Community-acquired acute kidney injury in India: data from ISN-acute kidney injury registry

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Summary

Background Acute kidney injury (AKI), particularly community-acquired AKI (CA-AKI), is a major health concern globally. The International Society of Nephrology's "0 by 25" initiative to reduce preventable deaths from AKI to zero by 2025 is not achievable in low and middle income countries, such as India, possibly due to a lack of data and measures to tackle this urgent public health issue. In India, CA-AKI predisposes younger patients to hospitalization, morbidity, and mortality. This is the first multicenter, prospective, cohort study investigating CA-AKI and its consequences in India.

Methods This study included data from patients with CA-AKI (>12 years of age) housed in the Indian Society of Nephrology-AKI registry, involving 9 participating tertiary care centers in India, for the period between November 2016 and October 2019. The etiological spectrum and renal and patient outcomes of CA-AKI at the index visit and at 1-month and 3-month follow-ups were analyzed. The impact of socioeconomic status (SES) on outcomes was also analyzed.

Findings Data from 3711 patients (mean [±SD] age 44.7 ± 16.5 years; 66.6% male) were analyzed. The most common comorbidities included hypertension (21.1%) and diabetes (19.1%). AKI occurred in medical, surgical, and obstetrical settings in 86.7%, 7.3%, and 6%, respectively. The most common causes of AKI were associated with sepsis (34.7%) and tropical fever (9.8%). Mortality at the index admission was 10.8%. Complete recovery (CR), partial recovery (PR), and dialysis dependency among survivors at the time of discharge were 22.1%, 57.7%, and 9.4%, respectively. Overall, at 3 months of follow-up, mortality rate, CR, PR, and dialysis dependency rates were 11.4%, 72.2%, 7.2%, and 1%, respectively. Multivariate analysis revealed that age >65 years, alcoholism, anuria, hypotension at presentation, thrombocytopenia, vasopressor use, transaminitis, and low SES were associated with mortality at the index admission.

Interpretation Sepsis and tropical fever were the most common causes of CA-AKI. Presentation of CA-AKI to tertiary care units was associated with high mortality, and a significant number of patients progressed to CKD. Individuals with a low SES had increased risk of mortality and require immediate attention and intervention.

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Keywords: AKI registry; Community-acquired AKI; Socioeconomic status; Sepsis-associated AKI

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Research in context

Evidence before this study

CA-AKI is common in India and other Low and Middle-Income countries (LMIC). Data on the etiology and outcomes of CA-AKI is limited to single-centre studies, and no nationwide registry exists. In most, a wide variation in the etiological spectrum and outcomes have been noted. Tropical fever, delayed referral, envenomation, use of alternative medications for common medical ailments, inappropriate use of antibiotics for respiratory and urinary tract infections, and easy availability of NSAIDs over the counter all contribute to the AKI burden in India.

Added value of this study

This study is the first study on CA-AKI from registry-based data in India. The commonest cause of CA-AKI noted in India was sepsis and tropical fever-associated CA-AKI. Most peoples with CA-AKI are young males and mostly belong to low socioeconomic category. This study found that 10.8% of patients died at Index admission, and 8.2% of survivors remained with residual renal damage at 3 months. The factors associated with mortality were the age of more than 65 years, alcohol abuse, anuria, hypotension at presentation, thrombocytopenia, vasopressor usage, transaminitis, and low socio-economic status.

Implications of all the available evidence

CA-AKI in India is a serious health burden with recognisable long-term consequences. CA-AKI affects younger males of low socioeconomic groups, who may be the target population to intervene. Equity in healthcare availability, early referral, and long-term follow-up of patients recovering from AKI may mitigate the risks associated with poor outcomes and the transition from CA-AKI to CKD in the region.

Introduction

Acute kidney injury (AKI) is an independent risk factor for morbidity, hospitalization, and mortality. It is also associated with high costs to patients and healthcare systems,[1] and is considered to be a novel risk factor for chronic kidney disease (CKD).[2] AKI is estimated to occur in approximately 13.3 million individuals worldwide and contributes to approximately 1.7 million deaths annually.[3] The global perspective of AKI as a "silent killer" has recently become a focal point for researchers.[4–7] Older studies have reported a varied incidence of AKI in different countries and centers, mainly due to various definitions of AKI. However, after standardization of the definition of AKI by the Acute Dialysis Quality Initiatives (ADQI) in 2005, and the Kidney Disease: Improving Global Outcomes (KDIGO) in 2012, recent studies have reported varying incidence and etiology of AKI in different parts of the world.[8] AKI, with a prolonged course of 7–90 days, is defined as acute kidney disease (AKD) and has been identified as a risk factor for new-onset CKD, again posing a greater threat to an already overburdened population with CKD.[9]

AKI may be community-acquired (CA-AKI), which occurs in the community or home setting outside the hospital, or hospital-acquired (HA-AKI), which occurs in a hospital setting. CA-AKI is reportedly more common in low-income and middle-income countries (LMICs), whereas HA-AKI is relatively more common in high-income countries (HICs).[10,11] Most patients who develop AKI at the community level require hospitalization and intensive care. Studies investigating the epidemiology of AKI more often refer to HA-AKI, which is approximately 5–10 times more common in HICs. These results may not be representative of CA-AKI, for which the disease spectrum that causes this condition differs. For example, malaria, leptospirosis, dengue, animal envenomation, acute gastroenteritis causing dehydration, and herbal and alternative medication-related AKI, are all conditions commonly encountered in community settings. Challenges facing healthcare systems in LMICs, such as India, the most populous country in the world with varied climates in different regions, are addressing both forms of AKI.[11–13] The challenges inherent to CA-AKI include delayed diagnosis and referral, inadvertent nephrotoxic drug prescription, inadequate resource allocation, and improper follow-up of survivors. The contribution of CA-AKI to the burden of CKD is currently unclear.

There are no large, multicenter data regarding CA-AKI from India. The Indian Society of Nephrology (ISN) started the AKI registry in 2016 to capture data regarding the epidemiology of AKI, its socioeconomic determinants, and the immediate and 3-month follow-up outcomes of AKI from tertiary care hospitals in different parts of the country.

Methods

Data source

The study was initiated as a pilot project to establish an AKI registry and retrieve data prospectively from nine tertiary care hospitals (Supplementary File 1). A standard operating procedure (SOP) was prepared and discussed with seven members of the ISN's Scientific Committee. The SOP was discussed with the principal investigator (PI) at each participating institute. Data entry operators, educated beforehand, or senior residents of the institute, entered the data under the supervision of the PIs at each center. Initially, 12 centers were chosen; however, three never entered data into the registry and, as such, were excluded. The AKI registry website was created under the domain name

<http://www.akiregistryindia.com>. Data from all patients with AKI, who visited the individual centers between November 2016 and October 2019, were captured and entered into the website. This study was approved by the institutional ethics committee (ethics approval code-2016-113-EMP-97). Each participating center also received ethical approval from their respective ethics committee(s). Informed consent was obtained from each participating center. Seven of the nine were public sector tertiary care institutes, two were private sector tertiary care hospitals, and all had robust follow-up of patients.

Inclusion and exclusion criteria

All patients >12 years of age with CA-AKI, defined as AKI occurring outside the hospital setting—typically in the community or home setting—and admitted to either the inpatient or emergency departments of the participating hospitals registered in the AKI registry, were included in the study. Patients who had HA-AKI, developed AKI at any time after 48 h of hospitalization, were admitted with normal renal function, preexisting CKD, renal transplant recipients, and those with incomplete records were excluded.

Data collection

The following data were collected: clinical, demographic, and socioeconomic profiles; risk factors and etiology of AKI; comorbidities; laboratory investigation results; associated complications; management; and patient outcomes. Patients with pre-existing diabetes mellitus, hypertension, or other cardiovascular diseases were also recorded. CKD was defined as kidney function and/or structural abnormalities persisting >3 months. Demographic and clinical data included age, sex, BMI, blood pressure, and general and systemic physical examinations. Laboratory parameters included baseline and follow-up hemoglobin levels and leukocyte counts, blood urea nitrogen (BUN), serum creatinine, proteinuria, serum uric acid, alkaline phosphatase, and any other special investigation(s) required for diagnosis at the discretion of the treating clinician.

Height and weight measurements were collected from each patient to calculate BMI using the following equation: BMI = weight (kg)/height (m^2). Patients were categorized as underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2), and obese (BMI ≥25 kg/m^2), as per the Indian Council of Medical Research guidelines for the categorization of BMI.[14]

Socioeconomic status (SES)

Socioeconomic data included educational qualifications, marital status, occupation, and income. Socioeconomic classification was performed according to the Modified Kuppuswamy Scale 2015 updated version (Supplementary File 1), a well-known socioeconomic status indicator standardized for the Indian population.[15]

Renal function assessment

AKI was defined and classified using the KDIGO guidelines, which used serum creatinine (increase in serum creatinine by ≥0.3 mg/dl within 48 h or increase in serum creatinine to ≥1.5 × baseline) and urinary output <0.5 ml/kg/h for 6 h.[8] For patients with serum creatinine values before admission, the most recent value was considered the baseline level. For patients without baseline creatinine in the 7–365 days before admission, baseline creatinine was imputed by back calculation using the Modification of Diet in Renal Disease (MDRD) equation and glomerular filtration rate (GFR) of 75 ml/min/1.73 m^2, as suggested by Pickering et al.[16] Staging of AKI was based on the following: an elevation of serum creatinine level 1.5–1.9 × baseline or ≥0.3 mg/dl elevation (stage 1); elevation of serum creatinine 2.0–2.9 × baseline (Stage 2); and 3.0 × baseline or increase in serum creatinine to ≥4.0 mg/dl or the initiation of renal replacement therapy (Stage 3).

Etiological assessment

The settings and specific etiologies of CA-AKI were noted. When AKI was multifactorial, the factor attributed by the treating clinician as the most contributory factor was considered the etiology of AKI. If no clear single etiology was ascertained, it was considered undetermined. Sepsis was defined according to the Third International Consensus Definition as a documented source of infection with a quick Sequential Organ Failure Assessment (qSOFA) score ≥2.[17]

Follow-up and outcome measures

Each patient was followed up for renal outcomes at discharge and at 1 and 3 months after the onset of AKI, as ensured by the individual center. Patient outcome(s) were classified as survivor or non-survivor. Among the survivors, complete recovery (CR) was defined as adequate urine output (>1 ml/kg/h) with serum creatinine <1.4 mg/dl without persistent proteinuria or microscopic hematuria. Partial recovery (PR) was defined as both a decrease in serum creatinine by ≥50%, with improved urine output (≥0.5 ml/kg/h) and no need for dialysis for patients who were started on dialysis. Dialysis dependency was defined as the need for any form of dialysis for >28 days. Proteinuria was defined as urine protein excretion of ≥1+ on urine dipstick examination. Microscopic hematuria was defined as >5 red blood cells/high-power field on spun urine evaluation. A flow-diagram illustrating the study process is presented in Supplementary File 1.

Statistical analysis

Baseline characteristics are presented by comparing the stages of AKI at presentation. Values are expressed as

mean and standard deviation (SD) for normally distributed continuous variables and as median and IQR for nonparametric distributions. Categorical values are expressed as percentages and proportions. The Kolmogorov–Smirnov test was used to test the normality of data distribution. The two groups comprised survivors and non-survivors. Student's t-test was used to compare parametric mean values between the two groups. The Kruskal–Wallis test was used to compare nonparametric values between >2 groups. Chi-squared and Fisher's exact tests were used to compare proportions between the 2 groups according to the application required. The Mann–Whitney U test was used to compare nonparametric values between the two groups. Predictors of mortality were determined using multivariate logistic regression analysis, with all significant variables in the univariate logistic regression analysis. The collinearity of the independent variables was examined using a correlation matrix and variance inflation factor (VIF). The correlation coefficients for each predictor variable were <0.8 in the correlation matrix, and the VIF values were <5, indicating that the multicollinearity assumptions were met. Differences with $P < 0.05$ were considered to be statistically significant. Statistical analyses were performed using SPSS version 25 (IBM Corporation, Armonk, NY, USA). Patients with insufficient data regarding the definition and classification of AKI were excluded. Missing data in the independent variables were handled with a series mean method using SPSS software.

Role of funding source

There was no role of the funder in the design, conduct, analysis, or interpretation of the study, or in the decision to submit the results for publication.

Results

Data from 4087 patients with AKI were archived in the AKI registry website during the study period. Data from 376 patients were not included in the analysis (data from 249 were not included and 127 did not return for follow-up). Thus, data from 3711 patients with AKI were analyzed.

Demographics of the study population

The baseline characteristics of the patients are summarized in Table 1. The mean (±SD) age of the study population was 44.7 ± 16.5 years (range 12–86 years), with the highest prevalence of AKI in those 55–64 years of age. Female patients were more likely to present with advanced AKI stage 3. The mean BMI of the patients was 23.10 ± 9.4 kg/m^2.

Associated comorbidities

The most common pre-existing comorbidity was hypertension (21.4%), followed by diabetes mellitus (19.1%), chronic liver disease (CLD) (11.7%), and coronary artery disease (CAD) (4.2%). Patients with diabetes mellitus and hypertension were more likely to develop stage 3 AKI (Table 1).

SES profile and lifestyle risk factors

Of the 3711 patients with AKI, 58.1% lived in rural areas. The patients were stratified into five socioeconomic categories based on the 2015 updated version of the modified Kuppuswamy scale. Approximately one-third (36.7% [831/2262]) of patients with AKI consumed alcohol regularly (Fig. 1).

AKI evaluation and staging

Among the 3711 patients, 2034 (54.8%) had stage 3 AKI, 1143 (30.8%) had stage 2, and 534 (14.4%) had stage 1. Biochemical parameters of the patients are summarized in Table 1. Notably, hyperkalemia (11.6%), transaminitis (24.4%), hypocalcemia (27.9%), hyperphosphatemia (19.4%), and hypoalbuminemia (27.4%) were observed on admission (Tables 1 and 4).

Etiology of AKI

AKI occurred in medical, surgical, and obstetrical settings in 3216 (86.7%), 270 (7.3%), and 225 (6%) cases, respectively. Sepsis was the most common etiology in the medical setting (Table 2).

In the surgical setting, the most common etiology of AKI was obstructive uropathy in 92 (2.5%) patients, followed by prerenal/blood loss in 82 (2.2%). In the obstetrical setting, puerperal sepsis was the most common cause (n = 73 [2%]).

Drug-induced AKI

Drug-induced AKI was observed in 292 (7.9%) individuals. Among these, drugs implicated in the cause of AKI included the following: non-steroidal anti-inflammatory drugs (NSAIDs) (n = 130 [44.8%]); aminoglycosides (n = 67 [22.9%]); proton pump inhibitors (PPI) (n = 30 [10.2%]); rifampicin (n = 18 [6.1%]); native and herbal medication (n = 35 [12%]); and other drugs (n = 12 [0.4%]).

Renal biopsy profile

Renal biopsy data were available for 582 of the 3711 patients (15.6%). The decision to perform a biopsy was at the clinician's discretion, and biopsy findings were recorded based on the predominant biopsy findings as reported by the pathologist at the individual centers. Broadly, the indications for biopsy were nonrecovery of renal function, uncertain diagnosis, suspected glomerular disease, and AKI with systemic symptoms. Acute tubular necrosis in 207 (35.6%) patients was the most common histopathological finding, followed by acute interstitial nephritis in 74 (12.7%). Glomerular etiology was observed in 178 (30.5%) cases, and TMA in 36 (6.2%) cases on biopsy (Table 3).

	Total (N = 3711)	KDIGO stage 1 (N = 534)	KDIGO stage 2 (N = 1143)	KDIGO stage 3 (N = 2034)	P value
Age (mean ± SD) years	44.7 (16.5)	47 (16)	42 (17)	45 (16.3)	0.164
Gender, male, n (%)	2472 (66.6)	375 (70.2)	804 (70.3)	1293 (63.6)	0.001
BMI	23.10 (±9.4)	22.3 (±8.9)	24.1 (±7.8)	20.9 (±10.8)	0.64
Hypertension, n (%)	795 (21.4)	84 (15.7)	252 (22)	459 (22.6)	0.002
Diabetes mellitus, n (%)	708 (19.1)	81 (15.2)	171 (15.0)	456 (22.4)	0.001
CLD, n (%)	435 (11.7)	69 (12.9)	123 (10.8)	243 (11.9)	0.394
Hypotension at presentation, n (%)	246 (6.6)	39 (7.3)	87 (7.6)	120 (5.8)	0.141
CAD, n (%)	156 (4.2)	24 (4.5)	39 (3.4)	93 (4.6)	0.276
Hemoglobin, g%	10.01 (7.9–12.6)	12.2 (8.5–14.4)	10.8 (8.4–12.9)	9.5 (7.4–11.4)	0.04
TLC (*10^3), per cu.mm	12 (8.7–16)	11.1 (8.6–16.2)	12.3 (9.8–16.2)	12.4 (8.7–15.5)	0.34
Platelet count (lakhs/cu.mm)	1.8 (0.98–2.6)	2.1 (1.2–2.9)	1.4 (0.88–2.4)	1.65 (1.0–2.7)	0.14
S. creatinine, mg %	3.4 (2.1–6.4)	1.6 (1.4–1.8)	2.25 (2.0–2.4)	5.4 (3.9–7.2)	0.001
BUN, mg %	39.70 (24.50–55.4)	22 (18.1–40.4)	30.6 (23.9–44.8)	44.1 (35.4–67.2)	0.05
Total calcium, mg %	8.6 (8.0–9.1)	8.6 (8.2–9.2)	8.4 (7.9–8.9)	8.6 (7.9–9.1)	0.241
Phosphate, mg %	4.2 (3.8–5.4)	4.2 (3.8–4.8)	4.1 (3.6–4.9)	4.6 (4.0–6.0)	0.45
Sodium, mmol/L	133 (129–136)	134 (130–136)	133 (130–135)	131 (129–134)	0.21
Potassium, mmol/L	4.3 (3.9–5.0)	4.0 (3.6–4.6)	4.5 (3.9–5.0)	4.6 (4.0–5.2)	0.5
Uric acid, mg %	5.15 (4.0–6.8)	4.3 (3.6–5.6)	4.6 (3.8–6.1)	5.8 (4.2–7.0)	0.06
Bilirubin, mg %	1.0 (0.6–1.8)	0.8 (0.6–1.1)	1.1 (0.7–2.1)	1.1 (0.7–1.8)	0.34
Albumin, g%	3.7 (3.2–4.1)	3.6 (3.4–4.1)	3.9 (3.4–4.2)	3.6 (3.1–4.0)	0.12
AST, IU/L	39.5 (22–64)	35 (20–57)	35 (20–89)	40 (24–62)	0.31
ALT, IU/L	26 (21–43)	23.5 (18–42)	30 (21–60)	26 (21–42)	0.3

Data are represented in the form of median (IQR Q1–Q3) unless specified. CAD, coronary artery disease; CLD, chronic liver disease; BMI, body mass index; AST, aspartate transaminase; ALT, alanine transaminase; TLC, total leukocyte count; BMI, body mass index.

Table 1: **Baseline characteristics of patients according to AKI staging (KDIGO 2012 classification).**

Management during hospital stay

The median duration of hospitalization was 9 days (range, 1–107 days). Of the patients, 70.2% received antibiotics appropriate for treating the underlying cause of AKI, 12% received antifungals, 18.73% required diuretics for volume management, and 15.57% required blood components during hospitalization. Intensive care unit (ICU) support was also required by 8.2% of

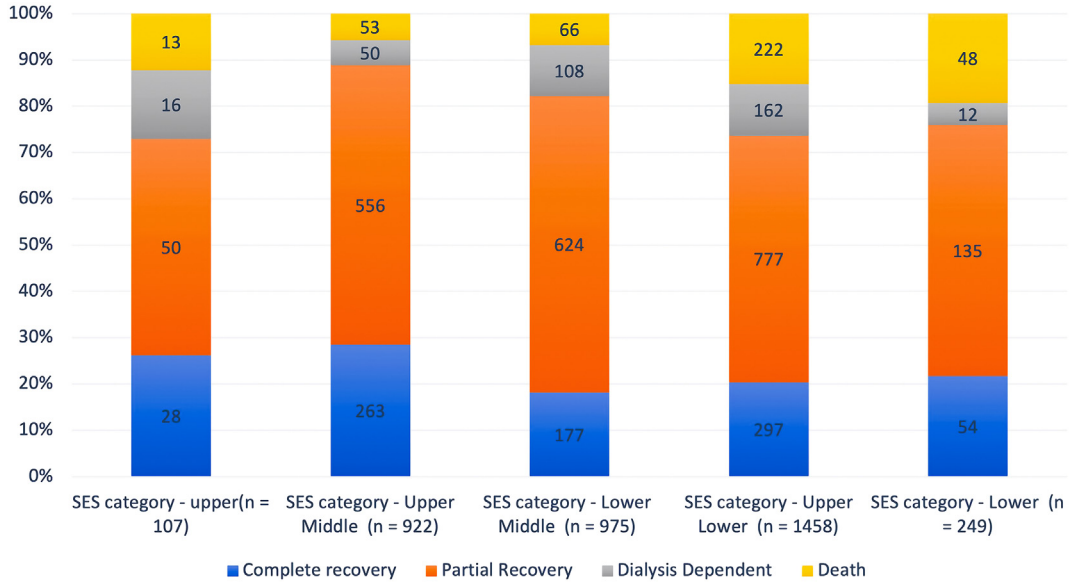

Fig. 1: **Outcomes of patients at discharge according to Socio-economic categories**. Patients classified into five categories (upper, upper middle, lower middle, upper lower and lower) according to the modified Kuppuswamy scale 2015.

AKI setting	Etiology of AKI	Frequency (n = 3711) N (%)	Mortality (n = 402) N (%)
Medical n = 3216 (86.7%)	Sepsis—urinary tract infection	610 (16.4)	71 (17.6)
	Sepsis—other foci	681 (18.3)	64 (15.9)
	Tropical fever	362 (9.8)	30 (7.4)
	Acute gastro-enteritis	294 (7.9)	14 (3.4)
	AKI with liver diseases	339 (9.1)	29 (7.2)
	Drug-induced	292 (7.9)	10 (2.5)
	Cardiorenal syndrome	188 (5.1)	23 (5.7)
	TMA	153 (4.1)	16 (4.2)
	Snake bite	83 (2.2)	19 (4.7)
	Others/undetermined etiology	212 (5.7)	21 (5.2)
Surgical n = 270 (7.3%)	Obstructive uropathy	92 (2.5)	8 (2)
	Pre-renal/blood loss related	82 (2.2)	4 (1)
	Sepsis	59 (1.5)	18 (4.5)
	Others	37 (1)	15 (3.7)
Obstetric n = 225 (6.1%)	Puerperal sepsis	73 (2)	21 (5.2)
	Antepartum/postpartum hemorrhage	55 (1.4)	17 (4.2)
	Pre-eclampsia/HELLP	42 (1.1)	7 (1.7)
	TMA	31 (0.8)	3 (0.7)
	Others	24 (0.6)	2 (0.5)

TMA, thrombotic micro-angiopathy; HELLP, hemolysis, elevated liver enzymes and low platelets.

Table 2: **Etiological spectrum of acute kidney injury.**

patients, and 27.3% required vasopressor drugs. A total of 1162 patients (31.3%) underwent ≥1 hemodialysis session(s) during their hospital stay.

Clinical outcomes

Clinical characteristics demonstrating the differences between survivors and non-survivors are summarized in Table 4. A summary of the recovery outcomes at discharge, 1 month and 3 months is presented in Fig. 2. Among the 3711 patients, 402 (10.8%) died during the index admission. At discharge, CR was recorded in 819 (22.1%) patients, PR in 2142 (57.7%), and dialysis dependency in 348 (9.4%). Proteinuria was observed in 2058 (57.4%) patients and microscopic hematuria in 409 (11.02%). At discharge, the mean creatinine level among the non-dialysis-dependent survivors was 2.83 mg/dl (IQR 0.6–12.5 mg/dl).

At the 1-month follow-up after discharge, another 20 patients died, with a total mortality of 422 (11.4%). CR, PR, and dialysis dependency were noted in 2388 (64.4%), 733 (19.7%), and 66 (1.8%) patients, respectively. Proteinuria and microscopic hematuria were observed in 890 (23.9) and 209 (5.6%) patients, respectively, and an additional 102 (2.7%) were lost to follow-up. At the end of follow-up at 3 months, CR, PR and dialysis dependency were evident in 2683 (72.2%), 267 (7.2%), and 36 (1%) patients, respectively, and 779 (21%) had residual proteinuria and 189 (5.1%) had microscopic hematuria (Table 5). None of the patients died 1 month after discharge, although 8.2% (n = 303) could not be traced for the last follow-up.

S.No	Predominant renal biopsy finding	Frequency (N = 582) n (%)
1	Acute tubular necrosis	207 (35.6)
2	Acute interstitial nephritis	74 (12.7)
3	Acute tubulointerstitial nephritis	45 (7.7)
4	Thrombotic microangiopathy	36 (6.2)
5	Acute pyelonephritis	24 (4.1)
6	Pigment cast nephropathy	15 (2.6)
7	Crescentic glomerulonephritis	36 (6.2)
8	Focal segmental glomerulosclerosis	18 (3.1)
9	Infection related glomerulonephritis	9 (1.5)
10	Acute cortical necrosis	21 (3.6)
11	Diffuse proliferative glomerulonephritis	39 (6.7)
12	IgA nephropathy	9 (1.5)
13	Myeloma cast nephropathy	14 (2.4)
14	Lupus nephritis	7 (1.2)
15	Others/non-specific/descriptive/inconclusive (or) inadequate	28 (4.8)

Table 3: **Renal biopsy profile of AKI patients who underwent Renal biopsy on clinical indication.**

Predictors of mortality at the index admission

The mortality rate at index admission was 402/3711 (10.8%). Reported causes of death in the index admission were as follows: septic shock (n = 119 [29.6%]); multi-organ dysfunction syndrome (MODS) (n = 58 [14.4%]); hyperkalemia (n = 40 [9.95%]); acute respiratory distress syndrome (ARDS) (n = 31 [7.71%]); hypovolemic shock (n = 28 [6.96%]); cardiac arrhythmias (n = 65 [16.16%]); and any cause of death was not

	Total N = 3711	Survivors N = 3309	Non—survivors N = 402	P value
Age, in years mean (SD)	44.7 (16.5)	44.26	45.94	0.055
Age >65	501 (13.5)	432 (13.1)	69 (17.2)	0.02
Gender (Male)	2472 (66.6)	2190 (66.2)	282 (70.1)	0.06
Hypertension	795 (21.4)	759 (22.4)	36 (9.0)	0.001
Diabetes mellitus	708 (19.1)	633 (19.1)	75 (18.7)	0.44
CLD	435 (11.7)	339 (10.2)	96 (23.9)	0.001
CAD	156 (4.2)	129 (3.9)	27 (6.7)	0.008
Obesity	165 (5.3)	132 (4.7)	33 (8.2)	0.06
Alcohol abuse	831 (36.7)	642 (34.5)	189 (47.4)	0.001
Tobacco consumption	(28.7)	(27.9)	(32.3)	0.04
Low SES	249 (7.0)	201 (6.4)	48 (12.2)	0.001
KDIGO stage 1	534 (14.4)	492 (14.9)	42 (10.4)	0.12
KDIGO stage 2	1143 (30.8)	1071 (32.4)	72 (17.9)	0.05
KDIGO stage 3	2034 (54.8)	1746 (52.8)	288 (71.6)	0.001
Hypotension at presentation	246 (6.6)	159 (4.8)	87 (21.6)	0.001
Anuric presentation	126 (3.4)	105 (3.2)	21 (5.2)	0.02
Hyperkalemia at presentation	432 (11.6)	354 (10.7)	78 (19.4)	0.001
CNS involvement	101 (2.7)	92 (2.8)	9 (2.2)	0.33
Vasopressor usage	1014 (27.3)	738 (22.3)	276 (68.7)	0.001
Dialysis requiring AKI	1162 (31.3)	990 (29.9)	172 (42.8)	0.001
Severe anemia	318 (8.6)	249 (7.5)	69 (17.2)	0.001
Leucocytosis	1731 (46.6)	1500 (45.3)	231 (57.5)	0.001
Thrombocytopenia	1257 (33.9)	1095 (33.1)	162 (40.3)	0.004
Advanced renal failure	1437 (38.7)	1281 (38.7)	156 (38.8)	0.971
Jaundice	618 (16.7)	501 (15.1)	117 (29.1)	0.001
Transaminitis	905 (24.4)	710 (21.5)	195 (48.5)	0.001
Hypocalcemia	1036 (27.9)	943 (28.5)	93 (23.1)	0.24
Hyperphosphatemia	720 (19.4)	645 (19.4)	75 (18.6.)	0.31
Hypoalbuminemia	1003 (27)	892 (27)	111 (27.6)	0.780

CAD, coronary artery disease; CLD, chronic liver disease; Thrombocytopenia, platelet count <150,000/cmm; Leukocytosis, TLC >11,000; Severe anemia, Hb <7 g/dl; Jaundice, hyperbilirubinemia >2 mg/dl; Transaminitis, SGOT/SGPT >40 IU/ml; CNS, central nervous system; hypoalbuminemia, serum albumin <3 g/dl; Hypocalcemia, serum calcium <8.4 mg/dl; Hyperphosphatemia, serum phosphate >6 mg/dl; Advanced renal failure, serum Creatinine >4 mg/dl.

Table 4: **Factors associated with mortality in patients with acute kidney injury.**

recorded in the registry (n = 61 [15.17%]). On analyzing the factors between survivors and non-survivors, age >65 years, pre-existing hypertension, CLD, CAD, alcohol abuse, tobacco consumption, low SES, higher AKI stage, anuria and hyperkalemia at presentation, vasopressor requirement, dialysis requiring AKI, severe anemia, leukocytosis, thrombocytopenia, jaundice and transaminitis were higher in the non-survivor group of pateints with AKI (Table 4). However, multivariable analysis revealed that age >65 years, alcohol abuse, hypertension at presentation, anuria, hypotension at presentation, thrombocytopenia, vasopressor use, jaundice, transaminitis, and low SES were significant predictors of mortality (Table 6).

Discussion

In this study, we found that mean age of patients with CA-AKI was 44 (±16.5) years, they were predominantly male, from lower SES category, and rural background. Other studies have also reported that CA-AKI in the tropics affects younger age groups compared to high-income countries, where older individuals are affected more.[18] In our cohort, the majority of patients (54.8%) presented with stage 3 AKI, 37.4% required ≥1 dialysis sessions, 8.2% required ICU support after admission, and 18.4% required vasopressor support. Many patients experience persistent renal dysfunction after being discharged from hospital.

There are differences in the recognition, management, and outcomes of AKI in different health settings for both CA-AKI and HA-AKI, which are influenced by economic conditions in different countries. There are many regional disparities between the different states in India. Several reports have been generated based on the Delphi study protocol from India[19]; however, this is the first extensive registry-based study from all parts of India to generate the etiologies and outcomes of CA-AKI in India. Moreover, this was the first study to retrieve data from all patients for up to 3 months of follow-up to analyze residual damage from CA-AKI.

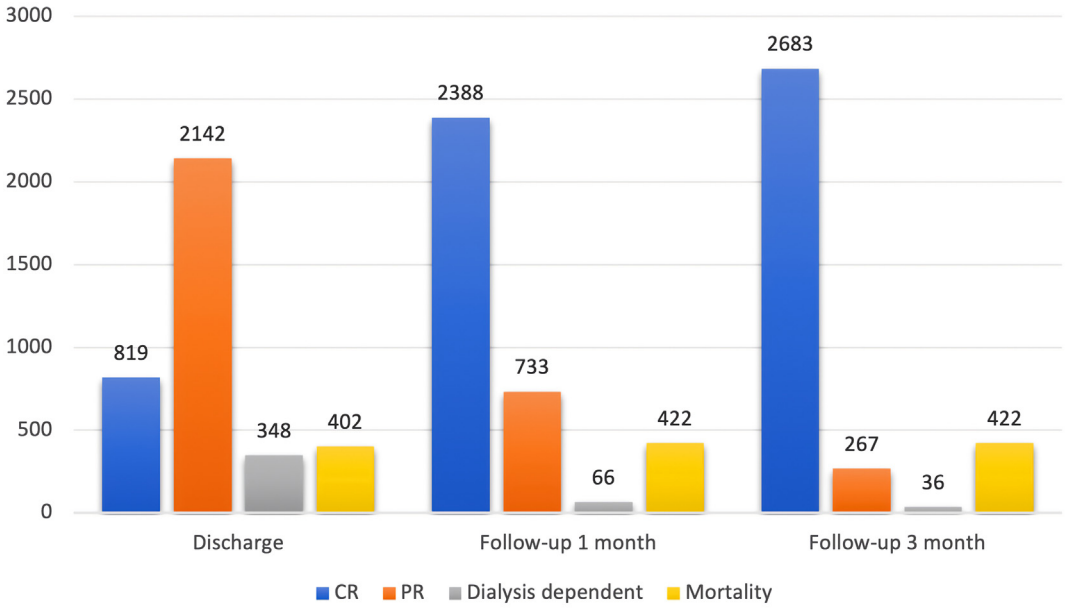

Fig. 2: **Outcomes of patients at discharge, 1 month and 3-month follow-up**. CR, complete recovery; PR, partial recovery.

Etiological spectrum

The most common etiological setting of AKI in our registry was medical, followed by surgical and obstetrical; the most common etiology was sepsis-associated AKI. Most studies investigating CA-AKI have reported sepsis as the most common etiology, including a single-center study conducted in India.[20] A single-center study[21] from Uttar Pradesh, India, reported diarrheal disease as the most common cause, whereas studies from the 1980s reported pre-renal AKI as the leading cause of CA-AKI.[21] In contrast, Kaaviya et al.[22] reported snake bites and animal envenomation as the most common causes of AKI in a study in southern India. At the same time, the present registry data revealed that only 1% of all cases of AKI were due to snake envenomation. Snake bite-induced AKI has mostly been reported in southern India. Geographical hotspots with a high incidence of snakebites require environmental action and government policies to tackle this preventable cause of AKI.

	Discharge	Follow-up at 1 month	Follow-up at 3 months
Serum creatinine, mg/dl mean (SD)[a]	2.83 (±3.59)	1.58 (±1.34)	1.15 (±0.61)
Complete recovery (CR) n (%)	819 (22.1)	2388 (64.4)	2683 (72.2)
Partial recovery (PR) n (%)	2142 (57.7)	733 (19.7)	267 (7.2)
Dialysis dependency n (%)	348 (9.4)	66 (1.8)	36 (1)
Chronic kidney disease n (%)	–	–	267 (7.2)
Death n (%)	402 (10.8)	422 (11.4)	422 (11.4)
Lost to follow-up n (%)	–	102 (2.7)	303 (8.2)

[a]Serum creatinine – only in non-dialysis-dependent survivors at various time points as indicated.

Table 5: **Status of patients at discharge, 1-month and 3-month follow-up.**

In nephrology practice, kidney biopsies are infrequently performed to ascertain the etiopathogenic process in the case of AKI and the AKI is typically diagnosed based on clinical assessment. The KDIGO clinical practice guidelines for AKI[8] recommend kidney biopsy if the cause of AKI remains unclear after careful evaluation, especially in patients whose pre- and post-renal causes of AKI have been excluded and the cause of intrinsic AKI remains ambiguous. It may be particularly useful when clinical assessment, urinalysis, and laboratory investigations suggest diagnoses other than sepsis, ischemic or nephrotoxic injury.[8] A biopsy was performed in 15% of the patients enrolled in the present study. The slightly higher incidence of kidney biopsy in our study may be due to the fact that all the participating centers were tertiary care hospitals. Tubulointerstitial etiology was observed in more than two-thirds of the patients, whereas glomerular or vascular causes were observed in one-third. The role of renal biopsy and its timing in AKI are evolving. Further studies investigating the effect of renal biopsy on guiding treatment decisions for AKI are needed to clarify this issue.

Patient outcomes

Mortality rates in patients with CA-AKI can vary based on factors, such as underlying health conditions, access to healthcare, treatment options, and demographics. Limited access to healthcare, lower SES conditions, and differences in healthcare practices can potentially affect mortality rates. The mortality rate during the index admission in our registry data was 10.8%. Another single-center study from Himachal Pradesh, India,

Variable	aOR (95% CI)	P value
Age >65	1.41 (1.01–1.94)	0.04
Gender (Males vs Female)	0.32 (0.25–1.2)	0.858
Hypertension (Yes vs No)	0.98 (0.8–1.23)	0.451
CAD (Yes vs NO)	0.591 (0.4–1.1)	0.442
CLD (Yes vs No)	1.090 (0.89–1.24)	0.296
Alcohol abuse (Yes vs No)	1.94 (1.48–2.56)	0.001
Tobacco consumption	0.735 (0.6–1.1)	0.09
Hypotension at presentation	2.03 (1.42–2.87)	0.001
Anuria at presentation	2.14 (1.23–3.71)	0.007
Severe anemia	0.51 (0.3–1.05)	0.12
Leucoyctosis	0.962 (0.7–1.1)	0.607
Thrombocytopenia	1.3 (1.1–1.62)	0.019
Vasopressor usage	5.03 (3.86–6.54)	0.001
Advanced renal failure (S creat >4 mg %)	1.38 (1.57–1.79)	0.09
Jaundice	1.6 (1.4–1.9)	0.04
Transaminitis	2.03 (1.57–2.6)	0.001
Dialysis requiring AKI	1.1 (0.91–1.2)	0.09
Low SES (Kuppusamy scale)	1.61 (1.3–1.92)	0.001

aOR, adjusted odds ratio; CAD, coronary artery disease; CLD, chronic liver disease; Thrombocytopenia, platelet count <150,000/cmm; Leucocytosis, TLC >11,000/cmm; Severe anemia, Hb <7 g/dl; Jaundice, hyperbilirubinemia >2 mg/dl; Transaminitis, AST/ALT >40 IU/ml.

Table 6: **Predictors of Mortality in Patients with Acute Kidney Injury on Multivariate logistic regression analysis.**

reported a mortality rate of 8.2%.[23] In contrast, a United-Kingdom-based Study by Wonacott et al. reported a mortality rate of 43.7% in CA-AKI, which was higher than HA-AKI.[24] A study from Taiwan reported higher mortality in HA-AKI (51%) compared with CA-AKI (26%). These findings suggest that mortality rates vary depending on the country, specific healthcare infrastructure, and patient demographics. The lower mortality in our cohort may be due to the younger age of the patients with fewer comorbidities compared to high income countries. Age >65 years, alcohol abuse, hypertension at presentation, anuria, hypotension at presentation, thrombocytopenia, vasopressor use, jaundice, transaminitis, and low SES were independent predictors of mortality. Late presentation may be the underlying reason for advanced renal failure and subsequent mortality. Community-level awareness is needed, especially in LMICs such as India, for early referral to nephrologists for CA-AKI. A large single-center study in Brazil identified that dialysis requirement, lower attendance time of nephrologists, age >60 years, and critical care unit admission were associated with higher mortality in patients with AKI.[25] A study from Gujarat in India reported a mortality rate of 11.8%. Mortality was associated with malaria-associated AKI requiring dialysis and, similar to our study, the requirement for inotropes and ventilatory support was associated with mortality.[26] They also noted high mortality during infection with *Plasmodium vivax*, a species previously considered to cause less cases of severe malaria compared to *Plasmodium falciparum*.[27] A large nationwide registry will inform us more about the outcomes of other specific AKI etiologies, help us understand regional variations, and enhance appropriate public health interventions.

Renal outcomes and post-AKI care

The recent KDIGO AKI conference emphasized the importance of AKD,[28] particularly in AKD-predisposed patients with CKD. We observed that many patients with CA-AKI had residual damage in the form of proteinuria and microscopic hematuria at the end of 3 months. There is associated with a significant risk of residual kidney damage. A persistent GFR decline of 35% from baseline between 7 days and 3 months was labelled AKD and was noted to have prognostic significance.[29] In our study, AKD was observed in 68% of the patients at the time of discharge; however, at 3 months follow-up, 8% had transitioned to CKD and 1% remained dialysis dependent. See et al. inferred a 2.67 (95% CI 1.99–3.58) times higher risk for CKD after an episode of AKI.[30] As early as 1967, Briggs et al. studied 50 patients with severe ATN and reported that at the years post AKI follow-up, 71% had lower GFR and 30% had a severe concentrating disability.[31] There are limited data regarding CKD progression from CA-AKI, and most studies have focused on HA-AKI progression to CKD.[24] Our findings suggest the need for regular follow-up in patients with CA-AKI. Better and closer follow-up protocols by nephrologists may help improve the short- and long-term outcomes of AKI.

Most patients with AKI do not undergo follow-up after discharge. A study from the United States by Siew et al.[32] noted that only 8.5% of AKI survivors received any nephrology consultation at follow-up post-discharge. In highly populated countries, such as India, follow-up of every patient with AKI after discharge may not be routinely possible. Therefore, determining the risk factors for complications and AKI/AKD that progress to CKD is of paramount importance to better plan and implement post-AKI follow-up.

Socioeconomic status and AKI outcomes

We found high mortality in those who belonged to the lower socioeconomic category according to the Kuppuswamy scale compared with <10% in those who belonged to the upper and upper middle socioeconomic category (Fig. 2). This observation is made even in countries with lower levels of inequality. A study from the United Kingdom reported a higher incidence and lesser survival among socially deprived individuals, as determined by the Index of Multiple Deprivation. The authors found that the adjusted mortality risk in patients with AKI was higher in the most deprived group, with a hazard ratio of 1.2.[33] We used the Kuppuswamy Scale, which is the most widely used and periodically updated classification system for SES in India.[34]

This is the largest registry-based study to report CA-AKI in India. The registry included multiple centers representative of rural and urban populations and major tertiary care centers from north to south and west to eastern parts of India. Sixty-nine percent of the data were obtained from two major high-volume public-sector hospitals. Because the registry was hospital-based, the cases may not represent the incidence of AKI in the community. A loss to follow-up of 8.2% at 3 months may undermine late mortality and underestimate CKD conversion. The cause of death after discharge could not be determined in many cases. Data regarding new-onset hypertension after recovery from AKI were not included in the registry. The most common etiology of CA-AKI in this nation-wide, registry-based study was sepsis-associated AKI, which is associated with a high mortality risk and transition to CKD. Anuria, hypotension, and hyperkalemia were independently associated with poor outcomes. This study also underscores the high mortality risk among patients from most deprived socio-economic groups, thereby urging immediate attention for targeted interventions.

Contributors

NP contributed to the conceptualization, funding arrangement, drafting and editing of the manuscript; Akhilesh Jaiswal, maintained the registry and analyzed data; Jeyakumar Meyyappan, drafted and edited the manuscript; Natrajan Gopalakrishnan, participated in the registry, provided data, and reviewed the manuscript; Arpita Roy Chaudhary, participated in the registry, provided data, and intellectual input; Edwin Fernando, data, drafting, and reviewing the manuscript; Manish Rathi, data, drafting, and reviewing; Shivendra Singh, contributed with patients, and reviewed the manuscript; Mohan Rajapurkar, intellectual input and guidance for the registry; Tarun Jeloka, drafting and editing the manuscript; Jai Kishun, biostatistics for the manuscript; Valentine Lobo, provided data, and reviewed, and edited.

Data sharing statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request. The data cannot be made public due to privacy and ethical restrictions.

Editor note

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Declaration of interests

The authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2024.100359.

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