked to resubmit their revision as a regular article.

Landmark Communications differ from regular articles in that they should be arranged in the following order:Title page, Abstract and keywords, Introduction, Short Methods, Results, Discussion (no headings necessary), Disclosure statement required, Acknowledgments, References, Tables (each including a title and legend), and Figure legends. The abstract should be brief (no more than 150 words). The main text should be limited to 1,500 words (including the abstract but not the acknowledgments, references, tables, and figure legends). These manuscripts normally have **no more than 3 display items** (Figure and/or Table—uploaded as individual files), and **25 references**. The study design, detailed methods, and/or supporting data should be included in **Online Supplementary Material** (each file uploaded separately).

Technical Note

Word limit: 1,500 words (8,400 characters) maximum including abstract but excluding references, tables, and figures.Abstract: 250 words (1,500 characters) maximum including spaces.Keywords: 3–6.References: 20 maximum.Disclosure statement required.Examples of appropriate subject matter

include descriptions of new laboratory or clinical methods, new apparatus, or critical modifications of established techniques. Organization of Technical Notes should be the same as for regular manuscripts.

Research Letter
Research Letters in *Kidney International* report results of studies similar to original investigations. Research Letters do not have abstracts and have online-only supplementary materials. Due to space restrictions, methods are straightforward or use data sources that can be referenced, statistical methods are not complicated, and interpretation is straightforward. Research Letters may involve pilot studies, or research focused on a few critical findings. Research Letters are cited in PubMed and are an effective way for authors to have concise, focused reports published in a high-profile journal. Both clinical and translational papers may be included in this category. Short original research reports—approximately 1,200 words. Word limit: 1,200 words. No abstract required.Graphical Abstract required. See Graphical Abstract section for more details. Methods must be provided as a separate supplementary file and must be excluded from the main manuscript. Provide all supplementary material in a single PDF and cite the individual supplementary material elements in the main text (e.g., Supplementary Methods, Supplementary References, etc.). In the main article in a Supplementary Material section immediately before the references, state the type of supplementary file [e.g., "Supplementary File (PDF)"] and the title "Supplementary Methods." Disclosure statement required.References: 9 maximum. Additional references must be provided in a separate supplementary file and formatted as supplementary references with the prefix "S" (e.g., S1, S2, etc.). In the main article in a Supplementary Material section immediately before the references, state the type of supplementary file [e.g., "Supplementary File (PDF)"] and the title "Supplementary References." Figures/tables: Limit of 2 tables and/or figures. Additional tables/figures should be provided in PDF format as Supplementary Material.

Clinical Trials
Word limit: 4,000 words (22,400 characters) maximum including spaces and abstract but excluding references, tables, and figures.Abstract: 250 words (1,500 characters) maximum including spaces.Keywords: 3–6.Results: Include headings about what is being tested in each individual experiment.References: no limit.Figures/tables: no limit. However, additional figures and tables may be considered as supplements for web-only publication. Disclosure statement required. Data Sharing Statement—Large biological datasets
Kidney International follows the ICMJE's data sharing statement policy for all clinical trials. To foster transparency, we require you to state the availability of your data in your manuscript. This may be a requirement of your funding body or institution. If your data are unavailable to access or unsuitable to post, you will need to indicate why, for example by stating that the research data are confidential. The statement will appear with your published article. For more information, visit the Data Statement page.Full-length reports of current research in either basic or clinical science.
Please read the Special Notice Regarding Clinical Trials below.

Special notice regarding clinical trials
As defined by the International Committee of Medical Journal Editors (ICMJE), a clinical trial is any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. A medical intervention is any intervention used to modify a health outcome and includes but is not limited to drugs, surgical procedures, devices, behavioral treatments, and process-of-care changes. A trial must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration. Nonrandomized trials are not exempt from the registration requirement if they meet the above criteria.

All clinical trials must be registered in a public registry prior to submission. The journal follows the trials registration policy of the ICMJE (http://www.icmje.org) and considers only trials that have been appropriately registered before submission, regardless of when the trial closed to enrollment. Acceptable registries must meet the following ICMJE requirements:be publicly available, searchable, and open to all prospective registrants;have a validation mechanism for registration data; andbe managed by a not-for-profit organization.

Examples of registries that meet these criteria include:the registry sponsored by the United States National Library of Medicine (http://www.clinicaltrials.gov),the International Standard Randomized Controlled Trial Number Registry (http://www.controlled-trials.com),the Cochrane Renal Group Registry (http://www.cochrane-renal.org), andthe European Clinical Trials Database (https://eudract.ema.europa.eu).
The trial registry number for eligible papers will be collected during the submission process.

Randomized Controlled Trials (RCTs) must adhere to the CONSORT statement (CONsolidated Standards Of Reporting Trials), and submissions must be accompanied by a completed CONSORT checklist (uploaded as a related manuscript file). Further information can be found at http://www.consort-statement.org.

Commentary (by invitation only)
Word limit: 1,500 words (8,400 characters) maximum including spaces and abstract but excluding references.Title: 115 characters maximum including spaces.Abstract: 75 words (420 characters) maximum.References: 9 maximum including the article discussed.Figures/tables: 1 figure required (will be redrawn).Commentaries discuss a paper published in a specific issue and should set the problems addressed by the paper in the wider context of the field. Disclosure statement required.

Letter to the Editor
Word limit: 250 words (1,500 characters) maximum including spaces.Abstract: no abstract required for this manuscript type.References: 4 maximum.Figures/tables: up to 1.Letters to the Editor will be considered for publication, subject to editing. Letters must contain information critical to a certain area or must be confirmatory of data recently published in *Kidney International*. A Letter must reference the original source, and a Response to a Letter must reference the Letter in the first few paragraphs, as well as the original source. Letters can use an arbitrary title, but a Response must cite the title of the Letter: e.g., Response to [title of Letter]. All Letters must contain a title page including title, all authors' names and affiliations, and corresponding author contact information.Note that *KI* does not accept Letters to the Editor regarding Nephrology Digest articles.

Editorial (by invitation only)
Word Limit: 1,600 words (8,960 characters) maximum including spaces.Abstract: no abstract required for this manuscript type.Keywords: 3–6.References: 5 maximum.Proposals for Editorials may be submitted; authors should only send an outline of the proposed paper for initial consideration.

Nephrology Image
Word limit: title: 70 characters including spaces; text: 300 words (1,700 characters) including spaces.Figures: The equivalent of 2 single-panel figures maximum. Additional figures may be included as supplementary images that will appear online but not in print. References: none.Abstract: no abstract required for this manuscript type.Illustrative images that are unique or highly illustrative of specific occurrences in nephrology such as renal pathology, radiology, specific-skin lesions, etc. They should be accompanied by a brief 1-paragraph description of relevant clinical information. Article must fit onto 1 page. You will be asked to cut text or part of your figure in the proof if the article is longer than 1 page.

Make Your Diagnosis
Word limit: title: 70 characters; The Case (page 1): 245 words (1,400 characters); The Diagnosis (page 2): 405 words (2,300 characters). Word limits include spaces but exclude references, tables, and figures.Abstract: no abstract required for this manuscript type.References: 3 maximum.Figures/tables: 1 single-panel figure maximum per page.This column provides readers with an opportunity to make clinical diagnoses based on an image accompanied by the history and physical exam, all of which will be on the first page. The second page will include the answers, a brief discussion, and any other relevant follow-up images and laboratory data.

Meeting Report (by invitation only)
Proceedings of meetings are solicited by the Editors, and the Meeting Report will undergo peer review.Word limit: 3000 words.Abstract: Unstructured, maximum of 150 words. Keywords: 3–6.Disclosure statement required. References: Maximum 50, should be important for establishing background of work discussed or published work from the meeting. General Structure: Provide an introduction that describes the purpose and context of the meeting. Identify the themes developed in the meeting and devote one section to each theme. The themes will serve as headings for the sections. Under each theme heading, highlight one presentation of particular significance. Within a theme, develop a figure or table that summarizes the rest or most of the rest of the presentations.

After the meeting themes and new ideas are presented, provide a section that summarizes where the field is currently, ongoing controversies in the field, and recommendations for future directions in the field.

Nephrologists sans Frontières (by invitation only)
Word limit: 1,500 words.Abstract: no abstract required for this manuscript type.Keywords: 3–6.References: no more than 9.Figures/tables: 1.

Policy Forum
Word limit: 1,500 words.Abstract: none.Keywords: 3–6.References: no more than 9.COI: A short disclosure statement is required.

Nephrology Digest (by invitation only)
Word limit: 600–900 words excluding references.Title: 100 characters maximum including spaces.Keywords: 3–6.References: 9 maximum including the article or presentation discussed.Figures/tables: 1 figure or table (figures may be redrawn).Nephrology Digests discuss a recent development in the field published or presented outside of *Kidney International* and should frame the issue in the wider context of the field. Nephrology Digest may also provide a forum for commentary on broader issues of relevance to research or clinical care in nephrology.Authors will not be charged for color images.Disclosure statement required.

Next Generation Clinicopathological Conference (by invitation only)
Word limit: No more than 2,500 words, excluding references and figures.No abstract.Keywords: 3–6.References: 9 maximum.Figures: 4–5.Disclosure statement required.

Format of Manuscripts

Manuscripts must be typed in English and double-spaced. All text including legends, footnotes, tables, and references are to be on one side of the page only. All manuscript pages must be numbered.

Open access

Please visit our Open Access page for more information.

Language (usage and editing services)
Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service available from Elsevier's Author Services.

Use of word processing software
It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required. Figures should not be embedded in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Title page

This should include (a) the complete manuscript title; (b) all authors' full names (listed as first name, middle initial, last name), highest academic degrees, and affiliations; (c) the name and address for correspondence, fax number, telephone number, and e-mail address; and (d) the sources of support that require acknowledgment. A running headline of no more than 50 characters (including spaces) should be supplied.

Abstract

The abstract should be no longer than 1,500 characters including spaces, stating the main problem, methods, results, and conclusions. There should be no subheadings in the abstract. It must be factual and comprehensive. The use of abbreviations and acronyms should be limited and general statements (e.g., “the significance of the results is discussed”) should be avoided. The editors reserve the right to edit the title and abstract to conform to journal style.

The abstract should state briefly the purpose of the research, the principal results, and major conclusions. An abstract is often presented separately from the article, so it must be able to stand alone. For this reason, references should be avoided, but if essential, then cite the author(s) and year(s). Also, nonstandard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Graphical Abstract

A Graphical Abstract graphical abstract is now mandatory for *Kidney International*. The Graphical Abstract should summarize the contents of the article in a concise, colorful pictorial form that appeals to the online publication format. It will help readers understand the take-home message of the paper, encourage browsing, and promote interdisciplinary scholarship. Authors must provide an original graphic separate from figure(s) in the paper that clearly represents the work described, preferably saved as a PowerPoint (.ppt) file.

Graphical abstracts should be submitted at the time of revision as a separate image file in the ScholarOne manuscript submission system. We prefer that you create your Graphical Abstract using the PowerPoint template provided. If you choose to create an image without the template provided, be sure to follow the specifications indicated below.

Graphical Abstracts are subject to editorial review for accuracy and quality but will be published as provided without copy editing once they have been accepted for publication.

Specifications:
The Graphical Abstract should be a single file that summarizes the research findings using colorful images rather than text. For ease of browsing, the Graphical Abstract should have a clear start and end, preferably "reading" from top to bottom or left to right. Avoid cluttering elements or images. Refer to Graphical Library in the PowerPoint template for optional layout options. **Image size**: If using PowerPoint, size slide for widescreen (16:9 ratio) with high-resolution images (minimum of 300 dpi, preferably 600 dpi). If using another program, provide images with a minimum of 531 × 1328 pixels (H×W) and a minimum resolution of 300 dpi. For larger images, use 200 × 500 pixels (HxW). **Font**: Arial or Calibri fonts only with 18-pt size or larger. **File type**: preferred file types are PowerPoint, TIFF, or EPS. Save the image file name as Graphical Abstract for uploading. Do not include a heading "Graphical Abstract" within the image file. Use exact title of accepted manuscript as the title. Place author's last name and the year of publication at the bottom. Place major conclusion or take-away point within in a "Conclusion" box.

Find icons and/or pictograms to use in Graphical Abstracts from unaffiliated services such as: The Noun Project Mindthegraph.com Canva.com Piktochart.com Easel.ly Infogram.com
Ensure that you follow all applicable attributions and licenses when using these services.

Authors can make use of Elsevier's Illustration Services for a fee at https://webshop.elsevier.com/illustration-services/ to ensure the best presentation of your image is in accordance with all technical requirements.**Examples:**
Following are some examples of Graphical Abstracts using the *Kidney International* template, originally designed for the ISN by Edgar Lerma, Divya Bajpai, Krishna Penmatsa, Aakash Shingada, and Fernanda Arce-Amaré, and modified for use in *KI*.

Translational Statement (only for Basic Research articles)

The Editors require a short paragraph on the translational impact of your study. Please include this paragraph of no more than 100 words under the heading "Translational Statement" and place it in the manuscript following the abstract for editorial review. The Translational Statement should describe how you envision your work affecting clinical care now or in the future and could include a statement on next steps. The goal of this new feature is to make your basic science accessible to all of the Journal's readership by putting it in the context of clinical care. Please note that the Translational Statement may be disseminated after publication to highlight your work.

Text

The manuscript should be organized under the following 11 headings:Graphical AbstractTitle pageAbstractTranslational Statement (only for Basic Research articles)IntroductionMethodsResultsDiscussionDisclosure statementReferencesAcknowledgements

Abbreviations

Abbreviations should be defined at first mention in the text and in each table and figure. For a list of standard abbreviations, please consult the Council of Biology Editors Style Guide (available from the Council of Science Editors, 9650 Rockville Pike, Bethesda, MD 20814) or other standard sources. Write out the full term for each abbreviation at its first use unless it is a standard unit of measure. Refrain from overuse of abbreviations.

Disclosure

For original articles, technical notes, commentaries, and reviews, the submitting author must include a disclosure statement in the body of the manuscript. The statement will describe all of the authors' relationships with companies that may have a financial interest in the information contained in the manuscript. This information should be provided under the heading titled “Disclosure”, which should appear after the Discussion section and before the References section. The absence of any interest to disclose must also be stated. In addition, any financial interests must be detailed in the Financial Disclosure form, which must be uploaded for each author upon submission. It is the responsibility of each author to provide complete and accurate financial and consulting information.

References

References should be listed in order of appearance (AMA style). Indicate references by (consecutive) superscript Arabic numerals in the order in which they appear in the text. The numerals are to be used outside periods and commas, inside colons and semicolons. For further detail and examples you are referred to the AMA Manual of Style, A Guide for Authors and Editors, Tenth Edition, ISBN 0-978-0-19-517633-9 (see http://www.amamanualofstyle.com).

The reference list (starting on a separate page) should contain the references in the order in which they are cited in the text. Only published works (as well as manuscripts already accepted for publication) which are referred to in the text should be listed in the reference list. The reference list must not contain any abstract citations, unpublished observations, personal communications, etc. Kindly cite such sources solely within the text (in parentheses), not in the reference list. Do not list more than 3 authors per reference. Should there be 4 or more, please include only the first 3 followed by "et al."

Please do not use reference linking software such as EndNote to format the citations and references. Please type them manually. If you use reference management software, please ensure that you remove ALL field codes before submitting the electronic manuscript. Please note that once you remove all hidden codes and unlink the field codes, you can no longer reformat or unformat the citations or bibliography, so always make a copy of your document prior to removing any codes. When using EndNote, you may use the EndNote tool to remove field codes, or you many manually remove the codes: Make a copy of the final manuscript. From the File menu in Word, select the Save As command. Give the file a new name. In the new file, hit CTRL+A to select all. Press Ctrl+Shift+F9 or Cmd+6 to unlink all fields. The in-text citations and bibliography become regular text, without field codes or any hidden links.
If authors still have questions about removing the field codes, technical support is available free of charge. The link to reach support is http://endnote.com/support.

Citation in text

Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Reference links

Increased discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links to abstracting and indexing services, such as Scopus, CrossRef and PubMed, please ensure that data provided in the references are correct. Please

note that incorrect surnames, journal/book titles, publication year and pagination may prevent link creation. When copying references, please be careful as they may already contain errors. Use of the DOI is highly encouraged.

A DOI is guaranteed never to change, so you can use it as a permanent link to any electronic article. An example of a citation using DOI for an article not yet in an issue is: VanDecar J.C., Russo R.M., James D.E., Ambeh W.B., Franke M. (2003). Aseismic continuation of the Lesser Antilles slab beneath northeastern Venezuela. Journal of Geophysical Research, https://doi.org/10.1029/2001JB000884. Please note the format of such citations should be in the same style as all other references in the paper.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data References
Please cite underlying or relevant datasets in your text and include said references in your Reference List. Data references should include the following: author name, title, repository, version, persistent identifier, year. Add the word "dataset" in brackets (i.e., [dataset]) immediately before the reference so that it can be properly identified. This identifier will not appear in your published article.

List
Number the references in the list in the order in which they appear in the text.

Examples
Reference to a journal publication:
1. Fan SL, Almond MK, Ball E, et al. Pamidronate therapy as prevention of bone loss following renal transplantation. *Kidney Int*. 2000;57:684–690.

Reference to a supplement article:
2. Fogo AB. Glomerular hypertension abnormal glomerular growth, and progression of renal diseases. *Kidney Int*. 2000;57(suppl 75):S15–S21.

Reference to a book:
3. Lameire N, Mehta RL, eds. *Complications of Dialysis*. New York, NY: Marcel Dekker, Inc; 2000.

Reference to a chapter in an edited book:
4. Weidner N, Buckalew VM Jr. Sickle cell anemia, sickle cell trait, and polycythemic states. In: Tisher CC, Brenner BM, eds. *Renal Pathology*. Vol 2. Philadelphia, PA: JB Lippincott Company; 1989:1417–1436.

Reference to a dataset:
[dataset] 5. Oguro M, Imahiro S, Saito S, et al. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.

Preprint references
Where a preprint has subsequently become available as a peer-reviewed publication, the formal publication should be used as the reference. If there are preprints that are central to your work or that cover crucial developments in the topic, but are not yet formally published, these may be referenced. Preprints should be clearly marked as such, for example by including the word preprint, or the name of the preprint server, as part of the reference. The preprint DOI should also be provided.

Journal abbreviations source
Journal names should be abbreviated according to the List of Title Word Abbreviations.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

ORIGINALITY

Submission declaration and verification

Submission of an article implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see https://www.elsevier.com/sharingpolicy), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. Permission for use within the submitted manuscript of any text, figures, tables, or data from other sources must be granted to the author, and must be on file prior to publication. If a modified, redrawn, or adapted figure is substantially similar to the original figure, permission from the original source is required. A simple color change or change of labels on an X and Y axis is not sufficient. Even in the rare circumstances where a figure has been modified, redrawn, or adapted enough so as not to require permission, the original source of the figure should nonetheless be acknowledged (e.g. ”Based on…“). When re-using a ”courtesy image“ from a non-Elsevier product, or from one Elsevier product in a different Elsevier product, permission must be obtained directly from the named individual or institution. To verify originality, your article may be checked by the originality detection service CrossCheck https://www.elsevier.com/editors/plagdetect.

KI accepts preprint manuscript submissions directly from medRxiv and bioRxiv through the M2J and B2J direct transfer partner program. This program can save authors time in submitting papers to the journal by transmitting their manuscript files and metadata directly from medRxiv or bioRxiv. This means authors do not have to spend time re-loading manuscript files and re-entering author information during submission. Authors can visit https://www.medrxiv.org/submit-a-manuscript or https://www.biorxiv.org/submit-a-manuscript to submit their preprint and then request transfer to *KI*.

Authorship

Requirements for all categories of articles should conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," developed by the ICMJE (http://www.icmje.org).

Each author must have contributed sufficiently to the intellectual content of the submission. The corresponding author should list all authors and their contributions to the work. The corresponding author must confirm that he or she has had full access to the data in the study and final responsibility for the decision to submit for publication. To qualify as a contributing author, one must meet all of the following criteria: Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results.Drafted or revised the manuscript.Approved the final version.Contributions by individuals who made direct contributions to the work but do not meet all of the above criteria should be noted in the Acknowledgments section of the manuscript. Medical writers and industry employees can be contributors. Their roles, affiliations, and potential conflicts of interest should be included in the author list or noted in the Acknowledgments and/or Contributors section concurrent with their contribution to the work submitted. Signed statements from any medical writers or editors declaring that they have given permission to be named as an author, as a contributor, or in the Acknowledgments section is also required. Failure to acknowledge these contributors can be considered inappropriate, which conflicts with the journal's editorial policy.

Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with *Kidney International*, its editors, the International Society of Nephrology, or Elsevier.

Changes to authorship

This policy concerns the addition, deletion, or rearrangement of author names in the authorship of accepted manuscripts:
Before the accepted manuscript is published in an online issue: Requests to add or remove an author, or to rearrange the author names, must be sent to the Journal Manager from the corresponding author of the accepted manuscript and must include: (a) the reason the name should be added or removed, or the author names rearranged and (b) written confirmation (e-mail, fax, letter) from all authors that they agree with the addition, removal or rearrangement. In the case of addition or removal of authors, this includes confirmation from the author being added or removed. Requests that are not sent by the corresponding author will be forwarded by the Journal Manager to the corresponding author, who must follow the procedure as described above. Note that: (1) Journal Managers will inform the Journal Editors of any such requests and (2) publication of the accepted manuscript in an online issue is suspended until authorship has been agreed.

After the accepted manuscript is published in an online issue: Any requests to add, delete, or rearrange author names in an article published in an online issue will follow the same policies as noted above and result in a corrigendum.

Ethics in publishing

Please see our information on Ethics in publishing.

This journal is a member of, and subscribes to the principles of, the Committee on Publications Ethics (COPE) http://www.publicationethics.org.

Human and animal rights

If the work involves the use of animal or human subjects, the author should ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-invol EU Directive 2010/63/EU for animal experiments http://ec.europa.eu/environment/chemicals/lab_animals/legislation_en.htm; Uniform Requirements for manuscripts submitted to Biomedical journals http://www.icmje.org, and in the case of renal transplant the Declaration of Istanbul (as published in KI Vol. 74 No. 7 [2008]). *Kidney International* will not consider manuscripts containing data derived from transplants obtained from executed prisoners. If authors wish to submit a manuscript related to this issue such as an editorial or review examining the consequences of such practices, they must contact the Editorial Office to obtain permission prior to submitting the manuscript. All manuscripts dealing with transplanted patients must conform to the Declaration of Istanbul and be acknowledged in the submission questions by ticking the appropriate box. In addition, a statement that "the paper adheres to the Declaration of Istanbul" must be placed in the Methods section, and the source of donor kidneys must be clearly identified in the Methods section of the paper as well. Authors should include a statement in the manuscript that informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects must always be observed.

Guidelines for studies of DNA polymorphisms

For case-control studies investigating associations between DNA sequence polymorphisms and renal phenotypes, the following review criteria will be considered in prioritizing manuscripts for publication:Adequate sample size and explicit power calculation are required for all submitted manuscripts. Negative studies have to be adequately powered in order to be considered for publication.Appropriate correction of *P* values for multiple comparisons is also required. In many cases this will involve calculation of empiric *P* values by permutation.Typing multiple markers within a locus of interest is preferred over studies that examine a single polymorphism. Defining risk haplotypes and performing haplotypic association tests is encouraged.Assessment and correction for possible population stratification are strongly encouraged, unless the analysis involves a method that is robust to stratification effects (e.g., transmission-disequilibrium testing).Replication of the association in an independent cohort is required for new association findings.Priority will be given to studies that demonstrate a specific effect of the associated polymorphism on the expression or function of the relevant genes. A convincing biological validation will be considered in lieu of the replication requirement.

Microarray data

Authors submitting manuscripts containing microarray data must submit the data to the Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/) or ArrayExpress (http://www.ebi.ac.uk/arrayexpress/) databases and provide the accession number(s) upon submission to the journal. The data must be MIAME-compliant, with all variables completed.

Biomarker Guidelines

Background: The field of biomarkers is continuously expanding for all disease states, including kidney disease. Over the last two decades, a number of novel and traditional biomarkers have been discovered and tested in the setting of kidney disease with a wide a range disease spectrum. There are also an increasing number of cohort studies and randomized clinical trials examining kidney-related outcomes providing a rich environment for biomarker testing. In order to select and publish the most impactful papers on this subject, it is necessary to set some criteria that standardize the quality of manuscripts submitted to *Kidney International* and *Kidney International Reports*.

The biomarker manuscript could include one or more of the following features: diagnostic, prognostic, or mechanistic (relevant to disease pathogenesis).

The biomarker(s) under study could be in one of the following phases: Early phases include both discovery and proof-of-concept studies (phase 1) demonstrating differences in biomarker levels between patients with and without the outcome of interest (i.e., CKD, AKI, and CVD) and prospective studies (phase 2) to determine the association between levels, disease behavior, and future outcomes. Later phases consider aspects of clinical incorporation, including determining the incremental predictive value of a candidate marker beyond established risk predictors (phase 3) and if biomarker use changes therapy for at-risk patients, improves outcomes, and is cost-effective (phases 4 to 6).
Proposed evaluation criteria for biomarker studies submitted to *KI* for publication: Early-phase (discovery or POC) studies should include a novel biomarker with a well-defined case control or cohort design and a validation cohort that is linked to the exposure or endpoint being measured, or a novel discovery biomarker with potential mechanistic relevance. Later-phase (clinical) studies should outperform traditional risk factors in diagnosing the disease, or add prognostic information over and above the combined information obtained from all other known predictors at both the group- and individual-patient level, or prove that the biomarker(s) are cost-effective, and preferably include a validation cohort.

Data Sharing Statement—Large biological datasets

Kidney International endorses the FAIR (findable, accessible, interoperable and re-usable) Data Principles as a framework to promote the broadest reuse of research data. We strongly encourage the authors to deposit large datasets based on DNA (e.g., GWAS, next-generation sequencing), RNA (e.g., micro-arrays, RNASeq), metabolomics, proteomics, etc., in an appropriate public repository. For instance, microarray data should be deposited in an MIAME-compliant database. The deposited datasets should include the primary data and appropriate summary statistics. Relevant accession numbers and links to these datasets should appear in the Methods section of the accepted manuscript. Restrictions of data access may exist for ethical and security considerations, data protection issues, or data obtained from a third party.
A "Data availability statement" should appear at the end of the manuscript.

Data availability statement Sample statement(s):
The data supporting the findings of this study are openly available in repository (XXXName) at URL/DOI, reference number (if any).
The data were derived from the following resources available in the public domain: [list resources and URLs].

Machine Learning Methodologies
Papers that use machine learning methodologies **must** provide details of the following: training datasets, information of the cross-validation sets, and performance (discrimination and calibration) of both the test and validation sets and not just the error/accuracy rates alone.
An external, independent test set is **strongly encouraged.**

Authors must also provide the editors and reviewers, upon request, all custom computer codes and algorithms that were used to generate the data. Upon publication, it is also desirable to release the custom codes that allow readers to repeat and replicate the steps involved in the generation of the data and the datasets.

Style

The American Medical Association Manual of Style (10th edition), Stedman's Medical Dictionary (27th edition) and Merriam Webster's Collegiate Dictionary (10th edition) should be used as standard references. Refer to drugs and therapeutic agents by their accepted generic or chemical name, and do not abbreviate them (a proprietary name may be given only with the first use of the generic name). Code numbers should be used only when a generic name is not yet available (the chemical name and a figure giving the chemical structure of the drug are required). Copyright or trade names of drugs should be capitalized and placed in parentheses after the name of the drug. Names and locations (city and state in USA; city and country outside USA) of manufacturers of drugs, supplies, or equipment cited in a manuscript are required to comply with trademark law and should be provided in parentheses. Quantitative data may be reported in the units used in the original measurement, but SI units are preferred, including those applicable to body weight, mass (weight), and temperature.

Journal style

As the electronic submission will provide the basic material for typesetting, it is important that papers and artwork are prepared in the general editorial style of the journal.Each figure file must contain the term "Figure" and the figure number: Figure1.tif. For information on labeling figures, see the artwork guidelines:https://www.elsevier.com/artworkinstructions.Do not make rules in figures thinner than 1 pt (0.36 mm).Use a coarse hatching pattern rather than shading for tints in graphs.Color in figures should be distinct when used as an identifying tool.Use SI units throughout.Spaces, not commas, should be used to separate thousands.Abbreviations should be preceded by the words for which they stand in the first instance of use in the text. Overuse of abbreviations in the text is discouraged.**No abbreviations should be used in the title or the abstract.**The abstract should be written as a single paragraph; do not include headings.Text should be double spaced with a wide margin.

Units

Follow internationally accepted rules and conventions: use the international system of units (SI). If other units are mentioned, please give their equivalent in SI.

Artwork

Electronic artwork

*General points*Make sure you use uniform lettering and sizing of your original artwork.Embed the used fonts if the application provides that option.Aim to use the following fonts in your illustrations: Arial, Courier, Times New Roman, or Symbol, or use fonts that look similar.Number the illustrations according to their sequence in the text.Use a logical naming convention for your artwork files.Provide captions to illustrations separately.Size the illustrations close to the desired dimensions of the published version.Submit each illustration as a separate file. *Style points* Add lowercase part labels a, b, c, etc., to figure panels. Do not include parentheses. Set y- and x-axis labels in sentence case. Change day to d, months to mo, mL to ml, dL to dl, L to l, hours to h. Change letters to Greek symbols where applicable, e.g., use β instead of English letter "B." Remove commas from thousands. Change P in P value to italicized and capitalized *P*, insert space on both sides of operator, and insert zero before decimal point, eg, $P < 0.01$. Use letters, not symbols or numbers, for footnotes Mask out personal identifiers. Remove register mark.

Please be mindful that histological images look darker in print than online so please ensure they are submitted in as bright a format as possible.

All microscopy figures must contain scale bars, which must be defined in the legends.

It is strongly encouraged that data be displayed in their raw form and not in a way that conceals their distribution. We recommend that individual data be presented as dot plots next to the average for the group with appropriate error bars, as shown in this sample from *PLOS Biology*. Presenting data as columns with error bars (dynamite plunger plots) is NOT ALLOWED.

For Western blots and other gels, uncropped, annotated, full-length images with MW markers should be submitted as "Review Files" together with the figures at the time of the first submission. These full-length images will be used by the reviewers during the reviewing process but will not be published. *Kidney International* reserves the right to assess digital figures with image forensics software.

A detailed guide on electronic artwork is available on our website: https://www.elsevier.com/artworkinstructions. **You are urged to visit this site; some excerpts from the detailed information are given here.** Our policy is that no specific feature within an image may be enhanced, obscured, moved, removed, or introduced. Adjustments of brightness, contrast, or color balance are acceptable if and as long as they do not obscure or eliminate any information present in the original. Manipulating images for improved clarity is accepted, but manipulation for other purposes could be seen as scientific ethical abuse and will be dealt with accordingly.

Formats

If your electronic artwork is created in a Microsoft Office application (Word, PowerPoint, Excel) then please supply 'as is' in the native document format.

Regardless of the application used other than Microsoft Office, when your electronic artwork is finalized, please 'Save as' or convert the images to one of the following formats (note the resolution requirements for line drawings, halftones, and line/halftone combinations given below):EPS (or PDF): Vector drawings, embed all used fonts.TIFF (or JPEG): Color or grayscale photographs (halftones),

keep to a minimum of 300 dpi.TIFF (or JPEG): Bitmapped (pure black & white pixels) line drawings, keep to a minimum of 1,000 dpi.TIFF (or JPEG): Combinations bitmapped line/halftone (color or grayscale), keep to a minimum of 500 dpi.
Please do not: supply files that are optimized for screen use (e.g., GIF, BMP, PICT, WPG); these typically have a low number of pixels and limited set of colors; supply files that are too low in resolution; and submit graphics that are disproportionately large for the content.

Color artwork
Please make sure that artwork files are in an acceptable format (TIFF (or JPEG), EPS (or PDF) or MS Office files) and with the correct resolution. If, together with your accepted article, you submit usable color figures then Elsevier will ensure, at no additional charge, that these figures will appear in color online (e.g., ScienceDirect and other sites) in addition to color reproduction in print. Further information on the preparation of electronic artwork.

Illustration services
Elsevier's Author Services offers Illustration Services to authors preparing to submit a manuscript but concerned about the quality of the images accompanying their article. Elsevier's expert illustrators can produce scientific, technical and medical-style images, as well as a full range of charts, tables and graphs. Image 'polishing' is also available, where our illustrators take your image(s) and improve them to a professional standard. Please visit the website to find out more.

Figure captions
Ensure that each illustration has a caption. Supply captions separately, not attached to the figure. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used. Use scale markers in the image for electron micrographs and indicate the type of stain used.

Text graphics
Text graphics may be embedded in the text at the appropriate position. See further under Electronic artwork.

Tables
Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules. Place explanatory matter of tables in the footnotes rather than in the titles.

Video
Elsevier accepts video material and animation sequences to support and enhance your scientific research. Authors who have video or animation files that they wish to submit with their article are strongly encouraged to include links to these within the body of the article. This can be done in the same way as a figure or table by referring to the video or animation content and noting in the body text where it should be placed. All submitted files should be properly labeled so that they directly relate to the video file's content. In order to ensure that your video or animation material is directly usable, please provide the file in one of our recommended file formats with a preferred maximum size of 150 MB per file, 1 GB in total. Video and animation files supplied will be published online in the electronic version of your article in Elsevier Web products, including ScienceDirect. Please supply 'stills' with your files: you can choose any frame from the video or animation or make a separate image. These will be used instead of standard icons and will personalize the link to your video data. For more detailed instructions please visit our video instruction pages. Note: since video and animation cannot be embedded in the print version of the journal, please provide text for both the electronic and the print version for the portions of the article that refer to this content.

Supplementary material
Supplementary material such as applications, images and sound clips, can be published with your article to enhance it. Submitted supplementary items are published exactly as they are received (Excel or PowerPoint files will appear as such online). Please submit your material together with the article and supply a concise, descriptive caption for each supplementary file. If you wish to make changes to supplementary material during any stage of the process, please make sure to provide an updated file. Do not annotate any corrections on a previous version. Please switch off the 'Track Changes' option in Microsoft Office files as these will appear in the published version.

Data linking
If you have made your research data available in a data repository, you can link your article directly to the dataset. Elsevier collaborates with a number of repositories to link articles on ScienceDirect with relevant repositories, giving readers access to underlying data that gives them a better understanding of the research described.

There are different ways to link your datasets to your article. When available, you can directly link your dataset to your article by providing the relevant information in the submission system. For more information, visit the database linking page.

For supported data repositories a repository banner will automatically appear next to your published article on ScienceDirect.

In addition, you can link to relevant data or entities through identifiers within the text of your manuscript, using the following format: Database: xxxx (e.g., TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Supplementary information is peer-reviewed material directly relevant to the conclusion of an article that cannot be included in the printed version owing to space or format constraints. It is posted on the journal's web site and linked to the article when the article is published and may consist of data files, graphics, movies, or extensive tables. The printed article must be complete and self-explanatory without the supplementary information. Supplementary information enhances a reader's understanding of the paper but is not essential to that understanding. Supplementary information must be supplied to the editorial office in its final form for peer review. On acceptance, the final version of the peer-reviewed supplementary information should be submitted with the accepted paper. To ensure that the contents of the supplementary information files can be viewed by the editor(s), referees, and readers, please also submit a 'read-me' file containing brief instructions on how to use the file.

If your manuscript or any significant part of it has been under consideration for publication elsewhere, or has appeared elsewhere in a manner that could be construed as a prior or duplication publication of the same, or very similar, work, the said material must be included and marked appropriately as a supplemental file.

Authors should ensure that supplementary information is supplied in its FINAL format as it is not copyedited and will appear online exactly as originally submitted. It cannot be altered, nor can new supplementary information be added, after the paper has been accepted for publication. Please supply the supplementary information via the electronic manuscript submission and tracking system, in an acceptable file format.

Please provide a single PDF or Word file that contains all supplementary items, with the exception of a large data file or supplementary movies, which may be provided as individual files. The term "Supplementary" should be included in the supplementary file name. Supplementary Figures should contain a legend in addition to the figure. Supplementary Tables should include a table title in addition to the table. Supplementary Movies should include a movie legend. Please use the S prefix (e.g., Figure S1, Table S1, Movie S1) to differentiate the material from that of the regular article. All supplementary references should start with the "S" prefix to be differentiated from regular references. Copy and paste the supplementary figure legends, supplementary table titles, supplementary movie legends, and description of other supplementary material (e.g., Supplementary Data Set, Supplementary Methods, Supplementary References, etc.) into the manuscript file under the "Supplementary Material" heading and before the references.

SUPPLEMENTARY MATERIAL Supplementary File (PDF) **Supplementary Methods. Figure S1.** [Entire figure legend.] **Figure S2.** [Entire figure legend.] **Table S1.** [Entire table title.] **Table S2.** [Entire table title.] **Movie S1.** [Entire movie legend.] **Supplementary References.**

Each supplementary component (e.g., Supplementary Methods, Supplementary Figure S1, Supplementary Figure S2, Supplementary Table S1, Supplementary Movie S1, etc.) must be cited in the main text in sequential order and include the term "Supplementary" before each component. It is not enough to refer generally to "supplementary material." However, Supplementary References should *not* be cited individually throughout the main article.

Accepted file formats
Quick Time files (.mov), graphical image files (.gif), HTML files (.html), MPEG movie files (.mpg), JPEG image files (.jpg), sound files (.wav), plain ASCII text (.txt), MS Word documents (.doc), Postscript files (.ps), MS Excel spreadsheet documents (.xls), and PowerPoint files (.ppt). We cannot accept TeX and LaTeX.

File sizes must be as small as possible so that they can be downloaded quickly. Images should not exceed 640 × 480 pixels but we would recommend 480 × 360 pixels as the maximum frame size for movies. We would also recommend a frame rate of 15 frames per second. If applicable to the presentation of the supplementary information, use a 256-color palette. Please consider the use of lower specification for all of these points if the supplementary information can still be represented clearly. Our recommended maximum data rate is 150 KB/s.

The number of files should be limited to eight, and the total file size should not exceed 8 MB. Individual files should not exceed 1 MB. Please seek advice from the editorial office before sending files larger than our maximum size to avoid delays in publication.

Further questions about the submission or preparation of supplementary information should be directed to the editorial office.

SUBMISSION AND PUBLICATION

Submission of papers

If you are ready to submit an article please visit the Online Submission page: http://mc.manuscriptcentral.com/ki.
All text should be submitted in Microsoft Word (.doc) and figures as .tif or .jpg files.
Figures appearing in the online version of manuscripts will be published in 72 dpi as is standard for all .pdf files on the internet. All figures published in print are at least 300 dpi.

Please add your Twitter Handle ("@+twitter user name") and ORCID (Open Researcher and Contributor ID) to your user account in manuscript central. If you don't have an ORCID, you can sign up for free at https://orcid.org/.

Submission checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
• E-mail address
• Full postal address

All necessary files have been uploaded:
Manuscript:
• Include keywords
• All figures (include relevant captions)
• All tables (including titles, description, footnotes)
• Ensure all figure and table citations in the text match the files provided
• Indicate clearly if color should be used for any figures in print
Graphical Abstracts / Highlights files (where applicable)
Supplemental files (where applicable)

Further considerations
• Manuscript has been 'spell checked' and 'grammar checked'
• All references mentioned in the Reference List are cited in the text, and vice versa

• Permission has been obtained for use of copyrighted material from other sources (including the Internet)
• A competing interests statement is provided, even if the authors have no competing interests to declare
• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

For further information, visit our Support Center.

Format for Revised Manuscripts

We ask that two versions of a revised manuscript be uploaded, one with "tracked" changes and one "clean" version with all changes accepted and track changes turned off.

Article transfer service

This journal is part of our Article Transfer Service. This means that if the Editor feels your article is more suitable in one of our other participating journals, then you may be asked to consider transferring the article to one of those. If you agree, your article will be transferred automatically on your behalf with no need to reformat. Please note that your article will be reviewed again by the new journal. More information.

Copyright

Upon acceptance of an article, authors will be asked to complete a 'Journal Publishing Agreement' (see more information on this). An e-mail will be sent to the corresponding author confirming receipt of the manuscript together with a 'Journal Publishing Agreement' form or a link to the online version of this agreement.

Subscribers may reproduce tables of contents or prepare lists of articles including abstracts for internal circulation within their institutions. Permission of the Publisher is required for resale or distribution outside the institution and for all other derivative works, including compilations and translations. If excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article. Elsevier has preprinted forms for use by authors in these cases.

Author rights

As an author you (or your employer or institution) have certain rights to reuse your work. More information.

Elsevier supports responsible sharing

Find out how you can share your research published in Elsevier journals.

Role of the funding source

You are requested to identify who provided financial support for the conduct of the research and/or preparation of the article and to briefly describe the role of the sponsor(s), if any, in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. If the funding source(s) had no such involvement, it is recommended to state this.

Formatting of funding sources

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

For authors requiring a commercial CC BY license, you can apply after your manuscript is accepted for publication.

The open access fee for this journal is $2,600 for ISN members and $3,200 for non-ISN members, excluding taxes.

This journal has an embargo period of 12 months.

AFTER ACCEPTANCE

Article-in-press publication

This journal makes articles available online as soon as possible after acceptance. This concerns the accepted article (both in HTML and PDF format), which has not yet been copyedited, typeset, or proofread. A Digital Object Identifier (DOI) is allocated, thereby making it fully citable and searchable by title, author name(s), and the full text. The article's PDF also carries a disclaimer stating that it is an unedited article. Subsequent production stages will simply replace this version.

Manuscript deposition service

Elsevier's automated manuscript deposition service enables authors to meet the open access or public access policies of all of the participating funders, making it simple and free for researchers to comply.

Online proof correction

To ensure a fast publication process of the article, we kindly ask authors to provide us with their proof corrections within two days. Corresponding authors will receive an e-mail with a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to MS Word: in addition to editing text, you can also comment on figures/tables and answer questions from the Copy Editor. Web-based proofing provides a faster and less error-prone process by allowing you to directly type your corrections, eliminating the potential introduction of errors.
If preferred, you can still choose to annotate and upload your edits on the PDF version. All instructions for proofing will be given in the e-mail we send to authors, including alternative methods to the online version and PDF.
We will do everything possible to get your article published quickly and accurately. Please use this proof only for checking the typesetting, editing, completeness and correctness of the text, tables and figures. Significant changes to the article as accepted for publication will only be considered at this stage with permission from the Editor. It is important to ensure that all corrections are sent back to us in one communication. Please check carefully before replying, as inclusion of any subsequent corrections cannot be guaranteed. Proofreading is solely your responsibility.

Crossmark

Authors will see the *CrossMark* logo with their articles upon publication in an issue. *CrossMark* is a multipublisher initiative to provide a standard way for readers to locate the current version of a piece of content. By applying the *CrossMark* logo Elsevier Inc. is committing to maintaining the content it publishes and to alerting readers to changes if and when they occur. Clicking on the *CrossMark* logo will tell you the current status of a document and may also give you additional publication record information about the document.

Offprints

The corresponding author will, at no cost, receive a customized Share Link providing 50 days free access to the final published version of the article on ScienceDirect. The Share Link can be used for sharing the article via any communication channel, including email and social media. For an extra charge, paper offprints can be ordered via the offprint order form which is sent once the article is accepted for publication. Both corresponding and co-authors may order offprints at any time via Elsevier's Author Services. Corresponding authors who have published their article gold open access do not receive a Share Link as their final published version of the article is available open access on ScienceDirect and can be shared through the article DOI link.

AUTHOR INQUIRIES

Visit the Elsevier Support Center to find the answers you need. Here you will find everything from Frequently Asked Questions to ways to get in touch.
You can also find out when your accepted article will be published.