### Title

Acute kidney injury developed in the intensive care unit: a population-based prospective cohort study in the Brazilian Amazon.




### Journal

Scientific Reports, 14(1)



### Authors

Melo, Fernando

Burdmann, Emmanuel

Macedo, Etienne

et al.



### Publication Date

2024-10-03

### DOI

10.1038/s41598-024-74177-y

Peer reviewed

scientific reports

Check for updates

OPEN

# Acute kidney injury developed in the intensive care unit: a population-based prospective cohort study in the Brazilian Amazon

Fernando A. F. Melo[1], Emmanuel A. Burdmann[2], Etienne Macedo[3], Ravindra Mehta[3] & Dirce M. T. Zanetta[4]✉

**The Brazilian Amazon is a vast area with limited health care resources. To assess the epidemiology of critically ill acute kidney injury (AKI) patients in this area, a prospective cohort study of 1029 adult patients of the three intensive care units (ICUs) of Rio Branco city, the capital of Acre state, were evaluated from February 2014 to February 2016. The incidence of AKI was 53.3%. Risk factors for AKI included higher age, nonsurgical patients, admission to the ICU from the ward, higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores at ICU admission, and positive fluid balance > 1500 ml/24 hours in the days before AKI development in the ICU, with aOR of 1.3 (95% CI 1.03–1.23), 1.47 (95% CI 1.07–2.03), 1.96 (95% CI 1.40–2.74), 1.05 (95% CI 1.03–1.08) for each unit increase, and 1.62 (95% CI 1.16–2.26), respectively. AKI was associated with higher ICU mortality (aOR 2.03, 95% CI 1.29–3.18). AKI mortality was independently associated with higher age, nonsurgical patients, sepsis at ICU admission, presence of shock or use of vasoactive drugs, mechanical ventilation and mean positive fluid balance in the ICU > 1500 ml/24 hours, both during ICU follow-up, with aOR 1.27 (95% CI 1.14–1.43) for each 10-year increase, 1.64 (95% CI 1.07–2.52), 2.35 (95% CI 1.14–4.83), 1.88 (95% CI 1.03–3.44), 6.73 (95% CI 4.08–11.09), 2.31 (95% CI 1.52–3.53), respectively. Adjusted hazard ratios for AKI mortality 30 and 31–180 days after ICU discharge were 3.13 (95% CI 1.84–5.31) and 1.69 (95% CI 0.99–2.90), respectively. AKI incidence was strikingly high among critically ill patients in the Brazilian Amazon. The AKI etiology, risk factors and outcomes were similar to those described in high-income countries, but mortality rates were higher.**

**Keywords** Acute kidney injury, Epidemiology, Critically ill patients, Disadvantaged populations, Low-income and middle-income countries, Amazon

**Abbreviations**

| | |
|---|---|
| AKI | Acute kidney injury |
| aOR | Adjusted odds ratio |
| aHR | Adjusted hazard ratio |
| APACHE | Acute physiology and chronic health evaluation |
| CI | Confidence interval |
| CKD | Chronic kidney disease |
| ICU | Intensive care units |
| IDMS | Isotope dilution mass spectrometry |
| KDIGO | Kidney disease: improving global outcomes |
| KRT | Kidney replacement therapy |
| pmp | Patients per million people |

[1]Division of Urology, Acre Federal University, Rio Branco, Acre, Brazil. [2]Laboratório de Investigação (LIM) 12, Serviço de Nefrologia, Faculdade de Medicina da Universidade de Sao Paulo, São Paulo, Brazil. [3]Department of Medicine, University of California San Diego (UCSD), San Diego, CA, USA. [4]Department of Epidemiology, School of Public Health, University of São Paulo, São Paulo, São Paulo, Brazil. ✉email: dzanetta@usp.br

| | |
|---|---|
| SAPS | Simplified acute physiology score |
| sCr | Serum creatinine |

Acute kidney injury (AKI) is a common event in intensive care units (ICUs). In an extensive systematic review of 76 cohorts comprising 564,455 ICU patients, the AKI frequency reported was up to 82.5%[1], and in a recent and large multinational study, AKI affected up to 57% of ICU patients[2].

AKI is associated with more resource consumption and costs, longer ICU and hospital stays, higher rates of early and late mortality, the development of chronic kidney disease (CKD), and other long-term systemic complications[3,4].

Most of the epidemiological information on AKI in the ICU comes from high-income countries in the Northern Hemisphere. A recent meta-analysis on this topic found approximately two times more studies from developed than from developing countries. When the number of ICUs and patients was compared, the discrepancies were more marked: 990 vs. 86 ICUs and 1,057,332 vs. 34,539 patients in developed versus developing countries, respectively[5]. The AKI incidence and patient characteristics were similar in both types of countries, but the need for kidney replacement therapy (KRT), length of ICU stay, and mortality were higher in developing countries. A prospective multinational study of AKI in the ICU assessed 6647 patients from 14 large urban centers, nine from developed countries and five emerging countries (Brazil, India and China). Living in an emerging country was an independent risk factor for higher mortality and for the absence of kidney function recovery at hospital discharge[6].

Population-level epidemiological studies among AKI patients in the ICU are scarce, especially in low-income and middle-income countries, where more than 85% of the world's population resides[7]. The Brazilian Amazon is a resource-constrained region with limited health care facilities and specific risk factors and exposures for AKI, such as animal venoms and tropical infectious diseases[8]. Population-based epidemiological studies of AKI in this region have not been performed.

The aim of this study was to prospectively assess the incidence, risk factors and outcomes of AKI developed in the ICUs of one geopolitical area (Acre state) in the Brazilian Amazon.

## Methods

### Type of study, population and period

We conducted a prospective cohort study of all adult patients (> 18 years) admitted to all ICUs of Rio Branco, the capital of the state of Acre in the western Amazon in Brazil, over 18 months (in 2014, data collection took place during two months interspersed with two months without collection and from February 2015 to February 2016 it took place uninterruptedly). The patients were followed daily during the first seven days of ICU stay, discharge from the ICU, or death, whichever occurred first. Their length of stay in the ICU and in the hospital was recorded. Mortality up to 180 days of ICU discharge was recorded. A seven days-time frame was arbitrarily selected because we aimed to assess the incidence of AKI related to the cause(s) of the ICU admission. A longer time frame would capture AKI related to complications inherent to critically ill patients in the ICU.

The state of Acre has 22 cities, 88% forest cover, and a territory of 164,000,000 $km^2$, bordering Bolivia, Peru and the Brazilian states of Amazonas and Rondônia. It had an estimated population of 800,000 individuals (demographic density of 4.47 inhabitants/$km^2$), 72.6% of whom lived in urban areas, according to the National Census Bureau (Instituto Brasileiro de Geografia e Estatística, IBGE) in 2015[8]. The network coverage of piped water was 44.6%, and 78.7% of urban areas did not have sewage network coverage[9]. Rio Branco city, where the studied ICUs were located, had an estimated population of 370,550 inhabitants and its hospital network was responsible for approximately 83% of the state population.

Patients from all three ICUs of the state capital were evaluated. These ICUs receive patients from 88% of the state area. In 2015, there was only one other ICU in the state, with five beds, located in the western area of the state. The studied ICUs are adult general medical-surgical units located in multidisciplinary hospitals. They were located in a tertiary public teaching hospital (with 232 beds and 13 ICU beds), in a teaching emergency hospital (with 204 beds and 18 ICU beds) and in a mixed public–private hospital (with 162 beds and 10 ICU beds). These hospitals provide care to the capital and most of the municipalities of the state.

### Exclusion criteria

The exclusion criteria were as follows: age less than 18 years; length of stay in the ICU less than 48 h; CKD stage 5; residential address outside the state of Acre; patients in palliative treatment or with a short-term reserved prognosis; or kidney transplant recipients.

### Definitions

Incident AKI was diagnosed by Kidney Disease: Improving Global Outcomes (KDIGO)[10] criteria using daily serum creatinine (sCr) and urine output measurements. We used strictly KDIGO AKI definition, which considers a mobile window for the diagnosis. The reference SCr for diagnosis was that observed 48 h or seven days prior the observed elevation of 0.3 mg/dl or 50%. For patients admitted with sCr ≥ 4 mg/dL, the creatinine criterion considered was an increase in sCr of at least 1.5 times during follow-up.

Since urine output was recorded over a 24-hour period, we could not determine AKI severity, if stage 1 or 2, when KDIGO urine output criterion was the only one reached by the patient. The maximum KDIGO stage was the worst KDIGO stage reached by a patient during the seven-day follow-up in the ICU.

AKI was defined as transient when sCr levels and urine output normalized within 48 h after diagnosis and as persistent when sCr levels remained increased and/or urine output remained decreased for more than 48 h after diagnosis.

We considered that the patients were already admitted with AKI (AKI previous to ICU) if they had sCr measured during the seven days prior to ICU admission that increased up to the date of ICU admission according to the KDIGO criteria, or if the sCr level decreased by 0.3 mg/dL or more compared to the value measured at ICU admission during the observation time in the ICU according to a modified KDIGO criteria[11–13]. For patients admitted with sCr ≥ 4 mg/dL, AKI previous to ICU was considered if the sCr level decreased to half or more of the sCr upon admission.

If a patient was already admitted with AKI in the ICU, had a decrease of SCr ≥ 0.3 mg/dL during follow-up, and subsequently fulfilled the KDIGO criteria for AKI diagnosis, the patient was considered as having an ICU incident AKI.

When a patient with an ICU incident AKI returned SCr and/or urinary output to the levels presented before AKI and subsequently fulfilled the KDIGO criteria for AKI diagnosis, it was considered another AKI episode.

KRT was initiated and performed at the discretion of the medical staff caring for the patient. There were no standardized criteria to start or end KRT.

Fluid balance was the difference between fluid intake and fluid output. Endogenous water and insensible losses were not considered. Positive fluid balance occurred when this difference was positive.

The sCr samples of the laboratories of the hospitals participating in this study were tested by colorimetric assay based on Jaffé's kinetic method[14], standardized against the definitive method of isotope dilution mass spectrometry (IDMS)[10], which complied with international standards. To ensure that sCr assessment was comparable among the study centers, we analyzed 37 anonymous blood samples simultaneously in the three centers. The sCr results showed no difference among the centers.

Regarding sedation, the estimated Glasgow Coma Scale score was used before sedation.

## Data collection

Data were collected prospectively and recorded in the database by trained members of the research group.

The following data were recorded:

1. Upon ICU admission: age, sex, educational level, cause of hospital and ICU admission, comorbidities, source of hospital admission (emergency or elective surgery, emergency room, ward), Simplified Acute Physiology Score (SAPS) III score, and Acute Physiology and Chronic Health Evaluation (APACHE) II score.
2. During the first seven days of ICU stay: daily sCr levels, daily urine output, respiratory and hemodynamic parameters, need for mechanic ventilation, vasoactive drugs, diuretics, and nephrotoxic drugs. For patients with incident AKI, daily KDIGO stage and the time from admission to AKI diagnosis were recorded.
3. Upon ICU discharge or death: length of ICU stay.
4. Upon hospital discharge or death: length of hospital stay.
5. After ICU discharge: 30 and 180 days after ICU discharge, patients or relatives were contacted by telephone or by visiting their homes to obtain information on death if it had occurred.

## Endpoints

The primary endpoint was ICU AKI incidence.

The secondary endpoints were ICU AKI outcomes: ICU mortality, length of ICU and hospital stay, and early (30 days) and late (31–180 days, for those who survived the first 30 days) mortality after ICU discharge.

## Ethics

This study was conducted according to the guidelines of the Declaration of Helsinki. It was approved by the ethics committees of the hospitals involved in this study, as well as the Ethics Committee of the Federal University of Acre (process number 721.845). All patients or their responsible relatives signed an informed consent form and agreed to participate. Confidentiality and anonymity were ensured.

## Statistical analysis

Clinical characteristics and demographic data are presented as the means and standard deviations, medians and interquartile ranges or numbers and percentages, as appropriate. Continuous variables were compared using t, Mann–Whitney U or Kruskal–Wallis tests, and categorical variables were compared with the $\chi^2$ or Fisher's exact test, as indicated.

For the evaluation of factors associated with ICU AKI development, the exposure factors during ICU stay were assessed on the days that preceded the occurrence of AKI (for instance, if AKI developed on the 4th day of the ICU stay, exposures in the first three days were assessed) or during ICU stay up to 7-day follow-up of patients who did not develop AKI for both univariable and multiple analyses.

Multiple logistic regression analysis was performed to evaluate factors associated with AKI development in the ICU (using as a reference the patients who were not admitted with AKI and did not develop AKI in the ICU and excluding those who were admitted to the ICU already with AKI and did not develop another episode during follow-up). The initial model included age (evaluated for each 10-year increase), sex (reference = female), education level (medium, high/reference = low), APACHE II score (continuous variable, measured at admission), number of comorbidities (one, more than one, reference = no comorbidities), nonsurgical patients (reference = surgical patients), and admission from ward (reference = not from ward). The following variables evaluated during the follow-up in the ICU stay before AKI development (reference = absence) were also included: positive fluid balance greater than 1500 ml/24 hours, shock or use of vasoactive drugs, use of mechanical ventilation, use of potentially nephrotoxic drugs, diuretics or drugs that block the renin-angiotensin-aldosterone system.

Multiple logistic regression was also performed to evaluate factors associated with mortality in the ICU among patients who developed incident AKI (those who did not develop AKI and those who were admitted to the ICU already with AKI and did not develop another episode during follow-up were excluded from this analysis). The initial model included the following independent variables: age (evaluated for each 10-year increase), sex (reference = female), number of comorbidities (one, more than one, reference = no comorbidities), nonsurgical patients (reference = surgical patients), admission from ward (reference = not from ward), and presence of sepsis at ICU admission (reference = absence of sepsis), number of episodes of AKI (reference one), persistent AKI (reference transient), AKI development after the 3rd day in the ICU (reference up to the 3rd day) and maximum KDIGO stage during follow-up in the ICU (3/reference stage 1 or 2). The following variables evaluated during follow-up in the ICU stay (reference = absence) were also included: mean positive fluid balance greater than 1500 ml/24 hours, use of mechanical ventilation, use of KRT, presence of shock or use of vasoactive drugs.

The logistic regression models to evaluate factors associated with AKI development in the ICU and to evaluate factors associated with mortality in the ICU among patients who developed incident AKI were conducted using a backward stepwise strategy. When there was a change in a parameter estimation greater than 10% with the exclusion of a variable, that variable remained in the model for adjustment. The goodness of fit was evaluated by the Hosmer–Lemeshow test, and the significance of the variables was evaluated by the Wald test. The variables included in the regression model were selected among those with a p value $< 0.15$ in the univariate analysis and those considered clinically relevant or important to be included in the analysis.

The association between ICU incident AKI (reference no ICU AKI, excluding those who were admitted to the ICU already with AKI and did not develop another episode during follow-up) and mortality in the ICU was evaluated by multiple logistic regression analysis, adjusting for the presence of the following variables: age (continuous), nonsurgical patients (reference = surgical patients), presence of (reference = absence) history of hypertension, stroke, heart attack, diabetes and congestive heart failure on hospitalization, sepsis at ICU admission, and positive fluid balance greater than 1500 ml/24 hours, presence of shock or use of vasoactive drugs, and use of mechanical ventilation, evaluated during follow-up in the ICU.

To evaluate the prognostic role of AKI developed in the ICU in mortality, survival curves were estimated by the Kaplan–Meier method and compared with the log-rank test in the univariate analysis. The assumption of proportional hazards during the periods analyzed was assessed by the proportional hazards test and the graphical method (transformation ln (-ln) of cumulative survival). Cox proportional hazards regression was used to evaluate mortality up to 30 days or 31 to 180 days after discharge from the ICU and included all patients who were discharged from the ICU (those who survived ICU hospitalization), with censorship at 30 days and those who survived the first 30 days after discharge from the ICU, with censorship at 180 days. For each period analyzed, AKI was evaluated in four different models: (1) presence of ICU AKI, (2) by maximum KDIGO stage of ICU AKI, (3) transient or persistent ICU AKI and (4) ICU AKI developed until or after the 3rd day in the ICU, using the absence of AKI as a reference. The models that evaluated mortality up to 30 days after discharge from the ICU were adjusted by age (continuous), nonsurgical patients (reference = surgical patients), and variables evaluated during the seven-day follow-up in the ICU, using absence as reference: use of mechanical ventilation, use of vasoactive drugs or presence of shock, use of KRT, and use of diuretics. The models that evaluated mortality from 31 to 180 days after discharge from the ICU, for those who survived the first 30 days after discharge, were adjusted by age (continuous), use of mechanical ventilation (reference = absence), use of vasoactive drugs or presence of shock, and use of KRT (reference = absence), evaluated during the follow-up in the ICU.

This prospective study had minimal missing values. In the multiple logistic regression models evaluated, missing values ranged from 0.2 to 6.0%. The survival multiple regressions done had no missing values. So, no special method for dealing with them was used.

The differences were considered statistically significant with a p value $< 0.05$. The analysis was performed with IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA) and R Statistical Software (version 4.2.1; R Core Team 2021).

## Results

During the study period, 1494 patients were admitted to the three ICUs. Among them, 28 were less than 18 years old, 80 had CKD stage 5, 299 remained less than 48 h in the ICU, 9 had only one sCr measurement and 73 were from other Brazilian states or other countries, with some patients having more than one exclusion criterion. Of the 1,029 remaining patients, 36.4% (375) had AKI at ICU admission, and 177 of them had another episode in the ICU. The total incidence of AKI in the ICU was 53.3% (548) during the first seven days (ICU AKI). The prevalence of AKI in the first seven days in the ICU was 72.5%.

Among those 548 who developed AKI during the ICU stay, 52.0% had stage 1 at diagnosis, 9.9% had stage 2, and 25.4% had stage 3 (Table 1). AKI developed mostly on the first three days after ICU admission (74.1%), was more frequently mild (40.1% with maximum KDIGO stage 1) and transient (68.1%), and occurred only once during the seven-day follow-up period in 82.8% of the patients with ICU AKI.

As shown in Table 2, patients who developed AKI during the ICU stay were older and more frequently had two or more comorbidities at admission. Chronic pulmonary disease, cardiac failure and stroke were more frequent in the AKI group. Most AKI patients were admitted to the hospital due to nonsurgical conditions.

A total of 38.0% of patients were initially admitted to a clinical ward, 41.6% were originally admitted to a operating room (24.6% had emergency surgery and 17% had elective surgery), and 20.4% were originally admitted to an emergency room. The main causes for ICU admission among the ICU AKI patients were post-surgery care (30.7%), hemodynamic instability (22.6%) and respiratory failure (19.3%). Only 2.4% of AKI patients were admitted due to tropical diseases. Patients with AKI previous to ICU admission had a higher frequency of neurological trauma cause of ICU admission. The APACHE II and SAPS III scores at ICU admission were

| Characteristic | *n* (%) |
|---|---|
| KDIGO diagnosis criteria | |
| Serum creatinine | 287 (52.4) |
| Urinary output | 132 (24.1) |
| Both | 129 (23.5) |
| Initial KDIGO stage | |
| 1 | 285 (52.0) |
| 2 | 54 (9.9) |
| 3 | 139 (25.4) |
| Not classified[#] | 70 (12.8) |
| Maximum KDIGO stage | |
| 1 | 220 (40.1) |
| 2 | 66 (12.0) |
| 3 | 207 (37.8) |
| Not classified[#] | 55 (10.0) |
| Number of AKI episodes[$] | |
| 1 | 454 (82.8) |
| 2 or more | 94 (17.2) |
| Duration of AKI[$] | |
| Transient (up to 48 h) | 373 (68.1) |
| Persistent (> 48 h) | 143 (26.1) |
| Not classified** | 32 (5.8) |
| Starting day of AKI[$] | |
| Up to the third day of ICU stay[&] | 406 (74.1) |
| After the third day of ICU stay | 142 (25.9) |

**Table 1**. Characteristics of AKI developed in the ICU ($n = 548$)*. *First AKI episode developed in the ICU. [#]Urine output was recorded in a 24-hour period, and it was not possible to classify initial and maximum KDIGO stages 1 and 2 when only the urine output criterion was used. **Due to the follow-up time of the patients in this study, it was not possible to classify patients who developed AKI on the 6th day and did not recover on the 7th day or those who developed AKI on the 7th day of admission to the ICU. [$]*AKI* acute kidney injury, [&]*ICU* intensive care units.

higher among the patients with ICU AKI than among the non-AKI patients (20 vs. 10 and 47 vs. 40, respectively) (Table 3).

In the univariate analysis, AKI development was associated with a higher positive fluid balance, use of mechanical ventilation, vasoactive drugs and diuretics and lower use of antihypertensive and nonsteroidal anti-inflammatory drugs in the ICU stay before AKI development (Table 4).

The significant variables associated with AKI development in the ICU in the final multiple logistic regression analysis model were age (adjusted odds ratio (aOR) 1.13, 95% confidence interval (CI) 1.03–1.23 for each 10-year increase), nonsurgical patients (aOR 1.47, 95% CI 1.07–2.03), admission to the ICU from the ward (aOR 1.96, 95% CI 1.40–2.74), higher APACHE II scores on ICU admission (aOR 1.05, 95% CI 1.03–1.08 for each unit increase) and a positive fluid balance over 1,500 ml/24 hours on the ICU days before AKI development (aOR 1.62, 95% CI 1.16–2.26).

KRT was performed for 10.9% of the ICU AKI patients and for 9.6% of those admitted in the ICU with AKI. The ICU mortality of patients submitted to KRT was 60% (36/60) for the ICU AKI patients and 42.1% (8/19) for patients with AKI previous to ICU admission.

The median ICU length of stay was 7.5 days among patients with ICU AKI and 8 days among those admitted with AKI. The median length of stay for non-AKI patients was 4 days (Table 5).

There was a significant difference among the medians of hospitalization time of patients who developed AKI in the ICU (16 days), those admitted to the ICU with AKI (18 days) and those who did not develop AKI (13 days) (Table 5).

ICU mortality and overall hospital mortality were higher among patients who developed AKI in the ICU than in the no-AKI group (41.1% vs. 14.5% and 52.4% vs. 18.4%, respectively) (Table 5). Those who were admitted to the ICU with AKI had ICU and hospital stay mortality rates of 21.7% and 27.3%, respectively.

The occurrence of AKI in the ICU was an independent risk factor for death during the ICU stay. The aOR from the multiple logistic regression analysis was 2.03 (95% CI 1.29–3.18).

The significant variables in the final multiple logistic regression analysis model that evaluated factors associated with death in the ICU among the patients who developed AKI during the first seven days of ICU stay were age (aOR 1.27, 95% CI 1.14–1.43 for each 10-year increase), presence of sepsis on ICU admission (aOR 2.35, 95% CI 1.14–4.83), nonsurgical patients (aOR 1.64, 95% CI 1.07–2.52), presence of shock or use of vasoactive drugs (aOR 1.88, 95% CI 1.03–3.44) and use of mechanical ventilation (aOR = 6.73, 95% CI 4.08–

| Characteristics | Total ($n=1029$) | AKI previous to ICU* ($n=198$, 19.2%) | AKI in ICU ($n=548$, 53.3%) | No AKI ($n=283$, 27.5) | $p$ value[$] |
|---|---|---|---|---|---|
| Age (years, median, IQR) | 58.0 (40.0–72.0) | 55.0 (35.0–70.0) | 62.0 (46.5–74.0) | 51.0 (36.0–66.5) | <0.001[#,◊] |
| Male sex (%) | 578 (56.2) | 124 (62.6) | 302 (55.1) | 152 (53.7) | 0.117 |
| Ethnicity (%)[&] | | | | | 0.361 |
| White | 343 (33.3) | 58 (29.3) | 201 (36.7) | 84 (29.7) | |
| Black | 162 (15.7) | 34 (17.2) | 80 (14.6) | 48 (17.0) | |
| Asian | 27 (2.6) | 4 (2.0) | 14 (2.6) | 9 (3.2) | |
| Native Brazilian | 5 (0.5) | 1 (0.5) | 2 (0.4) | 2 (0.7) | |
| Mixed | 492 (47.8) | 101 (51.0) | 251 (45.8) | 140 (49.5) | |
| Education level (%)** | | | | | 0.025[#] |
| Low | 536 (52.2) | 110 (55.6) | 300 (54.9) | 126 (44.5) | |
| Medium | 254 (24.7) | 47 (23.7) | 120 (22.0) | 87 (30.7) | |
| High | 237 (23.1) | 41 (20.7) | 126 (23.1) | 70 (24.7) | |
| Comorbidities (%) | | | | | |
| Chronic kidney disease | 84 (8.2) | 16 (8.1) | 52 (9.5) | 16 (5.7) | 0.160 |
| Diabetes | 190 (18.5) | 41 (20.7) | 104 (19.0) | 45 (15.9) | 0.369 |
| Hypertension | 528 (51.3) | 95 (48.0) | 297 (54.2) | 136 (48.1) | 0.142 |
| Chronic pulmonary disease | 82 (8.0 | 10 (5.1) | 59 (10.8) | 13 (4.6) | 0.002[#,$] |
| Anemia | 751 (73.1) | 153 (77.3) | 403 (73.7) | 195 (68.9) | 0.112 |
| Cancer | 46 (4.5) | 7 (3.5) | 27 (4.9) | 12 (4.2) | 0.702 |
| Cardiac failure | 93 (9.0) | 16 (8.1) | 67 (12.2) | 10 (3.5) | <0.001[#,$] |
| Stroke | 62 (6.0) | 8 (4.0) | 43 (7.8) | 11 (3.0) | 0.032[#] |
| Neurological diseases | 26 (2.5) | 6 (3.0) | 13 (2.4) | 7 (2.5) | 0.878 |
| Liver diseases | 23 (2.2) | 6 (3.0) | 12 (2.2) | 5 (1.8) | 1.000*** |
| Number of comorbidities (%) | | | | | 0.012[#] |
| No comorbidities | 159 (15.5) | 28 (14.1) | 80 (14.6) | 51 (18.0) | |
| One comorbidity | 353 (34.3) | 70 (35.4) | 169 (30.8) | 114 (40.3) | |
| Two or more comorbidities | 517 (50.2) | 100 (50.5) | 299 (54.6) | 118 (41.7) | |

**Table 2**. Overall patient demographics and antecedents ($n=1029$). *Patients who were admitted to the ICU with AKI and did not develop another episode during the follow-up period; [&]Comparison excluding Native Brazilians due to their low number; **2 missing data; [$]$\chi_2$ or Kruskal–Wallis test; ***Fisher's exact test; significantly different: [#]AKI in ICU versus no AKI group, [$]AKI previous to ICU versus no AKI group, [◊]AKI in ICU versus AKI previous ICU group ($\chi_2$ or Mann–Whitney U test, with Bonferroni correction).

11.09), and mean positive fluid balance in the ICU > 1500 ml/24 hours (aOR 2.31, 95% CI 1.52–3.53), both during the seven-day follow-up in the ICU.

AKI in the ICU was significantly associated with early mortality (up to 30 days after ICU discharge) in the four models evaluated. Higher risks were obtained when the model compared patients with AKI in the ICU with those who did not develop AKI. Patients with persistent AKI in the ICU had higher risks than those with transient AKI, and both had higher risks than the patients with no AKI. The development of AKI during the first three days after ICU admission had higher risks. When considering KDIGO stages, both stage 1 and 2 and stages 3 had an increased risk for early mortality (Table 6). These results can be seen in Fig. 1, which shows the survival curves of the first 30 days after ICU discharge obtained in the Cox regression models, separated by the presence of AKI, as evaluated in the four models.

Mortality between 31 and 180 days after ICU discharge of those who survived the first 30 days after discharge was higher among patients who developed persistent AKI and AKI up to the third day of ICU (Table 5). Figure 2 shows the late survival curves (31 to 180 days after discharge from the ICU) of the Cox regression models, separated by the presence of AKI, as evaluated in the four models.

## Discussion

The ICUs enrolled in this study cover 88% of the state of Acre, allowing a comprehensive prospective evaluation of critically ill patients admitted to the ICUs in this region. The study design permitted the estimation of the prevalence and incidence of AKI, and its risk factors and outcomes among ICU AKI patients of this Amazon population. This kind of information is scant, especially in developing countries, which represent more than 85% of the world's population.

Our study found a high prevalence and incidence of AKI by the KDIGO definition (using both the sCr and urine output criteria). In contrast to most of the recent previous epidemiological studies, which did not assess this aspect, we showed that most patients developed AKI after ICU admission instead of already being admitted with AKI. In fact, the overall ICU AKI prevalence was 72.5%, the AKI incidence during the first seven days in the ICU was 53.3%, and 74.1% of the cases occurred on the first three days after ICU admission. The high number of

| Characteristics | Total ($n=1029$) | AKI previous to ICU* ($n=198$, 19.2%) | AKI in ICU ($n=548$, 53.3%) | No AKI ($n=283$, 27.5) | $p$ value[$] |
|---|---|---|---|---|---|
| Hospital admission causes (%) | | | | | <0.001[#,$] |
| Nonsurgical (nontropical diseases) | 522 (50.7) | 94 (47.5) | 307 (56.0) | 121 (42.8) | |
| Nonsurgical (tropical diseases) | 18 (1.7) | 4 (2.0) | 13 (2.4) | 1 (0.4) | |
| Surgical (elective surgery) | 330 (32.1) | 56 (28.3) | 166 (30.3) | 108 (38.2) | |
| Surgical (emergency surgery) | 137 (13.3) | 37 (18.7) | 55 (10.0) | 45 (15.9) | |
| Obstetric/gynecological | 22 (2.1) | 7 (3.5) | 7 (1.3) | 8 (2.8) | |
| Original hospital admission location (%) | | | | | <0.001[#,$,◊] |
| Emergency surgery room | 309 (30.0) | 77 (38.9) | 135 (24.6) | 97 (34.3) | |
| Elective surgery room | 180 (17.5) | 23 (11.6) | 93 (17.0) | 64 (22.6) | |
| Emergency room | 246 (23.9) | 49 (24.7) | 112 (20.4) | 85 (30.0) | |
| Ward | 194 (28.6) | 49 (24.7) | 208 (38.0) | 37 (13.1) | |
| ICU admission causes (%) | | | | | |
| Sepsis | 100 (9.7) | 25 (12.6) | 49 (8.9) | 26 (9.2) | 0.305 |
| Hemodynamic instability | 202 (19.6) | 37 (18.7) | 124 (22.6) | 41 (14.5) | 0.019[#] |
| Respiratory failure | 157 (15.3) | 24 (12.1) | 106 (19.3) | 27 (9.5) | 0.248 |
| Neurological trauma | 72 (7.0) | 25 (12.6) | 28 (5.1) | 19 (6.7) | 0.002[$,◊] |
| Stroke | 85 (8.3) | 19 (9.6) | 43 (7.8) | 23 (8.1) | 0.742 |
| Neurological clinical diseases | 42 (4.1) | 4 (2.0) | 28 (5.1) | 10 (3.5) | 0.146 |
| Postsurgery care | 368 (35.8) | 63 (31.8) | 168 (30.7) | 137 (48.4) | <0.001[#,$] |
| APACHE II score (median, IQR) | 17.0 (8.0–25.0) | 18.0 (9.0–25.0) | 20.0 (10.0–27.0) | 10.0 (6.0–19.0) | <0.001[#,$] |
| SAPS III score (median, IQR) | 44.0 (36.0–55.0) | 45.0 (37.0–55.0) | 47.0 (38.0–58.0) | 40.0 (33.0–47.0) | <0.001[#,$] |

**Table 3**. Causes of UCI admission ($n=1029$). *Patients who were admitted to the ICU with AKI and did not develop another episode during the follow-up period; [$]$\chi_2$ or Kruskal–Wallis test; significantly different: [#]AKI in ICU versus no AKI group, [$]AKI previous to ICU versus no AKI group, [◊]AKI in ICU versus AKI previous ICU group ($\chi_2$ or Mann–Whitney U test, with Bonferroni correction).

| Exposure and risk factor | Total ($n=831$)[&] | AKI in ICU ($n=548$) | No AKI ($n=283$) | $p$ value[$] |
|---|---|---|---|---|
| Fluid balance (ml/24 hours, median, IQR) | 1257.0 (559.0–2065.0) | 1443.0 (560.0–2390.0) | 1162.3 (476.5–2117.5) | <0.001 |
| Mechanical ventilation (%) | 372 (44.8) | 285 (52.0) | 87 (30.7) | <0.001 |
| Liver failure (%) | 23 (2.8) | 18 (3.3) | 5 (1.8) | 0.206 |
| Antibiotic use* (%) | 494 (59.4) | 324 (59.1) | 170 (60.1) | 0.792 |
| Diuretic use[§] (%) | 298 (35.9) | 221 (40.3) | 77 (27.2) | <0.001 |
| Antihypertensive drug use[¤] (%) | 283 (34.1) | 169 (30.8) | 114 (40.3) | 0.006 |
| Nonsteroidal anti-inflammatory drug use (%) | 146 (17.6) | 86 (15.7) | 60 (21.2) | 0.048 |
| Ischemia[◊] (%) | 548 (65.9) | 350 (69.7) | 198 (60.2) | 0.005 |

**Table 4**. Exposure and risk factors for AKI development in the ICU[#]. [#]Exposure was assessed on the days of hospitalization that preceded the first occurrence of AKI in ICU or during the follow-up of patients who did not develop AKI; [&]Patients with AKI at ICU admission who did not develop another episode in the ICU were excluded from this analysis; [$]($\chi_2$ or Mann–Whitney U test). *Antibiotics: gentamicin, amikacin, vancomycin, first generation cephalosporins. [§]Diuretics: furosemide, hydrochlorothiazide, chlorthalidone. [¤]Antihypertensives: losartan, irbesartan, aliskiren, captopril, enalapril, lisinopril, ramipril. [◊]Ischemia = use of vasoactive drugs (noradrenalin, dobutamine or dopamine) or shock.

AKI patients found in the present study might be related to the severity of the patients upon hospitalization, as suggested by the severity score numbers, use of KDIGO criteria[15] and use of the urine output KDIGO criterion, which represented approximately 25% of the incident AKI detected. Koeze et al. showed that the detection of AKI in the ICU doubled when urine output was added to the SCr criterion[16]. It is possible that the higher severity scores at ICU hospitalization reflected late arrival at the tertiary health center or delay in ICU transfer from the ward.

Somewhat surprisingly, the etiology of AKI in the present study was similar to that described in developed countries or in tertiary hospitals in large urban centers in high-resource areas of Brazil. The AKI etiology was mostly multifactorial and associated with sepsis and kidney hypoperfusion. Only 1.7% of ICU admissions were related to tropical diseases. In a survey designed to assess KRT for AKI in Latin America, only approximately 10% of the studied units reported patients with leptospirosis, and less than 10% reported treating patients with snakebite- or dengue-associated AKI[17]. In prospective epidemiological studies of AKI in the ICU in Southeast

| Outcome | Total ($n=1029$) | AKI previous to ICUadmission[$] ($n=198$) | AKI in ICU ($n=548$) | No AKI ($n=283$) | $p$ value[&] |
|---|---|---|---|---|---|
| KRT use (%) | 79 (7.7) | 19 (9.6) | 60 (10.9) | 0 | 0.596[*] |
| ICU length of stay (median, IQI) | 7.0 (3.0–15.0) | 8.0 (4.0–16.0) | 7.5 (4.0–15.0) | 4.0 (2.0–11.0) | <0.001[#,$] |
| Hospital length of stay (IQI) | 15.0 (8.0–30.0) | 18.0 (9.0–34.5) | 16.0 (8.0–30.0) | 13.0 (6.5–25.0) | <0.001[#,$] |
| ICU mortality (%) | 309 (30.0) | 43 (21.7) | 225 (41.1) | 41 (14.5) | <0.001[#,$,◊] |
| Hospital mortality (%) | 393 (38.2) | 54 (27.3) | 287 (52.4) | 52 (18.4) | <0.001[#,$,◊] |
| Mortality 30 days after ICU discharge (%)** | 80 (11.1) | 6 (3.9) | 60 (18.6) | 14 (5.8) | <0.001[#,◊] |
| Mortality 31 to 180 days after ICU discharge (%)[¤] | 55 (8.6) | 12 (8.1) | 30 (11.4) | 13 (5.7) | 0.077 |

**Table 5**. Outcomes. [$]Patients who were admitted to the ICU with AKI and did not develop another episode during the follow-up period; [&]$\chi_2$ or Kruskal–Wallis test; [*]Comparison between ICU AKI and AKI previous to ICU group only. Significant differences: [#]ICU AKI versus no AKI group, [$]AKI previous to ICU versus no AKI group, [◊]ICU AKI versus AKI previous to ICU group ($\chi_2$ or Mann–Whitney U test, with Bonferroni correction). **Estimated for patients who was discharged from ICU, $n=720$; [¤]Estimated for patients who survived the first 30 days after discharge, $n=640$.

| Models[◊] | Early mortality[#] | | Late mortality[*] | |
|---|---|---|---|---|
| | aHR (95% CI)[$] | p value | aHR (95% CI)[$] | p value |
| AKI in the ICU | 3.13 (1.84–5.31) | <0.001 | 1.69 (0.99–2.90) | 0.056 |
| Stage 1 or 2KDIGO | 2.32 (1.30–4.16) | 0.005 | 1.71 (0.95–3.08) | 0.076 |
| Stage 3 KDIGO | 5.28 (2.88–9.71) | <0.001 | 1.65 (0.74–3.71) | 0.223 |
| Up to the 3rd day of ICU stay | 3.67 (2.13–6.32) | <0.001 | 1.96 (1.11–3.47) | 0.021 |
| After the 3rd day of ICU stay | 1.83 (0.84–3.98) | 0.127 | 1.10 (0.45–2.70) | 0.841 |
| Transient AKI[&] | 3.07 (1.77–5.34) | <0.001 | 1.59 (0.89–2.87) | 0.120 |
| Persistent AKI | 3.86 (1.92–7.76) | <0.001 | 2.48 (1.09–5.64) | 0.030 |

**Table 6**. Association of AKI during ICU stay and early and late mortality after ICU discharge. [◊]AKI was evaluated in four different Cox regression models: (1) presence of AKI; (2) by maximum KDIGO stage; (3) transient or persistent AKI and (4) up to or after the 3rd day in the ICU AKI, using the absence of AKI as a reference in the four models. [#]Analysis of early mortality (up to 30 days after discharge from the ICU) was adjusted by age, nonsurgical patients, use of mechanical ventilation, use of vasoactive drugs or presence of shock, use of KRT, and use of diuretics during follow-up (first seven days of ICU stay), censored at 30 days. [*]Analysis of late mortality (from 31 to 180 days after discharge from the ICU) was adjusted by age, use of mechanical ventilation, use of vasoactive drugs or presence of shock, and use of KRT during follow-up (first seven days of ICU stay), censored at 180 days. [$]aHR (adjusted hazard ratio); *CI* (confidence interval); *AKI* acute kidney injury. [&]Transient = serum creatinine and urine output normalized within 48 h after AKI diagnosis; Persistent = serum creatinine remained increased and/or urine output remained decreased for more than 48 h after AKI diagnosis.

Asia, a geographic area severely affected by poisonous snakebites and infectious tropical diseases[18], the incidence of tropical disease-associated AKI ranged from only 1.2 to 1.4%[19,20].

These results contradicted the expectation of finding a substantial number of unifactorial AKI cases associated with infectious diseases such as malaria, leptospirosis, dengue, or yellow fever or snake venoms, which occur in the community and affect mostly young and socially and economically vulnerable individuals[18]. There were 12,218 cases of dengue (513 severe cases) and 858 cases of leptospirosis (67 severe cases) reported in Acre in 2015[21], but there were only three cases of dengue, and 12 cases of leptospirosis admitted to the studied ICUs. In 2014 and 2015, almost one thousand snakebites were reported in Acre, and despite venomous snakebite-associated AKI being relatively frequent[18], no cases were seen in the assessed ICUs.

It is conceivable that most expected cases did not reach the primary health system or had no access to tertiary hospitals due to a belief in natural medicine, costs and transport difficulties[7,11]. The concept of accessibility is complex and influenced by the relationship between the distance of the supply and the location of users, affordability, acceptability and repressed demand. Our study area has peculiar geographical characteristics, with rivers that are not navigable most of the year, long rain periods and no paved roads, making it difficult to access larger cities. In rural areas, the distances to health care facilities and the poor condition of roads mean that the time, effort, and cost required to arrive at the point of health delivery can be substantial. In Brazil, studies have shown that people from the lowest income groups seek fewer health services or are less likely to use them[22,23]. An important point to consider is the culture and social norms of Brazilian natives and other Amazonian people, who prefer the use of traditional medicine/shamanism over Western modern therapies. The finding that the use of traditional therapies usually declines with higher income and education suggests that those social norms

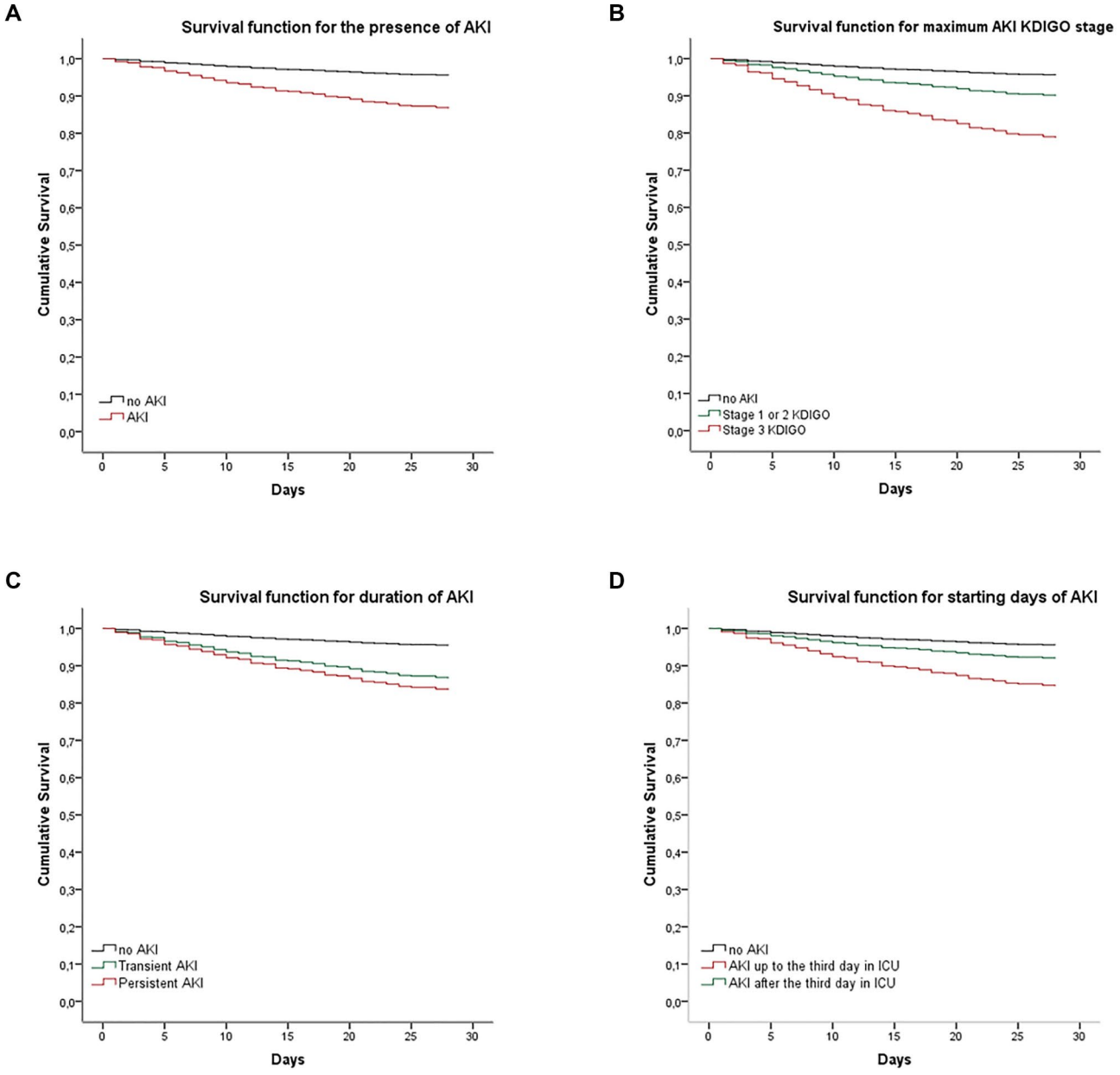


**Fig. 1**. Survival curves for the first 30 days after discharge from the ICU. AKI[$] was evaluated in four different Cox regression models: (**A**) AKI development in the ICU; (**B**) AKI categorized by maximum KDIGO stage; (**C**) AKI categorized as transient (duration up to 48 h) or persistent (more than 48 h); and (**D**) AKI categorized as those developed up to or after the third day of ICU[#] stay, using the absence of AKI as a reference. The Cox analyses were adjusted by age, nonsurgical patients, use of mechanical ventilation, use of vasoactive drugs or presence of shock, use of KRT, and use of diuretics during follow-up (first seven days of ICU stay), censored at 30 days. [$]*AKI* acute kidney disease, [#]*ICU* intensive care units.

are not inviolable[23]. The evidence confirms the expected negative impact of the discussed aspects on healthcare utilization[24,25].

In addition, since these diseases are the cause of community-acquired AKI, it is conceivable that most patients did not reach the ICU due to lack of recognition of AKI by primary care health services[26,27].

Finally, the gap between the supply and demand of ICU beds and the consequent failure to provide adequate intensive care is common in most developing countries[28,29]. This gap is driven by increasing population size, increased life expectancy and high prevalence of noncommunicable chronic diseases, such as diabetes, coronary heart disease, stroke and obesity[30]. Brazil is a large country with a large population. There is a marked difference between highly populated cities in the southeast/south of the country and the poorer regions in the north[30]. In 2016, the Brazilian Intensive Care Association (AMIB) census found a rate of ICU beds per 10,000 inhabitants in Brazil of 2.03, within the recommendation by the Brazilian Ministry of Health of a minimum of 1–3 ICU beds per 10,000 inhabitants. Nevertheless, the majority of states in the northern region are below this limit. In the

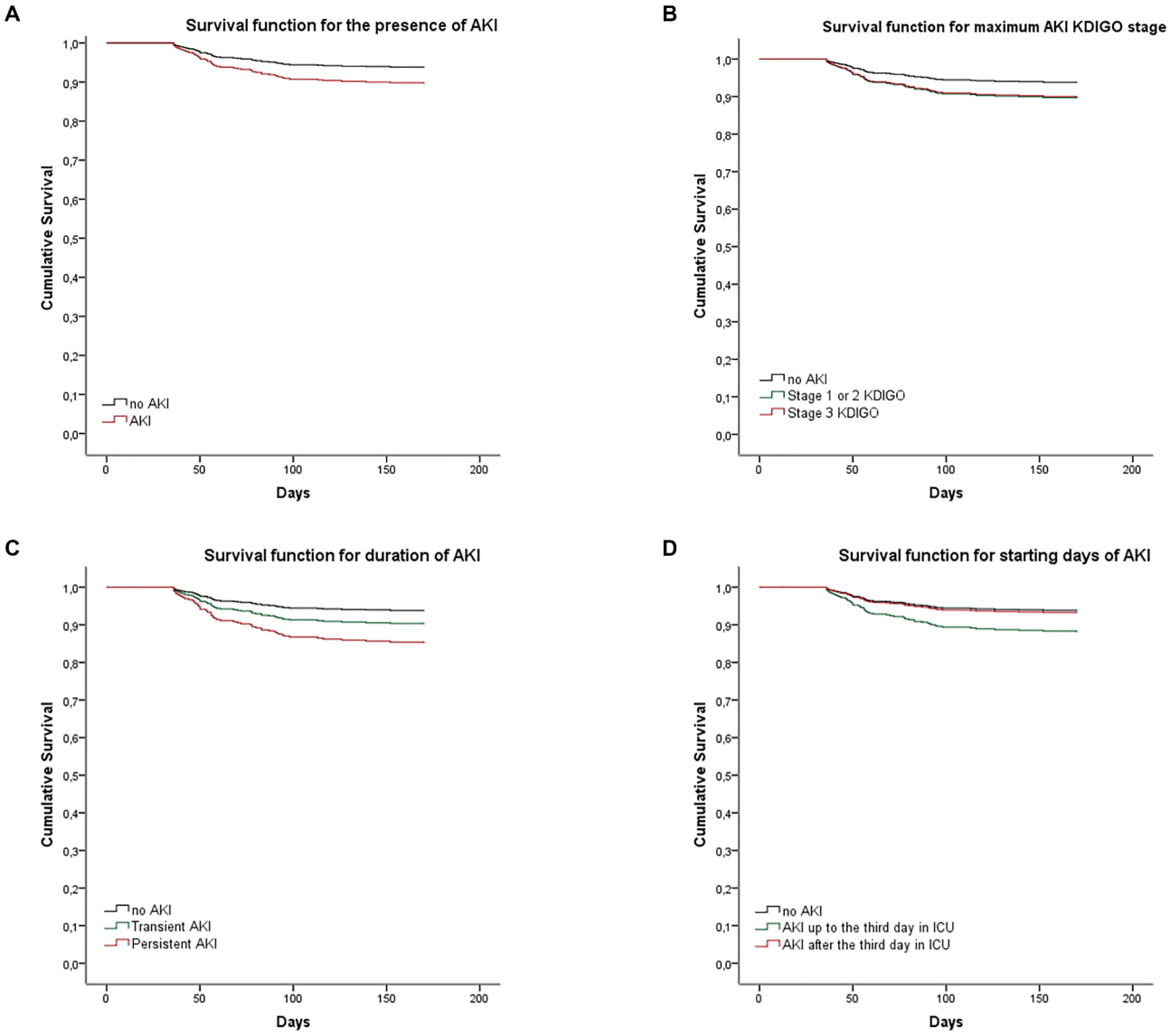


**Fig. 2**. Survival curves for 31 to 180 days after discharge from the ICU for patients who survived the first 30 days. AKI[$] was evaluated in four different Cox regression models: (**A**) AKI development in the ICU; (**B**) AKI categorized by maximum KDIGO stage; (**C**) AKI categorized as transient (duration up to 48 h) or persistent (more than 48 h); and (**D**) AKI categorized as those developed up to or after the third day of ICU[#] stay, using the absence of AKI as a reference. The Cox analyses of patients who survived the first 30 days after ICU discharge were adjusted by age, use of mechanical ventilation, use of vasoactive drugs or presence of shock, and use of KRT during follow-up (first seven days of ICU stay), censored at 180 days. [$]*AKI* acute kidney disease, [#]*ICU* intensive care units.

state of Acre, the rate of ICU beds per 10,000 inhabitants was only 0.89[31]. These characteristics are likely related to the worse outcomes compared to those in developed countries[32,33].

There was a low frequency of KRT use among ICU AKI patients (7.7%), although one-third had KDIGO stage 3 (37.8%). Our results are similar to those reported in Laos and in Southeast Asia, where KRT for ICU AKI patients was only 1.8% and 7.9%, respectively[20,34]. In the meta-analysis by Melo et al.[5], KRT was 8.8% in developed countries versus 23.8% in developing countries. Other studies also showed a higher rate of KRT use in developing countries[6,11]. This low frequency of KRT use in severe AKI cases may reflect the challenge of providing it in the Amazon region, with low availability of KRT equipment and trained healthcare personnel and nephrologists[7,35,36]. Mehta et al. found in the International Society of Nephrology 0by25 Global Snapshot[11] that 8% of the indicated KRT procedures were not performed due to a lack of resources or the inability to afford them. It is important to stress that the low frequency of KRT occurred in this study even though this treatment is funded by the Brazilian Health System, with no costs for the patients.

The low proportion of KRT use for chronic disease in the state of Acre also suggests a direct effect of the lack of resources on KRT use. The number of CKD patients in the KRT program in our study area is approximately

94 patients per million people (pmp), which is much lower than the average in Brazil (610 pmp)[35]. According to the Institute of Advanced Economics Research (IPEA), the most frequent causes for this are lack of physicians (58.1%), delay in care in clinics, lack of health centers and hospitals (35.4%) and the delay in having an appointment with experts (33.8%)[37].

In our study, ICU mortality rates, as well as length of ICU and hospital stay, were similar to those reported previously in developing countries but higher than those reported in developed countries[2,5,38]. The risk factors associated with mortality among these patients were not different from those in high-income areas: age, use of mechanical ventilation, sepsis at admission, nonsurgical patients, use of vasoactive drugs or shock and higher mean positive fluid balance. These worse outcomes, when compared with those in developed countries, might be explained primarily by two factors: the poor infrastructure of health systems and accessibility. The development of AKI in the ICU was also associated with increased risks for early (up to 30 days) mortality after ICU discharge, which were higher when AKI was stage 3 of the KDIGO criteria in early and precocious or persistent in both early and late mortality.

This study has several strengths. First, this study was designed specifically to prospectively capture AKI incidence, considering the demographic area and clinical characteristics to represent critically ill ICU patients with AKI in the study region. Second, covering all ICUs in the area, we conducted a population-based study in contrast to many other studies that covered only a relatively small sample of the population with retrospectively collected information and a small number of participants. Third, to assess factors associated with AKI development, we used the exposure on the days that preceded the occurrence of AKI. Fourth, in addition to measuring the incidence, we were able to estimate the prevalence, as we could identify those patients admitted to the ICU with AKI and those who developed AKI during the ICU stay. Fifth, in this prospective study, the frequency of missing data was minimal.

However, our study also has limitations. First, we collected clinical information during the first seven days after ICU admission, which may not represent all factors that affected outcomes. Second, the studied sample represented the patients who were able to access healthcare, which probably underestimates the actual characteristics of critically ill patients in the area. Third, we did not analyze the recovery of kidney function, which is important to identify factors that influence mortality. Additionally, the prevalence and incidence may be underestimated, as 299 patients could not be evaluated for being less than 48 h in the ICU. Among them may be some AKI cases. The SCr decrease used for the identification of patients already admitted with AKI at the ICU might result from factors unrelated to kidney function, such as muscle mass reduction or fluid overload. Finally, these data are from pre COVID pandemic, so may not reflect accurately the present situation.

In conclusion, the present study highlights an underrecognized area of critical care in developing countries. AKI is extremely common among ICU patients in the western Brazilian Amazon. There were few cases of tropical diseases associated with AKI. The risk factors and etiologies for AKI were similar to those reported in developed countries. The use of KRT was low. Mortality rates were higher than those reported in developed countries.

These data suggest that actions aimed at improving the early detection of high-risk and AKI patients, simple protocols for the prevention/minimization of AKI severity at the primary care level and early detection and transport of more severely critically ill patients are urgently needed in this area of the country and in areas with similar socioeconomic characteristics.

## Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Received: 23 October 2023; Accepted: 24 September 2024
Published online: 03 October 2024

## References

1. Komaru, Y. et al. Inverse correlation between incidence and mortality of acute kidney injury in critically ill patients: a systematic review. *Shock* **54** (3), 280–284 (2020).
2. Hoste, E. A. et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med.* **41** (8), 1411–1423 (2015).
3. Hoste, E. A. J. et al. Global epidemiology and outcomes of acute kidney injury. *Nat. Rev. Nephrol.* **14** (10), 607–625 (2018).
4. Shiao, C. C. et al. Long-term remote organ consequences following acute kidney injury. *Crit. Care* **19**, 438 (2015).
5. Melo, F. A. F. et al. A systematic review and meta-analysis of acute kidney injury in the intensive care units of developed and developing countries. *PLoS One* **15** (1), e0226325 (2020).
6. Bouchard, J. et al. A prospective international multicenter study of AKI in the intensive care unit. *Clin. J. Am. Soc. Nephrol.* **10** (8), 1324–1331 (2015).
7. Mehta, R. L. et al. International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. *Lancet* **385** (9987), 2616–2643 (2015).
8. IBGE Estados@. https://cidades.ibge.gov.br/brasil/ac/pesquisa/23/25124?detalhes=true (Assessed 22 December 2022) (2015).
9. Ministry of Cities- Brazilian Government. Sistema Nacional de Informações sobre Saneamento Brazil: Ministry of Cities – Brazilian Government; 2014. https://www.gov.br/mdr/pt-br/assuntos/saneamento/snis/painel (Assessed 22 December 2022) (2016).
10. Kidney Disease. Improving global outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int. Suppl.* **2**, 1–138 (2012).
11. Mehta, R. L. et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. *Lancet* **387** (10032), 2017–2025 (2016).
12. Macedo, E. et al. Recognition and management of community-acquired acute kidney injury in low-resource settings in the ISN 0by25 trial: a multi-country feasibility study. *PLoS Med.* **18** (1), e1003408 (2021).
13. Wainstein, M. et al. Use of an extended KDIGO definition to diagnose acute kidney injury in patients with COVID-19: a multinational study using the ISARIC-WHO clinical characterisation protocol. *PLoS Med.* **19** (4), e1003969 (2022).

14. Knapp, M. L. & Mayne, P. D. Development of an automated kinetic Jaffé method designed to minimise bilirubin interference in plasma creatinine assays. *Clin. Chim. Acta* **168** (2), 239–246 (1987).
15. Luo, X. et al. A comparison of different diagnostic criteria of acute kidney injury in critically ill patients. *Crit. Care* **18** (4), R144 (2014).
16. Koeze, J. et al. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. *BMC Nephrol.* **18** (1), 70 (2017).
17. Lombardi, R. et al. Acute kidney injury in Latin America: a view on renal replacement therapy resources. *Nephrol. Dial. Transpl.* **29** (7), 1369–1376 (2014).
18. Burdmann, E. A. & Jha, V. Acute kidney injury due to tropical infectious diseases and animal venoms: a tale of 2 continents. *Kidney Int.* **91** (5), 1033–1046 (2017).
19. Srisawat, N. et al. The epidemiology and characteristics of acute kidney injury in the Southeast Asia intensive care unit: a prospective multicentre study. *Nephrol. Dial. Transpl.* **35** (10), 1729–1738 (2020).
20. Sengthavisouk, N. et al. Epidemiology and short-term outcomes of acute kidney injury among patients in the intensive care unit in Laos: a nationwide multicenter, prospective, and observational study. *BMC Med.* **18** (1), 180 (2020).
21. Health Agency of the State of Acre. Epidemiological bulletin. SUS [Internet]. https://agencia.ac.gov.br/ (Assessed 22 December 2022).
22. Assis, M. M. A. & Jesus, W. L. A. Access to health services: approaches, concepts, policies and analysis model. *Ciênc Saúde Coletiva* **17** (11), 2865–2875 (2012).
23. O'Donnell, O. & Greece, T. Access to health care in developing countries: breaking down demand side barriers. *Cad. Saúde Públ.* **23** (12), 2820–2834 (2007).
24. Wong, E. L., Popkin, B. M., Guilkey, D. K. & Akin, J. S. Accessibility, quality of care and prenatal care use in the Philippines. *Soc. Sci. Med.* **24** (11), 927–944 (1987).
25. Ducan, T., Lavy, V. & Strauss, J. Public policy and anthropometric outcomes in the Côte d'Ivoire. *J. Public Econ.* **61** (2), 155–192 (1996).
26. Cerdá, J. et al. Acute kidney injury recognition in low- and middle-income countries. *Kidney Int. Rep.* **2** (4), 530–543 (2017).
27. Kashani, K. et al. Acute kidney injury risk assessment: differences and similarities between resource-limited and resource-rich countries. *Kidney Int. Rep.* **2** (4), 519–529 (2017).
28. Angus, D. C., Kelley, M. A., Schmitz, R. J., White, A. & Popovich, J. Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA* **284** (21), 2762–2770 (2000).
29. Laake, J. H. & Bugge, J. F. [Acute renal failure in critically ill patients]. *Tidsskr nor. Laegeforen* **130** (2), 158–161 (2010).
30. Rhodes, A. & Moreno, R. P. Intensive care provision: a global problem. *Rev. Bras. Ter. Intensiva* **24** (4), 322–325 (2012).
31. Associação de Medicina Intensiva Brasileira, Censo, A. M. I. B. & Brazil. https://www.amib.org.br/censo-amid (Assessed 22 December 2022) (2016).
32. Adhikari, N. K., Fowler, R. A., Bhagwanjee, S. & Rubenfeld, G. D. Critical care and the global burden of critical illness in adults. *Lancet* **376** (9749), 1339–1346 (2010).
33. Vincent, J. L. et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA* **302** (21), 2323–2329 (2009).
34. Srisawat, N. et al. The epidemiology and characteristics of acute kidney injury in the Southeast Asia intensive care unit: a prospective multicentre study. *Nephrol. Dial. Transpl.* **35**, 1729–1738 (2020).
35. Thomé, F. S., Sesso, R. C., Lopes, A. A., Lugon, J. R. & Martins, C. T. Brazilian chronic dialysis survey 2017. *Braz. J. Nephrol.* **41** (2), 208–214 (2019).
36. Mehta, R. L. et al. Nephrology consultation in acute renal failure: does timing matter? Am. *J. Med.* **113** (6), 456–461 (2002).
37. Almeida, N. D. & Pernambuco, U. F. D. A saúde no Brasil, impasses e desafios enfrentados pelo Sistema Único De Saúde: SUS. Ver. *Psicol. Saúde* **5** (1), 01–9 (2013).
38. Lombardi, R., Yu, L., Younes-Ibrahim, M., Schor, N. & Burdmann, E. A. Epidemiology of acute kidney injury in Latin America. *Semin. Nephrol.* **28** (4), 320–329 (2008).


## Author contributions

FAFM: study conceptualization, data collection, formal analysis, project administration, original draft writing, final manuscript review and editing.EAB and DMTZ: study conceptualization, formal analysis, project administration, original draft writing, final manuscript review and editing.EM and RM: study conceptualization, formal analysis, original draft writing, final manuscript review and editing.All authors read and approved the final manuscript.

## Funding

This study was funded by the São Paulo Research Foundation, FAPESP (process number 2014/19286-4) and Fundação de Amparo à Pesquisa do Acre, FAPAC. EAB is a recipient of grant #304743/2017-8 from the National Council for Scientific and Technological Development, CNPq. The funding institutions did not influence the design of the study, the collection, analysis, or interpretation of the data or the writing of this manuscript in any way.

## Declarations

## Competing interests

The authors declare no competing interests.

## Ethics approval and consent to participate

This project was approved by the ethics committees of the hospitals involved in this study, as well as the Ethics Committee of the University of São Paulo and the Federal University of Acre (process number 721.845). All patients or their responsible relatives signed an informed consent form and agreed to participate.

## Additional information

**Correspondence** and requests for materials should be addressed to D.M.T.Z.