BMJ Open

Development and validation of a clinical prediction model of acute kidney injury in intensive care unit patients at a rural tertiary teaching hospital in South Africa: a study protocol

Busisiwe Mrara ,[1] Fathima Paruk,[2] Constance Sewani-Rusike,[3] Olanrewaju Oladimeji[4]

To cite: Mrara B, Paruk F, Sewani-Rusike C, *et al*. Development and validation of a clinical prediction model of acute kidney injury in intensive care unit patients at a rural tertiary teaching hospital in South Africa: a study protocol. *BMJ Open* 2022;**12**:e060788. doi:10.1136/bmjopen-2022-060788

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-060788).

Received 03 January 2022
Accepted 01 June 2022

[1]Anaesthesiology and Critcal Care, Walter Sisulu University, Mthatha, Eastern Cape, South Africa
[2]Department of Critical Care, University of Pretoria, Pretoria, Gauteng, South Africa
[3]Human Biology, Walter Sisulu University, Mthatha, Eastern Cape, South Africa
[4]Department of Public Health, Walter Sisulu University, Mthatha, Eastern Cape, South Africa

Correspondence to
Busisiwe Mrara;
bmrara@wsu.ac.za

ABSTRACT

Introduction Acute kidney injury (AKI) is a decline in renal function lasting hours to days. The rising global incidence of AKI, and associated costs of renal replacement therapy, is a public health priority. With the only therapeutic option being supportive therapy, prevention and early diagnosis will facilitate timely interventions to prevent progression to chronic kidney disease. While many factors have been identified as predictive of AKI, none have shown adequate sensitivity or specificity on their own. Many tools have been developed in developed-country cohorts with higher rates of non-communicable disease, and few have been validated and practically implemented. The development and validation of a predictive tool incorporating clinical, biochemical and imaging parameters, as well as quantification of their impact on the development of AKI, should make timely and improved prediction of AKI possible. This study is positioned to develop and validate an AKI prediction tool in critically ill patients at a rural tertiary hospital in South Africa.

Method and analysis Critically ill patients will be followed from admission until discharge or death. Risk factors for AKI will be identified and their impact quantified using statistical modelling. Internal validation of the developed model will be done on separate patients admitted at a different time. Furthermore, patients developing AKI will be monitored for 3 months to assess renal recovery and quality of life. The study will also explore the utility of endothelial monitoring using the biomarker Syndecan-1 and capillary leak measurements in predicting persistent AKI.

Ethics and dissemination The study has been approved by the Walter Sisulu University Faculty of Health Science Research Ethics and Biosafety Committee (WSU No. 005/2021), and the Eastern Cape Department of Health Research Ethics (approval number: EC 202103006). The findings will be shared with facility management, and presented at relevant conferences and seminars.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The data will be collected prospectively, assuring quality and the collection of specific predictor data for building the model.
⇒ The predictive model will be internally and externally validated.
⇒ First such study to be conducted in a resource-limited setting.
⇒ This is a single-centre study with limited heterogeneity in the cohort and the possibility of model overfitting.
⇒ The sample size is relatively small, due to the additional testing of biomarkers.

INTRODUCTION

Acute kidney injury incidence in third world ICUs

The Kidney Disease Improving Global Outcomes guidelines define acute kidney injury (AKI) as an abrupt decline in renal function that occurs over hours to days, resulting in the accumulation of nitrogenous wastes and fluid overload.[1] Data from predominantly high-income countries suggest that AKI occurs in about 21% of adults and 34% of children, with associated mortality rates of 24% and 14%, respectively.[2] The incidence of AKI in critically ill patients is even higher than in general hospital admissions and has been reported to be over 50%, with a four-fold increase in mortality risk compared with patients without AKI.[3]

The availability of resources is believed to be an important factor contributing to the rising AKI incidences.[2] A world incidence of AKI meta-analysis found an inverse relationship between AKI incidence and total health expenditure in the country.[2] Furthermore, data from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) in the UK suggest that in-hospital AKI incidence is linked to poor healthcare quality as more than half of AKI cases were potentially avoidable had there been simple

interventions such as meticulous fluid titration and avoiding nephrotoxins.[4]

AKI management costs are simply unaffordable in low-income countries. Data from a tertiary hospital in South Africa, an upper-middle-income country, revealed that more than half of patients admitted with AKI required intensive care admission and dialysis;[5] both interventions are in short supply in the country. In 2016, the cost of dialysis for an adult patient in South Africa was estimated to be four times the national health budget allocation per person.[6]

To date, there is no effective treatment for established AKI, other than supportive renal replacement therapy (RRT), with limited impact on mortality. There is no recent evidence of successful AKI pharmacotherapy. The heterogeneity of AKI pathogenesis could be one of the reasons for the difficulty in finding a cure. Furthermore, the difficulties in early diagnosis often result in AKI presenting in an established untreatable state. Thus, the only intervention currently available to improve patient outcomes is the early identification of patients at risk, renal injury preventive strategies and the early diagnosis of AKI to halt further injury.

Pathophysiology of acute kidney injury: opportunities for exploration

There is ongoing biomedical research to elucidate AKI mechanisms, identify molecular targets for pharmacotherapy and ascertain interventions to prevent and treat AKI. Significant progress has been made in understanding renal cellular and mitochondrial function and new therapeutic solutions are in the pipeline.[7] Multiple physiological pathways such as oxidative stress, inflammation, apoptosis and necroptosis are involved in the evolution of AKI. The complexity of AKI pathophysiology makes finding a cure difficult, as multiple phenotypes that do not fit into one pathophysiological pathway have been described.[8] Regardless of the cause, the main pathophysiological mechanisms in AKI, ischaemia and toxic injury, have common histopathologic findings: inflammation, vascular and tubular injury. Furthermore, AKI in sepsis displays a combination of relative ischaemia due to microvascular dysfunction, and inflammation, with oxidative stress.[9] Sutton *et al* described four phases of tubular injury due to an ischaemic insult: initiation, extension, maintenance and recovery.[10] These clinical phases are directly related to cellular events during the injury and recovery process and correlate with the degree of renal perfusion reduction.[10 11] Endothelial injury and inflammation characterise the extension phase, which may be the defining event that converts transient AKI to persistent AKI.[11] Endothelial injury alters renal perfusion thus propagating tissue hypoxia and inflammation. When endothelial injury occurs, haemodynamic therapies such as fluids and vasopressors are ineffective and could be detrimental to renal recovery. Endothelial injury monitoring therefore is a relatively unexplored tool of early AKI diagnosis. A biomarker of endothelial injury in current use is Syndecan-1, a proteoglycan component of the endothelial glycocalyx (eGCX), the physiologically active layer lining the endothelium. Circulating levels of Syndecan-1 and heparan sulphate are proportionally related to the degree of eGCX damage and are associated with a proinflammatory state.[12] Syndecan-1 is a promising biomarker for AKI prediction in the setting of multiorgan failure and has been explored in sepsis, heart failure and paediatric cardiac surgery with variable results.[13–15]

Distant organ failure preceding biochemical AKI, common in critically ill patients, is mediated via generalised inflammation and endothelial dysfunction. With respiratory failure being the most common organ failure preceding AKI,[16] detecting pulmonary oedema and capillary permeability from endothelial dysfunction could enhance vigilance for AKI and modification of haemodynamic support. Investigating endothelial dysfunction, and respiratory failure as early AKI predictors, has the potential to improve haemodynamic management to prevent AKI progression.

Acute kidney injury predictive tools in the intensive care unit

Over 20 AKI predictive models have been published, with the majority based on chronic illness markers, acute physiological changes and biomarkers. These models were developed for specific patient subsets, and do not always work well in mixed intensive care unit (ICU) populations. Furthermore, some had low incidences of AKI in the derivation cohort and used creatinine as both a predictor and outcome variable. Moreover, many predictive models have not been validated and used. Predictive tools that combine biomarkers and clinical parameters are known to outperform tools that rely on a single type of parameter. Urinary cell-cycle arrest markers, such as nephrocheck, a combination of urine insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP), are currently the most accurate predictive biomarkers used in critical care patients.[17 18] NephroCheck detects cell cycle arrest, a hibernation phase in renal tubular cells subjected to ischaemia.

The applicability of currently available AKI predictive models cannot be assumed for patients from lower-resource countries as the patients are often younger, sicker from limited access to healthcare and ICU and have fewer comorbidities. Furthermore, HIV-related illneses often present in an advanced state, due to limited access to anti-retroviral therapy, possibly influencing the occurence and complications of AKI. Additionally, unique risk factors such as herbal and traditional medications, and hypertensive disorders of pregnancy, highly prevalent in low-income and middle-income countries, need to be explored.[19] Thus, the participants and predictors are uniquely different from the cohorts used to develop AKI prediction models in high-income settings.

The objectives of the study are to:

1. Determine the predictors of AKI in critically ill patients, in a resource-limited setting, using existing ICU data.

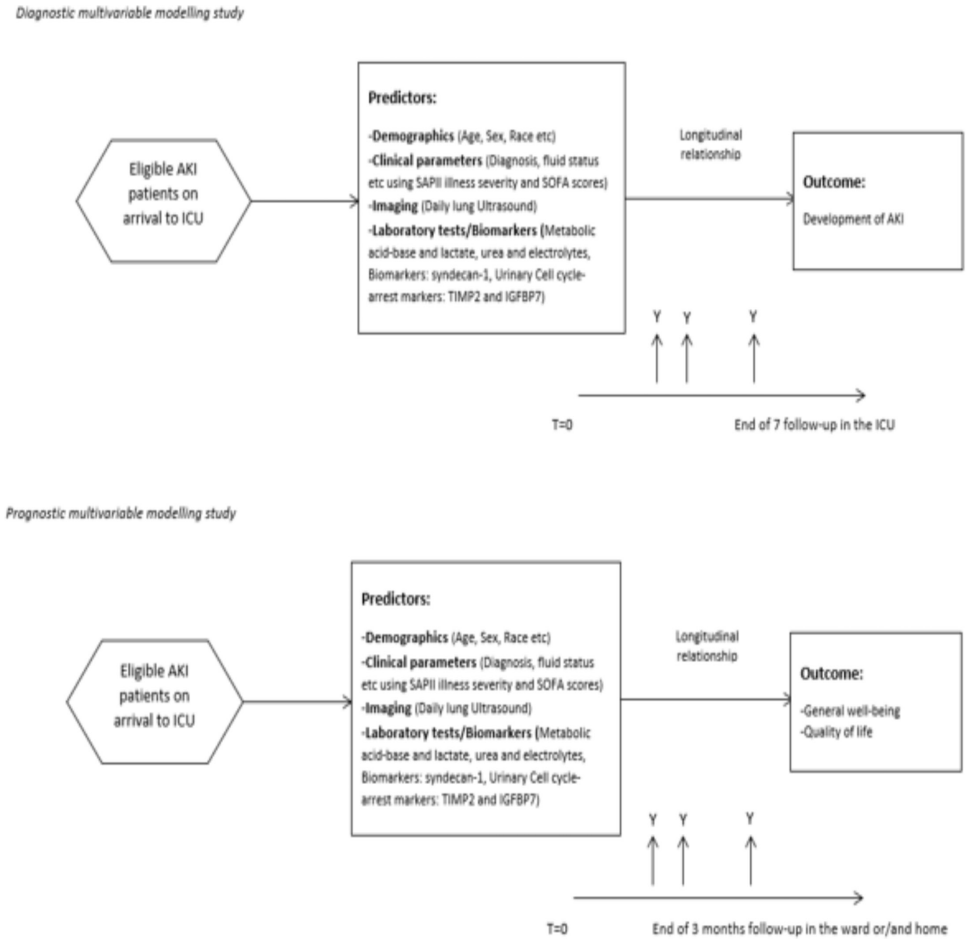

Figure 1 Visual aid outlining the study plan. AKI, acute kidney injury; ICU, intensive care unit.

2. Investigate distant organ dysfunction and pulmonary oedema as early AKI predictors.
3. Investigate Syndecan-1, an endothelial shedding biomarker as an AKI predictor, and compare its performance to the known AKI biomarker, NephroCheck (a combination of urine IGFBP7 and TIMP).
4. Investigate the association of abnormal renal vascular reactivity with endothelial dysfunction, and as an AKI predictor.
5. Develop and validate a multivariable clinical prediction model using the strong predictors in the cohort.
6. Determine 3-month outcomes of patients developing AKI in the ICU (mortality, and quality of life)

METHODS AND ANALYSIS

Study design and implementation flow

We plan to conduct the study in four phases as shown in figure 1.

Sources of data

The study will be carried out in the multidisciplinary ICU at Nelson Mandela Academic Hospital (NMAH), a 600-bed tertiary-level teaching hospital in Mthatha, South Africa. The first phase will use retrospective data from ICU records, while phases 2–4 will collect clinical data from participants prospectively.

Participants

For phase 1, the study population will comprise all patients admitted to the ICU between 2019 and 2020. For phases 2–4 all eligible patients where consent can be obtained will be enrolled for the prospective study.

Inclusion criteria

1. Phase 1: all patients>12 years old, admitted to the ICU for at least 24 hours. The ICU at NMAH admits patients from 12 years and above. The renal function of adolescents is like that of young adults.[20]
2. Phases 2–4, all patients above 12 years old from whom appropriate consent/ascent can be obtained, admitted to the ICU for at least 24 hours, requiring support for one or more organs.

Exclusion criteria

1. Patients with stage 2 AKI (or higher) on admission to the ICU
2. Patients with chronic kidney disease.

Outcome assessment

1. Primary outcome: new AKI stage 1 and worse (a SCr rise of >1.5 times the baseline or of >26 micromoles/L,

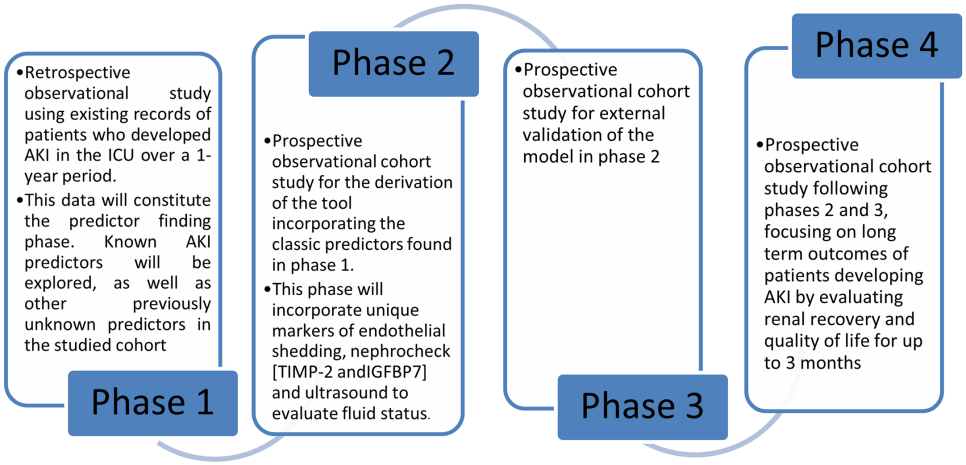

Figure 2 Illustration of timeline for recruitment and follow-up in phases 2–4. ICU, intensive care unit; IGFBP7, insulin-like growth factor-binding protein 7; TIMP, tissue inhibitor of metalloproteinases-2.

within 48 hours or a urine output of <0.5 L/kg/h for 6–12 hours)

The value used for baseline SCr, as used in previous publications, will be from the previous 7 days. If there are no recent results, a test value from the previous 2 months in the laboratory records will be used, failing which, an estimate from age and gender will be made using the Modification of Diet in Renal Disease formula using an estimated glomerular filtration rate of 75 mL/min/1.73 m^2.[20 21]

1. 2. Secondary outcomes: (i) need for RRT as assessed by the clinician. (ii) The outcomes will be assessed from the third day of ICU admission and followed up to discharge from the ICU, hospital or death, as indicated in the visual flow diagram in figure 2.

Baseline characteristics, laboratory parameters predictors, outcome assessment and follow-up

Phase 1: retrospective case–control study

Retrospective data to be collected from the ICU database:

1. All patients developing AKI in 2019 and 2020 (the period preceding the commencement of the prospective study phase) stage 1 or worse, during the ICU stay, identified from the database.
2. Comparator: patients admitted within the same period, who did not develop AKI.
3. Clinical and laboratory parameters will be compared between the two groups. The following data will be collected.

- Demographic data: age, sex, race comorbidities.
- Clinical data: diagnosis, referring discipline and hospital, surgical intervention details and other pre-ICU clinical details.
- Acute illness severity score on admission, Acute Physiology and Chronic Health Evaluation II (APACHE II), daily Sequential Organ Failure Assessment (SOFA) scores, daily urine output and cumulative fluid balance.
- ICU interventions: ventilation, inotropes, antibiotics, dialysis details, where applicable.
- Laboratory parameters: serum urea/creatinine ratios, chloride, albumin, microbiology results, HIV status and viral loads.

Phase 2: prospective cohort study: with the derivation of the predictive model

This phase will include the evaluation of significant predictors identified from phase 1. Additionally, the following data will be collected within 12 hours of admission to ICU, and daily during the ICU stay, until the 3–7 days, discharge or death:

- Demographic data: age, sex, race, referring hospital and discipline, timing of admission to the referring and tertiary hospitals, ascertaining admission delays.
- Clinical parameters: diagnosis, surgical intervention, physiological parameters, fluid resuscitation before ICU (type and amount of fluid), weight, fluid status assessment on admission (eg, passive leg raise, Central Venous Pressure, systolic pressure variation), ultrasound-guided inferior vena cava assessment for fluid status. Daily organ support parameters will be recorded to compute SOFA scores.
- Laboratory/imaging: acid-base, lactate, urea and electrolytes, lung ultrasound (daily), Doppler Renal Resistive Index (RI), Extravascular Lung Water Index (EVLWi) measured with transpulmonary thermodilution.

  Biomarkers: serum Syndecan-1, urinary cell cycle-arrest markers: TIMP2 and IGFBP7, nephrocheck. Serum and urine samples will be collected on the second and third days of ICU admission.

Syndecan-1 is a biomarker of eGCX shedding (Abcam, Cambridge, MA, USA). Its detection range is 4–256 ng/mL and the intra-assay coefficient of variation is 6.2%. It is quantified using a commercially available enzyme-linked immunosorbent assay (Diaclone SAS, Besancon, France; lower limit of detection 4.94 ng/mL).

Urinary [TIMP-2] •[IGFBP7] will be measured in units of (ng/mL)2/1000 using the NephroCheck Test (Astute Medical, San Diego, CA). The test procedure involves

adding fresh urine samples to a buffer mixed with a fluorescent antibody conjugate. The sample is applied to a cartridge and inserted into a designated platform for incubation, reading, result calculation and result display. The plastic cartridge is single-use and contains sandwiched immunoassays for TIMP-2 and IGFBP7. The test score, called AKI Risk Score, is derived from multiplying the concentrations of the two biomarker levels. An AKI Risk Score of 0.3 or less indicates a low risk of developing moderate to severe (AKI stage 2 and AKI stage 3) AKI within 12 hours of the assessment, while an AKI Risk Score of greater than 0.3 suggests a high risk of developing moderate to severe AKI within 12 hours. The AKI Risk Score exhibits approximately 10% coefficient of variation at the recommended cut-off value of 0.3 and the lower limit of quantitation is 0.002.[22]

Abdominal Doppler ultrasound for renal vascular reactivity will be performed on the second and third days with a 7.5 MHz transducer using a previously described measurement technique for the RI.[23 24] Sonography and colour Doppler mode will be used to localise each kidney and its interlobar arteries. Pulse-wave Doppler will measure blood flow velocities in the interlobar arteries. Peak systolic and end-diastolic velocities will be measured on five consecutive pulses. RI = (peak systolic velocity–end-diastolic velocity)/peak systolic velocity. The recorded RI values will be the average of the five measurements for each kidney. RI measurements will be performed by an appropriately qualified sonographer.

Cardiac output (CO) and EVLWi will be measured by transpulmonary thermodilution using the validated EV1000 VolumeView system.[25 26] The measurements are performed by injecting 20 mL cold saline (<8°C) into a central vein draining into the superior vena cava. The VolumeView system provides EVLWi measurements, after averaging three consecutive injections. VolumeView uses the area under the curve (AUC) of the transpulmonary thermodilution curve to measure CO, and the slope of the transpulmonary thermodilution curve to calculate the intrathoracic fluid volume and intrathoracic blood volume. The difference between the two volumes signifies extravascular fluid in the chest and is referred to as EVLWi. The value of EVLWi considered normal is <7 mL/kg of predicted body weight.[27]

Phase 3: validation of the predictive model

The clinical model developed will be validated in this phase using a new cohort of ICU patients. The same data will be collected as in phase 2, to test the model developed in phase 2. The predictive ability of the model will be compared with the actual occurrence of AKI.

Phase 4: prospective cohort study: follow-up on participants with AKI

Patients who developed AKI will be followed up for up to 3 months after discharge:

1. Assessing for general well-being, and quality of life.
2. Renal function, serum urea, creatinine, and electrolytes at or after 3 months.

Ethics and dissemination

The study has been approved by the Walter Sisulu University Faculty of Health Science Research Ethics and Biosafety Committee (WSU No. 005/2021), and the Eastern Cape Department of Health Research Ethics (approval number: EC 202103006). The findings will be shared with facility management, presented at relevant conferences and seminars.

Participant confidentiality

Before enrolment, written informed consent will be obtained from each participant or from the patient's next-of-kin, where it is not possible from the patient.

Participant and record data will be collected on either an electronic or paper case record form (CRF) for every patient recruited. Paper CRFs will be stored within a locked office in the hospital as they will include identifiable patient data in order to allow follow-up of clinical outcomes. Electronic data will be pseudoanonymised by the generation and use of a unique numeric code that is delinked to the participant's name in the electronic CRF. The numeric code allocated to each participant will be stored electronically, separately from the electronic CRF, in a secure, password-protected, internet-based file on the Research Electronic Data Capture (REDCap) platform. Each patient will thus only be identified on the electronic CRF by their numeric code.

Patient and public involvement

Study conception and design did not involve patients. As is required by South African ethics committees and stated in the study consent forms, a plain English summary and a Xhosa (local language) translation of the study will be provided to all study participants (and their next-of-kin) at the conclusion of the study. Wider dissemination of the study results to the community will be done via the media, patient support groups and open events at the hospital.

Sampling and sample size estimation

Participants meeting the inclusion criteria will be conveniently enrolled on the study. Patients over the age of 12 who were admitted to the ICU and stayed for at least 24 hours will be recruited for phase 1. Participants in phases 2–4 will be like those in phase 1, with informed or proxy consent.

Phase 1: The sample size and power for a case–control study were calculated using the Epi Info software V.7.02 STAT CALC. A retrospective collection of 55 matched patients (cases) who developed AKI after being admitted to the ICU between 2019 and 2020 with 55 patients who did not developed AKI during the same period (control).

Phases 2 and 3: To improve the statistical power of the sample size, we used the most mentioned 'rule of thumb, 10 events needed per predictor'.[28–31] Considering four[4] potential predictors to include in the model which equates to 40 (4*10) cases of AKI. In our facility,

the reported prevalence of AKI is 50%. A sample size of at least 80 (100/50*40) participants is needed for each of the derivation and validation phases of the study. A minimum of 160 AKI patients would be sufficient to build the model.

Analysis plan

Data management, handling missing data and attrition from follow-up

Data will be collected using REDCap and subsequently downloaded into CSV for exploration in Excel.

Because of suboptimal record archiving systems in our setting, to retain as many records as possible without biasing the model, we will apply a threshold of 40% of the missing parameters for each record in phase 1, that is, any record with more than 40% missing parameters would be excluded from the data analysis process since such large amounts of missingness will reduce statistical power and increase standard errors. When cases with missing data are ignored, information is lost, reducing statistical power and increasing standard errors.[32] However, when more than 10% of the data is missing, according to Bennett, statistical analysis is likely to be skewed or biased. In an event where we have a lower proportion of missing data, multiple imputation (MI) using multiple correspondence analysis will be considered, and the data's goodness-of-fit will be tested.[33]

Missing data in phases 2–4 (prospective phases) will be handled using an MI method. The method considers the circumstances surrounding missing data and provides more accurate parameter estimates. MI procedures do not directly replace a missing value; rather, they use information from observable data along with statistical assumptions to statistically estimate population parameters and the missing data mechanism for the most accurate representation of the available data sets.[34]

The MIs create numerous completed candidate data sets according to the missing data situation, and then combine these candidate data sets into one estimate for the missing data, rather than imputing a single value for each missing data.[35] In this context, validation using MI will be checked by verifying the goodness-of-fit of the imputation models using regression model assumptions. The standard regression diagnostics that will be used include investigations of residuals, outliers and influential instances. If the diagnostics indicate a poor model fit, the algorithms will need to be run several times before the imputations are generated.[36]

Patient attrition during the 3 months follow-up would be considered in the sample pool estimation; however, comprehensive discharge planning and a home follow-up protocol (calls, text messages and home visits, as appropriate) will be implemented to improve patients' care transitions and reduce attrition rates.[37 38]

Data analysis

Stata V.13 (StataCorp, College Station, TX) and the R project for statistical computing software will be used for the data analysis.

Descriptive statistics will be used for the sample groups (mean and SD or median and IQRs, as appropriate). Unpaired t-tests will be used to compare continuous variable group means if the data are normally distributed; otherwise, non-parametric (Mann Whitney U) methods will be considered. The χ^2 test for categorical variables and analysis of variance with post hoc Scheffe analysis for normally distributed continuous variables will be used to compare patient characteristics and outcomes between patients who develop AKI and those who do not develop AKI.

Multivariate regression analysis will be performed by comparing variables with univariate associations with the outcome to elucidate the association. Multiple regression models will be used to determine the individual contribution of the selected independent variables in AKI development. Following that, a statistical model will be developed based on the weighted strong predictors. A Kaplan–Meier estimator and the Cox proportional-hazards model will be used to determine survival characteristics for AKI patients. The Hosmer–Lemeshow test will be used to determine the goodness of fit for logistic regression models. In all analyses, a p value of 0.05 will be considered statistically significant. The model will first be validated in the testing (derivative) set, and the new model's performance will be evaluated in the validation data set. The test characteristics of the predictive parameters as AKI predictors (sensitivity, specificity, positive predictive value and negative predictive value) will be determined by calculating the receiver-operator characteristics curve and AUC. The Decision Curve Analysis (DCA) will be used to display the entire range of prediction thresholds that the new model will use to predict the risk of AKI. The model will be calibrated using a penalised logistic regression model and the selection operator (lasso) method for the variables in the final model to minimise the residual sum of squares and improve the clinical predictive accuracy of AKI risk in ICU patients.

Participants drop-out will be adjusted for at the analysis stage. We will equally consider the MI process if needed.[39 40] To evaluate group differences at various time points of follow-up, descriptive statistics and bivariate tests of associations will be used as needed. The relationships between key variables and study outcomes will be examined with appropriate univariate, multivariate and mixed model multilevel analyses.

Study timeline

We estimate that the study will last 2 years. Phase 2 patient enrolment began in June 2021 and will take 9–12 months, followed by 3 months for data cleaning and analysis, and preparation of manuscripts and abstracts.

DISCUSSION

This project is a first-of-its-kind in the management of critically ill patients with AKI in a rural resource-limited

setting. It is the first time that a predictive model will be developed and validated specifically for clinical prediction of AKI, rather than adapting models developed for patients in other settings. The tool will be developed in a resource-constrained setting where patients are younger, have a high HIV prevalence and may be exposed to novel nephrotoxins from herbal medications. The project's goal is to improve AKI screening to prevent further harm from nephrotoxic iatrogenic interventions such as drugs and fluids. The tool will hopefully, reduce AKI morbidity and mortality while also saving costs for the health system. Furthermore, as a follow-up project, patients with AKI will be followed for up to 3 months to assess renal recovery and quality of life, thereby improving the understanding of these patients' long-term outcomes.

Recognising multiple pathways in the pathophysiology of AKI, the study is positioned to investigate the utility of novel predictors such as the endothelial shedding biomarker, Syndecan-1, and explore the possibilities of improved fluid management guidance and haemodynamic support for the kidney presented by the early diagnosis of distant organ dysfunction preceding AKI.

This study will adhere to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement guidelines for transparent reporting of diagnostic predictive models.[41]

Contributors BM, CS-R and FP conceived the project idea; BM and OO initiated the discussion to publish this protocol; BM, FP and OO created the first draft and attended to the revisions of this submission. All authors have provided critical review and approved this final version.

Funding The research reported in this publication is supported by the Discovery (grant no: 038208). The content is solely the responsibility of the authors and does not necessarily represent the official views of Discovery.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD

Busisiwe Mrara http://orcid.org/0000-0002-2130-1756

REFERENCES

1 , Fliser D, Laville M, *et al*, Ad-hoc working group of ERBP. A European renal best practice (ERBP) position statement on the kidney disease improving global outcomes (KDIGO) clinical practice guidelines on acute kidney injury: Part 1: definitions, conservative management and contrast-induced nephropathy.. *Nephrol Dial Transplant* 2012;27:4263–72.
2 Susantitaphong P, Cruz DN, Cerda J, *et al*. World incidence of AKI: a meta-analysis. *CJASN* 2013;8:1482–93.
3 Bagshaw SMEAJ, Bellomo R, Bellomo R, Colman DNC K, *et al*. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med* 2015;41:1411–23.
4 Stewart GF, N J, Smith KK, Mason M. Acute kidney injury: adding insult to injury. National Confidential enquiry into patient outcome and death 2009:1–100.
5 Dlamini TAL, Heering PJ, Chivese T, *et al*. A prospective study of the demographics, management and outcome of patients with acute kidney injury in Cape town, South Africa. *PLoS One* 2017;12:e0177460.
6 Wearne N, Okpechi IG, Swanepoel CR. Nephrology in South Africa: Not Yet *ubuntu*. *Kidney Dis* 2019;5:189–96.
7 Kellum JA, Fuhrman DY. The handwriting is on the wall: there will soon be a drug for AKI. *Nat Rev Nephrol* 2019;15:65–6.
8 Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. *Clin Biochem Rev* 2016;37:85–98.
9 Peerapornratana S, Manrique-Caballero CL, Gómez H, *et al*. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019;96:1083–99.
10 Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int* 2002;62:1539–49.
11 Basile DP, Anderson MD, Sutton TA. Pathophysiology of acute kidney injury. *Compr Physiol* 2012;2:1303–53.
12 Torres Filho IP, Torres LN, Salgado C, *et al*. Plasma syndecan-1 and heparan sulfate correlate with microvascular glycocalyx degradation in hemorrhaged rats after different resuscitation fluids. *Am J Physiol Heart Circ Physiol* 2016;310:H1468–78.
13 Puskarich MA, Cornelius DC, Tharp J, *et al*. Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation. *J Crit Care* 2016;36:125–9.
14 de Melo Bezerra Cavalcante CT, Castelo Branco KM, Pinto Júnior VC, de Souza NM, de Oliveira Neves FM, Meneses GC, *et al*. Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. *J Thorac Cardiovasc Surg* 2016;152:178–86.
15 Neves FMdeO, Meneses GC, Sousa NEA, *et al*. Syndecan-1 in Acute Decompensated Heart Failure--Association With Renal Function and Mortality. *Circ J* 2015;79:1511–9.
16 Lee SA, Cozzi M, Bush EL, *et al*. Distant organ dysfunction in acute kidney injury: a review. *Am J Kidney Dis* 2018;72:846–56.
17 Hoste EAJ, McCullough PA, Kashani K, *et al*. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. *Nephrol Dial Transplant* 2014;29:2054–61.
18 Zhang D, Yuan Y, Guo L, *et al*. Comparison of urinary TIMP-2 and IGFBP7 cut-offs to predict acute kidney injury in critically ill patients: a PRISMA-compliant systematic review and meta-analysis. *Medicine* 2019;98:e16232.
19 Noubiap JJ, Bigna JJ, Nyaga UF, *et al*. The burden of hypertensive disorders of pregnancy in Africa: a systematic review and meta-analysis. *J Clin Hypertens* 2019;21:479–88.
20 Levey AS, Coresh J, Greene T, *et al*. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006;145:247–54.
21 Lamb EJ, Levey AS, Stevens PE. The kidney disease improving global outcomes (KDIGO) guideline update for chronic kidney disease: evolution not revolution. *Clin Chem* 2013;59:462–5.
22 Uettwiller-Geiger DL, Vijayendran R, Kellum JA, *et al*. Analytical characteristics of a biomarker-based risk assessment test for acute kidney injury (AKI). *Clinica Chimica Acta* 2016;455:93–8.
23 Mastorakou I, Lindsell DR, Piepoli M, *et al*. Pulsatility and resistance indices in intrarenal arteries of normal adults. *Abdom Imaging* 1994;19:369–73.
24 Schnell D, Darmon M. Renal Doppler to assess renal perfusion in the critically ill: a reappraisal. *Intensive Care Med* 2012;38:1751–60.
25 Bendjelid K, Giraud R, Siegenthaler N, *et al*. Validation of a new transpulmonary Thermodilution system to assess global end-diastolic volume and extravascular lung water. *Crit Care* 2010;14:R209.
26 Kiefer N, Hofer CK, Marx G, *et al*. Clinical validation of a new Thermodilution system for the assessment of cardiac output and volumetric parameters. *Crit Care* 2012;16:R98.
27 Sakka SG, Rühl CC, Pfeiffer UJ, *et al*. Assessment of cardiac preload and extravascular lung water by single transpulmonary Thermodilution. *Intensive Care Med* 2000;26:180–7.
28 Trongtrakul K, Patumanond J, Kongsayreepong S, *et al*. Acute kidney injury risk prediction score for critically-ill surgical patients. *BMC Anesthesiol* 2020;20:140.
29 Concato J, Peduzzi P, Holford TR, *et al*. Importance of events per independent variable in proportional hazards analysis. I. background, goals, and general strategy. *J Clin Epidemiol* 1995;48:1495–501.

30 Mallett S, Royston P, Waters R, *et al*. Reporting performance of prognostic models in cancer: a review. *BMC Med* 2010;8:21.
31 Bouwmeester W, Zuithoff NPA, Mallett S, *et al*. Reporting and methods in clinical prediction research: a systematic review. *PLoS Med* 2012;9:e1001221:12.
32 Peng C-YJ, Harwell M, Liou S-M, Ehman LH, editors. Advances in missing data methods and implications for educational research; 2006.
33 Bennett DA. How can I deal with missing data in my study? *Aust N Z J Public Health* 2001;25:464–9.
34 Dong Y, Peng C-YJ. Principled missing data methods for researchers. *Springerplus* 2013;2:222.
35 Janssen KJM, Vergouwe Y, Donders ART, *et al*. Dealing with missing predictor values when applying clinical prediction models. *Clin Chem* 2009;55:994–1001.
36 Nguyen CD, Carlin JB, Lee KJ. Model checking in multiple imputation: an overview and case study. *Emerg Themes Epidemiol* 2017;14:8.
37 Howard SJ, Elvey R, Ohrnberger J, *et al*. Post-Discharge care following acute kidney injury: quality improvement in primary care. *BMJ Open Qual* 2020;9:e000891.
38 Greer RC, Liu Y, Crews DC, *et al*. Hospital discharge communications during care transitions for patients with acute kidney injury: a cross-sectional study. *BMC Health Serv Res* 2016;16:1–9.
39 Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ* 2006;332:969–71.
40 Kristman VL, Manno M, Côté P. Methods to account for attrition in longitudinal data: do they work? A simulation study. *Eur J Epidemiol* 2005;20:657–62.
41 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ* 2014;350:g7594.