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Community-Acquired Acute Kidney Injury at Hospital Admission: What Happens One Year After?

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ABSTRACT

Community-acquired acute kidney injury is a frequent diagnosis at hospital admission in developed countries. Due to the multiple comorbidities, patients admitted to internal medicine departments have a higher susceptibility to acute kidney injury.

To determine the prevalence, risk factors, and impact of community-acquired acute kidney injury, we developed a retrospective observational case-control study in an internal medicine ward at a tertiary hospital comparing patients admitted with community-acquired acute kidney injury with patients without acute kidney injury at hospital admission. Patients who needed dialysis were excluded.

Community-acquired acute kidney injury was present in 19.6% of patients, mostly prerenal acute kidney injury (68.8%) and Kidney Disease Improving Global Outcomes classification stage 1 (51.9%). Dementia (OR 3.3, [0.2–0.6]) and loop diuretics as outpatient medication (OR 2.2, [0.2–0.9]) were risk factors for community-acquired acute kidney injury. These patients presented higher mortality after hospital discharge (p=0.003), and 35.1% of deaths occurred in the first 90 days. At one-year follow-up, chronic kidney disease progression was more frequent in the community-acquired acute kidney injury group (24.6% versus 2.6%, p=0.002); otherwise, new-onset chronic kidney disease was similar between groups.

The long-term consequences of community-acquired acute kidney injury can be severe, including renal disease progression and mortality after hospital discharge (mostly in the first 90 days); thus, it is important to implement programs to provide early evaluation for these patients. Patients taking diuretics are at increased risk of acute kidney injury. Also, patient and caregiver education on hydration of demented patients could prevent community-acquired acute kidney injury.

Keywords: acute kidney injury, aging, dementia, diuretics

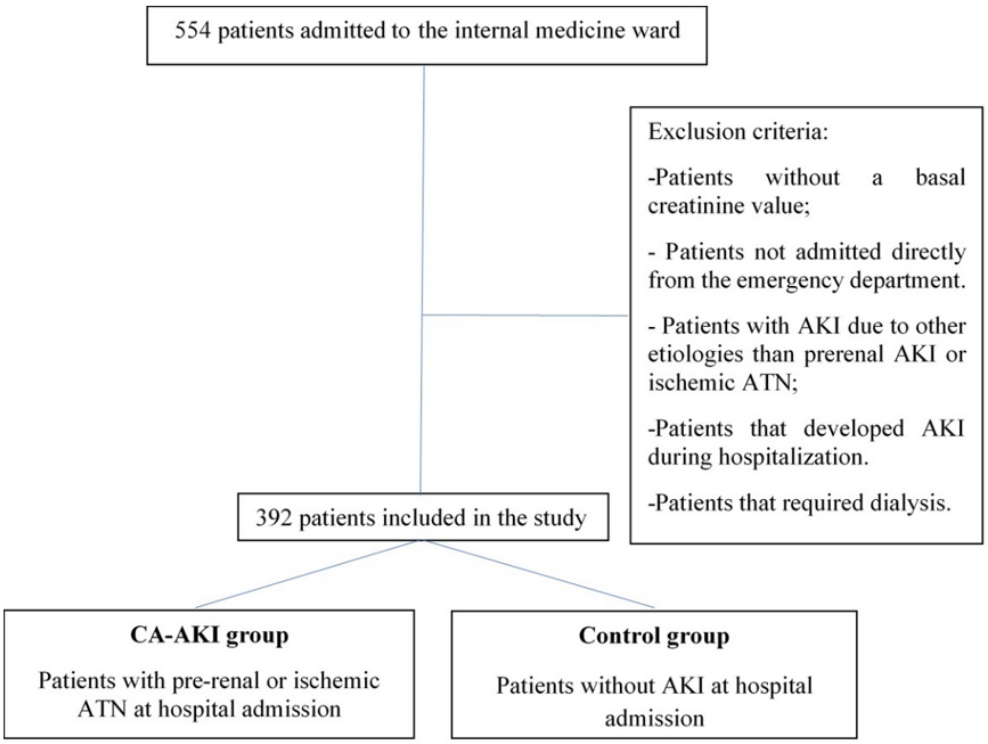
INTRODUCTION

Acute kidney injury (AKI) is a complex clinical condition defined by a 50% increase in serum creatinine within 7 days or an increase in serum creatinine of 0.3 mg/dl within 2 days [1]. AKI has been reported in 5 to 20% of hospitalized patients, depending on which AKI definition is used [2-4]. It is a rising public health problem because pathologies such as diabetes, heart failure, and sepsis (risk factors for AKI) are more and more frequent in developed countries [5]. The International Society of Nephrology has put forward the “0 by 25” campaign to highlight the importance of AKI in preventable causes of death in the community [6]. Such an effort can be accomplished only through a deep knowledge of community-acquired acute kidney injury (CA-AKI) prevalence and risk factors. Most studies exploring AKI outcomes have considered either hospital acquired AKI requiring dialysis or homogenous patient populations such as those exposed to radiocontrast agents, cardiac surgery, or intensive care and examined outcomes such as short-term mortality and costs [7-13]. Few studies have examined the impact of CA-AKI in long-term outcomes after hospital discharge, such as mortality, the progression of pre-existing chronic kidney disease (CKD), and the development of new-onset CKD [14-20]. Rather than distinct entities, AKI and CKD are now recognized as interconnected syndromes because AKI is a risk factor for CKD progression, and CKD is a risk factor for new episodes of AKI [21-25]. This study aims to evaluate patients one year after hospital admission and compare survival, re-admission rates, new-onset CKD, and CKD progression between patients with CA-AKI and a control group. This study also evaluates prevalence and predictive factors for developing CA-AKI.

MATERIALS AND METHODS

Study Design and Population Selection

We conducted a retrospective observational unmatched case-control study in an internal medicine ward from a tertiary



Abbreviations: AKI – acute kidney injury, ATN – acute tubular necrosis, CA-AKI – community-acquired acute kidney injury

Figure 1. Study design

hospital from July 1, 2017, to December 31, 2017. From all patients admitted during this period, we excluded those who did not present a basal creatinine value, who were not admitted directly from the emergency department, who developed AKI during hospitalization, who required dialysis, and who presented AKI etiologies other than prerenal AKI or ischemic acute tubular necrosis (ATN). The study design is presented in **Figure 1**. Each patient was followed until dead or up to one year after the index hospitalization.

Our research has been conducted in accordance with the World Medical Association Declaration of Helsinki. Since it was an observational study, ethical approval for the study was waived under the local laws. Informed consent was obtained in all patients.

Definitions

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) classification as a serum creatinine increase of 0.3 mg/dL within 48 hours or an increase in serum creatinine of 1.5 times the baseline value [1]. Urine output criteria was not used as patients had already presented with AKI at hospital admission and previous urine output was impossible to obtain. AKI was classified as prerenal or ATN based on clinical examination, renal ultrasound, and urinalysis results. In addition, prerenal AKI was defined as episodes associated with decreased renal perfusion with creatinine return to basal values by 48 to 72 hours and ischemic ATN as AKI associated with decreased renal perfusion and return to basal creatinine after 72 hours. Basal creatinine was defined as serum creatinine measured 7 to 365 days before hospital admission. Hypertension was defined as blood pressure higher than 140/90 mmHg or use of any anti-hypertensive drug. Cardiovascular disease was defined as presence of one or more of the following: coronary heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease, or cardiomyopathies. Diabetes mellitus was defined as previous glycated hemoglobin superior to 6.5% or use of antidiabetic drugs. CKD was defined as glomerular filtration rate less than 60 mL/min/1.73m^2 for 3 months. Dementia was defined as a description of the clinical process of previous deterioration in cognitive function beyond what might be expected from normal aging. Malignancy is defined as solid or hematologic tumors diagnosed within one year before hospitalization. The index hospitalization was the first admission to the internal medicine ward between July 1, 2017, and December 31, 2017. Concerning clinical outcomes one year after the index hospitalization, a new AKI episode was defined by the KDIGO criteria, CKD progression was defined as a decline in glomerular filtration rate higher than 5 mL/min/1.73m^2 at one year in a patient with a previous CKD diagnosis, new-onset CKD was defined as *de novo* glomerular filtration rate higher than 60 mL/min/1.73m^2 for 3 months, and new hospitalization was defined as a new urgent hospital admission.

Data Collection

Data was collected by consulting the individual electronic clinical process. For each patient was recorded: age, gender, comorbidities (hypertension, cardiovascular disease, diabetes mellitus, CKD, dementia, and malignancy), outpatient medication (loop diuretics and angiotensin conversing enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARB)) and main diagnosis code by the International Classification of Diseases, Tenth Revision, Clinical Modification 2016 (ICD-10-CM 2016). Serum creatinine and urinalysis was recorded at admission and serum creatinine was also recorded at discharge and one year after the index hospitalization. Clinical outcomes (new AKI episode, new hospital admission, CKD progression and new-onset CKD) were reported after

consulting the individual electronic clinical process one year after the index hospitalization.

Statistical Analysis

Categorical variables (gender, comorbidities, outpatient medication, and clinical outcomes) were presented as frequencies and percentages and were compared between CA-AKI and control groups with the use of Fisher's exact test or the chi-square test, as appropriate. Normal distribution was checked using the Kolmogorov-Smirnov test or skewness and kurtosis. Age, the only continuous variable that exhibited skewed distribution, was presented as median and 25th and 75th percentile and was compared using the Mann-Whitney test. Binary logistic regression was performed to compare CA-AKI and control group baseline characteristics and variables were selected from bivariate analysis ($p<0.1$). Kaplan–Meier estimates were used to evaluate survival curves between the CA-AKI and control groups. Cox proportional hazards were utilized to determine risk factors for mortality. All reported p-values were two-tailed, and a p-value less than 0.05 indicated statistical significance. Statistical analyses were performed by SPSS for Windows software version 23.0 (SPSS Inc., Chicago, IL).

RESULTS

During the study period, a total of 554 patients were admitted to the internal medicine ward, and 392 of them were included in the study. Global population characteristics are shown in **Table 1**. Patients were elderly (median age 77 years old), and the most frequent comorbidities were hypertension (77.2%, n=304), cardiovascular disease (55.3%, n=210), diabetes mellitus (46.4%, n=183), and CKD (45.7%, n=180). Most patients were taking loop diuretics (60.8%, n=239) and ACEi/ARB (54.2%, n=213) as outpatient medications. The major admission causes were sepsis caused by pneumonia (22.0%, n=86) and acute heart failure (22.0%, n=86).

CA-AKI was present at admission in 19.6% (n=77) patients. Most presented prerenal AKI (68.8%, n= 53). KDIGO classification stage 1 (51.9% n=40) was the most frequent. **Table 2** compares the CA-AKI group with the control group. After adjusting for covariables, dementia and loop diuretics as outpatient medications were the only risk factors for AKI at hospital admission.

Table 1. Demographic and clinical characteristics of the global population

Population Characteristics	N=392
Age, median, range	77, 27–97
Male gender, n %	199, 50.5
Comorbidities	
Hypertension, n %	304, 77.2
Cardiovascular Disease, n %	210, 55.3
Diabetes Mellitus, n %	183, 46.4
CKD, n %	180, 45.7
Dementia, n %	71, 18.0
Malignancy, n %	62, 15.7
Outpatient medication	
Loop diuretics, n %	239, 60.8
ACEi/ARB, n %	213, 54.2
Causes of hospital admission	
Sepsis caused by pneumonia, n %	86, 22.0
Acute heart failure, n %	86, 22.0
Sepsis caused by urinary tract infection, n %	28, 7.1

Abbreviations: ACEi – angiotensin conversing enzyme inhibitor; ARB – angiotensin receptor blockers; CKD – chronic kidney disease

Patients with CA-AKI had a higher mortality after hospital discharge (log rank 9.0, p=0.003). Survival after hospital discharge was 64.9% in the CA-AKI group versus 79.8% in the control group at 90 days and 54.4% versus 70.6% at one year. In the CA-AKI group, 40.9% (n=9) of deaths occurred in the first 90 days (**Figure 2**). Even after adjusting for covariables, CA-AKI remained a mortality risk factor (**Table 3**).

Patients who survived were evaluated one year after the index hospitalization. CKD progression was more frequent in the CA-AKI group (24.6% versus 2.6%, p=0.002); otherwise, new-onset CKD rates were similar between groups (**Table 4**).

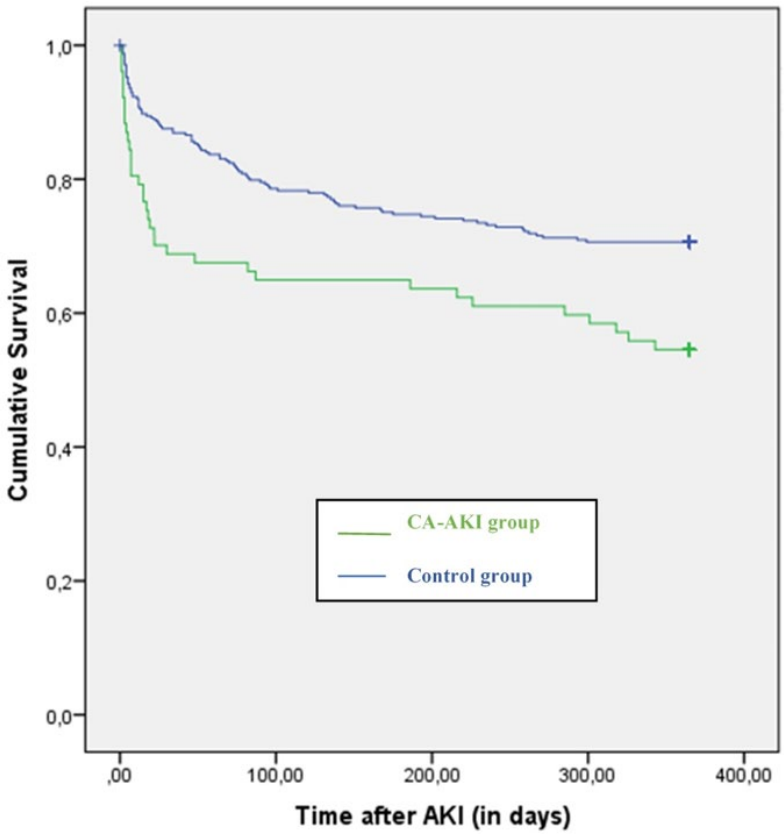
DISCUSSION

We evaluated the prevalence, clinical predictors, survival, and clinical outcomes of CA-AKI patients admitted to an internal medicine ward. Our results reveal that prerenal CA-AKI and ischemic ATN increased risk of death and CKD progression even one year after the index event and identified demented patients and loop diuretics use as risk factors for CA-AKI. Few recent studies focus on CA-AKI as opposed to hospital-acquired AKI, which has been explored in diverse clinical settings such as heart surgery and intensive care units [7-13].

Table 2. Comparison of baseline population characteristics between CA-AKI and control group and bivariate logistic regression for predictors for CA-AKI development

	CA-AKI group n=77	Control group n=315	p-value	OR, CI 95%
Age, median [IQR]	78 [69-85]	75 [64-84]	0.115	
Male gender, n %	40, 51.9	154, 48.7	0.613	
Comorbidities				
Hypertension, n %	67, 87.0	237, 75.0	0.024	0.7, [0.3–1.5]
Cardiovascular Disease, n %	41, 53.2	169, 53.5	0.971	
Diabetes Mellitus, n %	40, 51.9	143, 45.3	0.291	
CKD, n %	43, 55.8	137, 43.4	0.049	1.1, [0.6–1.9]
Dementia, n %	26, 33.8	45, 14.2	<0.001	3.3, [0.2–0.6]
Malignancy, n %	12, 15.6	50, 15.8	0.959	
Outpatient Medication				
Loop diuretics, n %	58, 75.3	180, 57.3	0.004	2.2, [0.2–0.9]
ACEi/ARB, n %	47,61.0	166,52.5	0.179	

Abbreviations: ACEi - Angiotensin conversing enzyme inhibitor, ARB- angiotensin receptor blockers; CA-AKI - community-acquired - acute kidney injury; CKD- chronic kidney disease, IQR – interquartile range, OR – odds ratio



Abbreviation: CA-AKI - community-acquired acute kidney injury

Figure 2. Kaplan-Meier survival comparison between CA-AKI and control group

Table 3. Survival analysis using Cox regression model. Age, male gender, malignancy, and AKI are risk factors for mortality

	p-value	HR, CI 95%
Age	0.006	1.0 [1.1–1.2]
Male gender	0.001	1.9 [1.3–2.7]
Hypertension	0.154	1.4 [0.9–2.3]
Cardiovascular Disease	0.864	1.0 [0.7–1.4]
Diabetes Mellitus	0.476	0.9 [0.6–1.3]
CKD	0.729	0.9 [0.6–1.4]
Dementia	0.049	0.7[0.4–1.0]
Malignancy	<0.001	0.4 [0.3–0.6]
CA – AKI	0.025	0.6 [0.4–0.9]

Abbreviations: CA – AKI community-acquired acute kidney injury, CKD – chronic kidney disease; HR – hazard ratio

Table 4. Comparison of clinical outcomes one year after the index hospitalization between surviving patients from the CA-AKI and control groups

	CA-AKI group n=61	Control group n=268	p-value
New AKI episode, n %	17, 27.8	48, 17.9	0.145
New hospital admission, n %	24, 39.3	92, 34.3	0.723
CKD progression, n %	15, 24.6	7, 2.6	0.002
New-onset CKD, n %	1, 1.6	2, 0.7	0.651

Abbreviations: AKI – acute kidney injury, CA-AKI – Community-acquired acute kidney injury, CKD-chronic kidney disease

CA-AKI prevalence varies among studies because of population heterogeneity and different AKI definitions [14-20]. We found a high prevalence of CA-AKI (19.6%), which could be motivated by the advanced age and multiple comorbidities of our population.

The independent risk factors associated with prerenal CA-AKI and ischemic ATN were the pre-admission use of loop diuretics and dementia. Use of ACEi/ARB was not a risk factor for CA-AKI. These results are in line with those of Stucker et al., who also studied an elderly population (median age 83) where the use of diuretics but not the use of ACEi/ARB was associated with CA-AKI [25]. Patients taking loop diuretics usually have a chronic decrease in effective circulating volume and therefore could be predisposed to prerenal AKI and ATN [26-28]. Dementia was also an independent risk factor for CA-AKI. Elderly people have a diminished sensation of thirst, and the normal adaptive response to volume depletion is compromised [5,29,30]. Dementia aggravates those problems since patients with cognitive alterations are predisposed to dehydration [31]. These findings reinforce the importance of timely intervention with “sick day guidance” for temporary discontinuation of diuretics during inter-current illnesses that limit fluid and food intake and the importance of monitoring the hydration status of patients with dementia [32,33]. Involvement of a patient’s general medicine doctors and caregiver will be critical in reducing the incidence of this disorder by early recognition of high-risk individuals and risk modification where possible.

Increased mortality in patients who develop AKI has been previously documented [34-36]. While most patients presented with AKI KDIGO classification stage 1 and patients who needed dialysis were excluded, the mortality risk associated with CA-AKI was significant. These results are in accordance with reports showing that even a small elevation in creatinine increases mortality risk [7,35,36]. In our study, CA-AKI patients presented a 35.1% mortality rate in the first 90 days. Talabani et al. report a 3-month mortality rate of 16.5%, but they

included patients with less severe illness since many were managed in outpatient care [20]. These results are also in line with a study by Lafrance et al., in which the mortality risk persisted after discharge and was higher within the first 90 days [34]. Our study points to the necessity of an early evaluation of CA-AKI patients and indicates that more programs should implement a post-AKI consultation since reports indicates that only a minority of patients with AKI (even AKI severe enough to require dialysis) are seen by a nephrologist after discharge [37].

The connection between CA-AKI and CKD is supported by several studies [22-24]. We found that, in surviving patients, the risk of CKD progression is significant but not the risk of new-onset CKD. We hypothesized that patients with previously normal renal function have a great capacity for renal recovery, especially since most patients present prerenal AKI [38,39]. Otherwise, patients with previous CKD present a lower renal functional reserve and have less capacity for complete renal function recovery [38,39].

This study has some limitations because it is a single-center, observational study. Also, patients with severe renal impairment at admission or with previous severe CKD are generally admitted to the nephrology department and therefore were not included in our study. We also are aware that although we have found AKI to be an independent mortality risk factor, it is often a marker of multisystemic disease severity, and some unidentified confounders may persist within this study.

CONCLUSION

We found that the long-term consequences of CA-AKI can be severe as it increases the risk of death and CKD progression even one year after the index event. Thus, it is important to implement programs to provide an early evaluation for those patients. These results also highlight the importance of patient and caregiver education on monitoring the hydration status of demented patients and those taking loop diuretics as a possible strategy to prevent CA-AKI.

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