Original Article

Acute Kidney Injury in a Tertiary Care Center of South India

Abstract

Background and Objective: Data regarding the epidemiology and outcomes of acute kidney injury (AKI) from our part of the world are limited. The irking consequences of AKI, both on the patient and the health care system, are being increasingly recognized. We aimed to study the epidemiology and short-term outcomes of AKI and to analyze the factors associated with adverse renal outcomes. **Materials and Methods:** We retrospectively studied AKI patients stratified according to the Kidney Disease: Improving Global Outcomes (KDIGO) stage, regarding clinicodemographic data, renal replacement therapy (RRT), and 90-day outcomes. Those with preexisting CKD Stage 4 (defined by estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) and above, prior renal transplant (s), or acute glomerulonephritis were excluded. The primary outcome was a composite of *de novo* CKD (eGFR <60 mL/min/1.73 m^2) or CKD progression (decline in eGFR category to any higher stage) in patients with baseline CKD at 90 days. The secondary outcome was a composite of *de novo* CKD, CKD progression, or death at 90 days. **Results:** Of the 358 patients, 52.5% had Stage 3 AKI. Eighty-eight patients (24.6%) had baseline CKD. Sepsis (51.4%) was the predominant etiology followed by nephrotoxins (42.5%). Renal replacement therapy (RRT) was required in 94 (26.3%) patients with hemodialysis being the most common modality. After excluding lost to follow-up, 66 patients (20.3%) had the primary outcome, and 195 patients (60%) had the secondary outcome. The 90-day mortality was observed in 39.7% of patients. AKI stage (P = 0.002), baseline CKD (P = 0.000) and RRT need (P = 0.005) were significantly associated with the primary outcome, while age >60 (P = 0.018), SOFA (Sequential Organ Failure Assessment) ≥9 (P = 0.000), hypoalbuminemia (P = 0.024), baseline CKD (P = 0.000) and RRT need (P = 0.001) were associated with the secondary outcome. **Conclusion:** Sepsis was the dominant precipitant of AKI and a major proportion had preventable etiology. AKI severity, baseline CKD status, and RRT need were found to predict the development or progression of CKD.

Keywords: *AKI, epidemiology, outcomes, risk factors*

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Introduction

The epidemiology and outcomes of acute kidney injury (AKI), the most common and perhaps the most serious renal event with short- and long-term repercussions, are determined to a large extent by the geographical, sociocultural, economic, genetic, and practice patterns in a country. Significant dissimilarities have been observed between countries, within different regions of a country, and even in a single center across different time periods.[1,2] AKI, in low- to middle-income countries like ours, is frequently a community-acquired problem affecting relatively younger people with fewer comorbidities, precipitated by a single identifiable cause and associated with lower mortality, in comparison with developed nations, where older, hospitalized individuals with significant comorbidities are affected with excess mortality.[1,3,4] Globally, AKI is estimated to affect 13.3 million individuals in a year, 5% to 10% of hospitalized patients, and 60% of intensive care patients, and >85% of this burden is contributed by developing countries.[5-7] In-hospital mortality of AKI remains unacceptably high exceeding 50% in critically ill patients.[8] Since the central AKI registry in our country is in its infancy, a void exists regarding the epidemiology and outcomes of AKI. Existing literature from our country has inherent limitations including, but not limited to, single-center data, under reporting, under recognition, retrospective design, and varied definitions.[1,4]

Although the short-term morbidity and mortality of AKI are better recognized, a critical knowledge gap exists regarding the long-term consequences

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in AKI survivors that have clinical and public health implications.[9] The conventional ideology of benign outcomes in AKI survivors has been recently challenged by observational studies. An episode of AKI elevates the risk of AKI recurrence, development of *de novo* CKD, or progression of existing CKD.[8,9] AKI and CKD are now recognized as interconnected syndromes with either being the risk factor of the other.[8] AKI has also been linked to nonrenal consequences such as increased risk of cardiovascular events, hypertension, poor quality of life, and mortality.[9-14] Even patients who had apparent complete recovery of renal function are at an increased risk of these adverse outcomes.[10,15] Hence, AKI survivors represent a high-risk population predisposed to potential ominous complications imparting a significant burden on the patient and public health resources, calling for risk stratification and mitigation measures.[16]

This study aims to analyze the etiology and short-term (90-day) outcomes in patients with AKI in a tertiary care center. Furthermore, the study intends to identify the risk factors associated with CKD development or progression and mortality in these patients.

Materials and Methods

This study was a retrospective study conducted in our tertiary care hospital between January 2018 and December 2019.

Patient selection and data collection

Adult patients (age ≥18 years) with AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) admitted either primarily in the nephrology unit or various other units seeking nephrology referral were included and staged as follows: Stage 1 (creatinine increase ≥0.3 mg/dL within past 48 hours or an increase of 1.5–1.9 times the baseline or a urine output <0.5 mL/kg/hour for 6–12 hours), Stage 2 (creatinine increase of 2.0–2.9 × baseline value or a urine output <0.5 mL/kg/hour for ≥12 hours), and Stage 3 (creatinine increase of 3 × baseline value or serum creatinine ≥4 mg/dL or RRT initiation or a urine output <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours). Those with preexisting CKD Stage 4 (defined by estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) and above, prior renal transplant (s), or acute glomerulonephritis were excluded from the study. Data on demographic characteristics, etiology, clinical features, comorbidities, biochemical parameters, histopathology, the treatment provided, vasopressor use, RRT, and outcomes were retrieved from patients' case records using a standardized data form. AKI at the time of admission or within 48 hours of admission was categorized as community-acquired AKI (CA-AKI) and that developing after 48 hours of hospitalization was categorized as hospital-acquired AKI (HA-AKI). Renal biopsy was performed when AKI did not improve by 14 days or earlier if there was a suspicion of a different disease process as per treating nephrologist's discretion. Baseline CKD was identified from serum creatinine measurement available within the preceding year from patients' records, finding of contracted kidneys on imaging, or chronicity (global glomerulosclerosis/moderate to severe interstitial fibrosis with tubular atrophy) on histology. Those with contracted kidneys or chronicity on biopsy without creatinine measurements were excluded as their CKD stage could not be ascertained. All eGFR measures were calculated using the Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine equation.

Outcome

The data were analyzed regarding the demographic features, etiology, histopathology, RRT, and 90-day outcomes. The primary outcome was a composite of *de novo* CKD (defined by eGFR <60 mL/min/1.73 m^2) or CKD progression (decline in eGFR category to any higher stage) in patients with baseline CKD at 90 days. The composite outcome of *de novo* CKD (defined by eGFR <60 mL/min/1.73 m^2) or, CKD progression (decline in eGFR category to any higher stage) in patients with baseline CKD or death at 90 days was studied as the secondary outcome.

Statistical methods

To describe the data, descriptive statistics, frequency analysis, and percentage analysis were used for categorical variables and mean with standard deviation (SD) or median with interquartile range (IQR) were used for continuous variables. Chi-square, Fisher exact, and Student *t* tests were used as appropriate. The risk factors with $P < 0.1$ for primary and secondary outcomes identified with univariate analysis using Chi-square test were further assessed using binary regression analysis. Collinearity was analyzed between the covariates. Statistical significance was considered at a $P < 0.05$, and odds ratios with 95% confidence interval were also calculated. Statistical analysis was done using IBM SPSS statistics software Version 26.0.

Results

Of the 358 patients included in the study, 77 patients (21.5%) had Stage 1, 93 (26%) had Stage 2, and 188 (52.5%) had Stage 3 AKI. The mean age of the study population was 46.09 ± 17 years; 213 (59.5%) of the total cohort were male, with a male: female ratio of 1.47:1. Among the comorbidities, diabetes mellitus was the most common in 99 patients (27.7%) followed by hypertension (n = 95, 26.5%). Among the entire study cohort, 88 patients (24.6%) had baseline CKD, 63.6% (56 patients) of them were in Stage 3 AKI group. The demographic and clinical characteristics are summarized in Table 1.

The etiology was multifactorial in most cases. Sepsis was the most common precipitating event (51.4%) with skin

Table 1: Patient characteristics and outcomes

Parameter		Total	KDIGO 1	KDIGO 2	KDIGO 3
n (%)		358	77 (21.5%)	93 (26%)	188 (52.5%)
Age in years (Mean±SD)		46.09±17	46.78±18	46.87±17.87	45.42±16.24
Gender	Male (*n*, %)	213 (59.5%)	41 (53.2%)	57 (61.3%)	115 (61.2%)
	Female (*n*, %)	145 (40.5%)	36 (46.8%)	36 (38.7%)	73 (38.8%)
	Male: Female ratio	1.47:1	1.14:1	1.58:1	1.57:1
Residence	Urban (*n*, %)	163 (45.5%)	47 (61%)	35 (37.6%)	81 (43.1%)
	Rural (*n*, %)	195 (54.5%)	30 (39%)	58 (62.4%)	107 (56.9%)
Setting	Medical (*n*, %)	257 (71.8%)	51 (66.2%)	69 (74.2%)	137 (72.9%)
	Surgical (*n*, %)	79 (22.1%)	19 (24.7%)	18 (19.3%)	42 (22.3%)
	Obstetric (*n*, %)	22 (6.1%)	7 (9.1%)	6 (6.5%)	9 (4.8%)
Community-acquired AKI		232 (64.8%)	49 (63.6%)	54 (58.1%)	129 (68.6%)
Hospital-acquired AKI		126 (35.2%)	28 (36.4%)	39 (41.9%)	59 (31.4%)
Comorbidities	Diabetes mellitus (*n*, %)	99 (27.7%)	25 (32.5%)	27 (29%)	47 (25%)
	Hypertension (*n*, %)	95 (26.5%)	28 (36.4%)	24 (25.8%)	43 (22.9%)
	Cardiovascular disease (*n*, %)	51 (14.3%)	14 (18.1%)	16 (17.2%)	21 (11.2%)
	Chronic liver disease (*n*, %)	32 (8.9%)	5 (6.5%)	10 (10.8%)	17 (9%)
	Cerebrovascular disease (*n*, %)	18 (5%)	7 (9.1%)	5 (5.3%)	6 (3.2%)
	Malignancy (*n*, %)	11 (3%)	3 (3.9%)	3 (3.2%)	5 (2.6%)
	Others (*n*, %)	20 (5.6%)	5 (6.5%)	9 (9.7%)	6 (3.2%)
Smoking (*n*, %)		160 (44.7%)	32 (41.6%)	43 (46.2%)	85 (45.2%)
Alcohol (*n*, %)		146 (40.8%)	36 (46.7%)	41 (44.1%)	69 (36.7%)
Baseline CKD (eGFR=60-89 mL/min/1.73 m^2) (*n*, %)		88 (24.6%)	12 (15.6%)	20 (21.5%)	56 (29.8%)
Recurrence (*n*, %)		58 (16.2%)	6 (7.8%)	18 (19.3%)	34 (18.1%)
SOFA (Median, IQR)		8 (5-11)	5 (3-8)	7 (4.5-9.5)	9 (6-12)
Vasopressor use (*n*, %)		121 (33.8%)	19 (24.7%)	37 (39.8%)	65 (34.6%)
Albumin in g/dL (Mean±SD)		3.65±0.6	3.81±0.52	3.69±0.61	3.56±0.62
Length of stay in days (Median, IQR)		10 (6-12)	9 (6-12)	9 (6-12)	10 (6-14)
Need for RRT (*n*, %)		94 (26.3%)	-	-	94 (50%)
Hemodialysis	*n*	68	-	-	68/94 (72.3%)
	Duration in hours (Mean±SD)	20.5±16.4	-	-	20.5±16.4
Intermittent peritoneal dialysis	*n*	26	-	-	26/94 (27.7%)
	Duration in hours (Mean±SD)	17±11.2	-	-	17±11.2

KDIGO=Kidney Disease: Improving Global Outcomes, AKI=acute kidney injury, CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate, SOFA=Sequential Organ Failure Assessment, RRT=renal replacement therapy, SD=standard deviation, IQR=interquartile range

and soft tissue being the predominant source (*n* = 78/184, 42.4%). Next to sepsis, nephrotoxins contributed to AKI in 152 patients (42.5%) with drugs contributing to the majority (*n* = 53/152, 34.9%). Among poisons consumed, paraquat ingestion (44.7%) was the most common. Table 2 provides a summary of the various AKI etiologies. Acute tubular injury was the most common histologic finding (23.9%) among patients who underwent renal biopsy (*n* = 46, 12.8%) [Table 3].

Outcome

Of the 94 patients (26.3%) requiring RRT, hemodialysis was the most common modality employed (72.3%). Acute intermittent peritoneal dialysis was done in 27.7% of patients who had hemodynamic instability or other contraindications to hemodialysis [Table 1]. At 90 days, 33 patients (9.2%) were lost to follow-up. Of the remaining 325 patients, 66 patients (20.3%) and 195 patients (60%) met the primary and secondary composite outcomes, respectively. Eighteen (5.5%) AKI patients without baseline CKD developed *de novo* CKD at 90 days. Sixteen of the 18 patients had Stage 3 AKI, whereas the remaining two patients had Stage 2 AKI, and all these patients progressed to CKD without AKI recovery. At 90 days, 129 patients (39.7%) had mortality, of which 79 patients (61.2%) expired during their hospital stay. The 30-day and 60-day mortality were observed in 101 patients (31.1%) and 117 patients (36%), respectively. The outcomes according to stage are tabulated in Table 4.

Risk factors associated with primary and secondary outcomes

In multivariate analysis, stage of AKI (P = 0.002), presence of baseline CKD (P = 0.000) and need for RRT (P = 0.005) were significantly associated with the primary outcome, whereas age >60 (P = 0.018), Sequential Organ Failure Assessment (SOFA) ≥9 (P = 0.000), hypoalbuminemia (P = 0.024), baseline CKD (P = 0.000),

Table 2: Etiological risk factors

Etiology		Total	KDIGO 1	KDIGO 2	KDIGO 3
Sepsis		184 (51.4%)	29 (37.7%)	46 (49.5%)	109 (58%)
Skin and soft tissue		78 (21.8%)	14	27	37
Urinary tract		54 (15.1%)	7	14	33
Abdominal		18 (5%)	2	3	13
Pulmonary		18 (5%)	3	1	14
Others		16 (4.5%)	3	1	12
Nephrotoxin		152 (42.5%)	33 (42.9%)	41 (44.1%)	64 (34%)
Drugs		53 (14.8%)	22	19	12
NSAID		18 (5%)	9	6	3
Mannitol		12 (3.3%)	6	4	2
Aminoglycoside		10 (2.8%)	4	4	2
Rifampicin		4 (1.1%)	-	1	3
Amphotericin B		3 (0.8%)	1	2	-
Cisplatin		4 (1.1%)	2	2	-
Colistin		1 (0.3%)	-	-	1
Vancomycin		1 (0.3%)	-	-	1
Exogenous toxins		47 (13.1%)	6	14	26
Paraquat		21 (5.9%)	3	5	13
Zinc phosphide		15 (4.2%)	2	4	9
Copper sulfate		6 (1.7%)	1	3	2
Para-phenylenediamine		2 (0.6%)	-	2	-
Cleistanthus collinus		1 (0.3%)	-	-	1
Unknown		2 (0.6%)	-	1	1
Endogenous toxins		36 (10.1%)	5	7	26
Myoglobin		21 (5.9%)	4	3	14
Heme		11 (3.1%)	1	3	7
Bile		4 (1.1%)	-	1	3
Light chain		2 (0.6%)	-	-	2
Contrast		16 (4.5%)	8	6	2
Bite/sting	Snake bite	15 (4.2%)	1	3	11
	Unknown	3 (0.8%)	-	2	1
Decreased effective circulating volume		62 (17.3%)	24 (31.2%)	10 (10.7%)	28 (14.9%)
Infection		49 (13.7%)	8 (10.4%)	14 (15%)	27 (14.4%)
Pyelonephritis		25 (7%)	4	5	16
Leptospirosis		8 (2.2%)	2	2	4
Malaria		7 (1.9%)	-	2	5
Dengue		4 (1.1%)	-	4	-
Scrub typhus		2 (0.6%)	-	-	2
HIV		3 (0.8%)	2	1	-
Cardiac-related causes		41 (11.4%)	14 (18.2%)	22 (23.7%)	5 (2.7%)
Liver-related causes		36 (10.1%)	9 (11.7%)	10 (10.7%)	17 (9%)
Obstetric causes		22 (6.1%)	9 (11.7%)	7 (7.5%)	6 (3.2%)
Pre-eclampsia-eclampsia related		12 (3.3%)	5	5	2
Puerperal sepsis		6 (1.7%)	2	1	3
Obstetric hemorrhage		3 (0.8%)	1	1	1
Acute fatty liver of pregnancy		1 (0.3%)	1	-	-
Thrombotic microangiopathy		8 (2.2%)	-	-	8 (4.3%)
Pancreatitis related		21 (5.9%)	8 (10.4%)	4 (4.3%)	9 (4.8%)
Obstruction		15 (4.2%)	-	4 (4.3%)	11 (5.9%)
Supravesical	Bilateral ureteric calculi	7 (1.9%)	-	1	6
	Bilateral malignant ureteral obstruction	4 (1.1%)	-	-	4

Contd...

Table 2: Contd...

Etiology		Total	KDIGO 1	KDIGO 2	KDIGO 3
Infravesical	Prostatic obstruction	3 (0.8%)	-	2	1
	Urethral stricture	1 (0.3%)	-	1	-

KDIGO=Kidney Disease: Improving Global Outcomes, NSAID=nonsteroidal anti-inflammatory drugs, HIV=human immunodeficiency virus. Patients may have more than one etiological factor and the total percentage may exceed 100%. Rhabdomyolysis=status epilepticus, trauma, undue exertion, leptospirosis, viral infections, drugs, alcohol, poisons (copper sulfate and paraphenylene diamine), and acute pancreatitis. Decreased effective circulating volume=blood loss, tube drainage, ostomy, anaphylaxis, and acute gastroenteritis

Table 3: Histopathology

Histology	*n* (46 patients)
Acute tubular injury	11
Pigment cast nephropathy	
Heme	8
Myoglobin	3
Bile	3
Tubular epithelial cell	2
Light chain cast	2
RBC	1
Thrombotic microangiopathy	6 (3 had cortical necrosis)
Acute tubulointerstitial nephritis	4
Acute pyelonephritis	4
IgA nephropathy	2

IgA nephropathy - one patient had acute tubular injury due to unknown poisoning with immunofluorescence evidence of IgA staining and the other patient had acute kidney injury due to gross hematuria. RBC=red blood cell

and need for RRT (P = 0.001) were associated with the secondary outcome [Table 5].

Discussion

Accumulating evidence on the adverse long-term consequences of AKI, both renal and nonrenal, has changed our perception of this syndrome, once considered to have a benign outcome. The development and validation of consensus definitions of AKI, apart from use in epidemiologic studies and trials, has increased our understanding of the short- and long-term outcomes of AKI.[7,9,17]

More than half of our study population belonged to the KDIGO Stage 3, reasons being delayed recognition, inadequate management of the precipitating cause, difficulty in health care access, resorting to alternative medicine, and delayed referral including in-hospital nephrology referral. The mean age of our cohort was 46 years, which was comparable with most of the Indian studies, although some studies have reported considerably lesser and greater mean age than ours.[2,5,18-21] Compared with data from developed countries, our patients were about two decades younger.[22] Males were represented more than females (1.47:1) in our study, as has been observed in other studies, which may be related to more health care access for males or to the hormonal differences in susceptibility as shown in few animal studies.[1,19,23,24] Majority of the AKI were related to medical causes (71.8%), followed by surgical (22.1%) and obstetric (6.1%) causes. This relative contribution has varied between 73% and 87% for medical causes, 3% and 9% for surgical causes, and 3% and 20% for obstetrical causes across various studies done in different regions of our country.[1,18,20] Two thirds of the AKI were community acquired during our study period, the proportion has varied between 53% and 92% among recent studies, which might be due to regional epidemiological variations.[5,18,23] One fourth of our study population had baseline CKD Stage 2 or 3, of which the majority had advanced AKI, which was one of our strengths as many studies excluded CKD patients.

The etiology of AKI was multifactorial in the vast majority. In our study, sepsis was the most common precipitating cause (51.4%). In the epidemiological studies conducted after 2010 at various centers of our country, the major etiological factor was sepsis contributing variably between 22% and 53%.[2,5,18,23] In the multicentric study by Bagshaw *et al.*,[22] 47.5% of AKI were attributable to sepsis, with chest and abdomen being the most involved sites. Among the different sites, skin and soft tissue was the most common sepsis source in our cohort, which could have been largely prevented had they been managed appropriately early. In the study by Priyamvada *et al.*,[5] skin and soft tissue was the most common foci, whereas other studies have cited urogenital, lung, or abdomen as the predominant site.[19,25,26] Scrub typhus was shown to be the major cause in a study from Shimla by Vikrant *et al.*,[18] probably related to the geographical terrain of the study location. Nephrotoxins including drugs, exogenous or endogenous toxins, and radiocontrast media contributed next to sepsis as the major cause. One third of the nephrotoxic AKI was drug induced, the major culprit being nonsteroidal anti-inflammatory drugs followed by mannitol, aminoglycoside, rifampicin, cisplatin, and other antimicrobials. Among different studies, nephrotoxic drugs were the precipitating agent in 1.5% to 13.4% of AKI compared with 14.8% in our study.[1,2,18,20] It has been shown that the odds of developing AKI are 53% greater with each nephrotoxin administered, and the risk gets compounded with each additional agent added.[10,27] Snake envenomation as a cause of AKI was observed in 4.2% of the cohort, with about three fourth of them presenting with Stage 3 AKI, mostly related to late referral or to use of local folk remedies instead of seeking health care.

Table 4: The 90-day outcomes of the study population

90-day outcomes	Total	KDIGO 1	KDIGO 2	KDIGO 3
n	358	77	93	188
Lost to follow-up	33 (9.2%)	8 (10.4%)	11 (11.8%)	14 (7.4%)
n (after excluding lost to follow-up)	325	69	82	174
Recovered	130 (40%)	48 (69.6%)	31 (37.8%)	51 (29.3%)
Primary outcome [*de novo* CKD (eGFR <60 mL/min/1.73 m^2) or CKD progression (decline in eGFR category to any higher stage) in patients with baseline CKD]	66 (20.3%)	-	16 (19.5%)	50 (28.7%)
Mortality	129 (39.7%)	21 (30.4%)	35 (42.7%)	73 (41.9%)
Secondary outcome [*de novo* CKD (eGFR <60 mL/min/1.73 m^2) or CKD progression (decline in eGFR category to any higher stage) in patients with baseline CKD or death]	195 (60%)	21 (30.4%)	51 (62.2%)	123 (70.7%)
Dialysis dependency	13 (4%)	-	3 (3.7%)	10 (5.7%)

KDIGO=Kidney Disease: Improving Global Outcomes, CKD=chronic kidney disease, eGFR=estimated glomerular filtration rate

Table 5: Analysis of risk factors associated with primary and secondary outcomes

Risk factor	Primary outcome					Secondary outcome				
	Univariate *P*	Multivariate *P*	OR	CI		Univariate *P*	Multivariate *P*	OR	CI	
				Lower	Upper				Lower	Upper
Age >60 years	0.003	0.178	3.29	0.58	18.75	0.000	0.018	3.33	1.23	9.01
Male Gender	0.993	-	-	-	-	0.493	-	-	-	-
Diabetes mellitus	0.000	0.218	2.58	0.57	11.63	0.001	0.418	1.49	0.57	3.88
Hypertension	0.001	0.186	2.92	0.59	14.32	0.012	0.498	1.39	0.54	3.6
Cardiovascular disease	0.290	-	-	-	-	0.037	0.326	0.56	0.18	1.77
Chronic liver disease	0.181	-	-	-	-	0.003	0.677	1.47	0.24	8.96
Smoking	0.824	-	-	-	-	0.437	-	-	-	-
Alcohol	0.657	-	-	-	-	0.378	-	-	-	-
SOFA ≥9	0.000	0.731	1.28	0.31	5.32	0.000	0.000	23.71	9.86	57
Low albumin	0.000	0.111	2.94	0.78	11.12	0.000	0.024	2.51	1.13	5.61
Vasopressor use	0.003	0.173	2.96	0.62	14.13	0.000	0.105	2.02	0.86	4.73
KDIGO stage	0.000	0.002	12.99	2.68	63.5	0.000	0.410	1.26	0.73	2.15
Recurrence	0.000	0.065	7.69	0.88	67.14	0.000	0.469	1.57	0.46	5.36
Baseline CKD	0.000	0.000	95.69	12.42	737.18	0.000	0.000	10.56	3.48	32.04
Need for RRT	0.000	0.005	7.29	1.83	29.09	0.000	0.001	3.70	1.37	9.99

For primary outcome: Hosmer and Lemeshow Test - 0.936, Variance inflation - 1.19-1.596 and Condition index (max) - 4.346. For secondary outcome: Hosmer and Lemeshow Test - 0.954, Variance inflation - 1.24-1.49; Condition index (max) - 4.478. SOFA=Sequential Organ Failure Assessment, KDIGO=Kidney Disease: Improving Global Outcomes, CKD=chronic kidney disease, RRT=renal replacement therapy, OR=odds ratio, CI=confidence interval

Tropical infections including malaria, leptospirosis, scrub typhus, and dengue contributed to 5.9% of cases, which was similar to that reported by Eswarappa *et al.*[23] (6.4%) and Umesh *et al.*[2] (7.6%), whereas tropical infections were the most common etiology in the studies by Vikrant *et al.*[18] and Bhadade *et al.*[19] In the study by Prakash *et al.*,[1] malaria contributed to 17% of cases, while they did not observe a single case of leptospiral AKI over 26 years. More than half of obstetrical causes were related to pre-eclampsia–eclampsia followed by puerperal sepsis and obstetric hemorrhage. However, puerperal sepsis was contributing most to obstetrical AKI in few studies.[2,18] Acute pancreatitis contributed to about 5% of cases in our study. AKI in acute pancreatitis occurs due to increased vascular permeability, inflammation, intense renal vasoconstriction, abdominal compartment syndrome, thrombotic microangiopathy, and rhabdomyolysis, and is a poor prognostic factor.[28]

In our current study, 26.3% of patients needed RRT, which was preferably provided as intermittent hemodialysis in the majority. Few studies reported similar RRT rates, whereas few others have reported rates as high as 72% to 80%.[1,2,18,19,29] At 90 days, 9.2% of the cohort were lost to follow-up. Eighteen (5.5%) AKI patients without baseline CKD developed *de novo* CKD at 90 days. Eswarappa *et al.*[23] reported CKD as an outcome in 2.4% of patients. Lai *et al.*[30] in his study on nondialysis requiring AKI survivors of surgical intensive care unit patients observed CKD Stage 3 and above at 90 days in 38.5% of patients, which was quite high. In a study of U.S. veterans, Amdur *et al.*[31] observed that 20% of patients with acute tubular necrosis progressed to CKD Stage 4 within a period of 20 months. Heung *et al.*,[32] in his analysis of Veterans Health Administration data, showed that 18.2% AKI patients had CKD Stage 3 or higher at 1 year. Experimental models have shown maladaptive repair, disordered

regeneration, or both, due to renin–angiotensin activation, tubular G2/M arrest, inflammation, epigenetic changes, and mitochondrial dysfunction among others, culminate in vascular dropout, glomerulosclerosis, and interstitial fibrosis with tubular atrophy, each of which contributes to progressive renal dysfunction by perpetuating injury and hampering repair.[8,33] Different drivers of nephron damage have a differential incidence and rate of progression, where the relative mix alters according to time after injury but can operate simultaneously. In clinical context, AKI progresses to CKD through at least two trajectories, either non-recovering AKI progressing to CKD, which is well recognized or after an "apparent" recovery following AKI, the trajectory of normal renal function decline is hastened, which is being increasingly appreciated.[15] In our study, we have observed only the first pathway of non-recovering AKI progressing to CKD. Another problem with apparent "complete" recovery is that, factors such as muscle mass loss, changes in volume of distribution, and hyperfiltration may confound with creatinine used as surrogate for renal recovery.[7,10] There is a need for better biomarkers to identify ongoing renal injury, which may help in risk stratifying patients for intervention.[10,33]

Acute kidney disease (AKD), a relatively newer concept was introduced in KDIGO 2012 AKI guidelines to identify patients with kidney structure and/or function abnormalities that do not meet the criteria for AKI or CKD but need medical attention to reverse renal damage to prevent adverse outcomes.[34,35] KDIGO defined AKD as either AKI or new or previously unrecognized decrease in glomerular filtration rate or increase in creatinine of less than 3 months duration. Both AKI and AKD without AKI can be superimposed on CKD.[34] The 16th Acute Dialysis Quality Initiative (ADQI) workgroup identified AKD as a vulnerable transition period for patients who have suffered AKI wherein critical interventions might be initiated to alter the natural history of kidney disease.[10] The National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) and the Canadian Society of Nephrology in their commentaries on AKD concept cautioned against the confusion created by the introduction of new terminology and the risk of overlooking other nephrology syndromes when evaluating patients first presenting with kidney disease and mislabeling unique pathologies under the umbrella term of AKD.[34] Although the concept of AKD can be used in epidemiological research, important knowledge gaps need to be addressed before adoption into clinical practice, as AKD has not been systematically studied.[10,34]

We observed 90-day mortality rate in 39.7% of the study population, of which 61% expired during the hospital stay. Indian studies from different centers have reported mortality rates varying between 8.7% and 90%.[18,21,23]

The epidemiologic change over time can be discerned by comparing our study results with the 10-year data of Jayakumar *et al.*[20] conducted at a tertiary care center catering to the same population as ours. The mean age was a decade less compared to our study. Hospital-acquired AKI saw a drastic increase from 7.9% to 35.2%, perhaps as a sequel of advances in medicine capable of providing advanced and prolonged life support, among others.[17] Although medical causes were contributing the most, acute diarrheal disease was the most common etiology in about 28.6% of patients compared with only 5% in the present study, which might be related to better personal and public health care measures. Surgical causes have increased from 3.4% to 22.1% owing to the progress made in the field resulting in more complicated cases being operated on. Sepsis contributed to only 8.8% in the previous study, whereas in ours, it was the major etiology in over half of the cases. The contribution of nephrotoxic drugs was similar to our study. Among the ingested toxins, copper sulfate was the most common in yesteryears, whereas paraquat, a mitochondrial poison with grave prognosis was predominant in our study (5.9%). Myoglobinuric AKI, a negligible entity in the previous study (0.62%), was contributing to 5.9% in the present study, which could be attributed to improved diagnostics. RRT requirement was about 2.5 times more in the previous study compared with ours. Mortality in the past cohort was only half of that observed in our study, which might be related to younger age, exclusion of patients with comorbidities, and majority being community-acquired AKI with an identifiable cause.[20]

On analyzing the risk factors associated with 90-day outcomes, advanced AKI stage, presence of baseline CKD, and need for RRT were associated with *de novo* CKD or progression. For the combined outcome of *de novo* CKD or progression or mortality, advanced age, SOFA ≥9, hypoalbuminemia, baseline CKD, and RRT need were the significant risk factors identified. Chawla *et al.*,[36] in his study of 5,351 U.S. war veterans who had AKI without CKD, showed that advanced age, hypoalbuminemia, diabetes mellitus, and severity of AKI by RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) score were predictive of adverse renal outcomes, and RRT need was associated with over 500-fold increased risk of CKD progression. In the study by Lo *et al.*,[37] in a community-based cohort of more than 5.5 lakh adults, an episode of dialysis requiring ARF increased the risk of developing Stage 4 or 5 CKD by 28 times, and the mortality risk was twice as compared with patients not requiring dialysis. They also observed that ESRD did not develop in patients with a baseline eGFR of 45 mL/min or more over an 8-year follow-up unless ARF requiring dialysis supervened. Ishani *et al.*,[38] in their study of elderly Medicare beneficiaries, showed that the ESRD risk was 13 times more in patients who had an AKI compared with non-AKI patients and that the risk increased to 41 times if they had baseline CKD. In a Canadian study by

Wald *et al.*,[39] the risk of chronic dialysis was almost three times in patients with dialysis requiring AKI compared with non-AKI patients; however, the mortality risk was similar between the two groups. Thakar *et al.*[40] showed that recurrent AKI was independently associated with a cumulative risk of developing advanced-stage CKD in their study of 4,082 diabetics over a 9-year period. Recurrent AKI, though significantly associated with the primary outcome of our study on univariate analysis, did not reach statistical significance on multivariate analysis. In Heung *et al.*'s[32] study, the timing of AKI recovery was found to predict the risk of developing CKD Stage 3 and above, even for Stage 1 AKI. In a systematic review and meta-analysis of 13 cohort studies, Coca *et al.*[41] showed that compared with non-AKI patients, AKI patients had 8.8 times the risk for ensuing CKD, thrice the risk for ESRD, and twice the risk for mortality. Most published studies on AKI outcomes suffer from methodological difficulties including retrospective study design, varying definitions, lack of comparator group, code creep, and ascertainment bias.[8,42] These issues are likely to be addressed by the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI), a prospective study to characterize the short-term and long-term outcomes of AKI, including development and progression of CKD, cardiovascular outcomes, mortality and other patient-centered outcomes compared with non-AKI patients to evaluate the utility of biomarkers in predicting progression and risk stratification of AKI patients.[42]

Despite burgeoning evidence accumulating on poor long-term outcomes of AKI, barriers and knowledge gap exist about interventions to improve outcomes.[16] The strategies include avoiding preventable factors pre-AKI, mitigating the severity during AKI, and post-AKI care in survivors [Table 6].[3] AKI survivors are a high-risk population, but unfortunately the care provided during AKI does not extend to the follow-up period, which is amenable to interventions to forestall the development of CKD and other adverse consequences.[10,16] Even in developed countries, the follow-up care is lacking.[9,16] Documentation of the AKI episode in the patient's record to alert future caregivers, patient/primary care physician education on AKI and its consequences, post-AKI risk stratification, improved processes of care including regular monitoring of blood pressure, glycemic control, proteinuria and renal function, and medication reconciliation are strategies to improve the quality of outcomes in AKI survivors as echoed in the consensus statements of the 18th ADQI workgroup.[3,6,9,10,16,36] The KDIGO 2012 AKI guidelines endorse this view by advising to evaluate AKI patients at 3 months, and even if CKD is not detected, these individuals are to be considered at risk for CKD and receive appropriate care. Novel strategies such as nephrology specialty ambulatory clinics are being studied in developed countries.[9] Two randomized control trials, FUSION and AFTER AKI trials, are underway to assess the impact of specialized nephrology follow-up and care bundles on major adverse kidney events.[9]

Our study did have few limitations, including retrospective study design, single-center study, small sample size, and being a tertiary care center, and a study population that may not be representative of the general population.

Table 6: Strategies to prevent the development/progression of chronic kidney disease after acute kidney injury

Pre-AKI	During AKI	Post-AKI
Public health measures	Early recognition	AKI documentation in patient's health care record
Safe drinking water	Risk stratification (biomarkers, FST)	Patient and primary care physician education
Sanitation and hygiene	Prompt treatment	Post-AKI risk stratification*
Vector control measures	Prevention of further renal injury	Lifestyle and dietary modification
Housing	Volume management	Medication reconciliation
Nutrition	Sepsis treatment	Prevention of recurrent AKI
Lifestyle modification	Avoiding nephrotoxin exposure (drugs, contrast)	Cardiovascular risk reduction
Restricted access to toxins	Cardiac and other organ dysfunction management	Periodic follow-up: renal and nonrenal events
Prenatal care improvement	Early referral	Serum creatinine
Strengthening primary health care		Urine protein
Availability of antivenom, antibiotics, parenteral fluids		Blood pressure
Comorbidities management		Blood sugar
Public health education		Imaging
		Comorbidities management
		Mobile nephrology care unit
		Post-AKI nephrology care bundle

*Post-AKI risk stratification based on patient factors (age, comorbidities), severity of the AKI episode (AKI stage, RRT requirement, duration) and degree of renal recovery (dialysis dependence, degree of serum creatinine decrease). AKI=acute kidney injury FST=Frusemide Stress Test

Conclusion

The present study has thrown light on the epidemiological differences compared with other studies and across time periods in the same population. Sepsis leads the etiology list, necessitating attention to prevention, early recognition, and aggressive management of the same. In the current study, a significant proportion had preventable precipitating events. The severity of AKI, baseline CKD status, and the need for RRT were found to predict the development or progression of CKD in our study. Longer follow-up of "apparently" recovered patients is needed to better characterize the impact of AKI. Knowledge of epidemiology and outcomes is essential to frame policies to overcome the barriers and care gaps to improve outcomes.

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Conflicts of interest

There are no conflicts of interest.

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