University of Cape Town
Faculty of Health Sciences

The prevalence and severity of the symptom burden in patients with End Stage Kidney Disease (ESKD) in a resource limited setting

Minor dissertation submitted in partial fulfilment of the requirements for the degree of Master of Medicine (MMed) in the Department of Medicine, Division of General Medicine

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Submitted: 26/09/2024

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The contents of this minor dissertation are presented in the ‘publication-ready’ format.

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Acknowledgements:

The authors would like to acknowledge the patients who took part in the study. We would also like to thank the staff in E13 Renal unit for their input and continued hard work.

Abstract

Introduction
Globally, kidney failure is Increasing. In South Africa, limited access to kidney replacement therapy (KRT) necessitates urgent improvement in kidney supportive and palliative care.

Methods
This prospective, cross-sectional, mixed-method study was conducted at two Cape Town hospitals from June 2021 to June 2023. Participants with end-stage kidney failure (n=75) were categorized into three groups: receiving dialysis, on the waiting list, and ineligible for state-funded KRT (category 3). Data collection included demographics, comorbidities, and social circumstances. The Integrated Palliative care Outcome Scale Renal (IPOS-Renal) questionnaire assessed symptom burden, complemented by qualitative insights from open-ended interviews, which underwent thematic analysis.

Results
The cohort was young, with a median age of 40 (33-45) years, and faced significant poverty, commonly experiencing weakness/lack of energy (64%). Patients on the waiting list and those in category 3 had a higher symptom burden. Category 3 patients had the highest prevalence of shortness of breath ($p=0.006$), dry mouth ($p<0.001$), poor mobility ($p=0.007$), and restless legs ($p=0.038$). Emotional symptoms were prevalent across all groups. Category 3 patients experienced the most severe physical symptoms, including shortness of breath ($p=0.003$), sore/dry mouth ($p<0.001$), drowsiness ($p=0.028$), and poor mobility ($p<0.001$). They also experienced the highest levels of personal anxiety ($p<0.001$), patient perception of family anxiety ($p=0.037$), and appointment time wastage ($p=0.021$). Qualitative findings highlighted concerns for families, fears about unfulfilled lives, and the need for better access to information.

Conclusion
Limited literature exists on symptom burden in conservative kidney care with dialysis rationing. Recommendations advocate early multidisciplinary team involvement, improved patient and family support, and enhanced palliative care training.

Publication ready document:

The prevalence and severity of the symptom burden in patients with End Stage Kidney Disease (ESKD) in a resource limited setting

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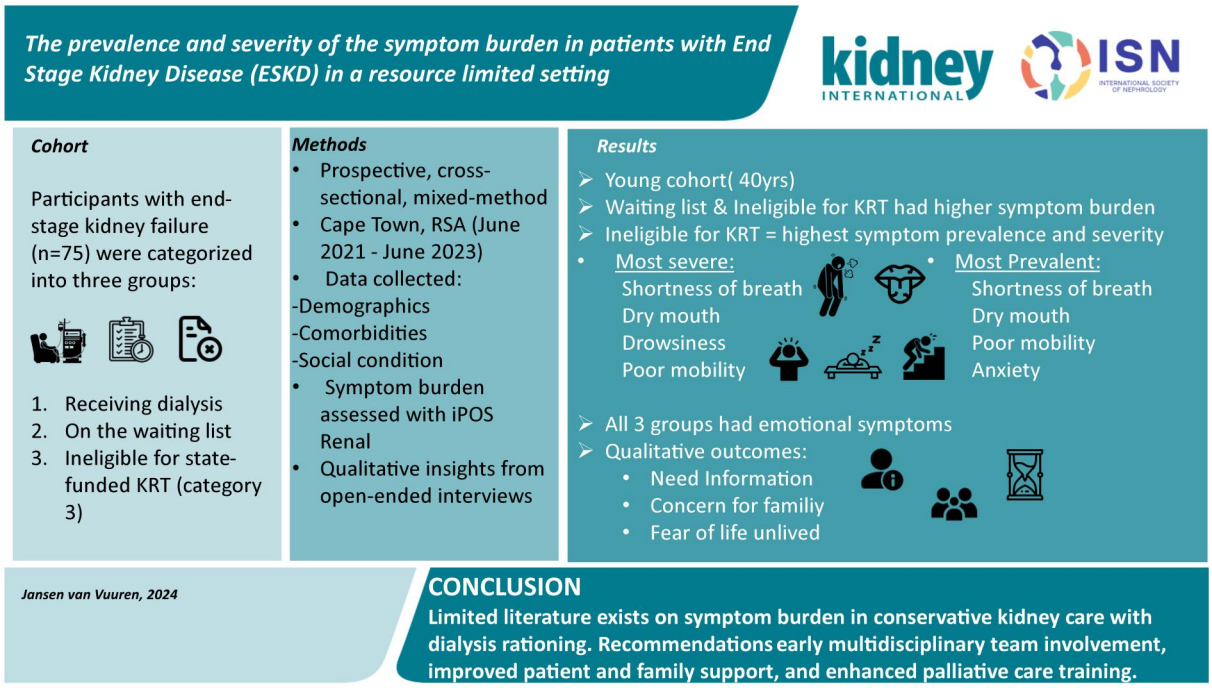
Word Count: 4057

Graphical Abstract



Title page:

The prevalence and severity of the symptom burden in patients with End Stage Kidney Disease (ESKD) in a resource limited setting

Running title: ESKD in resource limited setting

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Article type: Original article

Keywords: End stage kidney disease, symptom, palliation, Africa, CKD

Declaration

Ethics Considerations
The Health Research Ethics Committee of the University of Cape Town approved the study. (HREC reference number: 322/2021 A)

Funding
This study was self-funded and received no external funding or grants.

Acknowledgements
The authors would like to acknowledge the patients who took part in the study. We would also like to thank the staff in E13 Renal unit for their input and continued hard work.

Data availability
The data is available on request from the authors.

Conflicts of interest
The authors declare that they have no conflict of interests.

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The cohort was young, with a median age of 40 (33-45) years, and faced significant poverty, commonly experiencing weakness/lack of energy (64%). Patients on the waiting list and those in category 3 had a higher symptom burden. Category 3 patients had the highest prevalence of shortness of breath ($p=0.006$), dry mouth ($p<0.001$), poor mobility ($p=0.007$), and restless legs ($p=0.038$). Emotional symptoms were prevalent across all groups. Category 3 patients experienced the most severe physical symptoms, including shortness of breath ($p=0.003$), sore/dry mouth ($p<0.001$), drowsiness ($p=0.028$), and poor mobility ($p<0.001$). They also experienced the highest levels of personal anxiety ($p<0.001$), patient perception of family anxiety ($p=0.037$), and appointment time wastage ($p=0.021$). Qualitative findings highlighted concerns for families, fears about unfulfilled lives, and the need for better access to information.

Conclusion

Limited literature exists on symptom burden in conservative kidney care with dialysis rationing. Recommendations advocate early multidisciplinary team involvement, improved patient and family support, and enhanced palliative care training.

Introduction:

Kidney failure is defined as a glomerular filtration of <15milliliters/min per 1.73m^2 for a period of longer than 3 months. (1) Globally, there is a growing prevalence of kidney failure (KF), and South Africa is no exception.(2) This is even more concerning given the limited screening, preventative and therapeutic strategies available in South Africa, in particular, there is limited dialysis capacity in the state sector where dialysis is rationed. In 2017, the South African Renal Registry stated that the prevalence of kidney replacement therapy (KRT) in the public sector was 66 per million population (pmp).(3) Furthermore, between 1994 and 2017, there has been limited growth in numbers of KRT in the state sector, compared to exponential growth in the private sector.(4) Unsurprising, access to dialysis in Africa is poor. The median prevalence of haemodialysis (HD) in Africa is 12 pmp compared to 322.7 pmp globally.(5) Low socio-economic status, lack of education, poor government spending on health and low nephrology workforce all lead to disparities in kidney care in Africa.(6, 7) Resulting in rapid progression of chronic kidney disease (CKD) and increased mortality.(6, 7) In the state service in South Africa, due to a lack of primary care screening programmes, patients present late with end-stage kidney disease (ESKD), as their index presentations.(8) The combination of limited access to KRT and late presentation, leaves many patients and families suffering from complex bio-psychosocial and spiritual problems impacting their quality of life (QOL).(9) The pain and suffering experienced by these patients with KF are well documented in international studies, but how this impacts South African patients requires further exploration.(10)

Understanding the need for comprehensive kidney supportive and palliative care in South Africa, is complicated by the health inequity and limited health resources available for state patients, especially ESKD patients.(3, 4) In the state sector, KRT is rationed and often requires ‘choice-restricted conservative management’. This is ethically endorsed by applying the principle of utilitarianism, managed by a multi-disciplinary team, and strictly enforced by the health care management in state facilities, in South Africa. This implies that only patients eligible for kidney transplantation will be considered for chronic dialysis. This contrasts with patients in the private sector (approximately 15% of the population) who have open access

to dialysis.(3) A published manuscript from our institution reported that more than half (53·9%) of the patients presented for KRT, were not selected for the chronic dialysis program.(2) Furthermore, these numbers may be grossly underestimated as many patients, who are not transplantable, are not formally presented for KRT and remain in the primary care setting. Additionally, there are patients that are accepted for KRT, but need to wait on a waiting list until a dialysis slot becomes available. These patients often have significant symptoms and are in the precarious position of waiting for a slot, which may or may not become available.

Kidney supportive and palliative care aims to maintain residual kidney function and improve the QOL of patients and their families suffering with ESKD.(10) Patients experience a variety of symptoms that may negatively impact their physical well-being, interpersonal relationships and functional capability.(3, 11) Documented symptoms experienced by these patients include uremic pruritus, sleep disorders, restless legs syndrome, anorexia, nausea and vomiting, uremic gastritis, constipation, diarrhoea, depression and pain.(12) Some studies suggest that the symptom burden and the impact on QOL in ESKD, is similar to terminal malignancy.(9, 13) QOL is not just a physical construct and is also impacted by the psycho-social and spiritual factors of life.(14, 15) In the South African setting, these factors may be impacted by the poor economic status, high incidence of alcohol and drug use, limited support systems and anger due to rationed care.(16)

The integrated Palliative Care Outcomes Scale (IPOS) is a Patient Reported Outcomes measure (PROM) that was developed in the United Kingdom (UK) for the purpose of easy yet thorough assessment of patients with any advanced disease receiving palliative care.(17) Subsequently, IPOS-Renal was developed based on the generic IPOS tool but with eight additional symptoms specific to ESKD. It also allows open-ended questions to ensure all concerns are identified. The IPOS-Renal questionnaire has been validated in multiple studies, including the UK, New Zealand and Australia. PROMs have been shown to have multiple benefits, including monitoring a patient's symptom burden and ensuring patient and health care worker priorities are aligned by shedding light on the patient's perspective about their illness. (11, 18, 19)

The study's main objective was to demonstrate the degree of symptoms burden experienced by patients with ESKD in Cape Town, South Africa. The secondary objectives were to compare the difference in emotional and physical symptom burden between the three different groups of ESKD patient. These include 1) patients receiving dialysis, 2) patients awaiting dialysis (category 2), and 3) patients who were declined for dialysis. This study aims to improve insight into the specific needs and support required by patients with ESKD in the local context and serve as an advocacy tool to improve access to kidney supportive and conservative kidney management.

Methods

This is a pilot prospective, cross-sectional, mixed-method study with a small sample size at two state funded hospitals, in the Western Cape, South Africa (SA). Groote Schuur Hospital (GSH), an academic teaching hospital and Mitchells Plain District Hospital, a large district level hospital. The study took place from June 2021 to June 2023. The study was approved by the University of Cape Town Human Research Ethics Committee (HREC 322/2021).

The study population included those older than 18 years with ESKD (stage 5 chronic kidney disease (CKD) with an eGFR < 15 mL/min/1.73 m2) and were divided into 3 groups.

1. Group 1: (Dialysis cohort) included patients with ESKD currently receiving chronic KRT (either peritoneal dialysis or HD)
2. Group 2: (Waiting list cohort/ category 2) included patients with ESKD who were eligible for KRT and currently on the waiting list to start KRT (starting KRT will only occur if a chronic HD slot becomes available, initiation is not guaranteed).
3. Group 3: (Category 3 cohort) were patients who were deemed ineligible for state funded KRT and therefore receiving conservative kidney management (CKM). The decision of ineligibility for KRT was through presentation at the KRT selection meeting, or if the patient had pre-existing exclusion criteria deeming them poor transplant candidates (i.e. age, numerous comorbidities, other end organ failure).

Each group was comprised of 25 patients. (Supplementary appendix 1 is the eligibility criteria for acceptance onto state funded dialysis.) Category 1 patients were recruited during 3 consecutive random dialysis shifts. Category 2 patients were recruited during outpatient

Nephrology clinic visits. Category 3 patients were recruited while admitted to hospital or during outpatient visits to the Nephrology clinic.

A total of 75 patients were interviewed. No patients withdrew during or after the interview process. The data collected included basic demographic information (i.e. age, sex) and baseline Charlson Comorbidity index. Treatment data collected included: date of initiation of KRT, mode of KRT, length of time on waiting list, reason for ineligibility for KRT and whether the patient was reviewed by a nephrologist or palliative care physician. Lastly, data on social circumstances collected included home structure (brick house versus informal home), access to running water, employment status, income range and access to disability grant. (Appendix 2)

The quantitative data was collected by the utilization of the IPOS-Renal questionnaire. (Appendix 3) This validated PROM assesses prevalence and severity of physical, emotional, spiritual and social symptoms. The IPOS-Renal includes 11 short, structured questions. The remaining 10 questions use Likert scales to assess answers. The scoring scales have both numerical scores and descriptive scores that range from 0 to 3 or 4. For example, when asked to score the symptom "pain", a score of 0 would be synonymous with "not at all" whereas a score of 4 would indicate pain that is "overwhelming". Emotional symptoms were ranked 0 for "mostly" and 4 indicating "not at all". Participants completed the questionnaire independently or with assistance from a research assistant.

Qualitative data was collected through the first question of the IPOS-Renal which is the only open-ended question of the tool, and through interviews assessing 6 open-ended questions at the end of the interview. (Appendix 3) The questions focused on any unanswered questions, recent negative or positive experiences and identified the main concern about their condition. Answers given were recorded in writing either scribed verbatim by the interviewer (n=72) or by the patients themselves (n=3). The data was then entered into a central online, password-protected database. Braun and Clark's method of inductive thematic analysis was employed (Braun & Clarke, 2006) to analyse the qualitative data.

Descriptive statistics were used to summarise the cohort. Frequencies and percentages were presented for categorical variables. Chi-squared or Fisher's exact test was used for categorical comparisons, as appropriate. Mean and standard deviation was presented for continuous variables and to summarise severity of symptom scores. The aggregated IPOS scores were compared between dialysis, waiting list and category 3 patients using one-way analysis of variance (ANOVA). P values <0.05 were interpreted as statistically significant.

Results

A total of 75 patients were enrolled in the cohort and divided into 3 groups: dialysis, waiting list (category 2) and category 3 cohorts. Table 1 describes the social and demographic characteristics of the cohort. The mean age was young, at 39 years. Statistically, patients on the waiting list and those receiving dialysis had the poorest living circumstances, however poverty was profound in the entire group. Patients that were declined for chronic dialysis were found to have better overall living circumstances with highest access to an inside toilet and the lowest proportion living in informal housing.

Table 1 describes the social and demographic characteristics of the cohort

	Total	**Dialysis cohort**	**Waiting list cohort**	**Category 3 cohort**	**p-value**
	N=75	N=25	N=25	N=25	
Age	39 (9)	37 (11)	39 (7)	42 (7)	0.290
Employed	23 (31%)	6 (24%)	11 (44%)	6 (24%)	0.210
Disability Grant	21 (28%)	7 (28%)	6 (24%)	8 (32%)	0.820
Household Income	41 (55%)	10 (40%)	16 (64%)	15 (60%)	0.190
Brick House	57 (76%)	18 (72%)	16 (64%)	23 (92%)	0.058
Shack/informal house	18 (24%)	7 (28%)	9 (36%)	2 (8%)	0.058
Running Water inside	59 (79%)	15 (60%)	22 (88%)	22 (88%)	0.020
Toilet inside	55 (73%)	15 (60%)	18 (72%)	22 (88%)	0.080

Table 2 demonstrates the prevalence of the burden of symptoms experienced by the cohort. Overall, the commonest physical symptom was weakness/ lack of energy 48/75 (64%). Statistically significant differences in physical symptom burden occurred with shortness of breath (p=0.006), dry mouth (p=<0.001), poor mobility (p= 0.007) and restless legs (p=0.038).

The waiting list and the category 3 patients experienced the highest burden of these symptoms. Category 3 patients had the highest prevalence of shortness of breath 18/25 (72 %) compared to patients on the waiting list 10/25 (40%) and dialysis patients 7/25 (28%). “Sore or dry mouth” was a prevalent symptom with most category 3 patients 17/25 (68%) experiencing this symptom. Despite vomiting not reaching statistical significance, a higher proportion of patients on waiting list (36%) and category 3 patients (24%) experienced this symptom.

The burden of emotional symptoms across the cohort was high for patients and their families. Overall, the most prominent symptom was patient perception of family anxiety 64/74 (85%), which was prevalent across all 3 cohorts. Personal anxiety, insufficient information and time wasting at appointments were the 3 statistically significant complaints. Personal anxiety was predominantly experienced by the waiting list cohort 21/25 (84 %), followed by category 3 patients 19/25 (76%). This is compared to only 28% of dialysis patients experiencing anxiety. Receiving insufficient information was a common complaint overall 55% (p< 0.001). It was predominantly reported by those on the waiting list and the category 3 patients, at 72% and 68 % respectively. Category 3 patients experienced the highest proportion of time wasting with appointments 60% (p=0.004).

Table 2 demonstrates the prevalence of symptoms experienced by the patients in the study.

	Total	Dialysis	Waiting list	Cat 3	p-value
	N=75	N=25	N=25	N=25	
Physical symptoms [b]					
Pain	43 (57%)	15 (60%)	17 (68%)	11 (44%)	0.220
Shortness of breath	35 (47%)	7 (28%)	10 (40%)	18 (72%)	0.006
Weakness or lack of energy	48 (64%)	14 (56%)	15 (60%)	19 (76%)	0.300
Nausea	29 (39%)	8 (32%)	13 (52%)	8 (32%)	0.250
Vomiting	17 (23%)	2 (8%)	9 (36%)	6 (24%)	0.060
Poor Appetite	28 (37%)	8 (32%)	11 (44%)	9 (36%)	0.670
Constipation	24 (32%)	7 (28%)	7 (28%)	10 (40%)	0.580
Sore or dry mouth	30 (40%)	4 (16%)	9 (36%)	17 (68%)	<0.001
Drowsiness	25 (33%)	4 (16%)	10 (40%)	11 (44%)	0.076
Poor mobility	33 (44%)	6 (24%)	10 (40%)	17 (68%)	0.007
Uraemic pruritis	29 (39%)	8 (32%)	8 (32%)	13 (52%)	0.250
Difficulty sleeping	36 (48%)	15 (60%)	10 (40%)	11 (44%)	0.330
Restless legs	34 (45%)	7 (28%)	11 (44%)	16 (64%)	0.038

Changes in skin	26 (35%)	12 (48%)	9 (36%)	5 (20%)	0.110
Diarrhoea	7 (9%)	4 (16%)	1 (4%)	2 (8%)	0.330
Emotional symptoms					
Personal anxiety [c]	47 (63%)	7 (28%)	21 (84%)	19 (76%)	<0.001
Patient perception of family anxiety [c]	64 (85%)	18 (72%)	23 (92%)	23 (92%)	0.0700
Depression [c]	38 (51%)	9 (36%)	14 (56%)	15 (60%)	0.190
Did not feel at peace [d]	51 (68%)	14 (56%)	17 (68%)	20 (80%)	0.190
Social and practical issues					
Unable to share feelings [d]	38 (51%)	16 (64%)	11 (44%)	11 (44%)	0.260
Insufficient information [d]	41 (55%)	6 (24%)	18 (72%)	17 (68%)	<0.001
Practical issues not addressed [e]	46 (61%)	15 (60%)	16 (64%)	15 (60%)	0.950
Time wasted at appointments	32 (43%)	4 (16%)	13 (52%)	15 (60%)	0.004

[a] Prevalence (%) is defined as symptoms reported as mild, moderate, severe, or overwhelming.
[b] Response options: 0=None, 1=Slightly, 2=Moderately, 3=Severely, 4=Overwhelmingly.
[c] Response options: 0=Not at all, 1=Occasionally, 2=Sometimes, 3=Mostly, 4=Always.
[d] Response options: 0=Always, 1=Mostly, 2=Sometimes, 3=Occasionally, 4=Not at all
[e] Response options: 0=No problems, 1=Mostly addressed, 2=Partly addressed, 3=Hardly addressed, 4=Not addressed
[f] Response options: 0=None, 2=Up To half a day wasted, 4=More than half a day wasted

Table 3 reports the severity of physical and emotional symptoms across all 3 groups by demonstrating the mean symptom scores. Category 3 patients experienced the most severe physical symptoms, (shortness of breath (p=0.003), sore/dry mouth (p=<0.001), drowsiness (p= 0.028) and poor mobility (<0.001)). These symptoms ranged in severity from slight to moderately severe. Figure 1a, b and c demonstrate the severity of physical symptoms for all 3 cohorts.

Table 3 demonstrates the severity of symptoms experienced by participants by evaluating the mean scores for each symptom.

	Total	**Dialysis cohort**	**Waiting list cohort**	**Category 3 cohort**	**p-value**
Physical symptoms [b]					
Pain	1.1 (1.2)	1.3 (1.3)	1.1 (1.1)	0.9 (1.3)	0.530
Shortness of breath	0.9 (1.2)	0.6 (1.0)	0.6 (0.9)	1.5 (1.4)	0.003
Weakness or lack of energy	1.2 (1.2)	1.0 (1.0)	1.2 (1.2)	1.6 (1.3)	0.140
Nausea	0.6 (0.9)	0.4 (0.7)	0.8 (0.9)	0.6 (1.0)	0.370
Vomiting	0.4 (0.7)	0.2 (0.6)	0.6 (0.8)	0.4 (0.8)	0.170
Poor Appetite	0.7 (1.0)	0.6 (1.1)	0.7 (1.1)	0.6 (1.0)	0.920
Constipation	0.7 (1.1)	0.5 (1.0)	0.6 (1.0)	1.0 (1.3)	0.330
Sore or dry mouth	0.7 (1.1)	0.3 (0.8)	0.5 (0.8)	1.4 (1.3)	<0.001
Drowsiness	0.5 (0.9)	0.2 (0.4)	0.6 (0.9)	0.8 (1.2)	0.028
Poor mobility	0.9 (1.3)	0.3 (0.6)	0.7 (0.9)	1.8 (1.6)	<0.001
Uraemic pruritis	0.7 (1.1)	0.6 (1.0)	0.6 (1.1)	0.9 (1.1)	0.570
Difficulty sleeping	0.9 (1.1)	0.9 (0.9)	0.8 (1.2)	0.9 (1.3)	0.960
Restless legs	0.8 (1.1)	0.5 (1.0)	0.7 (1.0)	1.2 (1.2)	0.082
Changes in skin	0.6 (1.0)	0.8 (0.9)	0.7 (1.0)	0.4 (1.0)	0.480
Diarrhoea	0.1 (0.6)	0.3 (0.9)	0.0 (0.2)	0.1 (0.3)	0.160
Summative score (out of 60)					

Emotional symptoms					
Personal anxiety[c]	1.5 (1.4)	0.6 (1.2)	2.0 (1.2)	1.8 (1.4)	<0.001
Patient perception of family anxiety[c]	2.5 (1.4)	2.0 (1.5)	2.9 (1.2)	2.8 (1.3)	0.037
Depression [c]	1.0 (1.2)	0.8 (1.3)	1.2 (1.1)	1.1 (1.1)	0.530
Felt at peace[d]	1.6 (1.4)	1.5 (1.6)	1.4 (1.2)	1.7 (1.3)	0.770
Summative score (out of 16)					
Social and practical issues					
share feelings[d]	1.2 (1.4)	1.5 (1.4)	1.2 (1.6)	1.0 (1.3)	0.380
sufficient information[d]	1.2 (1.4)	0.5 (1.0)	1.7 (1.5)	1.6 (1.4)	0.003
practical issues address[e]	1.5 (1.5)	1.6 (1.7)	1.5 (1.6)	1.3 (1.3)	0.750
Time wasted	1.1 (1.4)	0.5 (1.2)	1.4 (1.5)	1.5 (1.4)	0.021
Summative score (out of 12)					

[a] Data are presented as mean (SD).
[b] Response options: 0=None, 1=Slightly, 2=Moderately, 3=Severely, 4=Overwhelmingly.
[c] Response options: 0=Not at all, 1=Occasionally, 2=Sometimes, 3=Mostly, 4=Always.
[d] Response options: 0=Always, 1=Mostly, 2=Sometimes, 3=Occasionally, 4=Not at all
[e] Response options: 0=No problems, 1=Mostly addressed, 2=Partly addressed, 3=Hardly addressed, 4=Not addressed

Figure 1 describing the severity of physical symptoms in 1a) dialysis cohort, 1b) waiting list (category 2) patients and 1c) category 3 cohorts.

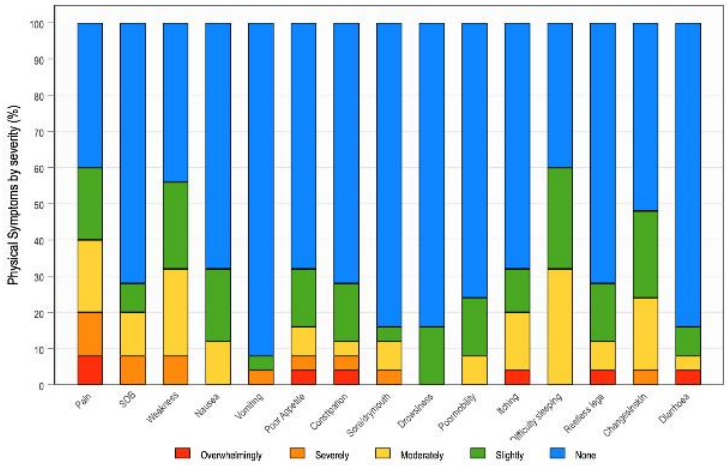

Figure S1a: Physical Symptoms in Dialysis patients

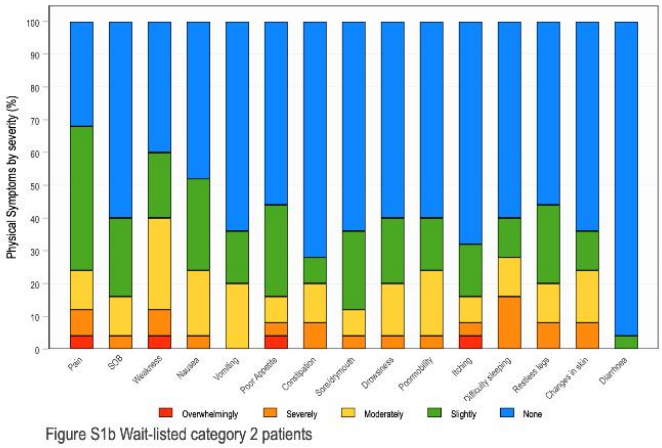

Figure S1b Wait-listed category 2 patients

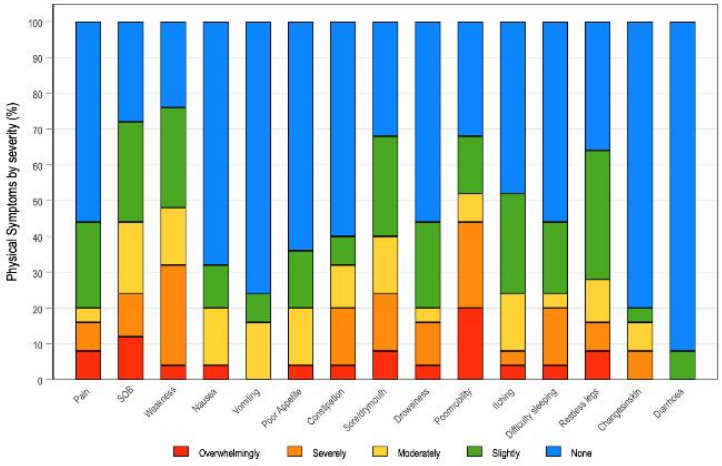

Figure S1c Physical symptoms in category 3 patients

Table 3 reports the severity of emotional symptoms. The emotional symptoms were more severe than the physical symptoms in all 3 groups. Both waiting list and category 3 patients reported moderate personal anxiety with a mean score of 2.0 and 1.8 ($p<0.001$) respectively. Similarly, **Patient perception of family anxiety** was reported in waiting list and category 3 cohorts, with mean scores of 2.9 and 2.8 ($p=0.037$). This implies that families experienced anxiety most of the time. Figure 2 a, b and c illustrate the severity of the emotional symptoms experienced by the 3 cohorts respectively.

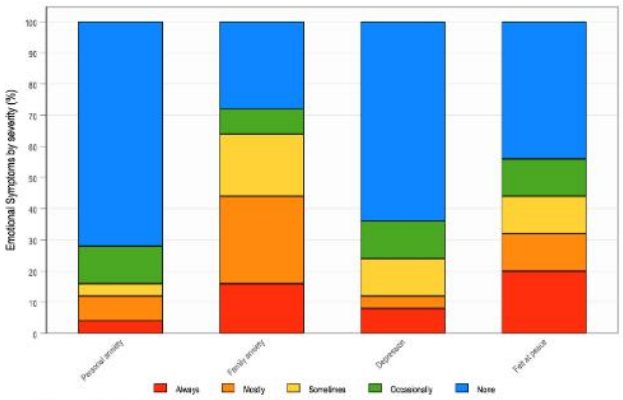

Figure S2a: Emotional Symptoms in Dialysis patients

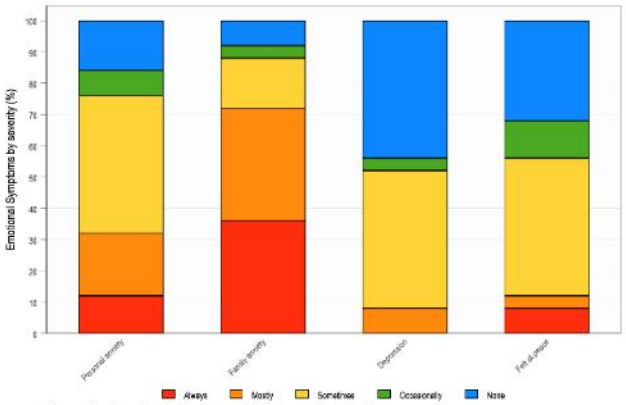

Figure 2b: Emotional Symptoms in Category 2 patients

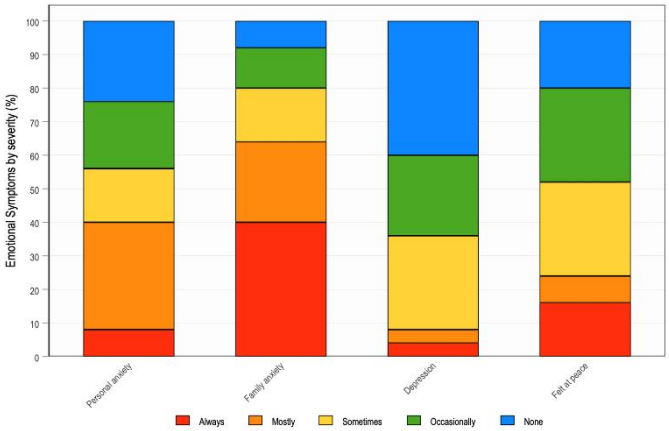

Figure S2c: Emotional Symptoms in Category 3 patients

Figures 2 a, b and c illustrate the severity of the emotional symptoms experienced in 1a) dialysis cohorts, 2b) waiting list/ category 2 cohorts and 2c) category 3 cohorts.

Supplementary figures 1 a, b and c demonstrate the severity of practical and social problems experienced. Although both groups of patients have a similar prevalence, the waiting list patients the greatest severity overall. Time wasting (p=0.021) and insufficient information (p =0.003) were severe for both those on the waiting list and the category 3 patients. Supplementary figure 2 graphically demonstrates the proportion of time patients felt was wasted on hospital appointments or investigations. The highest prevalence was found in the category 3 patients (60%) followed by the waiting list patients (52%).

Qualitative data

Participants (n= 75) were asked to answer 6 open ended questions at the end of the interview. After data scrutinization and evaluation, 5 prominent themes were agreed upon. In addition to the 5 main themes, several subthemes became apparent. Data excerpts were chosen to exemplify the themes that were identified.

Theme 1	**Theme 2**	**Theme 3**	**Theme 4**	**Theme 5**
Family and loved ones	Self-help	Fear of the life unlived	Need for Communication and Information	Maintaining and losing own identity
Sub-themes of theme 1	**Sub-themes of theme 2**	**Sub-themes of theme 3**	**Sub-themes of theme 4**	**Sub-themes of theme 5**
Financial implications	Access to dietary information	Limitations in daily life	Generic information about renal disease	Loss of independence
Disruption in family dynamics	Social self-help	Loss of future	Information about chronic dialysis structure/ Hospital systems	Regaining identity after decision regarding chronic dialysis
			Family involvement in education	Information about natural history of ESKD

Table 4: Themes and sub-themes identified from the qualitative data

1) **Family and loved ones**

The theme of family was brought up frequently during the open-ended questions. When answering the question about "what the biggest concern is about their illness", 16 participants mentioned their family. Under the main theme of *family and loved ones*, we identified the subtheme of *financial impact*. Many participants expressed fears of not being able to support their families financially either due to loss of employment, pension or in the event of death. In addition to the financial impact, many participants were concerned as to who would take over their role as primary caregiver to their young children or grandchildren. Even participants who were not the sole caregiver for their loved ones' welfare, expressed concern about how their family would cope without their presence and support. This draws attention to the distress that patients feel about the consequences of the *disruption to their family dynamics*.

Participant 74 commented: *"Who will look after my children. My 14-year-old son is still young. I want to see him grow up."*

2) **Self-help**

There was a strong need expressed by patients to exercise self-help, but many seemed to be lacking the tools for implementation. Queries regarding diet were mentioned by participants in all 3 groups. Common concerns were whether there is a specific diet that should be followed for their chronic kidney disease and which foods should be avoided. Food insecurity caused anxiety for many participants in the study. What came to the fore was the worry about how their lack of access to appropriate food, or in some cases any food at all, would negatively impact their health.

Participant 68 commented*: I'm worried about diet and what food to eat*. Participant 68

3) **Fear of the life unlived**

The definition of what "life unlived" means may be different for each person. Some participants who were regularly receiving dialysis expressed this, as well as those that were undergoing palliation. This fear seems to be very prominent in younger patients and those that were declined from the KRT programme.

Participant 17 commented*: Frustrated. Life just stopped and faded away*. Participant 17

4) **Need for Communication and Information**

Participants had a variety of questions about their condition during the interview process. The unanswered queries ranged from basic questions regarding the meaning of their diagnosis to complex questions regarding possible transplant. Some questions related to a patient-specific concern, but many others were generic, for example: the system for KRT at GSH and common side effects of medication.

I want my problem thoroughly explained as the diagnosis is new. Unclear as to what dialysis is. Participant 12 (on dialysis)

5) **Maintaining and losing one's identity**

The fifth theme was that of maintaining and losing one's identity, with sub-themes loss of independence, regaining identity post-initiation of KRT and the need for information about the natural history of ESKD. Fears regarding what the future of their health will hold, how rapidly their kidney function will decline and at what point external help will be required were all concerns raised by participants.

Won't be able to do anything for myself when the time comes and not sure when that will be. Participant 33.

My health has improved profoundly. Since starting dialysis, I am able to do my normal daily routine independently. Participant 8.

Discussion

This cross-sectional study was done in a resource-limited setting with choice-restricted kidney supportive care and aimed to determine the symptom burden of patients' with ESKD and explore their perceived needs. This adds to the dearth of data on symptom burden in ESKD in a health system with dialysis rationing. The findings include firstly the young age and poverty of our patient cohort. Secondly, the high symptom burden of those on the waiting list and those declined for dialysis and receiving CKM. Thirdly, the high emotional symptom burden to families and patients across all three groups. Fourthly, the qualitative themes highlighted concern for family and loved ones, for the life unlived and for losing personal identity. As well as the need for improved access to information to assist with empowering one-self.

Globally there is limited infrastructure in place for providing CKM care. An international working group has recently identified core components of CKM to promote international understanding, awareness and development.(1) The first South African consensus statement regarding renal palliative and supportive care was published in 2020 to provide assistance with management of both physical symptoms as well as biosocial issues.(20) This paper describes the complexities of choice restricted CKM in the South African context. Nkunu *et al* found that although many low and middle income countries provide some elements of CKM through management of CKD, there remains a paucity of data. Patients often had to be referred to more specialised centers to access CKM care, with central team members like social workers and community health care workers not being involved in care for patients with CKD.(21)

Comparative data on symptom burden in CKM globally

Despite the growing awareness of CKM, including choice restricted CKM, there is dearth of published literature on symptom burden, particularly in regions limited to choice restricted CKM. Supplementary Table 1 summarizes and compares the current literature reviewing symptom burden in CKD. Only 3 other published studies utilised the IPOS-Renal to evaluate symptom burden in patients with ESKD.(22-24) Our cohort, to our knowledge, was the only study evaluating the symptom burden of patients on a waiting list to access KRT. The other striking differences included the younger average age and degree of poverty. Most of the international CKM literature focuses on elderly patients. (22, 24, 25) Out of the seven studies, four had an average age over 70 years and 2 studies over 50 years, compared to our mean age of 40 years. The age discrepancy may partly be explained by the strict priority setting criteria for chronic dialysis used for state sector dialysis, in the Western Cape. In our setting, patients over the age of 60 years and all diabetic patients >50 years, receive choice restricted CKM by default. (Appendix 1) The consequences for our younger cohort were highlighted in the qualitative data. These included the mourning for unlived lives, the fear of loss of a care giver and the impact of the loss of income for the family.

There were marked similarities between our study and the other South African Study. Both studies describe cohorts 10 – 30 years younger than those studied elsewhere. They both

emphasize patients experiencing high level of anxiety, however the anxiety experienced by those on the "waiting list" was not described by Matthew *et al*. Additionally, they both highlighted the multiple socioeconomic challenges, our patients face, that make living with a chronic illness even more challenging. A published report from our unit detailed high rates of unemployment, lack of access to running water or an inside toilet and fear of living environment due to high crime rates.(26).

Physical symptoms comparative analysis

The high symptom burden in patients in a choice restricted setting in both those declined from KRT and those on the waiting list, has not been previously described. Although it is difficult make comparisons with studies using different PROMs, similarities were found between our findings and other published literature. Our study found that fatigue or lack of energy was the most prevalent symptom in ESKD, across all 3 groups. This is similar to a systematic review as well as other reported studies.(22, 24, 27, 28) The high prevalence and severity of poor mobility found in our cohort was echoed in the literature.(24) Most studies that evaluate symptom burden, report higher symptom prevalence and severity in patients receiving dialysis when compared to those on the CKM treatment pathway. (22, 23) There was however one study reporting similar symptom burden in both HD and those receiving CKM. (29)

One of the most prominent findings in this study was the high prevalence and severity of the emotional symptoms. Family related anxiety followed by personal anxiety was found in the entire cohort. Patient perception of family anxiety in ESKD is not often reported in the literature, however, a descriptive qualitative study in Australia, found a significant impact to the family life and dynamics of patients with CKD.(30) Anxiety and depressive symptoms in patients with ESKD are well described in the literature, with dialysis patients labelled as having the most severe emotional symptoms. (22, 24, 25, 28, 29, 31) We found emotional symptoms outweighed physical symptoms in our cohort, especially in the waiting list group.

Qualitative research on CKM explores patients' experiences, decision making processes, logistical challenges impacting care and their perspective of health care providers.(32, 33) This is important not only for those receiving CKM but also for those on the waiting list and dialysis. To our knowledge there is no qualitative data on choice restrictive CKM.(20) In contrast to our study, qualitative studies exploring CKM (not choice restricted) are usually focused on elderly patients > 70years.(32-34) The similarities include the patient's need for information and empowerment, the importance of holistic care and the need for family involvement.(33, 34)This has highlighted the importance of clear empathetic communication from the health care team and for a multi-disciplinary team (MDT) approach to care. (1, 20)

Recommendations to improve CKM in our setting:

This study highlighted the unmet severe emotional needs of our patients and their families. The integration of kidney supportive care is essential for all patients with ESKD and not just those receiving CKM. Early MDT involvement is needed to provide support, to patients and families and would ideally include a social worker, a psychologist /psychiatrist, palliative care team and nurse, community health workers and physio / occupational therapist and dietetics input. (1, 20, 21) This will provide patients with a holistic and complete care package but it may also slow down the progression of CKD.(35) In a low income setting with no established palliative MDT, early social worker and community health worker referral is essential involvement for all patients.(1, 21) This will assist with all aspects of social welfare for patients and their families, including disability grants for patients or grant-in-aid for caregivers, and could help ease some the concerns experienced by patients and support the burden of emotional distress.(21)

Patient perception of CKM is influenced positively when presented as an interactive and active process with MDT involvement.(33) Transparency regarding the KRT allocation in low resource settings is essential when creating a choice-restricted CKM service.(1) Therefore, having easy access to the KRT allocation criteria for patients on the CKM pathway should be considered.

Increased awareness and training of CKM for healthcare providers is essential. This requires CKM to be integrated into curriculums and to develop clear guidelines at a provincial and national level.(1) The International Society for Nephrology (ISN) has recently launched an international curriculum focused on CKM. (1)Identifying patients' biopsychosocial needs, facilitating family meetings, and prescribing end-of-life medication is a skill set that must be learned by all of us. Challenging situations still exist with limited availability of guideline-approved drugs.(36) This will require further lobbying for improved quality of care through all sectors of the health system. Ultimately, this requires policies that support the provision of CKM and should align with regional and national palliative care initiatives.

Limitations

This was a pilot study with a small cohort of patients. The small sample size and data from a real-world study, limited meaningful statistical significance. Some of the participants were inpatients, acutely unwell due to ESKD, this may have skewed their symptoms burden. But the strengths include that this is the first South African review of symptom burden using the IPOS-Renal, with open ended questions performed in patients native language, in a choice restricted setting.

Conclusion:

Patients with ESKD have a high symptom burden in all spheres including physical, emotional, social and practical. Patients on a waiting list for dialysis experienced severe patient perception of family anxiety and a higher than expected symptom burden. This highlighted the need for a comprehensive multi-disciplinary team to address not only the physical symptoms but also the emotional and social issues experienced of all ESKD patients, including those on dialysis.

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Acknowledgements:

The authors would like to acknowledge the patients who took part in the study. We would also like to thank the staff in E13 Renal unit for their input and continued hard work.

Supplementary content:

Supplementary Tables:

Supplementary Table 1: Literature on symptom burden in ESKD

Author **Country** **Year of publication**	S. So, et al Australia (2023) (22)	A. E. Bursic, et al USA (2022)(37)	N Matthew, et al SA (2023) (29)	M Jhamb, et al USA (2019) (28)	JE. Ma, et al USA (2023) (25)	J Liu, et al Australia (2024) (23)	JS. Scherer, et al USA (2018) (31)	Our study
Income status	High school or greater: CKM 57% Dialysis: 73%	Not mentioned	Unemployed HD 94% PD 84% CKM 78% Social Grant HD 74% PD 42% CKM 85%	High school or greater: CKD 91% Dialysis 84% GI cancer 81%	Financial stress experienced: 24% High School or greater: 90%	Social security Recipients: 41.4% Employed: 29.3% Unemployed: 9.5% Not employed outside the home: 9.5%	Not mentioned	Unemployed: 69% Disability grant: 28% Household income: 55%
Number participants	339	165	150	837	377	156	55	75
Mean age of cohort	CKM 83 years Dialysis 73 years	72 years	HD 45 years PD 44 years CKM 59 years	CKD 52 years Dialysis 56 years GI cancer 61 years	77 years	57 years	72 years	40 years
Groups of renal failure (CKM, dialysis?)	CKM (n=216) Dialysis (n= 123)	Dialysis n=26) CKD (n=139) (all stages)	Dialysis (HD =50 and PD n=50) CKM (n=50) (GFR<20)	CKD, n=82 (not on dialysis), Dialysis n=149 and GI cancer n=606	CKD receiving CKM stage 4/5 in >70 years olds	CKD Dialysis n=105 CKM n=47 Specifically in Working adults	Kidney palliative care clinic patients (KPC) CKD including but not limited to ESKD Dialysis, CKM	Dialysis (HD &PD) n=25, ESKD awaiting dialysis n=25 and CKM for palliation n=25
Tool used	I-POS renal And EQ-5D-5L	ESAS then IPOS-Renal	HADS KDQOL-SF36	FACTIF-F BDI PHQ-9 CES- D BPI SF 36 pain subscale	Symptom burden score IADLS ADLS	IPOS-Renal EQ-5D-5L	IPOS-Renal KPS	IPOS-Renal
Symptom prevalence	Lack of energy (CKM 79% Dialysis 87%) Poor mobility (CKM 70%, Dialysis 74%)	Fatigue 85% Mobility issues 66% Pain 58%	-	Fatigue 75% in CKD/ESKD group Pain 29% Depression 28%	3 classes identified: 1st: Physical function limitation. issues with Physical IADLS 2nd: General symptoms: shortness of breath, constipation, and dizziness.	Weakness (92.2%), poor mobility (83.3%), and pain (82.5%)	Nausea highest prevalence	Weakness/lack of energy 64%, most prevalent. Shortness of breath, poor mobility, and dry mouth =statistically significant Category 3 patients had the highest prevalence

					3rd: Complex needs: Pain, Psychological symptoms, functionality impairment polypharmacy			of symptoms, followed by Waiting list patients and then Dialysis patients
Most significant Symptoms	Statistically significant: restless leg	Poor mobility Fatigue Anxiety	-	Fatigue	Dependent on class but Shortness of breath, dizziness and constipation	Same as the prevalent symptoms: Weakness, poor mobility, and pain Those on dialysis had significantly higher symptom scores than those not receiving dialysis	Nausea, Shortness of breath	Shortness of breath, poor mobility, drowsiness, and dry mouth. Category 3 patients had most severe symptoms, followed by waiting list patients
Most significant emotional issues	Anxiety (IPOS-Renal) Poor functional ability (EQ-5D-5L)	Anxiety	Anxiety and depression. Noted highest prevalence and most severe anxiety in HD and CKM stage 5	Depression (only emotional symptom evaluated). Higher in GI cancer patient	Anxiety and depression	Anxiety and depression	Anxiety followed by depression	Patient perception of family anxiety, Personal anxiety Notably most severe in Waiting list and Category 3 patients
Recommendations	Reduced functional ability is associated with reduced HRQOL in patients with CKD Stage 5 managed with or without dialysis, and optimization of multidisciplinary teams within KSC units are likely to be of benefit.	Integration of palliative care into outpatient service.	Patient participation in KRT planning, Hb targeting and \nutritional intervention. Additional mental health support for young patients on KRT. PD first program.	Ongoing research in collaborative care intervention focusing on pain, fatigue, and depression.	Interdisciplinary team input especially for patients with complex needs. Palliative care, physiotherapists, social workers, occupational therapists, and pharmacists suggested for MDT	Debilitating symptoms in patients with ESKD while working that require specific support including a multidisciplinary approach	Plan to include spiritual and emotional support	*

EQ-5D-5L: Health related quality of life questionnaire; ESAS: Edmonton Symptom Assessment Scale; HADS: Hospital Anxiety and Depression scale; KDQOL-SF36: Kidney disease quality of life short form 36; FACTIF-F: Functional Assessment of Chronic Illness Therapy –Fatigue; BDI Beck Depression Inventory; PHQ-9: Patient Health Questionnaire 9; CES- D : Center for Epidemiologic Studies Depression Scale; BPI: Brief Pain Inventory; SF 36 pain subscale; IADLS: Instrumental activities of daily living; ADLS: Activities of daily living; HD: Haemodialysis; PD: Peritoneal Dialysis, CKM: conservative kidney management; USA: United States of America; SA: South Africa; ESKD: end stage kidney disease; KRT: Kidney replacement therapy; MDT: Multi-disciplinary team.

Supplementary figures:

Supplementary figure 1: The severity of the social and practical difficulties

1a) dialysis cohorts, 2b) waiting list (category 2) cohorts an d 2c) category 3 cohorts

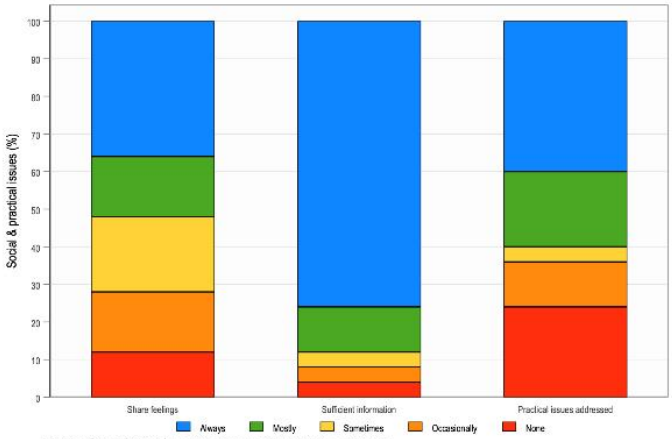


Figure S3a: Social/practical issues in dialysis patients

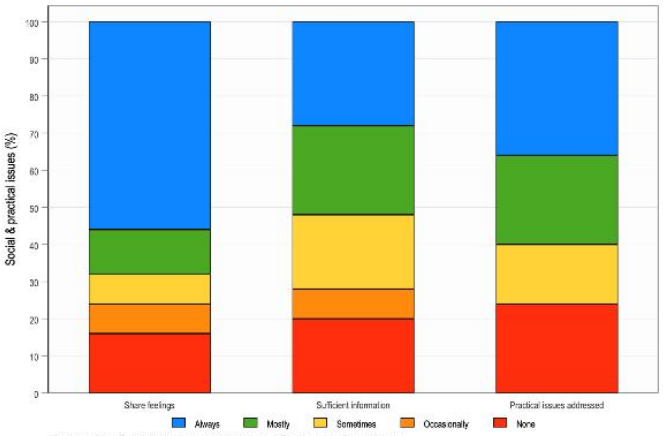


Figure 3b: Social/practical issues in Category 2 patients

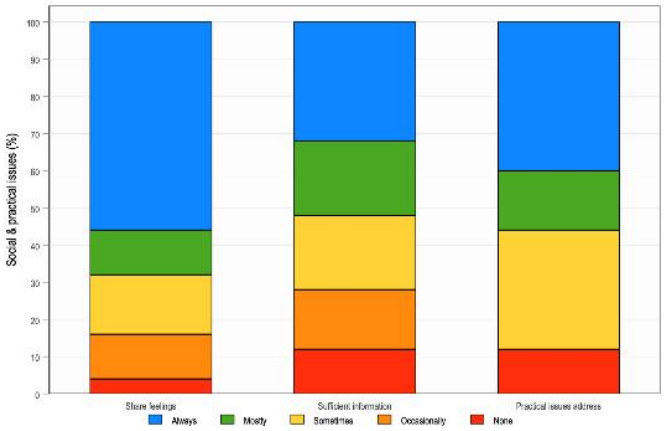
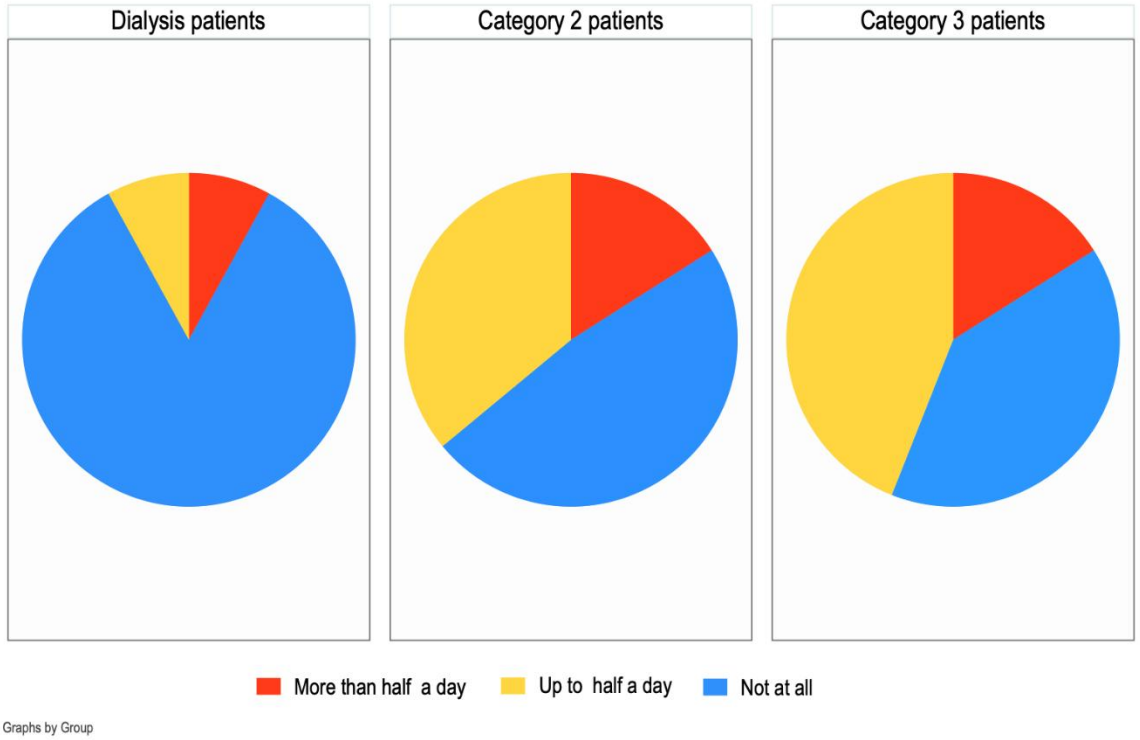


Figure S3c: Social/practical issues in Category 3 patients

Supplementary figure 2: The proportion of perceived time wasted

Dialysis, waiting list (category 2), and category 3 patients**.**


Dialysis patients
Category 2 patients
Category 3 patients
More than half a day
Up to half a day
Not at all
Graphs by Group

Appendices:

1) Western Cape Dialysis Criteria

RENAL ASSESSMENT TOOL

DATE: _____

PATIENT: _____
HOSPITAL NO.: _____
DOB.: _____

Creatinine: _____
Primary renal disease (code): _____

Nephrologist: _____
Registrar: _____

CATEGORY 3

Any **one** excludes patient:

Renal transplantation is contraindicated or carries unacceptable risks

- ☐ AIDS or HIV infection other than HIV+ patients with the medical characteristics described in category 2;
- ☐ Age ≥ 80 years;
- ☐ Substance abuse or dependency;
- ☐ Morbid obesity (BMI ≥ 35 kg/m2);
- ☐ HBsAg positive or cirrhosis, or HBsAg positive with a viral load > 2000 IU/ml and elevated ALT
- ☐ Diabetes mellitus age ≥ 50 years;
- ☐ Active, uncontrollable malignancy with reduced life expectancy;
- ☐ Advanced, irreversible or progressive disease of vital organs such as:
  - o Cardiac (ejection fraction <40%), cerebrovascular or peripheral vascular disease
  - o liver disease
  - o lung disease
  - o unresponsive infections
- ☐ Psychological Exclusion Criteria
  - o Any form of serious mental illness or incapacity which, as shown by psychiatric and medical examination, would preclude the patient and/or family or available support group from successfully managing the patient, considering his/her impairment, through dialysis, a transplant, and extended follow up care.
- ☐ Non-Adherence
  - o Patients with non-adherence to prescribed therapy, clinic visits or prescribed lifestyle therapy.
  - o Any factor that on careful consideration, compromises the patient's ability to comply with long-term follow up visits or in-patient therapy
  - o Patients on renal replacement who do not adhere to prescribed treatment will be reassessed, and treatment may be withdrawn.
- ☐ Kidney Transplantation
  - o Patients who, when offered one, refuse to accept a kidney transplant without valid reasons will be reassessed and treatment may be withdrawn

CATEGORY 2

The following factors, taken together, reduce the chances of being offered treatment:

MEDICAL FACTORS

- ☐ Age 51 - 60 years;
- ☐ BMI 30 - 35 kg/m2;
- ☐ Left ventricular systolic dysfunction (ejection fraction ≥40% and ≤ 50%)
- ☐ Hypertension with severe target organ damage;
- ☐ HBsAg/HCV positive with no cirrhosis;
- ☐ Smoking;
- ☐ Diabetes mellitus;
- ☐ HIV infected patients provided CD4 count ≥ 200/ml, VL undetectable and 6 months of treatment on first line ARV with good adherence and clinical response.
- ☐ First presentation with end-stage kidney failure requiring dialysis
- ☐ Comorbid disease e.g. stable ischaemic heart disease
- ☐ Previous kidney transplant

SOCIAL

- ☐ Good home circumstances (including access to storage space, running water, sanitation and electricity), needed to succeed with dialysis and transplantation
- ☐ The patient is well-motivated and has access to a good social support system required to do well on dialysis and transplantation.
- ☐ A patient whose life enhances the opportunities for others in his/her family and community to flourish
- ☐ Proximity to and/or evidence of financial means or other capability to regularly arrange transport to a renal unit as frequently as this may be needed (the unit is unable to fund or provide such transport).

CATEGORY 1

Must be accommodated

No Category 2 or 3 factors

PLUS **all** of:

- ☐ Age <50 years
- ☐ BMI less than 30kg/m²
- ☐ HIV negative
- ☐ HBsAG negative
- ☐ South African citizen

FINAL CATEGORY:

☐ **ACCEPTED**

- ☐ **Haemodialysis**
- ☐ **CAPD**
- ☐ **Living donor Tx**

Comments:

☐ **NOT ACCEPTED**

Comments:

2) Data collection form

Date of presentation:

Category if available:

Date of initiating dialysis:

Dialysis:
Date of initiating dialysis if applicable: dd/mm/yy
Mode: HD: Y/N PD: Y/N
Transplant: : Y/N

Conservative medical care:
Palliative service at the GSH
Seen at the CHC
• Ever reviewed by nephrologist Y/N

Primary Health Care:
Living situation:
Home: brick: Y/N shack: Y/N
Running water inside: Y/N
Toilet inside: Y/N
Household Income: Y/N
DG: Y/N Employment: Y/N

3) IPOS-Renal Questionnaire

IPOS-Renal Patient Version

www.pos-pal.org

Patient name :

Date (dd/mm/yyyy) :

Patient number : *(for staff use)*

Q1. What have been your main problems or concerns over the past 3 days?

1. .....

2. .....

3. .....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick the box that best describes how it has affected you over the past 3 days.

	Not at all	Slightly	Moderately	Severely	Overwhelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Itching	0☐	1☐	2☐	3☐	4☐
Difficulty Sleeping	0☐	1☐	2☐	3☐	4☐
Restless legs or difficulty keeping legs still	0☐	1☐	2☐	3☐	4☐
Changes in skin	0☐	1☐	2☐	3☐	4☐
Diarrhoea	0☐	1☐	2☐	3☐	4☐
Please list any other symptoms not mentioned above, and tick the box to show how they have affected you over the past 3 days.					
1._____	0☐	1☐	2☐	3☐	4☐
2._____	0☐	1☐	2☐	3☐	4☐
3._____	0☐	1☐	2☐	3☐	4☐

Over the past 3 days:

	Not at all	Occasionally	Sometimes	Most of the time	Always
Q3. Have you been feeling anxious or worried about your illness or treatment?	0☐	1☐	2☐	3☐	4☐
Q4. Have any of your family or friends been anxious or worried about you?	0☐	1☐	2☐	3☐	4☐
Q5. Have you been feeling depressed?	0☐	1☐	2☐	3☐	4☐

	Always	Most of the time	Sometimes	Occasionally	Not at all
Q6. Have you felt at peace?	0☐	1☐	2☐	3☐	4☐
Q7. Have you been able to share how you are feeling with your family or friends as much as you wanted?	0☐	1☐	2☐	3☐	4☐
Q8. Have you had as much information as you wanted?	0☐	1☐	2☐	3☐	4☐

	Problems addressed/ No problems	Problems mostly addressed	Problems partly addressed	Problems hardly addressed	Problems not addressed
Q9. Have any practical problems resulting from your illness been addressed? (such as financial or personal)	0☐	1☐	2☐	3☐	4☐

	None at all	Up to half a day wasted	More than half a day wasted
Q10. How much time do you feel has been wasted on appointments relating to your healthcare, e.g. waiting around for transport or repeating tests?	0☐	2☐	4☐

	On my own	With help from a friend or relative	With help from a member of staff
Q11. How did you complete this questionnaire?	☐	☐	☐

If you are worried about any of the issues raised on this questionnaire then please speak to your doctor or nurse

4) Structured open ended questions

Thank you for answering the questions so far.

1. Are there any unanswered concerns that you still want to share with us?
2. Is there anything that we could do to improve your care
3. Have you had any negative experiences in the Health system within the last 1 year.
4. What be your recommendation to improve your negative experience?

5. What do you think we are doing well with respect to your health? 6. What is your biggest concern/ problem with your illness

5) Ethics

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-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

19 May 2021

HREC REF: 322/2021

Dr B Davidson
Division of Nephrology and Hypertension
E-13 NGSH
Email: bianca.davidson@uct.ac.za
Student: anejvv@gmail.com

Dear Dr Davidson

PROJECT TITLE: TO DETERMINE THE PREVALENCE AND SEVERITY OF THE SYMPTOM BURDEN IN PATIENTS WITH END STAGE RENAL DISEASE (ESRD) IN A RESOURCE LIMITED SETTING-MASTER'S CANDIDATE-DR A JANSE VAN VUUREN

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 & 06 July 2020.

Approval is granted for one year until the 30 May 2022.

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)

The HREC acknowledge that the student: Dr Janse van Vuuren will also be involved in this study.

Please quote the HREC REF 322/2021 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/REF 322/2021sa

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

HREC/REF 322/2021sa

6) Instructions for authors:

Introduction

Frequency

Published monthly.

Impact factor

2021 Impact Factor: 18.998

3 of 90 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 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 and the highest level of original research studies in clinical and basic kidney 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. **Landmark Communications** present high-quality findings of exceptional interest, novelty, transformative value, and broad significance. **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. **Research Letters** report results of studies similar to original investigations that may involve pilot studies, or research focused on a few critical findings. **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 kidney research. **Controversial discussions** on hot topics or debated issues are written by two opposing authorities with a summary by the editors. **Nephrology Images** are presentations of interesting images in kidney pathology, radiology chosen for their illustrative nature or simply for their esthetic qualities. **Policy Forum** features 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 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.

Before you begin

Declaration of generative AI in scientific writing

The below guidance only refers to the writing process, and not to the use of AI tools to analyse and draw insights from data as part of the research process.

Where authors use generative artificial intelligence (AI) and AI-assisted technologies in the writing process, authors should only use these technologies to improve readability and language. Applying the technology should be done with human oversight and control, and authors should carefully review and edit the result, as AI can generate authoritative-sounding output that can be incorrect, incomplete or biased. AI and AI-assisted technologies should not be listed as an author or co-author, or be cited as an author. Authorship implies responsibilities and tasks that can only be attributed to and performed by humans, as outlined in Elsevier's AI policy for authors.

Authors should disclose in their manuscript the use of AI and AI-assisted technologies in the writing process by following the instructions below. A statement will appear in the published work. Please note that authors are ultimately responsible and accountable for the contents of the work.

Disclosure instructions

Authors must disclose the use of generative AI and AI-assisted technologies in the writing process by adding a statement at the end of their manuscript in the core manuscript file, before the References list. The statement should be placed in a new section entitled 'Declaration of Generative AI and AI-assisted technologies in the writing process'

Statement: During the preparation of this work the author(s) used [NAME TOOL / SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication

This declaration does not apply to the use of basic tools for checking grammar, spelling, references etc. If there is nothing to disclose, there is no need to add a statement.

Informed consent and patient details

Studies on patients or volunteers (including organ/tissue donors) require 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 the author has 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.

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.

Reporting sex- and gender-based analyses

Reporting guidance

For research involving or pertaining to humans, animals or eukaryotic cells, investigators should integrate sex and gender-based analyses (SGBA) into their research design according to funder/sponsor requirements and best practices within a field. Authors should address the sex and/or gender dimensions of their research in their article. In cases where they cannot, they should discuss this as a limitation to their research's generalizability. Importantly, authors should explicitly state what definitions of sex and/or gender they are applying to enhance the precision, rigor and reproducibility of their research and to avoid ambiguity or conflation of terms and the constructs to which they refer (see Definitions section below). Authors can refer to the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER guidelines checklist. These offer systematic approaches to the use and editorial review of sex and gender information in study design, data analysis, outcome reporting and research interpretation - however, please note there is no single, universally agreed-upon set of guidelines for defining sex and gender.

Definitions

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth"), most often based solely on the visible external anatomy of a newborn. Gender generally refers to socially constructed roles, behaviors, and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society. Sex and gender are often incorrectly portrayed as binary (female/male or woman/man) and unchanging

whereas these constructs actually exist along a spectrum and include additional sex categorizations and gender identities such as people who are intersex/have differences of sex development (DSD) or identify as non-binary. Moreover, the terms "sex" and "gender" can be ambiguous--thus it is important for authors to define the manner in which they are used. In addition to this definition guidance and the SAGER guidelines, the resources on this page offer further insight around sex and gender in research studies.

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.

Mendelian randomization studies

Mendelian Randomization (MR) is a method that uses genetic variation associated with a putative exposure as an instrument to infer a causal effect of that exposure on an outcome. In order for the MR inference to be valid, three key assumptions need to be met: (1) there is a strong and stable effect of an instrument on the exposure of interest, (2) there are no confounders that can create spurious associations of the instrument with the exposure and the outcome, and (3) there is no independent pathway between the instrument and the outcome other than through the exposure (i.e., no horizontal pleiotropy).

Violation of the key MR assumptions can lead to erroneous conclusions. Such violations may be difficult to detect when publicly available summary statistics are used without proper quality control, sensitivity analyses, and explicit testing. Moreover, given large numbers of GWAS traits (including proteome and metabolome-wide studies) and tens of thousands of

trait-associated variants (and their various combinations), the MR approach can theoretically test an infinite number of "causal hypotheses." The issue of multiple testing becomes then difficult to control, and there are currently no standards to address this issue. Therefore, in order to consider a manuscript reporting MR results, we require a strong starting "causal hypothesis" that is already supported by some independent evidence. Any MR report submitted to our journal must also conform to the STROBE-MR guidelines (Skrivankova *et al*., *JAMA*, 2021).

In summary, we advise authors to use the MR methods as an ancillary approach, adding to the evidence for a specific hypothesis in a multi-level study. Stand-alone **single hypothesis** MR studies based solely on secondary analyses of published summary statistics and/or without independent validation of the hypothesized effect are unlikely to be considered as high priority for *Kidney International*.

Reference:

Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, VanderWeele TJ, Higgins JPT, Timpson NJ, Dimou N, Langenberg C, Golub RM, Loder EW, Gallo V, Tybjaerg-Hansen A, Davey Smith G, Egger M, Richards JB. Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement. *JAMA*. 2021;326(16):1614–1621. doi: 10.1001/jama.2021.18236. PMID: 34698778.

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

Preparation of manuscripts

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. **Note that at least the most important sections of the Methods must ALWAYS be described in the text of the paper before the Results section, with the longer description in supplementary material as needed. Please note that this placement is not preferred but will be allowed if the word count is exceeded.**

The *American Medical Association Manual of Style* (11th 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

Kidney International publishes the following types of articles:

Review

- Word limit: Reviews should be between 3,000 and 5,000 words, and on average 4,000 words, excluding abstract, references, tables, and figures.
- Abstract: 250 words maximum.
- Keywords: 3–6
- References: 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, as well as a copy of their personal bibliography. 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 maximum, excluding abstract, references, tables, and figures.
- Abstract: 250 words maximum.
- 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](#Data Sharing)
- Graphical Abstract required. See [Graphical Abstract](#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,
- Brief abstract (no more than 150 words)
- Keywords: 3–6,
- Introduction,
- Short Methods,
- Results,
- Discussion (no headings necessary),
- Disclosure statement required,
- Acknowledgments,
- References (no more than 25),
- Tables (each including a title and legend), and
- Figure legends.
- 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 figures and/or tables**. Figures should be uploaded as individual files. **The study design, detailed methods, and/or supporting data should be included in a single file as online Supplementary Material.**
- A Graphical Abstract is required. See [Graphical Abstract](#Graphical Abstract) section for more details.

Technical note

- Word limit: 1,500 words maximum, excluding abstract, references, tables, and figures.
- Abstract: 250 words maximum.
- Keywords: 3–6.
- Include a Translational Statement (or Lay Summary if the Technical Note is clinically relevant)
- 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 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.
- Keywords: 3–6.
- No abstract. Enter "NA" in the submission form.
- Graphical Abstract required. See [Graphical Abstract](#Graphical Abstract) section for more details.
- Include a short description (1–3 sentences) of the study design in the Methods section. Indicate that full methods are provided in the Supplementary Material.
- Disclosure statement required.
- References: 9 maximum. Additional references must be excluded from the main manuscript and be provided in the Supplementary Material.
- All Supplementary Material must be provided in a single file and include the Supplementary Methods and Supplementary References, if applicable. Supplementary References must be formatted with the prefix "S" (e.g., S1, S2, etc.). Cite the individual supplementary material elements (e.g., Supplementary Methods, Supplementary References, etc.) in the main text. Under a Supplementary Material heading before the references, state the type of supplementary file [e.g., "Supplementary File (PDF)"] and list each supplementary component, e.g., "Supplementary Methods." and "Supplementary References."
- Figures/tables: Limit of 2 tables and/or figures. Additional tables/figures should be provided in the Supplementary Material file.

Clinical trials

- Word limit: 4,000 words maximum, excluding abstract, references, tables, and figures.
- Abstract: 250 words maximum.
- 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](#Data Sharing)

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 (https://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; and
- be managed by a not-for-profit organization.

Examples of registries that meet these criteria include:

1. the registry sponsored by the United States National Library of Medicine (http://www.clinicaltrials.gov),
2. the International Standard Randomized Controlled Trial Number Registry (http://www.controlled-trials.com),
3. the Cochrane Renal Group Registry (http://www.cochrane-renal.org), and
4. the 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 https://www.goodreports.org/reporting-checklists/consort/.

Commentary (by invitation only)

- Word limit: 250 words maximum, excluding abstract and references.
- Title: 115 characters maximum, including spaces.
- Abstract: 75 words 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 maximum. Supplementary Material (e.g., Supplementary Methods, Supplementary References, Supplementary Figures or Tables) is encouraged, to remain within the word limit.
- Abstract: no abstract required for this manuscript type.
- Provide all Supplementary Material in a single PDF and cite each individual supplementary material element (e.g., Supplementary Methods, Supplementary

References, Supplementary Figure S1, etc.) in the main text. 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 a caption of each element.

- References: 4 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 caption "Supplementary References."
- 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 maximum.
- 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.

Editorial: Special Report (by invitation only)

Proposals for Editorial: Special Report must be submitted to the Editorial Office (pmorriss@wustl.edu). Authors should send only an outline of the proposed paper for initial consideration.

- Maximum length: 1600 words, excluding abstract, tables, figures, and references.
- Title page with authors, affiliations, and corresponding contact details.
- Abstract: 150 words.
- Keywords: 3–6.
- Disclosure statement required.
- List of supplementary materials (if applicable).
- References: 5 maximum.
- Figures/tables: 2 maximum; original work preferred.

Nephrology image (by invitation only)

EFFECTIVE NOVEMBER 1, 2022—**Pre-submission proposals** for Nephrology Images must be emailed to the editorial office (lueg@wustl.edu). A limited number are accepted for publication. Proposals should include the main image(s) and a brief description of the case. KI seeks illustrative images that are unique or highly illustrative of specific occurrences in nephrology, such as renal pathology, radiology, specific skin lesions, etc. **Invited**

submissions are accompanied by a brief 1-paragraph description of relevant clinical information.

- The title has a 70-character limit.
- The text has a 300-word limit.
- Maximum the equivalent of 2 single-panel figures.
- Additional figures may be included as supplementary images to appear online but not in print.
- No references; no abstract.
- The article must fit on 1 printed journal page. Authors will be asked to shorten text or cut figures at the proof stage if the article exceeds 1 page.

Make your diagnosis (by invitation only)

EFFECTIVE NOVEMBER 1, 2022—**Pre-submission proposals** for Make Your Diagnosis articles must be emailed to the editorial office (lueg@wustl.edu). A limited number are accepted for publication. Proposals should include a brief description of the case and diagnosis. **Invited submissions** provide readers with an opportunity to make clinical diagnoses based on an image or data accompanied by the history and physical exam—all of which must appear on printed page 1 (The Case). Printed page 2 includes the answers, a brief discussion, and any other relevant follow-up images and laboratory data (The Diagnosis).

- The title has a 70-character limit.
- The case has 245-word limit.
- The diagnosis has 405-word limit.
- Maximum 1 single-panel figure or table per page.
- Maximum 3 references; no abstract.

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 (by invitation only)

- 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.

Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but British spelling will be revised to American spelling during the copyediting stage). 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 Language Editing service available from Elsevier's Language 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.

Open access

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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 250 words, 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 3 to 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.

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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.
Lay summary (for clinical investigation and clinical trial a

The Editors require this short paragraph of about 100–150 words to convey the article content, aimed at nonspecialists in the field and written in a way that they can easily understand. The structure of a lay summary should answer the main questions of "who/what/where/when/how many/why?" It should include one final sentence that explains why the research is important, and what the article has concluded. Please include this paragraph under the heading "Lay Summary" and place it in the manuscript following the abstract. For more information on Lay Summaries, see https://www.elsevier.com/connect/authors-update/in-a-nutshell-how-to-write-a-lay-summary.

Text

The manuscript should be organized under the following 11 headings:

- Graphical Abstract
- Title page
- Abstract
- Translational Statement (only for Basic Research articles)
- Introduction
- Methods
- Results
- Discussion
- Disclosure statement
- References
- Acknowledgements

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, Eleventh 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:

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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.

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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*. 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. 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

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.).

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*.

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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.

Authorship

Requirements for all categories of articles should conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," developed by the ICMJE (https://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:

1. Conceived and/or designed the work that led to the submission, acquired data, and/or played an important role in interpreting the results.
2. Drafted or revised the manuscript.

3. 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.

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-involving-human-subjects/; 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 https://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:

1. 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.
2. Appropriate correction of *P* values for multiple comparisons is also required. In many cases this will involve calculation of empiric *P* values by permutation.
3. 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.
4. 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).
5. Replication of the association in an independent cohort is required for new association findings.
6. 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 policy

Kidney International endorses the FAIR (findable, accessible, interoperable and re-usable) Data Principles as a framework to promote the broadest reuse of research data. Our journal **requires** and enables you to share data that supports your research publication and enables you to interlink the data with your published articles. Research data refers to the results of observations or experimentation that validate research findings. To facilitate reproducibility and data reuse, this journal **requires** you to also share any custom software/code, models, algorithms, protocols, and methods that were used to reach your conclusions. This policy applies to all original research published in *Kidney International* (Basic Research Investigation, Clinical Investigation, Clinical Trial, Landmark Communication, Technical Note, and Research Letter).

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