OPINION ARTICLE

REVISED "Acute Kidney Injury predictive models: advanced yet far from application in resource-constrained settings." [version 2; peer review: 2 approved]

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v2 **First published:** 13 Jun 2022, **11**:642
https://doi.org/10.12688/f1000research.122344.1
Latest published: 13 Jul 2022, **11**:642
https://doi.org/10.12688/f1000research.122344.2

Abstract

Acute kidney injury (AKI) remains a significant cause of morbidity and mortality in hospitalized patients, particularly critically ill patients. It poses a public health challenge in resource-constrained settings due to high administrative costs. AKI is commonly misdiagnosed due to its painless onset and late disruption of serum creatinine, which is the gold standard biomarker for AKI diagnosis. There is increasing research into the use of early biomarkers and the development of predictive models for early AKI diagnosis using clinical, laboratory, and imaging data. This field note provides insight into the challenges of using available AKI prediction models in resource-constrained environments, as well as perspectives that practitioners in these settings may find useful

Keywords

Acute Kidney Injury, predictive models, resource-constrained settings

This article is included in the Global Public Health gateway.

Open Peer Review

Approval Status ✓ ✓

	1	2
version 2 (revision) 13 Jul 2022	✓ view	✓ view
version 1 13 Jun 2022	? view	? view

1. **Jeffrey Lipman**, Royal Brisbane and Women's Hospital, Herston, Australia

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Any reports and responses or comments on the article can be found at the end of the article.

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Author roles: Mrara B: Conceptualization, Funding Acquisition, Methodology, Project Administration, Resources, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Paruk F**: Supervision, Writing – Review & Editing; **Oladimeji O**: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Research reported in this publication is supported by Discovery (Grant No:038208). The content is solely the responsibility of the authors and does not necessarily reflect the official views of Discovery, Walter Sisulu University and University of Pretoria.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

How to cite this article: Mrara B, Paruk F and Oladimeji O. **"Acute Kidney Injury predictive models: advanced yet far from application in resource-constrained settings." [version 2; peer review: 2 approved]** F1000Research 2022, **11**:642 https://doi.org/10.12688/f1000research.122344.2

First published: 13 Jun 2022, **11**:642 https://doi.org/10.12688/f1000research.122344.1

REVISED **Amendments from Version 1**

In this version we have

1. Added a reference to support the assertion that dialysis is costly.
2. The reviewers raised a concern about the linkage of HIV prevalence and low-income settings. We have reworded the reference to HIV prevalence to delink it from low-income settings.

Any further responses from the reviewers can be found at the end of the article

Background

Acute kidney injury (AKI) epidemiology in low-resource settings is underreported due to difficulties with paper-based reporting and diagnosis confirmation because of limited access to laboratory testing. This has been identified as one of the barriers to the advancement of global initiatives aimed at eliminating preventable AKI deaths by 2025.[1] Furthermore, epidemiologic research on the development of predictive models of AKI in resource-limited settings is lacking; the few publications on the subject are validations of models developed in well-resourced countries.

Several predictive models for the early prediction of AKI in critically ill patients have been developed, utilizing patient data available in intensive care units (ICUs) and, more recently, machine-learning algorithms.[2,3] The silent and delayed onset of AKI makes early intervention and management difficult, resulting in the progression to dialysis-requiring renal impairment and chronic kidney disease, which is an unaffordable cost in resource-constrained healthcare systems.[4] It is hoped that early detection will allow for interventions such as reducing the impact of nephrotoxic drugs and fluid titration.

Most AKI prediction models have been developed with predictors based on susceptibilities like chronic comorbidities and exposures such as surgical procedures and sepsis. These models demonstrated variable performance in the early prediction of AKI; however, their combination with biomarkers improved their predictive performance and focused biomarker use on patients with a high pre-test probability of AKI, thus streamlining biomarker use in the determination of AKI risk.[5,6]

Challenges with models' application in resource-constrained settings

Despite these advances, some models have been criticized for methodological flaws such as using creatinine as both a predictor and an outcome measure, having low rates of AKI in the development cohort, using single-centre data, and lacking validation.[7] Furthermore, there is limited data on the models' use for the intended purpose of directing interventions to prevent further kidney injury, presumably due to difficulties with the models' multiple variables. The models predict AKI up to 24 hours ahead of time, a short timeframe that may allow for changes in medication and fluid prescription but is unlikely to have a significant impact on an already evolving injury process.

The published models when integrated into health information systems with electronic alerts have not consistently demonstrated appreciable effects on AKI outcomes.[3] Electronic health records are prohibitively expensive in resource-constrained settings. The application of AKI bundle interventions has yielded mixed results in terms of benefit in reducing AKI rates,[8,9] with even less evidence of benefit from individual interventions such as avoidance of nephrotoxins and overzealous fluid resuscitation, raising the possibility of heightened awareness and improved care quality as the reason for improvement rather than the interdependence of the interventions.

For various concerns, the applicability of currently available predictive models in low-resource contexts remains debatable and needs to be refined. Patients in low-resource settings are frequently sicker (due to delayed presentation, limited access to health care or ICU, or both), younger, and have comorbid communicable diseases.

Advanced HIV-related illness is a significant factor that may influence the occurrence and progression of AKI. As a result, HIV should be further investigated in AKI predictive models. In South Africa, the prevalence of HIV is thought to be high with a prevalence of 21% in some areas,[10] compared to 5% in the USA, where some of the AKI risk models have been developed.

Additionally, HIV illness is comparatively more severe in underserved areas due to late presentation and regulated antiretroviral treatment initiation. As a result, research into HIV as a risk factor and its impact on AKI development in patients with severe acute illness requiring ICU admission in such settings is critical. Several researchers have identified HIV infection as an independent risk factor for AKI[11]; the risk is associated with HIV progression as measured by CD4

count and viral load, tenofovir disoproxil fumarate treatment, and hepatitis C co-infection. Other risk factors include the use of herbal and traditional medications with unknown nephrotoxic potential, as well as the high prevalence of infectious disease, traumatic injuries, and pregnancy-related hypertensive disorders. The disparities in AKI epidemiology and causation between high and low-income settings may also be influenced by health-care quality, which is linked to healthcare funding. As a result, the participants and predictors used to develop AKI prediction models in high-income settings are theoretically distinct from those prevalent in resource-constrained settings.

Furthermore, because the impact and practicability of these predictive tools in high-income settings has not been thoroughly studied, alternative models that are simple to use and incorporate concrete actions to prevent AKI would be advantageous. The cost of the biomarkers, including importation and implementation with specialized laboratory equipment and expertise, is also a barrier to their implementation in resource-constrained settings where basic laboratory tests such as 24-hour serum creatinine are difficult to achieve.

Conclusion

While AKI predictive modelling in high-income health systems is rapidly evolving, lower-income health systems should carefully consider the applicability and costs of these models within in resource-constrained settings. We would argue that in resource-constrained settings a pragmatic approach would be to mainly focus on raising awareness about AKI risk, meticulous patient monitoring, careful drug and fluid prescription practice, and general measures to improve health care quality, which is all that is currently feasible.

Author contributions

BM and OO initiated discussion of the idea; BM and OO created the first draft. BM, OO, and FP critically reviewed and approved this final version.

Data availability

Underlying data

No data are associated with this article.

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 20 July 2022

https://doi.org/10.5256/f1000research.136033.r144207

✔ **Nolubabalo Unati Nqebelele**
Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

All comments have been adequately addressed by the authors.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephrology, Chronic kidney disease, Acute Kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 20 July 2022

https://doi.org/10.5256/f1000research.136033.r144208

✔ **Jeffrey Lipman**
Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Herston, QLD, Australia

In my opinion, the manuscript in its current revision is acceptable for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Intensive Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 30 June 2022

https://doi.org/10.5256/f1000research.134322.r140611

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Nolubabalo Unati Nqebelele
Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

This is a clearly articulated opinion article on the challenges encountered with the use of AKI predictive models in resource-constrained settings. These models have gained popularity and are rapidly evolving in well-resourced environments. The authors discuss the challenges with the general applicability of these models in low-resourced settings.

In paragraph 2, the authors discuss the 'unaffordable cost of dialysis-requiring renal impairment in resource-constrained healthcare systems', without providing a reference. There are various publications on this issue and a reference should be provided.

In the challenges with the models' application in resource-constrained settings (paragraphs 6-7), there is a strong emphasis on HIV infection. Though important and should perhaps be considered in AKI predictive models, the prevalence of HIV varies extensively, even in low-resourced settings and this should be considered in the discussion.

It is commendable that the authors conclude that raising awareness of AKI and paying attention to patient monitoring and care is where most attention should be placed in resource-limited settings at this stage. Furthermore, the availability of less-than-ideal creatinine should be improved upon in resource-constrained healthcare systems.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Partly

Are arguments sufficiently supported by evidence from the published literature?

Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Nephrology, Chronic kidney disease, Acute Kidney disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jul 2022

busisiwe Mrara, Walter Sisulu University, Mthatha, South Africa

Thank you for your valuable input.

We have added a reference supporting the assertion regarding the astronomical costs of dialysis.

We accept that HIV prevalence is variable in low-income settings. We have reworded the paragraph to delink HIV prevalence and low-income settings. However, we would like to emphasise that the advanced presentation of HIV and its complications including Acute Kidney Injury, could be an issue in areas of inadequate health care access.

Competing Interests: No competing interests were disclosed.

Reviewer Report 22 June 2022

https://doi.org/10.5256/f1000research.134322.r140612

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Jeffrey Lipman
Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Herston, QLD, Australia

This is a nice description of the problems of Acute Kidney Injury (AKI) prediction models. As the authors state, AKI is not an uncommon phenomenon in ICU and potentially its prediction could be used to mitigate the consequences of AKI.

Creatinine is the common biomarker used for kidney function and hence used in the diagnosis of AKI. Its problems in kidney injury are commonly known, a crude marker with a delayed response –

today's creatinine is yesterday's renal function. In this opinion piece, the authors quite correctly point out the problems of using creatinine in the prediction of AKI, both from the point of view of its delayed response and that it is used in the prediction and the outcome of AKI.

I have merely one comment - the authors are from South Africa which could be described as a low-income/low-resource setting/region (accepted). In South Africa, there is a large HIV "burden". This may not be so in all similar low-resource regions. The authors link low resources with HIV infections – I would suggest this not to be the case and the authors should "delink" the two issues. Sure bring up the problems of HIV and kidney involvement, but separate the two issues for this manuscript.

Is the topic of the opinion article discussed accurately in the context of the current literature?
Yes

Are all factual statements correct and adequately supported by citations?
Partly

Are arguments sufficiently supported by evidence from the published literature?
Partly

Are the conclusions drawn balanced and justified on the basis of the presented arguments?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Intensive Care

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Jul 2022

busisiwe Mrara, Walter Sisulu University, Mthatha, South Africa

Thank you for sharing your insights.

It is correct that the prevalence of HIV is not directly linked to low-resource environments, and is not high in some low and middle-income countries. The problem we would like to emphasise is the advanced presentation of HIV in settings where health care access is inadequate and the consequent possible impact on the occurrence of Acute Kidney Injury.

Competing Interests: No competing interests