Protocol

Acute Kidney Injury – Epidemiology in ICU patients 2 – North America

Acronym: AKI-EPI-2 - North America

Version: 1.0 – Date 29 January 2026

Trial identifiers:

North America Sponsor:

Name: University of Alberta

Address: Department of Critical Care Medicine
Faculty of Medicine and Dentistry, College of Health Sciences
University of Alberta
2-124 Clinical Sciences Building, 8440-112 ST NW
Edmonton, Alberta, T6G2B7, Canada

North America Principal Investigator:

Name: Sean M Bagshaw, MD, MSc

Address: Department of Critical Care Medicine
Faculty of Medicine and Dentistry, College of Health Sciences
University of Alberta
2-124 Clinical Sciences Building, 8440-112 ST NW
Edmonton, Alberta, T6G2B7, Canada

Global Principal Investigators:

Name: Eric Hoste, MD, PhD

Address: C Heymanslaan 10, 9000 Ghent, Belgium

Telephone: +32 9 332 2769

Email: eric.hoste@uzgent.be

Name: Antoine Schneider, MD, PhD

Address: Adult Intensive Care Unit, Centre Hospitalier Universitaire Vaudois,

46 Avenue du Bugnon 1011 Lausanne, Switzerland

Telephone: +41 21 314 46 32

Email: antoine.schneider@chuv.ch

Study Synopsis

Title	Acute Kidney Injury – Epidemiology in ICU patients 2
Acronym	AKI-EPI-2 – North America
Sponsor (North America)	University of Alberta (Edmonton, Canada)
Sponsor (North America) PI	Sean M Bagshaw, MD, MSc
Global PIs	Eric Hoste, MD, PhD Antoine Schneider, MD, PhD
ClinicalTrials.Gov	NCT07207031
Medical condition under investigation	Acute Kidney Injury (AKI)
Purpose of clinical trial	To investigate the epidemiology and outcomes of acute kidney injury in critically ill patients.
Primary objective	To provide a contemporary update on the epidemiology (rates, severity, duration, and etiology) of AKI and associated outcomes in critically ill patients.
Secondary objectives	• To assess temporal aspects of AKI (timing relative to ICU admission and duration). • To describe utilization and practice of RRT (indications, timing, modality, anticoagulation, duration, discontinuation) • To explore differences in rates and outcomes between regions and health care systems according to geographical location and resources.
Trial design	• International, multicenter cohort study
Endpoints	<u>Co-primary outcomes</u>: • occurrence rate of AKI within 7 days of ICU admission • maximum severity of AKI within 7 days of ICU admission. <u>Secondary outcomes:</u> • Proportion of AKI in patients with and without known baseline serum creatinine • Duration of AKI episodes (within 7 days of ICU admission) • Proportion of episodes with rapid reversal (duration <48h) vs persistent AKI (duration ≥48h) • Incidence of acute kidney disease (AKD) at ICU discharge and hospital discharge, truncated at 90-days • Use of RRT within 7 days of ICU admission • Type and specifics of applied RRT (indications, timing, modality, method duration, anticoagulation, discontinuation) • Length of stay in the ICU, post ICU in the hospital, and total length of stay in the hospital • ICU readmission up to day 90 • Hospital readmission up to day 90

	• Serum creatinine level at ICU and hospital discharge (truncated at day 90) • RRT dependence at hospital discharge (any RRT applied within 72 hours of discharge) • Mortality at hospital discharge (truncated at 90-d) • Magnitude of AKI: area under the curve of AKI of severity over time • Incidence of AKI and maximum AKI severity stage defined by serum creatinine and/or urine output criteria only, within 7 days of ICU admission. <u>Additional endpoints</u> for patients included in the "long term outcomes sub study" (see below): • Serum creatinine level at day 90, and 1 y • RRT dependence at day 90, and 1y • Mortality at hospital discharge at day 90, and 1y • Survival analysis up to day 90 and 1 y • Health-related quality of life at day 90 and 1y (EQ5D) • Major Adverse Kidney Events (MAKE): a composite endpoint of death, use of RRT and decreased kidney function at day 90 (+/-14 days), and 1 year (+/-30 days).
Sample Size	• The North America study aims to recruit 1,250-1,500 patients (50 patients at 25 sites). • The Global study aims to recruit 10,642 critically ill patients worldwide
Summary of eligibility criteria	<u>Inclusion:</u> • Age ≥ 18 years. • Admitted to ICU. • Admitted to the ICU for more than 24-h, or anticipated length of stay in the ICU for 24-h or more. • Informed Consent, as necessary, according to local research ethics committee (REB). <u>Exclusion:</u> • End Stage Kidney Disease treated with maintenance RRT. • Readmission to the ICU during same hospitalization episode. • <u>Missing AKI defining data (no measured serum creatinine and <6 hours of documented urinary output).</u>
Version and date of final protocol (North America) (Global)	 Version 1.0, 29 January 2026 Version 1.0 17 June 2024

1. Background and rationale

Acute Kidney Injury (AKI) is a frequent complication in critically ill patients admitted to the intensive care unit (ICU). In large epidemiological studies [1–3], the occurrence rate of AKI during the first 5 or 7 days of ICU admission ranged between 40 and 60%. In patients who underwent major surgery, a lower but relevant incidence of AKI was observed (20%)[4]. Of note, these studies also included patients who were less ill (not critically ill) and supported in a high-dependency unit setting, which may underestimate the overall burden of AKI. In all cohorts, moderate-severe (≥ stage 2) AKI was associated with less favorable outcomes after adjustment for other major risk factors. These reported incidences and association with outcomes were highly heterogeneous across centers. In particular, geographical location and country socio-economic status appeared to play a major role. The FINNAKI, SEA-AKI and AKI-EPI studies, although of major importance in the field, present limitations. First, the data was acquired more than a decade ago. In this period, numerous changes in practice have occurred regarding AKI management. For instance, the importance of the application of the KDIGO care bundle was demonstrated in some populations [5,6]. Similarly, the lack of benefit for early initiation of renal replacement therapy (RRT) has been shown in large multicenter trials [7–9]. The number of elderly patients admitted to the hospital and for whom invasive procedures are proposed is increasing over time [10]. Altogether, these elements are likely to have modified the incidence and outcomes of AKI in critically ill patients [11]. Second, it has recently been proposed to integrate biomarkers of kidney damage in AKI definition [12]. The utilization of such biomarkers is also likely to have modified our ability to assess renal injury and apply protective measures. Third, none of the FINNAKI, SEA-AKI or the AKI-EPI studies evaluated the impact of AKI duration (or magnitude) on outcomes at day 90 post ICU admission (the current gold standard to define chronic kidney disease). Fourth, these studies also did not aim to describe the utilization and practice of acute renal replacement therapy (RRT) in ICU settings associated with AKI. Finally, in these studies, there was poor representation of low- and middle-income countries. Hence, there is strong rationale for an updated global snapshot of the epidemiology of AKI in critically ill patients.

Accordingly, we have designed the AKI-EPI 2 study, an international multicenter observational study.

2. Trial objectives and design

2.1 Trial objectives

The AKI-EPI 2 Global and North America will aim to:

1. Provide a contemporary update on the epidemiology (rates, severity, duration and etiology) of AKI and associated outcomes in critically ill patients
2. Assess temporal aspects of AKI (timing relative to ICU admission and duration),

3. Describe RRT practices (indications, timing, modality, anticoagulation, dose, duration, and discontinuation).
4. Explore differences in rates and outcomes between regions and health care systems according to geographical location and resources.

2.2 Primary outcomes

Our co-primary outcomes will be the occurrence rate of AKI and the maximum severity of AKI within 7 days of ICU admission.

2.3 Secondary outcomes

The following secondary outcomes will be considered.

- Proportion of patients with AKI among patients without known baseline serum creatinine
- Duration of AKI episodes (within first week of ICU admission)
- Proportion of AKI with rapid reversal (duration <48h) vs persistent AKI (duration ≥48h)
- Incidence of acute kidney disease (AKD) at ICU discharge and hospital discharge, truncated at 90-d
- Use of RRT within 7 days of ICU admission
- Type and specifics of applied RRT (indications, timing, modality, dose anticoagulation, duration, discontinuation)
- Length of stay in the ICU, post ICU in the hospital, and total length of stay in the hospital
- ICU readmission up to day 90
- Hospital readmission up to day 90
- Serum creatinine level at ICU and hospital discharge (truncated at day 90)
- RRT dependence at hospital discharge (any RRT applied within 72 hours of discharge)
- Mortality at hospital discharge (truncated at 90-d)
- Magnitude of AKI: area under the curve of AKI of severity over time
- Incidence of AKI and maximum AKI severity stage defined by serum creatinine and/or urine output criteria only, within 7 days of ICU admission.

In addition, for patients included in the "long term outcomes sub-study" (see below), the following additional secondary outcomes will be considered:

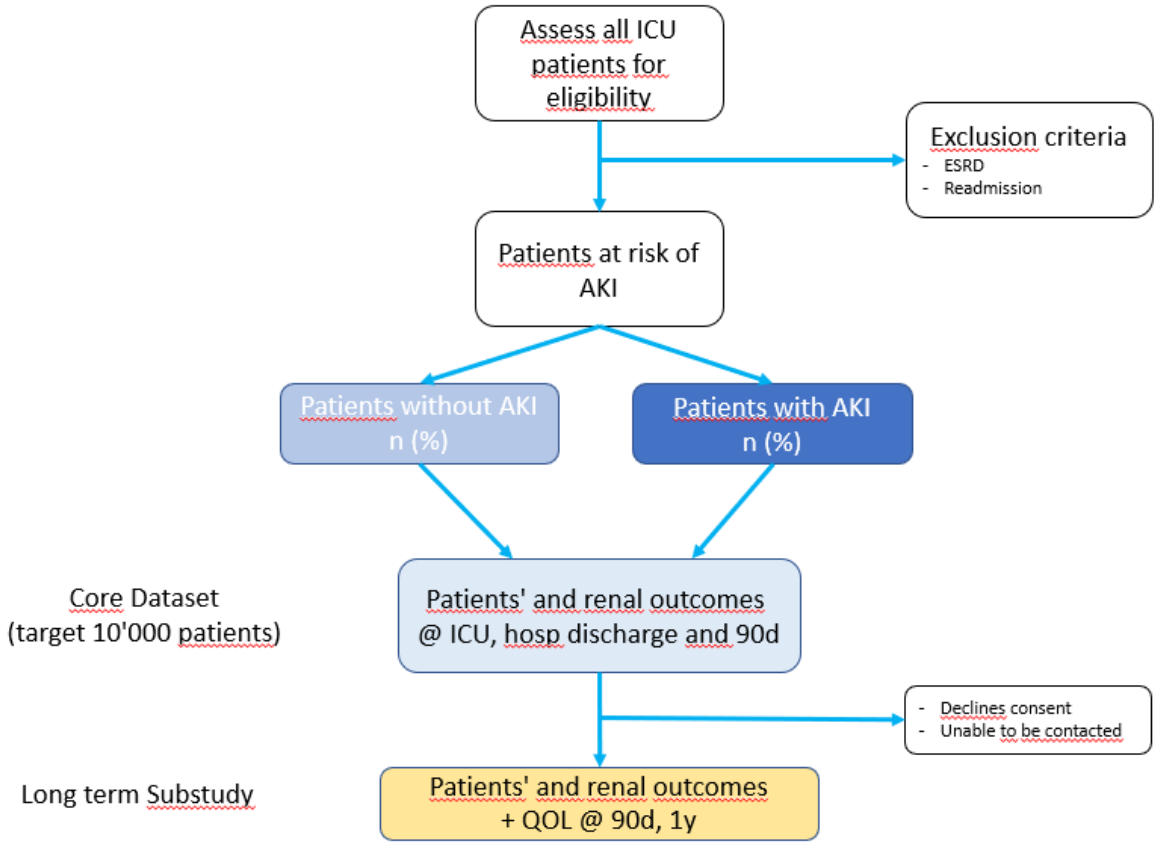
- Serum creatinine level at day 90, and 1 y
- RRT dependence at day 90, and 1y
- Mortality at hospital discharge at day 90, and 1y
- Survival analysis up to day 90 and 1 y
- Quality of life at day 90 and 1y (EQ5D)
- Major Adverse Kidney Events (MAKE): a composite endpoint of death, use of RRT and decreased kidney function at day 90, and 1 year.

2.4 Study design

This is a multinational observational cohort study. Data will be collected at baseline (ICU admission) as well as daily for ICU Day 1 to 7 (or ICU discharge, whichever comes first). Outcome data will be

collected at hospital discharge and, in a subgroup of patients long term follow up outcome data will be collected at day 90 and 1y.

2.5 Study diagram



3. Project Population and Study Procedures

3.1 Project population

We will include all consecutive patients fulfilling eligibility criteria (below). Recruitment will continue until the predetermined number of patients for the center has been reached (see below power calculation). The duration of the study period may vary from center to center.

Inclusion Criteria:

- Age >= 18 years.
- Admitted to one of the participating ICUs.
- Admitted to the ICU for more than 24-h, or anticipated length of stay in the ICU for 24-h or more.
- Informed consent, as necessary, according to the local research ethics board (REB).

Exclusion Criteria

- Readmission to the ICU during the same hospitalization episode.
- End Stage Kidney Disease treated with maintenance RRT.
- Missing AKI defining data (no measured serum creatinine and <6 hours of documented urinary output).

3.2 Recruitment screening and informed consent procedure

Minimal (core) dataset

The recruitment screening process will be adapted to each center. In general, all eligible patients will be included in the study for a minimal (core) dataset. According to local ethic committee and local regulations, this might or might not require formal written consent. Before inclusion in the study, the presence of documented opposition to research and data reutilization will be checked.

In general, waiver for written consent will be requested for the following reasons:

- The data collection tool will be developed with the view of complying with GDPR requirements and enable data pseudonymization. The study utilizes health related data routinely collected in clinical practice
- Informed consent may be difficult to obtain from the patient or the next of kin which could likely lead to uncomfortable discussion with a potential for harm.
- From a scientific point of view, to be able to report on incidence, we need to be able to include all consecutive patients.

Extended dataset and outcomes

In a subset of patients, we will attempt to obtain an extended dataset and longer follow-up. This includes attempts to obtain data 90 days and 1 y after ICU admission (see below). For these patients, according to local ethic committee and regulation, we will, in most instances be required to obtain formal consent.

3.3 Study Procedures

The study is purely observational, no intervention will be conducted.

Minimal dataset

The minimal dataset includes the following data (Table 1)

- Site characteristics: Geographic area (United Nations geographical subregions), country, area (rural/regional, urban), level (primary, tertiary), teaching/non-teaching, academic, community, regional.
- Patient baseline characteristics (age, sex, comorbidities, baseline creatinine)
- ICU admission characteristics (admission type, primary diagnosis, SOFA score)
- Daily creatinine and total urinary output measurements (for AKI diagnosis, staging, duration)
- RRT initiation data: ICU Day of initiation, severity of AKI, non-renal organ support, indications, modality, dose/ultrafiltration, anticoagulation)
- Daily use and practice parameters for RRT administration (modality, dose/ultrafiltration, anticoagulation, treatment interruption)
- RRT modality transition: ICU Day of transition, type of transition
- RRT termination: ICU date of termination, total duration

- At hospital discharge: ICU and hospital length of stay, vital status, use of RRT and serum creatinine, truncated at 90-days.

Extended datasets

Extended Follow-up

This dataset will be completed only for patients enrolled in centers participating in the "long term outcomes sub-study". Patients included in the main study and who survived to hospital discharge will be invited (and consented) for a follow-up visit or contacted over the phone by a study collaborator, whichever is most applicable. During this follow-up, the following outcomes will be ascertained:

- Day 90 (+/- 14 days): vital status, use of RRT, serum creatinine (if available) and administration of the EQ-5D-5L questionnaire. We will also ascertain patient-reported outcome measures following critical illness complicated by AKI (+/- treatment with RRT).
- 1 year (+/- 30 days): vital status, use of RRT, serum creatinine and administration of the EQ-5D-5L questionnaire. We will also ascertain patient-reported outcome measures following critical illness complicated by AKI (+/- treatment with RRT).

If we are unable to contact a patient after reasonable efforts (2 attempts to contact via a telephone call), we will attempt to contact his/her next of kin or general practitioner. For patients unable to respond to the survey, the next of kin will be contacted and the EQ-5D-5L will be administered to them by proxy. In case, no information can be obtained, this patient will be considered lost to follow up.

4. Statistics and Methodology

4.1 Power Calculation

The primary aim of the study is to estimate the incidence of AKI and to derive the corresponding exact two-sided 95% confidence interval (CI) according to Clopper-Pearson. Depending on the type of admission, AKI rates between 40 and 70% were reported in the literature [13]. Therefore, a rate of 50% was assumed for the sample size calculation as a conservative approach. Using this assumption, 10,642 patients are needed to limit the width of the 95% CI to 1.9%. Thus, with n = 10,642 patients, the incidence of AKI can be estimated with at least this precision. AKI-EPI-2 North America will aim to recruit ~ 1,250-1,500 participants across 25 sites in North America.

4.2 Statistical Analyses plan

Prior to the completion of recruitment and final database locking, a detailed statistical analysis plan (SAP) will be developed.

The analysis of the primary endpoint, defined as the occurrence of AKI within 7 days of ICU admission, will use the Clopper-Pearson exact method with a 95% confidence level. For multinomial proportion estimates (e.g., KDIGO stages (1/2/3) in AKI patients), simultaneous 95% CIs we will calculate using Goodman's methods [17].

We will describe the frequencies (percentages) and mean (SD) or median (IQR) for all baseline variables and secondary endpoints, as applicable. Survival curves will be constructed according to the Kaplan-Meier method. We will compare groups (e.g., AKI vs. no AKI; RRT vs. no RRT) using Fisher's exact test or Pearson's Chi-squared test for categorical variables, and for continuous variables, Student t-test or

Wilcoxon signed-rank test, depending on data distribution. To identify and assess the association of factors associated with AKI, multivariable logistic regression analysis will be performed. Variables considered will include demographic, baseline and clinical characteristics, and further include those previously described in the literature. To describe the association with AKI (by varying definitions and RRT use) with outcomes, multivariable logistic and linear regression analyses will be performed.

We will perform subgroup analyses according to the definition of AKI (based on serum creatinine or urine output only), severity of AKI, age, sex, case mix and admission diagnosis, illness severity, country GDP, hospital type, and other potential factors to be defined in the SAP.

A sensitivity analysis will be performed on patients with known baseline serum creatinine only.

5. Regulatory Aspects

5.1 Local regulations / Declaration of Helsinki

This research project will be conducted in accordance with the protocol, the Declaration of Helsinki, the principles of Good Clinical Practice, the Human Research Act (HRA) and the Human Research Ordinance (HRO) as well as other locally relevant regulations. The Coordinating Investigator acknowledges his responsibilities as both the Coordinating Investigator and the Sponsor.

5.2 Obligation to announce

Substantial changes to the project set-up, the protocol and any relevant project documents will be submitted to relevant Research Ethics Committees for approval before implementation.

Upon project termination, the Ethics Committee will be notified within 90 days.

5.3 Duration of conservation

Anonymized health related data and all study documents will be stored for at least 10 years after the completion of the study in the secured servers from Ghent University. In addition, each participating center needs to store all study related data such as Informed Consent Forms (ICF's), code lists, source documents etc. in a secured place and/or on secured servers for the time required by local regulations.

6. Further Aspects

6.1 Overall ethical consideration

This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

The Project Leaders affirm and uphold the principle of the participants' right to dignity, privacy and health and that the project team shall comply with applicable privacy laws. Especially, the anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Individual participant's medical information obtained because of this research project is considered confidential and disclosure to third parties is prohibited. Participant confidentiality will be further ensured by storing only pseudonymized patient data in computer files.

6.2 Risk-Benefit Assessment

Due to its observational design, the study is not associated with a specific risk for project participants.

7. Quality Control and Data Protection

7.1 Quality measures

For quality assurance representatives of the promoter, auditors, relevant Medical Ethics Committees may visit the research sites. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Data will be stored in a specific REDCap file. This is either a local mirror version of REDCap which will include patient identifiers, and which will be used for the purpose of data collection. Alternatively, pseudonymized data can be entered in the central study REDCap. Investigators may choose to enter data in coded form in an electronic excel or paper CRF. This data will only be kept locally (within the center) and serve for verification purposes.

In case, a local mirror REDCap is used, data will then be locally pseudonymized before being transferred to the central REDCap study database. The data is accessed through a web browser directly on the secure REDCap server. The server is hosted within the Ghent University Hospital campus and meets hospital level security and back-up requirements.

Access to this server requires institutional login and password. Access to the study folder will be electronically restricted to the dedicated study collaborators listed in study delegation logs. In addition, the database will be protected and this password will only be given to dedicated study collaborators listed in the study delegation log. Traceability of changes is guaranteed since Redcap has an audit trail.

Health related personal data captured during this project are strictly confidential and disclosure to third parties is prohibited; pseudonymization will safeguard participants' confidentiality.

Access to protocol, dataset, statistical code, and ID key code during the study will be restricted. All parties involved must keep the participant data strictly confidential.

Study data, in coded form can, upon request, be accessed by regulating authorities or scientific journals for review

8. Funding / Publication / Declaration of Interest

8.1 Funding:

This study will be initially funded by the research funds accessible to the PIs and Steering Committee. Further external (local or regional) funding support will be sought to support site-specific research infrastructure.

8.2 Publication

After completion of the study, several scientific articles will be written and submitted to peer-reviewed scientific journals. Members of the steering committee will be listed as co-authors and all

other collaborators under the group name “AKI-EPI-2 Study Investigators”. This will include integration of participant data from *AKI-EPI-2 – North America*.

8.3 Declaration of conflicts interest

There is no intellectual, financial or proprietary conflict of interest to declare.

9. References

1. The FINNAKI Study Group, Nisula S, Kaukonen K-M, Vaara ST, Korhonen A-M, Poukkanen M, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39:420–8.

2. Hoste EAJ, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med. 2015;41:1411–23.

3. Srisawat N, Kulvichit W, Mahamitra N, Hurst C, Praditpornsilpa K, Lumlertgul N, et al. The epidemiology and characteristics of acute kidney injury in the Southeast Asia intensive care unit: a prospective multicentre study. Nephrology Dialysis Transplantation. 2020;35:1729–38.

4. Zarbock A, Weiss R, Albert F, Rutledge K, Kellum JA, Bellomo R, et al. Epidemiology of surgery associated acute kidney injury (EPIS-AKI): a prospective international observational multi-center clinical study. Intensive Care Med. 2023;49:1441–55.

5. Zarbock A, Küllmar M, Ostermann M, Lucchese G, Baig K, Cennamo A, et al. Prevention of Cardiac Surgery–Associated Acute Kidney Injury by Implementing the KDIGO Guidelines in High-Risk Patients Identified by Biomarkers: The PrevAKI-Multicenter Randomized Controlled Trial. Anesthesia & Analgesia. 2021;133:292–302.

6. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med. 2017;43:1551–61.

7. Investigators S-A, Canadian Critical Care Trials G, Australian, New Zealand Intensive Care Society Clinical Trials G, United Kingdom Critical Care Research G, Canadian Nephrology Trials N, et al. Timing of Initiation of Renal-Replacement Therapy in Acute Kidney Injury. N Engl J Med. 2020/07/16 ed. 2020;383:240–51.

8. Gaudry S, Hajage D, Schortgen F, Martin-Lefevre L, Pons B, Boulet E, et al. Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. N Engl J Med. 2016;375:122–33.

9. Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. N Engl J Med. 2018;379:1431–42.

10. Naik H, Murray TM, Khan M, Daly-Grafstein D, Liu G, Kassen BO, et al. Population-Based Trends in Complexity of Hospital Inpatients. JAMA Intern Med [Internet]. 2024 [cited 2024 Jan 17]; Available

from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2813852

11. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? Kidney International. 2015;87:46–61.

12. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, et al. Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement. JAMA Netw Open. 20201001st ed. 2020;3:e2019209.

13. Hoste EAJ, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. Nat Rev Nephrol. 2018;14:607–25.