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# Acute Kidney Injury in Hospitalised Medical Patients: Aetiology and Prognosis

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***Authors' contributions***

*This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.*

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## ABSTRACT

**Background:** Acute Kidney Injury (AKI) increases the length of hospitalisation and mortality. The study aims to assess the incidence, risk factors and outcome of AKI in hospitalised medical patients.
**Methods:** AKI was measured in adult patients by using the serum creatinine criteria. Baseline data included age, sex, diagnosis during admission, pathological records, analytical data, use of nephrotoxic drugs, length of hospital stay, mortality at the hospital and during the follow-up, and the cause of death.
**Results:** A total of 100 patients were included with a mean age of 75.6 years. Majority of male patients (n= 23; 56%) were showed AKI development. The most frequent associated diseases were hypertension, type 2 diabetes mellitus, and heart failure. Hospital stay was greater than 10 days in 52 patients. The patients who developed AKI were older, and had an increased prevalence of heart failure, hypertension, diarrhoea, anaemia, increased BUN, impaired GFR, and were most frequent under ARBs or diuretics. Mortality was higher in the AKI group during hospitalisation.

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**Conclusions:** AKI is frequent in hospitalised medical patients. A previous history of hypertension, heart failure, presence of diarrhoea, anaemia, increased BUN, low eGFR, and the use of ARBs or diuretics are the risk factors for AKI. Patients who developed AKI had an increased likelihood of death during hospitalisation.

*Keywords: Acute kidney injury; incidence; mortality; risk factors; length of hospital stay.*

## 1. INTRODUCTION

Acute Kidney Injury (AKI) definition, was adjusted by de Acute Kidney Injury Network (AKIN) in 2007, considering that minor increases in serum creatinine over a short period of time were associated with various adverse effects [1]. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for AKI was published [2]. This guideline includes information and recommendations on the definition, risk assessment, evaluation, prevention, and management of AKI.

AKI is a common and serious complication of certain surgeries especially cardiac surgery, hip fracture surgery or orthopaedical surgeries, and critically ill patients, mainly in the elderly [3-6]. The mild AKI occurs in nearly one in five patients undergoing cardiac surgery and increases 19-fold short-term mortality [7].

Patients who develop AKI have an increased incidence of renal impairment, longer hospital stay, and AKI is also a risk factor for the development of chronic kidney disease (CKD) [8,9].

AKI frequency is rising, and it is present in up to 5% of hospital admissions and 5% to 20% of hospitalised patients [10-12]. Besides, the risk of developing AKI during hospitalisation is high, increasing mortality between 50% and 70% [13-15].

Most studies have been conducted in surgical or critically ill patients. The study aims to assess the prevalence, morbidity and mortality of AKI in hospitalised medical patients admitted in an Internal Medicine facility excluding patients under surgery or admitted in an Intensive Critical Unit (ICU).

## 2. MATERIALS AND METHODS

### 2.1 Setting and Population Study

This is a single centre, retrospective observational cohort study of patients admitted consecutively to an Internal Medicine department at Hospital Clínico of Santiago de Compostela, Spain, a tertiary general hospital, during January 1, 2018 to February 28, 2018. Patients included were 18 years of age or older. Exclusion criteria include: patients with end-stage renal disease treated with renal replacement therapy (transplantation, peritoneal or hemodialysis).

### 2.2 Outcome Definitions

AKI criteria were defined as follows: Stage 1- rise in serum creatinine (sCr) of ≥ 0.3 mg/dL or 1.5 times baseline sCr; Stage 2- increase of ≥ 2-3 fold from baseline sCr; Stage 3- increase of > 3 fold from baseline sCr, a serum creatinine of ≥ 4 mg/dL with an acute increase of at least 0.5 mg/dL, or initiation of RRT, all within 48h. The urine output criteria for AKI were not used in the present study. The estimated Glomerular Filtration Rate (eGFR), using initial serum creatinine, was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) to assess baseline renal function during admission [16].

### 2.3 Study Variables

Baseline data were recorded for all patients, including age, sex, medical diagnosis during admission, the presence of diabetes, hypertension (HTA), Chronic Obstructive Pulmonary Disease (COPD), heart failure, Coronary Artery Disease (CAD), Cerebrovascular Disease (CVD), Peripheral Artery Disease (PAD), malignancy (cancer), liver cirrhosis, and chronic kidney disease (CKD). Smoking, alcohol intake, and length of hospital stay were also recorded. Other variables included were fever, diarrhoea (loose, watery stools three or more times a day) during hospital admission, heart rate, leucocyte count, anaemia, serum urea nitrogen, sodium, potassium, and albumin. Serum creatinine was measured at the emergency room and during the following 48 hours. Blood samples were analysed in the same laboratory. The use of nephrotoxic drugs such as angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin-II receptor antagonists (ARBs), diuretics, non-steroidal anti-inflammatory

drugs (NSAIDs), and statins were obtained from the medical records. The study also highlights the mortality during hospital stay and after 1,3,6 and 12 months and determines the need for ICU admission or dialysis. Information regarding outcomes was obtained through Electronic Medical Records (EMR). Causes of death were identified from death certificates or EMR. Resolution of AKI was defined as an eGFR≥60 ml/min/1.73 $m^2$ at the end of the study.

## 2.4 Statistical Analyses

Continuous variables were expressed in means ± standard deviation, and categorical variables are reported as numbers and percentages. Differences were analysed by t-test for continuous variables and Chi-square test for categorical variables. It was considered that a finding to be statistically significant if the two-sided *p*-value was < 0.05. The relative risk and confidence intervals (CIs) were estimated at 95% level (CI 95%). All analyses were conducted using SPSS for Windows (ver. 22.0; SPSS Inc., Chicago, IL, USA).

## 2.5 Ethics Statement

The study was conducted in compliance with the Declaration of Helsinki.

Informed written consents were not obtained from the patients because this was a retrospective observational study. Identifiable patients' information was encrypted and analysed data were anonymous.

## 3. RESULTS

The study included a total of 100 patients. The mean age of the patients was 75.6 ± 14.9 years (range 24-94 years), 80% were aged ≥65 years, and 56 % were male. Smoking was present in 33% and alcohol intake was observed in 23% of patients. There were 34% patients with diabetes, 55% with hypertension, 16% with COPD, 31% with heart failure, 17% with ischemic heart disease, 13% with CKD, 12% with cerebrovascular disease, 8% with PAD, 20% with malignancies, and 6% with liver cirrhosis. Patients' characteristics and clinical outcomes according to the presence of AKI are shown in Table 1.

A total of 23 patients met the criteria for AKI based on serum creatinine. Based on the creatinine criteria, an incidence of AKIN stage 1 occurred in 13 patients (56.5%), stage 2 in 6 patients (26.1%), and stage 3 in 4 patients (17.4%). Differences according to the presence of AKI are shown in Table 2. No significant differences were observed in gender distribution, prevalence of diabetes, COPD, CAD, CKD, CVD, PAD, liver cirrhosis, presence of fever, SBP, DBP, heart rate, leucocyte count, hematocrit, serum sodium, potassium, protein, albumin, creatinine (both initial and peak), re-admission rate, length of hospital stay, use of ACEIs, NSAIDs, or statins. However, patients who developed AKI were older (RR 3.2 CI 95% 1.68-7.99), with a higher prevalence of hypertension (RR 2.9 CI 95% 1.03-8.16), heart failure (RR 3.33 CI 95% 1.26-8.77) and diarrhoea. Hypotension was associated with diarrhoea in 3/13 patients (23.07%). Most patients with diarrhoea (all of them included in the AKI group) were presented normal or high blood pressure. Anaemia (RR 2.57 CI 95% 1.99-3.67), higher BUN (RR 3.6 CI 95% 1.98-5.21), impaired eGFR, the use of ARBs (RR 2.88 CI 95% 1.0-8.3), and the use of diuretics (RR 2.63 CI 95% 0.99-6.95) were also most frequent in patients who developed AKI. Malignancy was most frequent in the non-AKI group. Main causes of admission according to the presence of AKI are shown in Table 3.

**Table 1. Basic patient characteristics (N = 100)**

| | |
|---|---|
| Age (mean, SD) | 75.61 (14.91) |
| Age ≥ 65 years (%) | 80 |
| Sex (female; male, %) | 44; 56 |
| Diabetes mellitus (%) | 34 |
| Hypertension (%) | 55 |
| COPD (%) | 16 |
| Heart failure (%) | 31 |
| Heart ischemic disease (%) | 17 |
| Chronic kidney disease (%) | 13 |
| Cerebrovascular disease (%) | 12 |
| Peripheral artery disease (%) | 8 |
| Malignancy (%) | 20 |
| Liver cirrhosis (%) | 6 |
| Smoking (%) | 33 |
| Alcohol consumption (%) | 23 |
| AKI (%) | 23 |
| AKI (stage 1, 2, 3, %) | 13, 6, 4 |
| Hospital mortality (%) | 12 |
| Overall mortality (%) | 46 |
| Hospital stay (≥10 days) | 52 |

*COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury*

During the study period, 46 patients were died, of which 12 patients were died during hospitalisation. Overall, the all-cause death rates

in 1, 3, 6, and 12 months were 18%, 25%, 33%, and 46% respectively. Mortality during hospitalisation was higher in the AKI group compared to the non-AKI group (p= 0.042). There were no differences in 1, 3, 6, or 12 month mortality between both groups (Table 4). In patients with AKI who died, the most frequent causes were heart failure (3 patients) followed by pulmonary aspiration (2 patients) and pneumonia (2 patients).

**Table 2. Patient's characteristics and clinical outcome according to AKI. Continuous variables are expressed as mean ± standard deviation**

| Variable | AKI (n = 23) | Non-AKI (n = 77) | *p* value |
|---|---|---|---|
| Age (years) | 77.00±11.1 | 75.19±15.9 | 0.039* |
| Age ≥65 years (%) | 21 (91.3) | 59 (76.6) | 0.122 |
| Gender, female, (%) | 11 (47.8) | 33 (42.8) | 0.324 |
| Diabetes mellitus (%) | 8 (34.7) | 26 (33.7) | 0.928 |
| Hypertension (%) | 17 (73.9) | 38 (49.3) | 0.038* |
| COPD (%) | 6 (26.0) | 10 (12.9) | 0.133 |
| Heart failure (%) | 12 (52.1) | 19 (24.6) | 0.012* |
| CAD (%) | 6 (26.0) | 11 (14.2) | 0.186 |
| CKD (%) | 5 (21.7) | 8 (10.3) | 0.156 |
| CVD (%) | 3 (13.0) | 9 (11.6) | 0.861 |
| PAD (%) | 2 (8.6) | 6 (7.7) | 0.889 |
| Malignancy (%) | 1 (4.3) | 19 (24.6) | 0.032* |
| Liver cirrhosis (%) | 2 (8.6) | 4 (5.1) | 0.535 |
| Diarrhoea (%) | 13 (56.5) | 0 (0) | 0.035* |
| Fiber (%) | 3 (13.0) | 17 (22.0) | 0.342 |
| Systolic BP (mmHg) | 122.61±23.88 | 121.71±26.62 | 0.631 |
| Systolic BP ≥ 140 (mmHg) | 6 (26.0) | 18 (23.3) | 0.789 |
| Systolic BP < 100(mmHg) | 6 (26.0) | 17 (22.0) | 0.763 |
| Diastolic BP (mmHg) | 64.33±14.51 | 68.81±15.14 | 0.688 |
| Heart rate (bpm) | 82.57±21.53 | 86.75±18.49 | 0.134 |
| Heart rate < 60 bpm (%) | 5 (21.7) | 5 (6.49) | 0.051 |
| Heart rate ≥ 100 bpm (%) | 8 (34.7) | 22 (28.5) | 0.062 |
| Leucocyte count (per $mm^3$) | 9.02±3.70 | 11.04±5.37 | 0.063 |
| Hemoglobin (g/L) | 11.03±2.65 | 12.75±2.37 | 0.049* |
| Hematocrit (%) | 33.01±7.45 | 37.46±6.74 | 0.181 |
| BUN (mg/dL) | 88.65±34.46 | 78.28±71.62 | 0.043* |
| Sodium (mEq/L) | 137.52±4.24 | 137.88±7.58 | 0.995 |
| Potassium (mEq/L) | 4.45±0.55 | 4.47±0.86 | 0.864 |
| Protein (g/L) | 6.32±0.83 | 6.07±0.71 | 0.127 |
| Albumin (g/L) | 3.28±0.67 | 3.11±0.65 | 0.475 |
| Creatinine (mg/dL), initial | 1.31±0.74 | 1.21±1.82 | 0.624 |
| Creatinine (mg/dL), peak | 1.69±1.12 | 1.53±2.09 | 0.239 |
| Creatinine (mg/dL) final | 1.53±1.02 | 1.16±0.93 | 0.421 |
| eGFR | 55.99±18.01 | 65.52±20.17 | 0.045* |
| Hospital mortality (%) | 5 (21.7) | 7 (9.0) | 0.042* |
| 12 month mortality (%) | 3 (13.0) | 10 (12.9) | 0.854 |
| Readmission (%) | 14 (60.8) | 42 (54.5) | 0.592 |
| Length of stay ≥ 10 days (days) | 12 (52.1) | 40 (51.9) | 0.985 |
| ACEIs (%) | 4 (17.3) | 12 (15.5) | 0.836 |
| ARBs (%) | 8 (34.7) | 12 (15.5) | 0.043* |
| Diuretics (%) | 15 (65.2) | 32 (41.5) | 0.046* |
| NSAIDS (%) | 6 (26.0) | 26 (33.7) | 0.488 |
| Statins | 9 (39.1) | 25 (32.4) | 0.554 |

*AKI, acute kidney injury; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebro vascular disease; PAD, peripheral artery disease; BP, blood pressure; BUN, blood urea nitrogen; eGFR, glomerular filtration rate; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin-II receptor antagonists; NSAIDS, non-steroidal anti-inflammatory drugs*

**Table 3. Main causes of admission according to the presence of AKI**

| Total | % | AKI group | % | Non-AKI group | % |
|---|---|---|---|---|---|
| Respiratory infection | 35 | Heart failure | 7 | Respiratory infection | 27 |
| Pneumonia | 15 | Respiratory infection | 5 | Pneumonia | 14 |
| Heart failure | 14 | Anaemia | 2 | Urinary tract infection | 7 |
| Diarrhoea | 8 | Diarrhoea | 2 | Heart failure | 5 |
| Urinary tract infection | 7 | Urinary tract infection | 2 | Malignancy | 3 |

**Table 4. Mortality during the study period in patients with or without AKI**

| Mortality period | AKI n/total (%) | Non-AKI n/total (%) | *p* value |
|---|---|---|---|
| Baseline (hospitalisation) | 5/23 (21.73) | 7/77 (9.09) | 0.042* |
| 1 month | 2/18 (11.11) | 4/70 (5.71) | 0.418 |
| 3 months | 0/16 (0%) | 8/66 (12.12) | 0.143 |
| 6 months | 2/16 (12.5) | 6/58 (10.34) | 0.806 |
| 12 months | 3/14 (21.42) | 10/52 (19.23) | 0.854 |
| Total mortality | 12/23 (52.17) | 35/77 (45.45) | 0.498 |

**statistically significant (p< 0.05)*

At the end of the study, 11 patients were survived in the AKI group. A total of 4 patients (36.36%) presented a full resolution of AKI whereas the others showed partial recovery.

Patients older than 65 years with AKI had more prevalence of hypertension, type 2 diabetes mellitus, high level of BUN, hypoalbuminemia, and the use of diuretics.

Malignancy rate was higher in the non-AKI group probably explained, at least in part, because of the elderly. A total of 5 patients were admitted to an ICU, 3 needed hemodialysis, and 10 needed a blood transfusion during hospitalisation. The rate of re-admission to hospital during the study period was 56%. Length of the hospital stay was greater than 10 days in 52 patients.

In cohort, AKI occurred in 23% of the patients according to the AKIN criteria. Most of them were classified as AKI stage 1 (13 patients), and only 1 patient progressed to AKI required hemodialysis. The other 2 patients who needed dialysis during hospitalisation did not develop AKI when admitted but several days after admission.

## 4. DISCUSSION

In this study, AKI occurred frequently in patients who required medical hospitalisation. The presence of AKI was most frequent in elderly patients and those with known hypertension or heart failure. The presence of diarrhoea during admission and the use of ARBs and diuretics were also associated with AKI development. Variables such as anaemia, high level of BUN, and an impaired eGFR were also associated with a higher rate of AKI development.

AKI development has been studied in patients undergoing hip fracture surgery with a reported prevalence ranging from 15.3% to 24.4% [17-22]. In patients undergoing cardiac surgery, the prevalence of 20.4% has been reported [2]. Critically ill patients are the most likely to develop AKI. In this group of patients, prevalence ranging from 29% to 77% using the AKIN definition has been reported earlier [23].

The overall prevalence of AKI varies with the definition used. In this study, the prevalence was 23%, including only sCr criteria. Elderly patients were particularly susceptible to developing AKI, as well as in this study, because of anatomical and physiological changes in the kidney, increased association of comorbidities, some of them affecting the kidney, and more frequent exposure to medications that can impair renal function [18,20,24-26].

Although several studies have shown the association of AKI with a longer hospital stay, progression of chronic kidney disease, and a higher rate of all-cause mortality [27-31], that does not supports the present study except the case of hospital mortality. In this study, patients who develop AKI had a higher mortality rate during hospital stay in compared to those patients who do not develop AKI. This fact could be explained in part because of the relatively small number of patients enrolled in the study but also for the fact that a significant number of

patients presented diarrhoea when admitted and this could be the cause of initial AKI in these patients.

The study population included mainly elderly patients. There is a change in renal physiology and muscle mass with age that affects eGFR calculation [32]. This fact can lead to a eGFR calculation less reliable in older patients and could potentially increase adverse effects related to common clinical situations (e.g. diarrhoea and subsequent dehydration) or the use of nephrotoxic drugs even in the presence of theoretically normal eGFR. eGFR measurement is commonly based on serum creatinine (Cockcroft–Gault, MDRD and CKD-EPI).

Recently, the use of laboratory biomarkers in the calculation of eGFR seemed to be more accurate and also useful for the assessment of AKI. In this sense, several biomarkers of kidney damage such as cystatin C -probably the most widely studied, galectin-3, proenkephalin, interleukin-18, alpha 1-microglobulin, kidney injury molecule -1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL), provide risk, diagnostic and prognostic information related to the episode of AKI [33]. Nevertheless, the use of biomarkers has current important limitations. One limitation is how to compare the biomarker performance to serum creatinine performance during the AKI event. To decide whether an increase in a biomarker is enough to allow intervention is not clarified at present. Biomarkers appropriate cut-offs should be identified [32,34]. There is also a current lack of information from longitudinal and interventional studies that validate the use of these biomarkers in clinical practice [35].

The main causes of in-hospital death were cardiac arrest (9 patients), pulmonary aspiration (6 patients), heart failure, and malignancy (both 5 patients). In AKI patients, the most frequent cause of death was heart failure (3 patients) whereas cardiac arrest (8 patients) was most frequent in non-AKI patients. The present study does not demonstrate a casual relationship between AKI and outcomes.

## 5. LIMITATIONS OF THE STUDY

Patients were recruited from a single centre, AKI was assessed within 48 hours only, and there was a low rate of stage 2 or 3 AKI. The relatively low number of patients included could limit AKI resolution in respect to time and outcomes. Urine output or urine biomarkers have not been estimated in this study. As in previous study [36], sCr AKI criteria and EMR data have been used, and this could underestimate the diagnosis of AKI. No kidney biopsies were performed to demonstrate the presence of acute tubular necrosis and its severity.

## 6. CONCLUSION

It is concluded that AKI is a common complication in patients hospitalised for medical disorders. In this study, elderly patients, previous history of hypertension or heart failure, the presence of diarrhoea, anaemia, elevated BUN, and low eGFR during admission, were the significant risk factors for developing AKI. The use of ARBs and diuretics, both drugs commonly used for the treatment of hypertension and/or heart failure, were also associated with AKI development. AKI development was associated with an increased likelihood of death during hospitalisation. No significant relationship between AKI and length of hospital stay, re-admissions or increased mortality following hospitalisation was recorded.

Prospective studies in medical patients (neither surgical nor ICU), should be done to evaluate the clinical outcomes and the possible benefit of early diagnosis and preventive management in these patients.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

The study was conducted in compliance with the Declaration of Helsinki.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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