Rwanda Medical Journal RMJ

REVIEW Open access

Short and long-term prognosis in acute kidney injury

Authors: V. Nsengiyumva[1]; G. Igiraneza[1]; N. Lameire[2]

Affiliations: *[1]Department of Internal Medicine, University Teaching Hospital of Kigali, Rwanda; [2]University Hospital, Gent, Belgium*

ABSTRACT

The first three papers in this continuing medical education series on acute kidney injury (AKI) discussed the epidemiology of AKI, the diagnostic approach and the non-dialytic and dialytic interventions in patients with AKI [1-3], respectively.

In this fourth and last paper we describe the short and long-term prognosis of these patients. The acute patient mortality remains unacceptably high in particular when AKI occurs in a critically ill patient. However, also outside the intensive care unit, every episode of AKI – mild or not - is not only associated with short-term but also long-term adverse outcomes. It has recently become clear that even if the patient survives and is discharged from the hospital, some of the consequent adverse effects of AKI are related to incomplete or no recovery of renal function.

Some of these long-term consequences of AKI leading to chronic kidney disease (CKD) are discussed in this paper with emphasis on data obtained in low-income countries. The necessary long-term renal follow up of AKI survivors imposes an additional burden on the overall health care system in these countries.

Keywords: Acute kidney injury; Chronic kidney disease end-stage renal disease; Renal Replacement therapy; low-income countries; socio-economic aspects of AKI;

INTRODUCTION

Acute patient mortality

As described in the first paper of this series, we found a global epidemiological study that pooled incidence rates of acute kidney injury (AKI), giving incidence rates of 21.6% in adults and 33.7% in children [4]. The pooled AKI-associated mortality rates were 24.3% in adults (95% CI, 22.1 to 25.7) and 14% in children (95% CI, 8.8 to 21.0). The AKI- associated mortality rate declined over time and was inversely related to the income of countries as well as the percentage of Gross Domestic Product (GDP) spent on total health expenditure. As described in the first paper, an overall AKI incidence of 2.8% was found within the hospitalized population in Rwanda, while the hospital AKI mortality rate was around 32% [5]. Despite literature describing an overall decline in the mortality rate of AKI [4, 6, 7], AKI is still associated with a markedly increased risk of death in hospitalized patients, particularly in those admitted to the intensive care unit (ICU) where in-hospital AKI mortality rates may exceed 50%. A recent multinational review of the epidemiological trends in 97 ICUs, with 1,802 patients originating from 33 different countries [8] reported that sepsis was the primary cause of AKI, and the in-hospital mortality of AKI was 26.9% in patients with AKI compared to 7% in patients without AKI. The short-term mortality of patients with severe sepsis increases with increasing AKI severity from 23% up to 64% [9-11].

While sepsis is a leading cause of AKI in critically ill patients, the relationship between AKI in less severely ill patients with infection was studied in 1836 hospitalized patients with severe and non-severe community-acquired pneumonia [12]. AKI was found in 631 patients (34%) of whom 329 had associated severe, and 302 had non-severe associated sepsis. The risk of death associated with AKI varied with the severity of pneumonia but patients with AKI had a higher risk of death; by hospital discharge (11% vs. 1.5 %, p<0.001), at 90 days (24% vs. 10% p<0.001), and at one-year (36.3% vs. 20.1%, P<0.001). Mortality at one year increased with increased severity of AKI and was 30%, 41% and 44% for the maximum RIFLE stages, respectively, (p<0.001).This risk was significantly higher immediately after hospitalization but gradually fell over time in the overall cohort and in those with

Corresponding author: Norbert Lameire, MD, PhD. E-mail: norbert.lameire@ugent.be; **Potential Conflicts of Interest (CoI):** All authors: no potential conflicts of interest disclosed; **Funding**: All authors: no funding was disclosed; **Academic Integrity**. All authors confirm that they have made substantial academic contributions to this manuscript as defined by the ICMJE; **Ethics of human subject participation:** The study was approved by the local Institutional Review Board. Informed consent was sought and gained where applicable; **Originality:** All authors: this manuscript is original has not been published elsewhere; **Type-editor**: Sean Batenhorst (USA)

Review: This manuscript was peer-reviewed by three reviewers in a double-blind review process;

Received: 21st January 2018; **Initial decision given**: 16th February 2018; **Revised manuscript received**:26th May 2018; **Accepted**: 5th February 2019

Copyright: © The Author(s). This is an Open Access article distributed under the terms of the Creative Commons Attribution License (CC BY-NC-ND) (click here).which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. **Publisher**: Rwanda Biomedical Centre (RBC)/Rwanda Health Communication Center, P.O.Box 4586, Kigali.

ISSN: 2079-097X (print); 2410-8626 (online)

Citation for this article: Nsengiyumva V; Igiraneza G; Lameire N. Short and long-term prognosis in acute kidney injury. *Rwanda Medical Journal, Vol 76, no 2, pp 1-8, 2019*

non-severe pneumonia. A significantly higher risk of death (hazard ratio 1.29) was also present in those never admitted to an intensive care unit [12].

Among patients in the intensive care unit (ICU) who develop AKI requiring dialysis, mortality rates range from 40% to >60 % [13-17]. In more recent trials in ICU patients requiring renal replacement therapy (RRT), the 90-day mortality was 45% in one study published in 2009 [18] and 52.5% in a trial in 2008 [19]. Moreover, of the survivors with severe AKI, 24.5% were still receiving RRT on day 60 [19].

Cardiac surgery-associated AKI (CSA-AKI) is the second most common cause of AKI in the ICU and is independently associated with increased morbidity and mortality [20]. Severe CSA-AKI is independently associated with a 3–8-fold higher perioperative mortality, a prolonged length of stay in the ICU and in-hospital, and increased cost of care [21]. The risk of death associated with AKI remains high for 10-years after cardiac surgery regardless of other risk factors, even for those patients with complete renal recovery [22].

In-hospital mortality rates are lower among patients with AKI in the general hospital population or those who have less severe AKI (15-30% versus 1-10% among patients without AKI) [6, 7, 23, 24]. A small, acute decrement in kidney function due to AKI may also increase in-hospital mortality [25].

In a recent analysis of mortality in hospital AKI cases; 19,249 hospitalizations encompassing 15,096 individual patients were included in the analysis [26]. Using more recent Acute Kidney Injury Network (AKIN) definitions of AKI, the overall incidence of AKI was 22% (AKIN stage 1, 15.8%; stage 2, 2.7%, and stage 3, 4.2%. The mortality rate for AKI was 10.8%, compared to 1.5% for cases without AKI. Larger increases in serum creatinine (sCr) were associated with higher mortality rates: stage 1, 6.5%; stage 2, 16.5%; and stage 3, 23.5%. After adjustment for age, sex, race, admission sCr concentration, and the severity of illness index, AKI was independently associated with in-hospital mortality (adjusted odds ratio 4.43, 95% confidence interval 3.68 – 5.35).

As recently reviewed [27], the associations between AKI and mortality have been observed across several patient populations, including general inpatients and critical care [28-31], myocardial infarction [32, 33], critical care [34], general surgery [35] and cardiac surgery [36].

AKI carries a substantial risk of mortality which persists after adjustment for co-morbidities. AKI is thus not only an indicator for severity of illness but also leads to earlier onset of multi-organ dysfunction with significant effects on mortality. For example, adults who suffered severe in-hospital AKI from January 1, 2004, to August 31, 2010, were identified at three hospitals in the University of Pennsylvania Health System (UPHS) [37]. Cox proportional hazards models predicting death, dialysis, or a combined endpoint of death or dialysis were applied within 14 days after onset of AKI. In adjusted analyses, strong predictors of the combined endpoint included intensive care unit location (versus floor), medical service, liver disease, higher creatinine, the higher rate of change in creatinine, and the more significant number of pressor medications. Higher absolute creatinine concentration was associated with greater use of dialysis, but lower overall mortality in adjusted analyses.

AKI is thus not an isolated event and results in remote organ dysfunction to the lungs, heart, liver, intestines, and brain through pro-inflammatory mechanisms that involve neutrophil cell migration, cytokine expression and increased oxidative stress. Recent reviews explore the mechanisms and the long-term consequences of AKI on other organ systems [38, 39].

Long-term mortality and cardiovascular events

AKI is also associated with long-term mortality and cardiovascular events. A recent meta-analysis of 25 cohort studies on mortality reported a 58% increased risk of heart failure, a 40% increased risk of myocardial infarction, and a 15% increased risk of stroke [40]. These elevated risks persisted among several subgroups, including AKI severity, recovery, and patients with and without pre-existing cardiovascular disease or chronic kidney disease (CKD).

Therefore, the association between AKI and cardiovascular events may not be explained merely by reduced kidney function after an episode of AKI. One potential mediator may be the effects of AKI on blood pressure. In a retrospective cohort study of 2,451 previously normotensive patients who survived an AKI hospitalization, Hsu and colleagues [41] found that survivors of AKI were more likely to develop hypertension over a 2-year follow-up period (46% vs. 41%) than patients without AKI. This difference became evident within 180 days (31% vs. 23%), persisted after multivariable adjustment, and remained present after exclusion of patients with pre-existing CKD. AKI and re-hospitalization risk

More short-term adverse outcomes after AKI include the morbidity and costs associated with re-hospitalization. A recent population-based study from Ontario, Canada, demonstrated that in 156,690 patients with AKI, 1 in 3 patients who survived a hospitalization complicated by AKI either died, were readmitted to hospital (median time to all-cause readmission of 11 days), or visited the emergency department within 30-days of hospital discharge [42]. Increased rates of 30-day readmission have also been noted in patients with KDIGO AKI Stage 1, [43], patients with AKI in the critical care unit, [44] and those with heart failure who experience AKI [45].

A recent study showed that the 30-day readmission rate in patients with heart failure was significantly higher in those who had either sustained (S-AKI) or transient AKI (T-AKI) compared to those without AKI [46]. Compared with no AKI (readmission rate of 17.5%; 95% CI 16.5% to 199%), the adjusted rate of readmission was highest in patients with S-AKI (23%, 95% CI 21% to 25%), followed by 20 (95% CI 17.5% to 23%; p =0.05) in T-AKI patients. Recurrent AKI is another important outcome to consider. Among 11,683 AKI hospitalizations in a regional Veterans Administration database, 25% of patients were re-hospitalized with AKI in the next year [47]. The median time to recurrent AKI was 64 days, and close to 60% of these episodes occurred within 90 days of hospital discharge. Reducing the risk

for these interim outcomes within the first few weeks to months after discharge may be an underappreciated opportunity to improve the long-term prognosis for these patients.

Long-term renal prognosis of AKI

An increasingly held view is that patients who survive an AKI episode are at considerable risk for developing de novo CKD [48], hastening the progression of pre-existing CKD [28, 31] and evolution towards end-stage kidney disease. Vice versa, background CKD by itself also strongly predisposes to the development of AKI [49]. Despite some reservations on the existence of a direct link between AKI and CKD (see below) recent prospective and retrospective studies have provided cogent arguments showing a clear relation between AKI and development of CKD later in life. A recent small but prospective single-center cohort study found that AKI is associated with deterioration in renal function after three years, even in an unselected population, with predominantly Stage 1 AKI. Non-recovery from AKI turned out to be an essential factor, determining adverse long-term outcomes [50].
Another prospective observational long-term follow-up study [51] demonstrated that community-acquired AKI in the setting of a tertiary care inner-city emergency department in Lisbon (Portugal) is associated with a substantially increased risk of death and of developing CKD stage ≥ 3.

At approximately 5-year follow-up, patients who initially presented with community-acquired AKI exhibited the highest incidence of CKD, with 40% of the patients in this group developing CKD stage ≥3, 39.5% exhibiting an estimated glomerular filtration rate (eGFR) loss of >25%, and 27% reaching the composite endpoint of CKD stage 5, ESRD, and dialysis requirement. Furthermore, the mortality rate in the AKI group was the highest, at 44.5% [51].
Also, the analysis by Shawney et al. [52] studied the long-term (10-year) trajectory of subsequent renal decline in post-AKI survivors and used the 1-year post-discharge eGFR rather than the pre-admission value as a new reference point. Death was more common than a subsequent 30% renal decline (37.5% vs. 11.5%) and CKD stage 4 (4.5%). Overall, 25.5% of AKI patients did not recover. The subsequent renal decline was more significant after AKI (vs. no AKI) (15% vs. 11%). Renal decline after AKI (vs. no AKI) was most significant among those with higher post-discharge eGFRs. The excess risk after AKI persisted over ten years of study, irrespective of AKI severity, or post-episode proteinuria. Thus, even if post-discharge kidney function returns to normal, hospital admission with AKI is associated with the increased renal progression that persists for up to ten years.

Concurrently, experimental data has revealed many similarities between the pathological processes that drive CKD progression and those that occur following an episode of AKI [49, 53, 54]. These mechanisms are multiple and varied but are mostly independent of the initial renal injury [49, 53, 54]. Of particular importance are the maladaptive repair processes resulting in tubulo-interstitial atrophy and fibrosis, which may arise because of pro-inflammatory signals preventing normal tubular cell regeneration/re-differentiation [54]. Alongside this, capillary rarefaction and vascular drop-out also occur, forming a vicious cycle and increasing the risk of subsequent ischemic injury [55]. Many other cellular and molecular pathways of renal repair after AKI have recently been reviewed extensively [56].

Some concerns about the direct link between AKI and CKD

Although recent literature provides a strong base for the AKI-CKD link, there is still controversy on the causality of this association. As recently pointed out by Coca [57], much of the older clinical literature, mainly based on retrospective analysis, has not been sufficiently stringent in identifying the extent by which CKD results after AKI. CKD post AKI may result from an irreversibly fixed defect due to non-recovery from tubular injury, manifesting as a steep drop and plateau of renal function at a new baseline. Alternatively, it may be the result of a "slow de novo further progression of AKI.

An extensive discussion of some critical factors influencing, and possibly obscuring, the relation between AKI and CKD is beyond the scope of this paper but have been recently discussed [58]. These factors include the sharing of a number of common risk factors between AKI and CKD making it difficult to conclude with certainty that AKI is causally related to CKD, the possible misclassification of AKI as preexisting CKD due to unknown baseline sCr values, the multiple trajectories that recovery of renal function may take, and the multitude of other factors that may influence the severity and duration of AKI with an impact on the recovery of renal function [58].

Follow up of the patients surviving AKI

Given the association between AKI and the later development of both non-renal (mostly cardiovascular), and renal complications, follow-up care for patients who sustain AKI in the hospital has important public health and socioeconomic impact, particularly in low-income countries like Rwanda [59, 60]. In 2012, the KDIGO AKI workgroup released guidelines recommending that patients be evaluated three months after AKI for the new onset of CKD or worsening of any pre-existing CKD [61]. It can be anticipated that referring all patients who suffered from an AKI episode for follow-up care to a nephrology clinic would create an overwhelming burden to the nephrology community. It is thus imperative to select those patients who are at the highest risk of a poor outcome for specific post-AKI care. High risk patients (severe AKI [KDIGO ≥ stage 2/RRT need], AKI in transplant recipients or, irrespective of the degree of AKI, age above 65 years, comorbidities like hypertension, diabetes mellitus, cardiovascular disease, liver cirrhosis, and those actively treated for cancer) should, before discharge, preferably be seen by a nephrologist and educated about AKI, the prevention of further AKI episodes, and the importance of follow-up.

Patients with CKD are to be managed according to the KDIGO Clinical Practice Guideline for the evaluation and management of chronic kidney diseases [62]. As explained above, the analysis of the significant reasons of post-discharge mortality and early readmission rates of the surviving AKI patients is of relevance for the organization of the post-AKI care and the referral pattern of these patients.

Multiple studies have observed low rates of nephrology follow-up care after an episode of AKI, across different settings and countries. The current reality is that patients are rarely seen by a nephrologist after an AKI episode even in AKI-RRT. Siew et al. [63] calculated that within the first year after an episode of AKI that required RRT, the cumulative incidence of nephrology referral was only 8.5% among survivors who were considered to be at risk for subsequent decline in kidney function. The severity of AKI did not affect referral rates. Follow-up increases with time, but the percentage of patients seen by a nephrologist at 12 months after an AKI hospitalization is still only 19% [27].

Although very important, nephrology follow-up alone will often not be sufficient and a patient-centered approach is addressing the still ongoing, frequently non-renal, illness of the patient is also needed. In addition to nephrology consultations for the patient who has sustained AKI, it is imperative that primary care practitioners understand the risks associated with even mild degrees of AKI suffered by their patients, both to initiate timely nephrology involvement and to optimally manage patients at risk for the development of CKD [64-66].

Reflections on AKI in sub-Saharan countries, including Rwanda.

As previously discussed [1, 60, 67] the actual epidemiology of AKI in sub-Saharan countries is not well understood because of late presentation of patients to tertiary centers, underreporting, and a reduced capacity to provide intensive care to severely ill patients.

AKI occurrences in the community (e.g., due to diarrheal states, malaria) remain under-recognized. There is incomplete knowledge not only of how common but also how costly AKI is in low-income countries. Two global meta-analyses [4, 68] and a recent survey covering sub-Saharan countries [69] have demonstrated that AKI registries are imperfect or even non-existent. Moreover, most of the available studies on AKI burden are limited because they seldom provide population-based data; instead, they focus on high-level medical centers, often the only ones offering dialysis and other advanced care, and thus do not reflect the reality of the country as a whole. For example, the epidemiological data obtained in Rwanda were limited to the patient population hospitalized in the four major hospitals of the country [5]. While scientifically valuable, these studies do not provide data allowing a reliable estimation of the population burden of AKI in the country. Although it may be assumed that the majority of cases of AKI in countries like Rwanda are community-acquired, the use of registries which only compile data on hospital-acquired cases in high-level medical centers leads to under-reporting and skewed views on prevalence and incidence. This limitation has essential consequences because these community-acquired forms of AKI are the most amenable to early, inexpensive yet very effective interventions.

Due to inadequate registry data both the short and long term non- renal and renal prognosis of AKI in sub-Saharan countries is mostly unknown. In a recent survey [69] on AKI in sub-Saharan countries, a pooled mortality of 32% in adults and of 34% in children with AKI was calculated. Pooled mortality decreased over time in both adults and children, although the ranges of mortalities in individual studies were highly variable. When stratified by whether dialysis, when indicated, was received or not, pooled mortality was significantly higher in adults (86% vs. 30%) and children (74% vs. 30%) who did not receive at least one dialysis session.

Renal recovery, defined as independence from dialysis, improvement in serum creatinine after AKI, or both, was reported in 17 studies based on populations from the sub-Saharan countries [69]. The pooled rate of renal recovery was 130 (55%) of 237 (six studies) in adult survivors and 667 (75%) of 886 (11 studies) in child survivors. The pooled rate of residual CKD, defined as persistence of renal dysfunction but not needing dialysis at the time of discharge, was 24 (13%) of 186 adults (three studies) and 68 (10%) of 676 children (five studies). These outcomes were not routinely reported or systematically defined, and some studies had a substantial loss to follow-up, so the true rates remain unknown [69].

Data is scarce on long-term renal prognosis associated with specific causes of AKI in low-income countries, such as malaria, leptospirosis and snake bite -induced AKI. Several types of kidney diseases are associated with malaria (for review [70]) and in malaria-associated AKI, RRT is required in up to 76% of cases, and complete renal functional recovery occurs in approximately 64% of cases in both P. falciparum and P. vivax malaria-associated AKI [71, 72].
A group of 44 patients with AKI caused by leptospirosis were followed for at least one year in outpatient clinics with regular assessments, including renal status [73].

The primary outcome measure was normalization of renal function at one year. Of the 44 patients, 31 were in the risk and injury stage (Group 1), and 13 had AKI in the failure stage (Group 2) under RIFLE criteria. The RIFLE criteria has been discussed in the first paper of this series [3]. In Group 2, 11 had abnormal renal functions on discharge with a mean serum creatinine of 392 mmol/l and GFR values of 20 ml/min/1.73 m^2 and nine patients required RRT. Seventeen out of the total of 44 patients had persistently abnormal renal functions on discharge, but 13 of them recovered their renal functions to normal. Four patients (9%) who belonged to group 2, had persistently abnormal renal functions compatible with stage 3 chronic kidney disease (CKD) after the first year. Renal histology of two of these patients showed tubulo-interstitial lymphocyte infiltrate, tubular atrophy and interstitial fibrosis.

Herath et al [74] also analyzed the 1-year renal prognosis in 54 patients who had AKI following a snakebite during the period 2004-2009. At one year, 20 patients (37%) had developed chronic kidney disease (CKD) while 34 (63%) had entirely recovered their kidney function. The acute stage serum creatinine was high in both groups with no difference between groups, but the CKD group showed significantly high serum creatinine at two months after AKI. Mean duration of RRT of the recovered group and CKD group were 7 and 16 days respectively. Renal histology of 6 CKD patients showed predominant glomerular sclerosis and interstitial nephritis.

Both the general analyses by Olowu et al [69] as well as the data on prognosis in specific causes of AKI indicate that renal function after AKI may not always completely recover. Also in low income countries, AKI may thus be a significant cause of long-term CKD and even end-stage renal disease (ESRD).

In comparison to AKI patients in high-income countries the majority of individuals affected by AKI in low-income countries like Rwanda are younger, and many more are children. The most frequent causes of AKI in sub-Saharan countries and more particularly in Rwanda have been discussed in the first paper of this series [--1]. Although the mortality among these patients may be lower than that of the older, critically ill patients in high-income countries, AKI still creates a huge burden of disease, not only in terms of high mortality, but, as discussed above, also in terms of the development of severe, often progressive CKD and ESRD and/or long-term cardiovascular diseases in surviving patients [75]. Although RRT for AKI is reimbursed in Rwanda in contrast with many other sub-Saharan countries, the evolving ESRD requires chronic RRT which is not reimbursed by the community-based health insurance. The majority of the families cannot afford dialysis, many patients probably die untreated, and the loss of family members due to death or invalidity adds to the additional socio-economic burden. The final outcome of the discharged patients suffering from CKD and/ or ESRD post-AKI is not known in many sub-Saharan countries, including Rwanda, due to incomplete or absent post-AKI follow up.

While the efforts of the social security system in Rwanda in providing a maximum of six weeks RRT for AKI have to be recognized, we believe that the incidence and severity of AKI in sub-Saharan countries like Rwanda may be significantly decreased by simple, inexpensive measures that can be implemented by unsophisticated caregivers. However, these community caregivers should be trained and continuously educated to acquire the knowledge needed for early recognition, timely intervention and effective follow-up of AKI patients [76].

On the individual level, relatively simple preventive strategies should be developed, including identification and correction of potentially reversible causes of kidney damage such as volume depletion, often due to gastrointestinal infections, and avoidance of nephrotoxins. Because health care is affected by social and economic factors, any preventive intervention needs to address all health determinants, including educational, economic, and environmental factors [77].

Expensive interventions to prevent or treat AKI could affect the ability of a health-care system to meet other needs. Conversely, the high mortality associated with primary diseases, such as malaria, HIV/acquired immune deficiency syndrome (AIDS), infectious gastroenteritis, and toxic self-medication is frequently caused by serious AKI that cannot be treated due to the lack of dialysis facilities [78]. Special attention needs to be given to the promotion of planned pregnancies with appropriate antenatal care by skilled midwives.
Because of the scarcity of resources and the presence of overwhelming health-related and other problems, on the community level, prevention of AKI should focus on the eradication of the most common causes (i.e. tropical and non-tropical infections, exposure to nephrotoxic substances, and pregnancy-related AKI), improving education and socioeconomic statuses, and supporting health-care structures and access. In rural centers, primary-care physicians or other primary health care providers need to be able to treat common causes of AKI and to transfer individuals requiring critical care at the right time to hospitals with secondary and tertiary capacity to deal with AKI, including RRT [77].

Innovative strategies, such as outreach programs, improved transportation, the involvement of community health workers, and the strengthening of first-level health units are needed to decrease the physical barriers to access of health services by rural populations.

Finally, until relevant studies accurately measure the incidence and consequences of AKI in low and middle-income countries, resulting in sufficient awareness among local populations, AKI will remain mostly unrecognized. Such under-recognition results in very low attention being paid to the problem by public healthcare workers, as well as the impaired implementation of region-wide initiatives destined to avoid the development of AKI. Pulled in different directions by many requests and dealing with limited economies, politicians, and administrators in these countries cannot give the problem adequate attention and resources, and the condition remains poorly managed. Poor recognition also extends to primary caregivers, who have insufficient awareness of the diagnosis and the management of AKI and thus fail to rapidly implement the simple, inexpensive measures that would have the highest beneficial impact [67].

OVERALL CONCLUSIONS OF THIS CME SERIES

The present paper is the last contribution in a continuous medical education series on acute kidney injury. The first paper provides recent information on definition, staging and epidemiology of AKI, focusing on the limited data available on AKI in Rwanda.

The second paper summarizes the most important clinical and relatively minimal technical steps in the diagnostic approach to a patient suspected to suffer from AKI.

The third paper summarizes in detail the non-dialytic and dialytic therapeutic interventions in AKI.

This last contribution describes the overall and renal short- and long-term prognosis of AKI. The last part of this paper summarizes some concerns about the impact of AKI on the general health care system in Rwanda and many other sub Saharan countries.

REFERENCES

[1] V. I. Nsengiyumva, Igiraneza Grace; Lameire, Norbert, "Definition and epidemiology of acute kidney injury," Rwanda Medical journal, vol. 75, no. 2, pp. 17-23, 2018.
[2] V.I. Nsengiyumva, Igiraneza, Grace, Lameire Norbert, "Approach to the patient with presumed AKI," Rwanda Medical Journal, vol. 75, no. 3, 2018.
[3] V.I. Nsengiyumva, Igiraneza Grace, Lameire Norbert, "Non-dialytic and dialytic management of AKI," Rwanda Medical Journal, vol. 76, no.1, 2019.

[4] P. Susantitaphong et al., "World incidence of AKI: a meta-analysis," (in eng), Clin J Am Soc Nephrol, vol. 8, no. 9, pp. 1482-93, Sep 2013.
[5] G. Igiraneza, "Incidence and short outcome of acute kidney injury in tertiary teaching hospitals in Rwanda," Thesis for MMed in Internal Medicine- College of Medicine and Health Sciences. University of Rwanda, vol. 1, pp. 1-55, 2015.
[6] S. S. Waikar, G. C. Curhan, R. Wald, E. P. McCarthy, and G. M. Chertow, "Declining mortality in patients with acute renal failure, 1988 to 2002," (in Eng), J Am Soc Nephrol, vol. 17, no. 4, pp. 1143-50, Apr 2006.
[7] J. L. Xue et al., "Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001," (in eng), J Am Soc Nephrol, vol. 17, no. 4, pp. 1135-42, Apr 2006.
[8] R. Bellomo et al., "Acute kidney injury in the ICU: from injury to recovery: reports from the 5th Paris International Conference," (in eng), Ann Intensive Care, vol. 7, no. 1, p. 49, Dec 2017.
[9] S. M. Bagshaw, C. George, and R. Bellomo, "Early acute kidney injury and sepsis: a multicentre evaluation," (in eng), Crit Care, vol. 12, no. 2, p. R47, 2008.
[10] J. A. Lopes et al., "Acute kidney injury in patients with sepsis: a contemporary analysis," (in eng), Int J Infect Dis, vol. 13, no. 2, pp. 176-81, Mar 2009.
[11] D. Payen et al., "A multicentre study of acute kidney injury in severe sepsis and septic shock: association with inflammatory phenotype and HLA genotype," (in eng), PLoS One, vol. 7, no. 6, p. e35838, 2012.
[12] R. Murugan et al., "Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival," (in eng), Kidney Int, vol. 77, no. 6, pp. 527-35, Mar 2010.
[13] S. M. Bagshaw et al., "Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study," (in eng), Crit Care, vol. 9, no. 6, pp. R700-9, 2005.
[14] A. de Mendonca et al., "Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score," (in eng), Intensive Care Med, vol. 26, no. 7, pp. 915-21, Jul 2000.
[15] P. G. Metnitz et al., "Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients," (in eng), Crit Care Med, vol. 30, no. 9, pp. 2051-8, Sep 2002.
[16] R. W. Schrier and W. Wang, "Acute renal failure and sepsis," (in eng), N Engl J Med, vol. 351, no. 2, pp. 159-69, Jul 08 2004.
[17] S. Uchino et al., "Acute renal failure in critically ill patients: a multinational, multicenter study," (in eng), Jama, vol. 294, no. 7, pp. 813-8, Aug 17 2005.
[18] R. Bellomo et al., "Intensity of continuous renal-replacement therapy in critically ill patients," (in eng), N Engl J Med, vol. 361, no. 17, pp. 1627-38, Oct 22 2009.
[19] P. M. Palevsky et al., "Intensity of renal support in critically ill patients with acute kidney injury," (in eng), N Engl J Med, vol. 359, no. 1, pp. 7-20, Jul 03 2008.
[20] H. Mao et al., "Cardiac surgery-associated acute kidney injury," (in eng), Cardiorenal Med, vol. 3, no. 3, pp. 178-99, Oct 2013.
[21] C. Ortega-Loubon, M. Fernandez-Molina, Y. Carrascal-Hinojal, and E. Fulquet-Carreras, "Cardiac surgery-associated acute kidney injury," (in eng), Ann Card Anaesth, vol. 19, no. 4, pp. 687-698, Oct-Dec 2016.
[22] C. E. Hobson et al., "Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery," (in eng), Circulation, vol. 119, no. 18, pp. 2444-53, May 12 2009.
[23] O. Liangos, R. Wald, J. W. O'Bell, L. Price, B. J. Pereira, and B. L. Jaber, "Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey," (in eng), Clin J Am Soc Nephrol, vol. 1, no. 1, pp. 43-51, Jan 2006.
[24] F. Liano and J. Pascual, "Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group," (in eng), Kidney Int, vol. 50, no. 3, pp. 811-8, Sep 1996.
[25] S. G. Coca, A. J. Peixoto, A. X. Garg, H. M. Krumholz, and C. R. Parikh, "The prognostic importance of a small acute decrement in kidney function in hospitalized patients: a systematic review and meta-analysis," (in eng), Am J Kidney Dis, vol. 50, no. 5, pp. 712-20, Nov 2007.
[26] H. E. Wang, P. Muntner, G. M. Chertow, and D. G. Warnock, "Acute kidney injury and mortality in hospitalized patients," (in eng), Am J Nephrol, vol. 35, no. 4, pp. 349-55, 2012.
[27] R. R. Acedillo et al., "Characteristics and Outcomes of Patients Discharged Home from an Emergency Department with AKI," (in eng), Clin J Am Soc Nephrol, Jul 20 2017.
[28] R. L. Amdur, L. S. Chawla, S. Amodeo, P. L. Kimmel, and C. E. Palant, "Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis," (in Eng), Kidney Int, vol. 76, no. 10, pp. 1089-97, Nov 2009.
[29] C. Y. Hsu, G. M. Chertow, C. E. McCulloch, D. Fan, J. D. Ordonez, and A. S. Go, "Nonrecovery of kidney function and death after acute on chronic renal failure," (in Eng), Clin J Am Soc Nephrol, vol. 4, no. 5, pp. 891-8, May 2009.
[30] A. Ishani et al., "Acute kidney injury increases risk of ESRD among elderly," (in eng), J Am Soc Nephrol, vol. 20, no. 1, pp. 223-8, Jan 2009.
[31] L. J. Lo et al., "Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease," (in Eng), Kidney Int, vol. 76, no. 8, pp. 893-9, Oct 2009.
[32] M. T. James et al., "Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography," (in eng), Circulation, vol. 123, no. 4, pp. 409-16, Feb 1 2011.
[33] B. B. Newsome et al., "Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction," (in eng), Arch Intern Med, vol. 168, no. 6, pp. 609-16, Mar 24 2008.
[34] R. Wald et al., "Chronic dialysis and death among survivors of acute kidney injury requiring dialysis," (in eng), Jama, vol. 302, no. 11, pp. 1179-85, Sep 16 2009.
[35] A. Bihorac et al., "Long-term risk of mortality and acute kidney injury during hospitalization after major surgery," (in eng), Ann Surg, vol. 249, no. 5, pp. 851-8, May 2009.
[36] A. Ishani et al., "The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death," (in eng), Arch Intern Med, vol. 171, no. 3, pp. 226-33, Feb 14 2011.
[37] F. P. Wilson, W. Yang, and H. I. Feldman, "Predictors of death and dialysis in severe AKI: the UPHS-AKI cohort," (in

Eng), Clin J Am Soc Nephrol, vol. 8, no. 4, pp. 527-37, Apr 2013.
[38] F. Depret, M. Prud'homme, and M. Legrand, "A Role of Remote Organs Effect in Acute Kidney Injury Outcome," (in eng), Nephron, vol. 137, no. 4, pp. 273-276, 2017.
[39] K. Doi and H. Rabb, "Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets," (in eng), Kidney Int, vol. 89, no. 3, pp. 555-64, Mar 2016.
[40] A. Odutayo et al., "AKI and Long-Term Risk for Cardiovascular Events and Mortality," (in eng), J Am Soc Nephrol, vol. 28, no. 1, pp. 377-387, Jan 2017.
[41] C. Y. Hsu, R. K. Hsu, J. Yang, J. D. Ordonez, S. Zheng, and A. S. Go, "Elevated BP after AKI," (in eng), J Am Soc Nephrol, vol. 27, no. 3, pp. 914-23, Mar 2016.
[42] S. A. Silver et al., "30-Day Readmissions After an Acute Kidney Injury Hospitalization," (in eng), Am J Med, vol. 130, no. 2, pp. 163-172.e4, Feb 2017.
[43] I. Koulouridis, L. L. Price, N. E. Madias, and B. L. Jaber, "Hospital-acquired acute kidney injury and hospital readmission: a cohort study," (in eng), Am J Kidney Dis, vol. 65, no. 2, pp. 275-82, Feb 2015.
[44] C. M. Horkan, S. W. Purtle, M. L. Mendu, T. Moromizato, F. K. Gibbons, and K. B. Christopher, "The association of acute kidney injury in the critically ill and postdischarge outcomes: a cohort study*," (in Eng), Crit Care Med, vol. 43, no. 2, pp. 354-64, Feb 2015.
[45] H. D. Kiers et al., "Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury," (in eng), Nephrol Dial Transplant, vol. 28, no. 2, pp. 345-51, Feb 2013.
[46] B. J. Freda, A. B. Knee, G. L. Braden, P. F. Visintainer, and C. V. Thakar, "Effect of Transient and Sustained Acute Kidney Injury on Readmissions in Acute Decompensated Heart Failure," (in eng), Am J Cardiol, vol. 119, no. 11, pp. 1809-1814, Jun 1 2017.
[47] E. D. Siew et al., "Predictors of Recurrent AKI," (in Eng), J Am Soc Nephrol, vol. 27, no. 4, pp. 1190-200, Apr 2016.
[48] L. S. Chawla, R. L. Amdur, S. Amodeo, P. L. Kimmel, and C. E. Palant, "The severity of acute kidney injury predicts progression to chronic kidney disease," (in eng), Kidney Int, vol. 79, no. 12, pp. 1361-9, Jun 2011.
[49] L. S. Chawla, P. W. Eggers, R. A. Star, and P. L. Kimmel, "Acute kidney injury and chronic kidney disease as interconnected syndromes," (in eng), N Engl J Med, vol. 371, no. 1, pp. 58-66, Jul 3 2014.
[50] K. L. Horne, R. Packington, J. Monaghan, T. Reilly, and N. M. Selby, "Three-year outcomes after acute kidney injury: results of a prospective parallel group cohort study," (in eng), BMJ Open, vol. 7, no. 3, p. e015316, Mar 29 2017.
[51] K. Soto et al., "The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury," (in eng), Kidney Int, vol. 90, no. 5, pp. 1090-1099, Nov 2016.
[52] S. Sawhney et al., "Post-discharge kidney function is associated with subsequent ten-year renal progression risk among survivors of acute kidney injury," (in eng), Kidney Int, Apr 14 2017.
[53] D. A. Ferenbach and J. V. Bonventre, "Kidney tubules: intertubular, vascular, and glomerular cross-talk," (in eng), Curr Opin Nephrol Hypertens, vol. 25, no. 3, pp. 194-202, May 2016.
[54] M. A. Venkatachalam, J. M. Weinberg, W. Kriz, and A. K. Bidani, "Failed Tubule Recovery, AKI-CKD Transition, and Kidney Disease Progression," (in eng), J Am Soc Nephrol, vol. 26, no. 8, pp. 1765-76, Aug 2015.
[55] D. P. Basile et al., "Progression after AKI: Understanding Maladaptive Repair Processes to Predict and Identify Therapeutic Treatments," (in eng), J Am Soc Nephrol, vol. 27, no. 3, pp. 687-97, Mar 2016.
[56] S. Kumar, "Cellular and molecular pathways of renal repair after acute kidney injury," (in eng), Kidney Int, vol. 93, no. 1, pp. 27-40, Jan 2018.
[57] S. G. Coca, "Outcomes and renal function trajectory after acute kidney injury: the narrow road to perdition," (in eng), Kidney Int, vol. 92, no. 2, pp. 288-291, Aug 2017.
[58] N. Lameire, J. Vanmassenhove, and A. Lewington, "Did KDIGO guidelines on acute kidney injury improve patient outcome?," (in eng), Intensive Care Med, vol. 43, no. 6, pp. 921-923, Jun 2017.
[59] C. P. Kirwan, J., "Acute kidney injury is a chronic disease that requires long-term follow-up.," Annual update in intensive care and emergency medicine 2013, pp. 723-737, 2013 2013. Springer, Berlin
[60] N. H. Lameire et al., "Acute kidney injury: an increasing global concern," (in eng), Lancet, vol. 382, no. 9887, pp. 170-9, Jul 13 2013.
[61] "KDIGO Clinical Practice Guidelines in Acute Kidney Injury," Kidney International supplement, vol. 2, no. 1, pp. 1-138, 2012.
[62] K. D. I. G. O. K. Workgroup, "Clinical Practice Guideline for the evaluation and management of chronic kidney disease," Kidney Int, vol. supplement, pp. 30-150, 2013.
[63] E. D. Siew et al., "Outpatient nephrology referral rates after acute kidney injury," (in Eng), J Am Soc Nephrol, vol. 23, no. 2, pp. 305-12, Feb 2012.
[64] B. T. Bowman, A. Kleiner, and W. K. Bolton, "Comanagement of diabetic kidney disease by the primary care provider and nephrologist," (in eng), Med Clin North Am, vol. 97, no. 1, pp. 157-73, Jan 2013.
[65] C. J. Diamantidis, N. R. Powe, B. G. Jaar, R. C. Greer, M. U. Troll, and L. E. Boulware, "Primary care-specialist collaboration in the care of patients with chronic kidney disease," (in eng), Clin J Am Soc Nephrol, vol. 6, no. 2, pp. 334-43, Feb 2011.
[66] N. Richards et al., "Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes," (in eng), Nephrol Dial Transplant, vol. 23, no. 2, pp. 549-55, Feb 2008.
[67] N. Lameire, W. Van Biesen, and R. Vanholder, "Epidemiology of acute kidney injury in children worldwide, including developing countries," (in eng), Pediatr Nephrol, vol. 32, no. 8, pp. 1301-1314, Aug 2017.
[68] R. L. Mehta et al., "International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology," (in eng), Lancet, vol. 385, no. 9987, pp. 2616-43, Jun 27 2015.
[69] W. A. Olowu et al., "Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic

review," (in Eng), Lancet Glob Health, vol. 4, no. 4, pp. e242-50, Apr 2016.
[70] G. B. D. J. Silva, J. R. Pinto, E. J. G. Barros, G. M. N. Farias, and E. F. Daher, "Kidney involvement in malaria: an update," (in eng), Rev Inst Med Trop Sao Paulo, vol. 59, p. e53, 2017.
[71] R. Naqvi, "Plasmodium Vivax causing acute kidney injury: A foe less addressed," (in eng), Pak J Med Sci, vol. 31, no. 6, pp. 1472-5, Nov-Dec 2015.
[72] R. Naqvi, M. Mubarak, E. Ahmed, F. Akhtar, A. Naqvi, and A. Rizvi, "Acute tubulointerstitial nephritis/drug induced acute kidney injury; an experience from a single center in Pakistan," (in eng), J Renal Inj Prev, vol. 5, no. 1, pp. 17-20, 2016.
[73] N. J. Herath, S. A. Kularatne, K. G. Weerakoon, A. Wazil, N. Subasinghe, and N. V. Ratnatunga, "Long term outcome of acute kidney injury due to leptospirosis? A longitudinal study in Sri Lanka," (in eng), BMC Res Notes, vol. 7, p. 398, Jun 25 2014.
[74] H. M. Herath et al., "Chronic kidney disease in snake envenomed patients with acute kidney injury in Sri Lanka: a descriptive study," (in eng), Postgrad Med J, vol. 88, no. 1037, pp. 138-42, Mar 2012.
[75] S. S. Patel, C. E. Palant, V. Mahajan, and L. S. Chawla, "Sequelae of AKI," (in eng), Best Pract Res Clin Anaesthesiol, vol. 31, no. 3, pp. 415-425, Sep 2017.
[76] N. Perico and G. Remuzzi, "Acute kidney injury in low-income and middle-income countries: no longer a death sentence," (in eng), Lancet Glob Health, vol. 4, no. 4, pp. e216-7, Apr 2016.
[77] J. De Maeseneer and M. Flinkenflogel, "Primary health care in Africa: do family physicians fit in?," (in eng), Br J Gen Pract, vol. 60, no. 573, pp. 286-92, Apr 2010.
[78] M. Carter and J. Callegari, "Proposed treatment program for acute renal failure (ARF) in the United Republic of Tanzania as a model for sub-Saharan Africa," (in eng), J Hosp Mark Public Relations, vol. 18, no. 1, pp. 81-8, 2007.