Personalised recommendations for hospitalised patients with Acute Kidney Injury using a Kidney Action Team (KAT-AKI): protocol and early data of a randomised controlled trial

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ABSTRACT

Introduction Although studies have examined the utility of clinical decision support tools in improving acute kidney injury (AKI) outcomes, no study has evaluated the effect of real-time, personalised AKI recommendations. This study aims to assess the impact of individualised AKI-specific recommendations delivered by trained clinicians and pharmacists immediately after AKI detection in hospitalised patients.

Methods and analysis KAT-AKI is a multicentre randomised investigator-blinded trial being conducted across eight hospitals at two major US hospital systems to enrol 4000 patients over 3 years (between 1 November 2021 and 1 November 2024). A real-time electronic AKI alert system informs a dedicated team composed of a physician and pharmacist who independently review the chart in real time, screen for eligibility and provide combined recommendations across the following domains: diagnostics, volume, potassium, acid–base and medications. Recommendations are delivered to the primary team in the alert arm or logged for at least one diagnostic intervention. More than half (51.6%) had recommendations to discontinue or dose-adjust a medication. The median time from AKI alert to randomisation was 28 (IQR 15.8–51.5) min.

Ethics and dissemination The study was approved by the ethics committee of each study site (Yale University and Johns Hopkins institutional review board (IRB) and a central IRB (BRANY, Biomedical Research Alliance of New York). We are committed to open dissemination of the data through clinicaltrials.gov and sharing of data on an open access repository as well as publication in a peer-reviewed journal on completion.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A major strength of our study is that it uses the electronic health record (EHR) system to diagnose and deliver personalised recommendations for acute kidney injury (AKI).
- Another strength is its potential to allow identification of actionable areas of improvement in the early management of AKI, especially for modifications of the area medication adjustments, not only nephrotoxins but also renally metabolised medications with extrarenal side effects that may contribute to AKI-associated morbidity and mortality.
- A limitation of the study is that patients often had multiple diagnostic and intervention recommendations which limited our ability to investigate if and how a specific recommendation was associated with an outcome.
- Our early data show that it is feasible to train a team of physicians and pharmacists that respond to AKI at the early stage, remotely screen patients on diagnosis and deliver recommendations within the EHR all within less than an hour of AKI detection, which could streamline care, allow prompt diagnosis and interventions to improve patient outcomes, and reduce cost.

INTRODUCTION

Acute kidney injury (AKI), an abrupt decline in kidney function, affects up to 20% of hospitalised patients and is associated with increased inpatient mortality. AKI can
progress to higher stages, potentially necessitating dialysis and contributing to prolonged hospital length of stay (LOS), as well as the development and progression of chronic kidney disease (CKD). 5–6

Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines define early-stage AKI as a rise in the serum concentration of creatinine by 0.3 mg/dL within 48 hours or a relative increase of 50% within 7 days. 7 Various guidelines have been put forth to not only standardise AKI definition but also promote early detection of AKI and proper use of diagnostic tools and medication adjustments early in the clinical course. 7–9 Ultimately, such guidelines are devised to encourage early recognition and interventions to promote an optimal path for recovery to reduce the risk of progression and associated adverse events. However, despite such well-recognised guidelines, clinicians often fail to recognise early stages of AKI, especially in those with low baseline creatinine values. 10–11

Previous clinical trials performed by our group and others have evaluated whether clinical decision support systems (CDSS) can improve clinician identification of AKI and AKI-associated outcomes in hospitalised patients as well as prevention of AKI in high-risk populations such as those post cardiac surgery. 12–16 Large studies including those that employed multimodality CDSS have shown mixed results with minimal clinical impact. 13–17,18

This may be due to significant variations in adherence to best practice guidelines as well as AKI progression and LOS. However, studies assessing a real-time electronic AKI alert alone have shown mixed results with minimal clinical impact. 13–17,18

The study design

KAT-AKI is a multicentre, randomised, investigator-blinded trial to assess the effectiveness of personalised recommendations for AKI in reducing AKI progression, dialysis and death in hospitalised patients. The study started enrolment on 1 November 2021 and planned to end enrolment on 1 November 2024. The study design is shown in figure 1. A synopsis of the study is provided in online supplemental file A.

Study population and setting

All adult (≥18 years old) patients hospitalised within six hospitals in the Yale New Haven Health System and two hospitals in the Johns Hopkins Health System who develop at least stage 1 KDIGO AKI are eligible for screening. The planned time to complete enrolment is 3 years. An automated alert notifies the Kidney Action Team (KAT) for all eligible patients using an algorithm that retrospectively searches for serum creatinine values within the lab results of the patient’s electronic health record (EHR) using a rolling minimum window to operationalise the KDIGO criteria for stage 1 AKI using a time frame of 48 hours for 0.3 mg/dL rise or 7 days for 50% rise from the lowest serum creatinine. 7,13

The algorithm fires a maximum of one time so that the study team is alerted only at the onset of AKI but not thereafter even if AKI is persistent. Patients are eligible only at the onset of the first episode of AKI during given hospital admission. As the majority of patients will not have serum creatinine measurement within 7 days prior to admission and as the aim is to intervene as close to AKI onset as possible, the cohort will likely represent those with hospital-acquired AKI. As the goal of the trial is early intervention, patients with community-acquired AKI are excluded unless they have a creatinine measurement within 7 days prior to admission.

Exclusion criteria

Patients who are on hospice care or have ‘comfort measure only’ orders, have received a solid organ transplant, have indications for urgent nephrology consult or dialysis (defined as serum potassium of ≥7 mEq/L, acute ingestion of dialysable toxins, refractory volume overload, metabolic acidosis with pH <7.15, blood urea nitrogen >150 mg/dL), have pre-existing stage V CKD, end-stage kidney disease on dialysis or initial hospital creatinine of ≥4.0 mg/dL, or have been seen by nephrology or already have a nephrology consult are excluded from enrolment. Additionally, we exclude individuals who were enrolled in the study during a previous hospitalisation.

Study personnel

The KAT is a team of trained physicians and pharmacists who receive real-time AKI alerts. At any given time, one physician and one pharmacist are ‘on call’ for the KAT. At this time, most of our enrolments have occurred in the morning, which is the time most patients get daily blood draws at our hospital system. Personnel limitations do not allow us to provide 24/7 coverage for the entire duration of the trial. However, we plan to ensure some representation of AKIs that occur in the afternoon, overnight and on weekends. Patients diagnosed with AKI outside of routine phlebotomy hours may represent a population.
that is systematically different from patients diagnosed on daily morning labs. Additionally, there may be differences in the care teams and their response to the laboratory result, as well as the intervention.

The trained physicians are nephrologists, second-year nephrology fellows or medical residents who have completed a rotation on an adult inpatient nephrology service. The pharmacist team includes clinical pharmacy specialists experienced in hospital pharmacology. All trainees additionally receive an AKI educational primer developed by the study team and access to a KAT manual which includes the clinical workflow as well as KAT standards for recommendations. This manual has been modified based on feedback received from nephrology fellows and attendings during a pilot period. The study personnel are blinded to group allocation during screening, chart review and creation of recommendations.

**Intervention**

The intervention is a set of structured recommendations created by the KAT. A full list of potential recommendations appears in online supplemental file B. The team reviews an alerted patient’s chart within 1 hour of receiving the alert. They screen the patient’s record for the eligibility criteria, including validation of the presence of AKI, and subsequently provide recommendations in the areas of diagnostic evaluation, volume, potassium and acid–base recommendation-based management as well as recommendations on whether prescribed medications should be dose adjusted, have levels monitored or be discontinued where applicable (online supplemental file B table 1). To maximise KAT efficiency, these recommendations are prestructured in the data entry system, such that the KAT only has to check which recommendations are appropriate for a particular patient. There is, however, a ‘free-text’ box in each category to add recommendations.
that have not been prepopulated (figure 2). Once both KAT members (ie, physician and pharmacist) submit their recommendations, patients are randomised within the data entry system to either the alert group or the usual care group. On randomisation to the alert group, a combined note is automatically generated and inserted into the EHR (figure 3). No note is created for patients in the control group, who will continue to receive the usual care. No specific interventions are required or prohibited during participation in this trial. The comparator group is usual care as the aim is to assess the real-world impact of personalised recommendations for AKI evaluation and management through AKI awareness and actions compared with current provider practices acknowledging potential hospital and provider-level variability in practices. Any alternative comparator strategy would lead to contamination and may be unsafe in hospitalised patients with evolving clinical status if not costly, particularly for AKI where a one-size-fits-all approach may be inappropriate and has not shown benefit. To encourage adherence to intervention, notes will be routed to the primary providers of the patients as in-basket messages, or the covering provider will be flagged for cosignature.

**Randomisation**

Randomisation is performed using Research Electronic Data Capture (REDCap V.10.5.8, Vanderbilt University, Nashville, Tennessee, USA), a Health Insurance Portability and Accountability Act (HIPAA)-compliant central server within the Clinical and Translational Research Accelerator at the Yale University School of Medicine. A computer-generated randomisation table uses permuted blocks of four, six and eight individuals. Randomisation is stratified by study hospital. The KAT workflow design creates recommendations prior to randomisation to preserve their blinding. The patients’ clinicians and
patients are not blinded as the recommendation appears in the chart of the patient randomised to the intervention arm and the note specifies that they will only receive this note for those randomised to intervention.

**Challenges of volume recommendations in the setting of electronic evaluation**

Volume evaluation and management is a critical component of AKI management and requires physical examination along with diagnostic aids to estimate intravascular volume status. In the absence of physical examination, it is challenging to make volume recommendations with accuracy. KAT physicians are trained to use a combination of blood pressure and heart rate, physical exams documented by multiple clinicians and nursing staff, weight trends if weights obtained while standing are recorded and diagnostics such as recent echocardiogram.
and chest X-ray results. Volume-specific recommendation checkboxes are mostly investigative and encourage clinicians to perform a clinical assessment, except in cases of documented pulmonary oedema or hypotension with evidence of weight loss, where diuresis or volume resuscitation may be recommended, respectively. All volume challenge recommendations also include the importance for re-evaluation of volume status afterwards as well as the statement ‘caution if concern for volume overload, decompensated heart failure or cirrhosis ...’.

**Additional survey data**

Before randomisation, physicians on the KAT are required to select what they think is the most likely aetiology of AKI from a list with an option to free text if their suspected aetiology is not listed (online supplemental file B figure 1). This will not be included in the recommendation note but will be used to assess recommendation patterns based on suspected AKI aetiologies and the associated outcomes.

**Primary outcomes**

The primary outcome for the clinical trial is a composite of progression of AKI, receipt of dialysis and death at 14 days after randomisation. Progression of AKI is defined as a higher KDIGO AKI stage than at the time of randomisation. Dialysis is operationally defined as haemodialysis, continuous renal replacement therapy or peritoneal dialysis. Isolated ultrafiltration for volume removal is not included. If a patient is discharged alive before 14 days after randomisation, we will carry forward the last observed status in terms of AKI progression and dialysis.

**Secondary outcomes**

Secondary outcomes include incidences of inpatient mortality within 14 days after randomisation, inpatient dialysis receipt within 14 days, inpatient progression of AKI within 14 days, rate of nephrology consults within 14 days, the percentage of recommendations adhered to within 24 hours of randomisation and rates of discharge to hospice care. Assessment of heterogeneity across the study sites is also performed to assess whether the benefit of the KAT is dependent on local resources and practices.

**Contamination**

As clinicians are not blinded to the intervention, contamination may occur over the course of the trial. When providers get exposed to the alert, over time, their recognition of AKI as well as their diagnosis and management of AKI may change. We expect this to affect our trial to a minor degree as this is a reasonably large multicentre trial where the chance of physicians’ re-exposure to this alert (ie, having multiple patients randomised to intervention) is likely low. Additionally, the study assesses the impact of recommendations for a syndrome/diagnosis that has a heterogeneous cause. Contamination cannot be avoided in the current trial design. However, to assess contamination, we plan to look at change in the effect size of the composite and individual outcomes over time.

We will also assess the average number of alert exposures per physician and its association with the outcome.

**Statistical analysis**

Primary analyses compare the proportion of patients experiencing the primary outcome at 14 days after randomisation. These will be compared using the Cochrane-Mantel-Haenszel χ² test, accounting for stratification by study hospital. Secondary analyses include percentages of each individual component of the primary composite outcome, each at 14 days, cost of admission and recommendation adherence (ie, percentage of recommendations implemented by the primary care team) within 24 hours (online supplemental file B table 2).

**Subgroup analyses**

The following subgroup analyses are planned to recognise a group of patients who may be undertreated or overtreated and may need a special alert notification mechanism. The prespecified subgroups include patients admitted to non-medicine floors with primary clinical teams that may have less experience in the management of AKI, teams with an especially busy and dynamic service (intensive care units (ICUs), patients on special renal haemodynamic medications (renin–angiotensin system blockers and sodium–glucose cotransporter-2 inhibitors), those that are diagnosed with AKI during later hours and weekends, and those with heart failure and cirrhosis, where a more specialised volume management algorithm may be necessary (online supplemental file B table 3).

**Power and sample size**

The overall sample size of the study is based on the composite outcome of AKI progression, dialysis and death. The baseline rate for this outcome is 21% based on preliminary data, and a 20% improvement rate would be considered clinically meaningful. To achieve 90% power, at an alpha of 0.05, we would need to enrol 1824 patients in each randomisation arm of the study for an overall total of 3648. However, given concerns about contamination, we have increased this overall number by almost 10% for a final total of 4000 patients. Enrolment of 4000 individuals allows us to maintain detection of a difference in the rate of adherence of 10% of 1 SD at an alpha of 0.05.

**ETHICS AND DISSEMINATION**

**Ethical considerations**

The conduct and ethics of the clinical trial are carefully considered by the study team. The trial protocol (V.1.1, 1 October 2021) was approved by the BRANY Central Institutional Review Board (IRB) as a single IRB for which Yale New Haven Health System and Johns Hopkins University School of Medicine provided reliance agreements. All IRBs provided a waiver of consent. Any amendment to the protocol will require IRB approval prior to implementation and will be shared with investigators. The trial operates under a waiver of informed consent because the trial
demonstrates minimal risk to the welfare of the patient. The clinical trial is performed in accordance with the Declaration of Helsinki and the most recently approved protocol, International Conference for Harmonisation—Good Clinical Practice, and all other applicable regulatory requirements.

Data safety monitoring plan
The study will be monitored by the internal team as well as a dedicated external data and safety monitoring board (DSMB), which will review the data conduct biannually. Participant safety will be continuously monitored by the external DSMB, which includes safety signal detection at any time during the study. The DSMB may unblind the intervention assignment for any participant with a serious adverse event (SAE). In situations where the SAE requires an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant’s intervention assignment will be sent to investigators in accordance with local regulations and/or sponsor policy.

Confidentiality and access to data
Data collected over the course of the study on REDCap are deidentified and stored on a server that is only accessible from within the Yale intranet by only study team members approved by Yale and Johns Hopkins University IRBs, and limited dataset is included for analysis. No protected health information will be included in the analysis or publication.

Dissemination policy
On completion of data collection and analysis, the study findings will be disseminated via presentations at local and national conferences and publications in peer-reviewed journals. These will be prepared and written by the study investigators without any involvement of professional writers.

Data availability
Deidentified data will be shared with reviewers on submission of final results to encourage thorough peer-review and inform future studies. The final deidentified dataset will be made available publicly available on an open data repository once the final results are published.

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

Unstratified early data
These data represent the first 500 enrolments between 1 November 2021 and 12 August 2022. At the time, 740 patients had been screened, of which 500 were enrolled. Enrolment rate was on average 48 patients per month for the first 7 months but has gradually improved to an average of 140 per month (median 140, IQR 126–181) as a result of KAT member recruitment efforts, which allowed an average of 4 days a week multisite coverage.

KAT clinicians’ disagreement with the electronic AKI diagnosis (20.7% of those screened) was the most common reason for exclusion. A majority (91%) had stage I AKI; 7% had stage II AKI; and 2% had stage III AKI. A distribution of the location of the patients who generated the alerts is shown in table 1. The largest frequency of all alerts (52.2%) was for general medical floor patients who were under the care of hospitalists (221, 44.2%) or general internal medicine teaching teams (40, 8%). The second most common location of all alerts (67, 13.4%)
were medical ICU and step-down units. The heart failure service was the third most common location contributing to 7% of all alerts, followed by oncology (5% of all alerts) and general surgery (5%).

Unstratified outcomes are presented in Table 2. AKI progression occurred in 16.0% of the cohort. Median LOS was 8.3 (IQR 5.0–15.3) days. The incidence of death and dialysis at 14 days were 6.8% and 2.4%, respectively. The composite outcome occurred in 18.8% of the study cohort. The median time to KAT action, defined as the time a member of the KAT starts filling out the electronic recommendation form, was 20 (IQR 8–40) min. The average time it takes to complete each form was 5 min for a physician and 3 min for a pharmacist.

Frequencies of recommendations in the five major areas of intervention, as well as nephrology consult are shown in Table 3. The most commonly recommended intervention was diagnostic evaluation, which was recommended for 99.0% of all enrolled patients. Volume-related interventions were the next common recommendation type (75.8%). This included empirical volume challenge with caution (18.4% of volume recommendations), volume challenge after confirming volume depletion (31.2%), daily weights (27.8%), avoiding or stopping intravenous fluids (6.0%) and diagnostics such as point-of-care ultrasound and CXR where appropriate (9.2% of volume recommendations). Potassium recommendations were given 16.0% of the time, of which 42.3% included potassium administration. Acid–base suggestions were recommended 14.2% of the time. Nephrology consult was recommended 3.4% of the time.

Medication discontinuation or medication dose adjustment was recommended in 51.6% of participants. There were 126 (25.2%) who had recommendations to discontinue medications, of which the medication was a
consult at the time of the alert. This suggests that there is significant room for improvement in AKI care at the earliest stage in the form of personalised recommendations. There were also some unexpected findings, such as that half of the potassium recommendations were to replete potassium. Although hypokalaemia has been associated with risk of CKD progression, its impact in AKI has not been explored. Additionally, the preliminary data demonstrate that it is feasible to institute an AKI response team that could provide comprehensive AKI recommendations within minutes of electronic diagnosis of AKI.

In-hospital AKI is common and is associated with significant morbidity and mortality. Despite current efforts to implement best practices and guidelines, clinicians are often unaware of early-stage AKI representing missed opportunities for identifying and managing hospital-acquired AKI. Thus far, the largest studies of AKI alerts and multimodality interventions have shown no mortality benefit with alerts, perhaps due to variable hospital practices in the management of AKI. Reasons for the variable outcomes with AKI alerts are unclear. One possibility is that AKI is often part of a systemic illness and is often multifactorial in aetiology, where a one-size-fits-all approach to management will not work.

This multicentre, randomised, investigator-blinded trial was designed considering these gaps in care. It investigates the utility of individualised AKI management recommendations provided by a team of trained physicians and pharmacists to optimise care at clinician and patient levels. A major concern of interventions that use alerts has been alert fatigue, where repeated exposure to interruptive alerts in a busy hospital environment leads to the bypassing of important alerts along with unimportant ones. Our previous large multicentre trial ELAIA-1 (Electronic Alerts for Acute Kidney Injury Amelioration) had similarly demonstrated that such pop-up alerts without guidance can be associated with harm and higher costs. Therefore, the type of intervention used in our study may mitigate these concerns through the use of actionable recommendations by a team of experts that are provided in the form of a research progress note. We believe this mechanism is well suited to assist busy clinicians, leading to more focused and timely interventions and a more cost-effective alternative to a care bundle, potentially avoiding unnecessary diagnostics and interventions and duplications of recently performed diagnostics.

**Limitations of the trial**

There are a few limitations to our trial. Randomisation to the intervention arm does not guarantee receipt of intervention. Although the care team is flagged to each research progress note, completion of the intervention depends on the appropriate clinician reviewing these recommendations promptly. Our intervention also does not guarantee that KAT recommendations will be followed by clinicians using their own clinical judgement while caring for the patients directly. There is also a small possibility that clinicians become accustomed to receiving

<table>
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<th>Table 3 Continued</th>
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<tr>
<td><strong>Intervention category</strong></td>
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<tr>
<td>Oral bicarbonate</td>
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<tr>
<td>Medications‡</td>
</tr>
<tr>
<td>Discontinue medication</td>
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<tr>
<td>NSAID</td>
</tr>
<tr>
<td>Other</td>
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<tr>
<td>Dose adjust±monitor level</td>
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<tr>
<td>Discontinue and dose adjust</td>
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<tr>
<td>Nephrology consult</td>
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*Percentages are per cent of individuals with the specific recommendations out of the total for the major categories and per cent of the category for the subcategories; percentages may not add up to 100% as patients may have more than one recommendation in each category.†Each volume administration recommendation is accompanied by a statement, ‘caution with fluids if any concern for volume overload such as with evidence of decompensated heart failure or cirrhosis’. ‡These are the number of individuals with at least one of the specified medication recommendations.

ABG, arterial blood gas; CK, creatine kinase; CXR, chest X-ray; I&O, intake and output; IVF, intravenous fluid; LDH, lactate dehydrogenase; LR, lactated Ringer’s; NSAID, non-steroidal anti-inflammatory drug; POCUS, point of care ultrasound; VBG, venous blood gas.

non-steroidal anti-inflammatory drug in 23.8% of these cases (6% of the entire cohort), and there were 172 (34.4%) with recommendations to dose-adjust medications with or without level monitoring where appropriate. The three most common class of medications recommended for discontinuation or dose adjustment were analgesics (35.2%), antimicrobials (27.2%) and anticoagulation (16.6%) (online supplemental file B table 4).

Relevant interventions implemented by the patients’ providers within 24 hours following randomisation are recorded for all participants, and adherence to recommendations is recorded for those randomised to the intervention arm (online supplemental file C).

So far, this study shows the feasibility of real-time, early, personalised recommendations for AKI using a trained team of physicians and pharmacists. Most of the AKIs were captured at stage I, demonstrating the opportunity for early intervention. Unstratified mortality rate was comparable to previous studies. The most frequent diagnostic recommendations have been benign and inexpensive, such as ruling out urinary retention using a bladder scan, collecting a urinalysis or checking orthostatic vitals. There were fewer recommendations for urine electrolytes. The most common volume recommendation was volume assessment. Importantly, over half of the cohort required at least one medication dose adjustment or discontinuation, and only 3.4% were determined by the expert team to benefit from a formal nephrology.
recommendation notes for AKI and become dependent on the alerts for AKI diagnosis, leading to missing AKI in the usual care arm. We attempt to mitigate this possibility by leaving a reminder in the alert note that this is a randomised trial, and the clinician will not receive alerts for all patients with AKI. Additionally, after IRB approval at the individual site and before starting enrolment at each site, a hospital-wide overview of the project was presented at each individual site as an introduction to the trial. Finally, we cannot tell which recommendations are truly impactful, and the outcome in many cases may only be related to the alert of AKI rather than the specific recommendation, but we plan to assess whether differences in outcomes are mediated through adherence to recommendations. However, the high rate of medication recommendations in the early data, in particular, suggests that the intervention will likely promote early discontinuation or dose adjustment of not only potential nephrotoxins but also medications with renally cleared metabolites associated with potential extrarenal adverse outcomes. The KAT-AKI clinical trial will examine whether individualised recommendation alerts for AKI could reduce the duration of AKI, dialysis usage and mortality. The EHR system offers an opportunity to screen for AKI in real-time and communicate timely personalised recommendations to covering clinicians directly into the EHR. If effective, clinical decision support tools could be a cost-effective and feasible solution for implementing AKI best practices. Providing targeted and comprehensive diagnostic and interventional recommendations, including pharmacological recommendations, may facilitate a favourable trajectory to recovery and overall improved AKI-associated outcomes.

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Contributors FPW is the grant holder, conceived the study, acquired funding and supervised this protocol article. AMA and KDO’C wrote the initial manuscript. AMA assisted with protocol revision, data collection instrument design, training and recruitment. MM, YY and CC-M contributed to protocol development. CP contributed to protocol development, techniques and manuscript editing. SM, KS, CJ, MLB, CPC-V, BK, MO, MG, JT, Asm, Asl, JL, SEC and DB contributed to patient recruitment and manuscript revisions. All authors reviewed and approved the final manuscript for publication.

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