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***XXXV Ciclo di Dottorato***

# IN-HOSPITAL ACUTE KIDNEY INJURY: STUDY OF PREVALENCE, SEX DIFFERECES AND MORTALITY.

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# SUMMARY

# INTRODUCTION

## Background

Acute kidney injury (AKI) is defined as an abrupt decline of renal function evaluated by the increase of serum creatinine levels and by the concomitant decrease of urinary output graded according to Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline criteria published in 2012 (Figure 1)[1].

| State | Creatinine | Urinary volume |
|---|---|---|
| 1 | >0.3 mg/dL,<br>1.5–1.9 times basal creatinine | <0.5 ml/kg/h for<br>6–12 h |
| 2 | 2.0–2.9 times basal creatinine | <0–5 ml/kg/h for<br>>12 h. |
| 3 | 3.0 times basal creatinine<br>Creatinine greater than<br>4.0 mg/dl<br>Start TRR,<br>Less than 18 years old TFG<br><35 ml/min/1.73 m$^2$ | <0.3 ml/kg/h for<br>>24 h.<br>Anuria for >12 h. |

KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int.* 2012;2(1):1–138.

**Figure 1. KDIGO criteria for AKI**

While definition of AKI can seem simple, it is a serious and complex health problem[2].

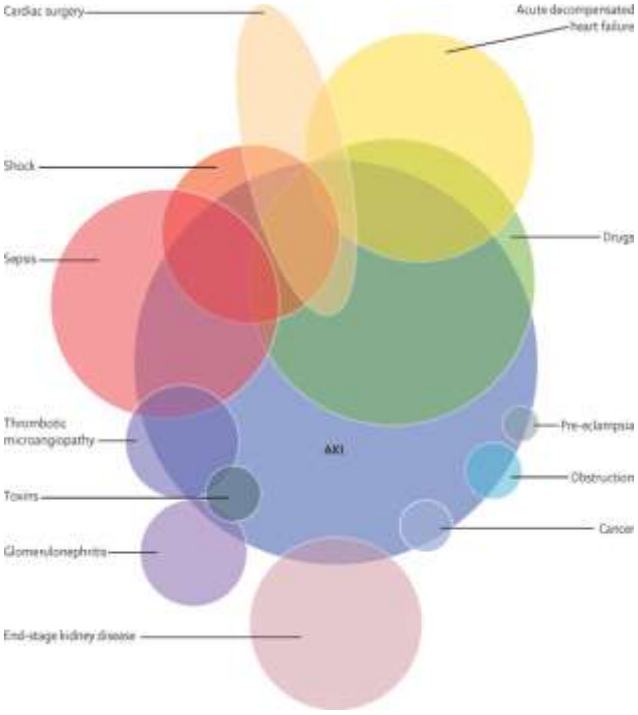


**Figure 2. The clinical spectrum of AKI syndrome**

Primary the cause of AKI is often multi-factorial and its onset can be influenced by several factors (Figure 2).

Secondly, AKI influences importantly other systems, and it has been defined as a proper syndrome with consequences that impact cardiovascular system, pulmonary exchanges, but also can cause brain and gut alteration, dysfunction of bone marrow[3] [4](Figure 3) and hence it can impact seriously on morbidity and mortality[5][6].

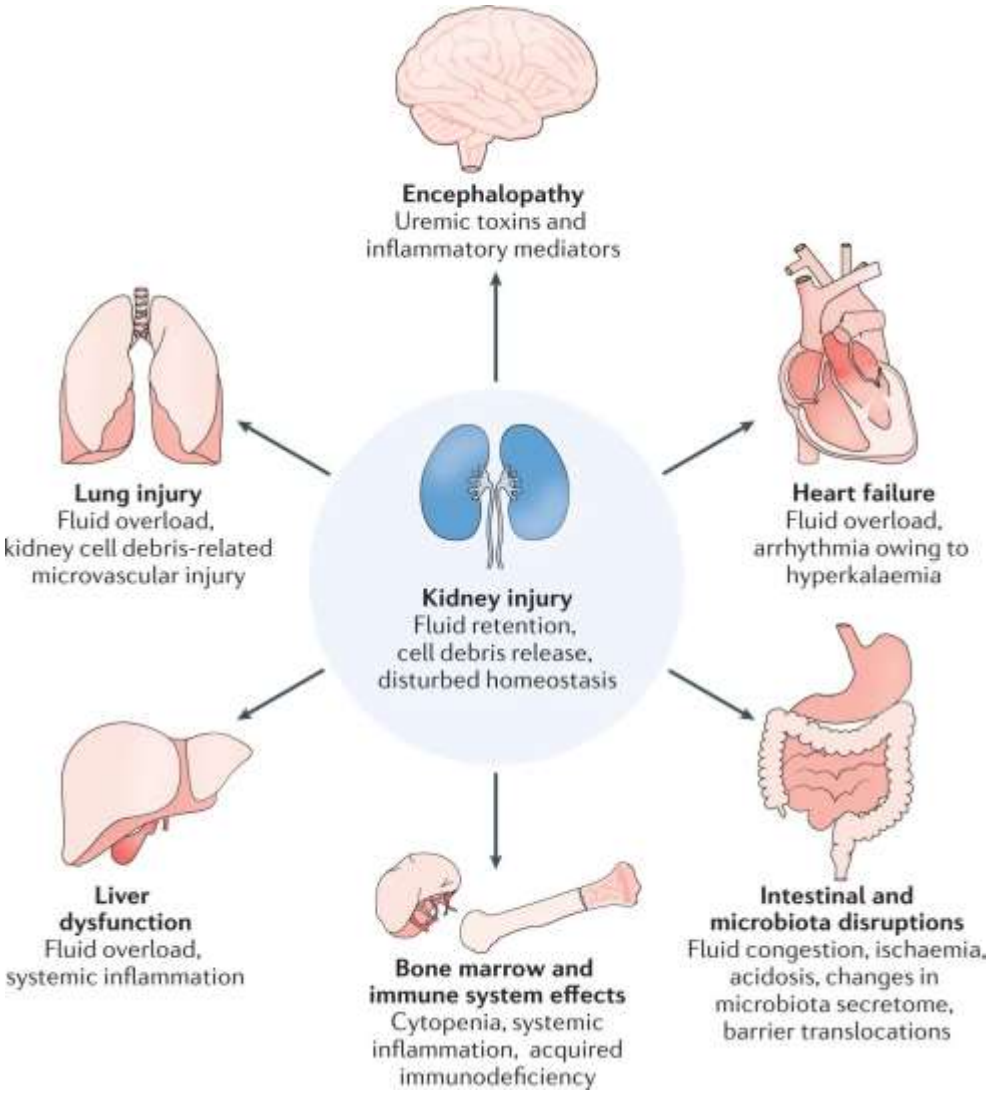


**Figure 3. Alteration in other systems during AKI**

If we consider AKI a complex entity, we can understand better that many factors influence the occurrence and epidemiology of AKI, further to the divergence in AKI diagnostic criteria, there are the clinical setting (hospital vs. community AKI), data sources, composition of the studied population, and concurrent conditions like sepsis or cance. [7] Moreover, a country's characteristics, encompassing resource availability and service accessibility, can impact AKI rates, leading to disparities between high-income and low-income nations.[8]

So, assumed these significant considerations, it is challenging to extrapolate data on AKI epidemiology, even from large-scale studies. In 2013, Susantitaphong et al. examined 312 studies published after 2004, comprising more than 49 million population, and found a mean AKI

incidence of 10.7%. However, when exclusively analyzing studies utilizing the KDIGO classification criteria, the incidence surged to 23.2%, while it decreased to 2.9% when AKI diagnosis relied solely on administrative data.[9]

In 2015, Mehta et al. updated the global analysis through the 0by25 project by the International Society of Nephrology, examining over 77 million individuals. [10] They observed a pooled AKI incidence of 21% among hospital admissions, with most cases categorized as mild and only 11% necessitating kidney replacement treatments (KRT). However, their analysis suffered limitations in representing low-income countries, impeding the study of regional variations in AKI epidemiology.

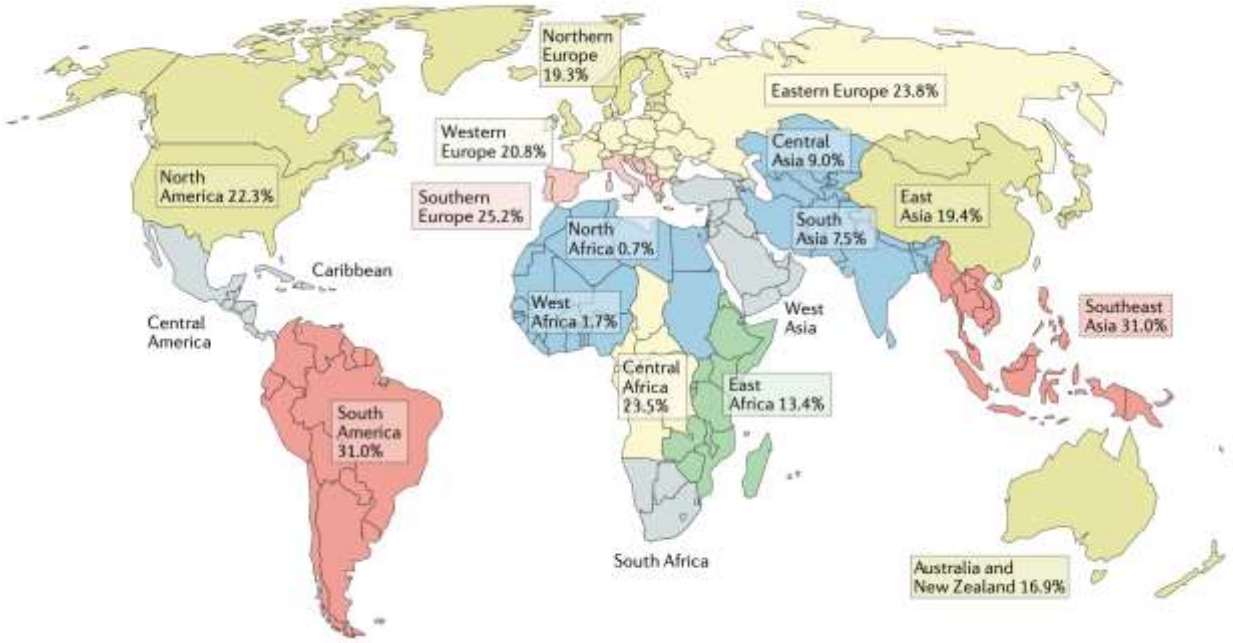


**Figure 4. Worldwide AKI epidemiology**

While in the community contest it is quite hard estimate the prevalence of its occurrence and its consequences[11,12], in the hospital population we can try investigating them, also because it can have severe consequences,[13] nonetheless AKI is probably one of the most frequent and underestimated syndromes in hospitalized patients[11,14,15].

Hospital AKI has been evaluated in various studies[16,17] which showed that the most severe forms of AKI (stages 2-3 KDIGO) are associated with increased risk of mortality, length of hospital stay

and healthcare costs mainly due to frequent re-hospitalizations and development of comorbidities.[18,19]

Moreover, AKI represents an independent risk factor for the progression toward chronic kidney disease (CKD)[20,21] After the acute phase of AKI there is a transition one to CKD defined as Acute Kidney Damage (AKD). AKD is status of acute or subacute kidney damage/dysfunction manifested by persistence of AKI stage 1 or greater beyond 7 to 90 days after the initial AKI diagnosis. If criteria of AKI persist beyond 90 days, it is considered incident or progressive CKD according to baseline kidney function.[22]

This process involves different pathways from the acute damage to the chronic one: the endothelial disfunction for the reduction of production of nitric oxide (NO), and the augmentation of TGFbeta, VEGF, PDGF, angiopoietin, etc; the interstitial inflammation with the recruitment of neutrophils, monocytes, lymphocytes B and T; successively there's the myofibroblasts arrival and matrix deposition with the consequent fibrosis; tubular epithelial damage and dysregulation repair. [23]

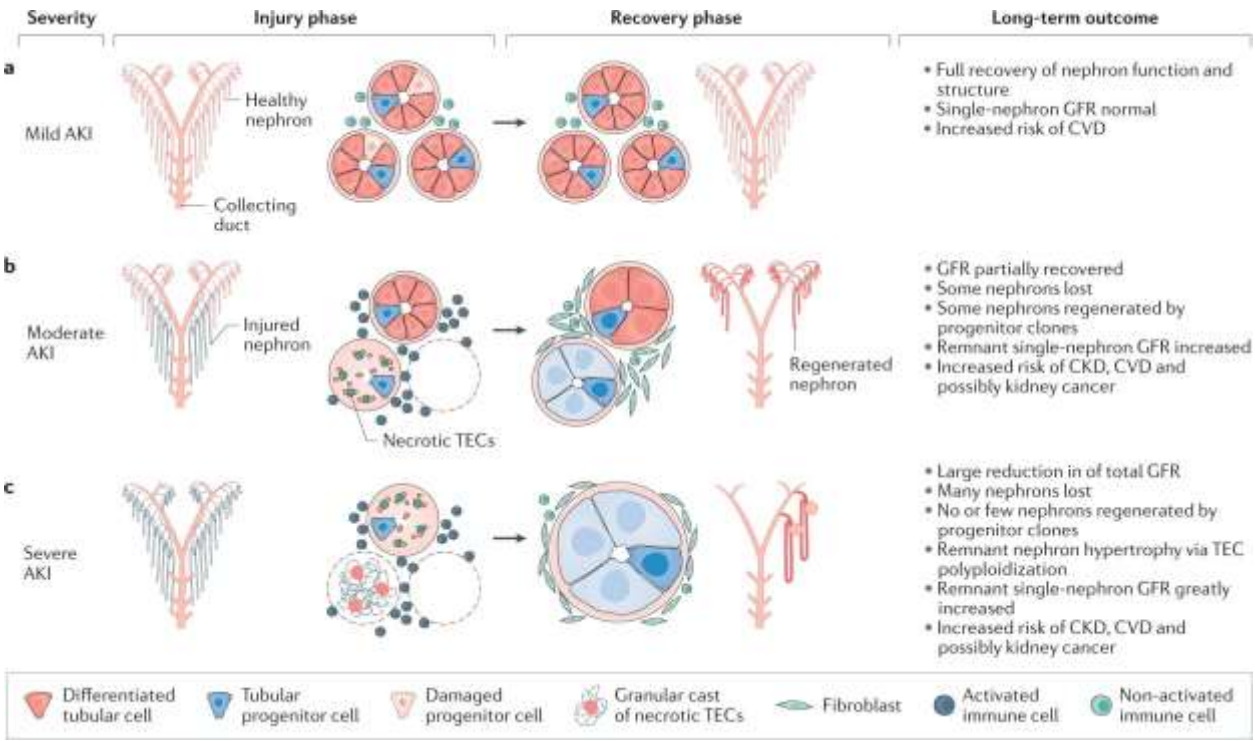


**Figure 5. Physiopathology of renal injure and repair**

We need to consider that these pathophysiological events have differences between sexes, in fact, several studies experimental on rats and on humans demonstrated that there are differences in NO's production, more propensity to vasodilatation caused by oestrogens and more production of prostaglandins and thromboxane. Moreover, females seem to have a protection for fibrosis made by oestrogens that inhibit TGFbeta.[24]

Moreover, if we consider AKI as a complex syndrome, we need to consider sex differences in different physiological areas as immunology, renal transport and metabolism. [25–27]

Some studies tried to analyse sex differences on AKI incidence, but the results are still discordant[28,29], indeed, KDIGO 2012 guidelines indicated that female sex was a susceptibility factor for AKI, especially in cardiac surgery, rhabdomyolysis and exposure to nephrotoxic agent.[1] Anyway, these results are not confirmed in every study population, especially in ICU[30,31]; actually a 2018 meta-analysis showed female sex as protective for in-hospital AKI.[32]

So, the evolution to chronicity and the increased mortality of AKI patients[33,34] are the principal reason why AKI has recently emerged as a major public health concern with high human and financial costs. In the US, AKI leads to an increase of the hospitalization costs that ranges $5.4 billion to $24 billion: the most expensive patients are those requiring renal replacement therapies (RRT) that are associated with longer hospital stay[15,18]. Based on this consideration, there is the urgent need of new studies to limit the incidence and progression of AKI and the opportunity for hospitals and policymakers to develop integrated healthcare processes with the aim to reduce AKI-related costs. This is particularly relevant for elderly patients who are more prone to develop AKI in consideration of the loss of renal functional reserve due to aging and the presence of different comorbidities: indeed, in a European hospitalized cohort, the average age of AKI patients was 76 years. Moreover, it has been shown that age-related yearly incidence of AKI increased from 17 per million in adults under age 50 to 949 per million in those aged 80-89[35].

**Figure 6. Evolution of AKI**

Many published studies on AKI referred to critically ill patients admitted to Intensive Care Units (ICU) in which the main drivers of the disease are represented by sepsis or septic shock, serious medical conditions characterized by an intense host systemic inflammatory response due to the presence of pathogenic microorganisms and by widely variable clinical manifestations including multiple organ failure and AKI. However, recent studies showed that AKI is a frequent complication also in low- and medium-intensity care settings, representing the first cause of Nephrology consultancy[36].

Nowadays, we still have some unmet needs in the management of AKI in hospitalized patients: first, an earlier diagnosis of AKI may limit the worsening of disease with the need of RRT, decreasing the length of hospital stay and thus improving outcomes. Secondly, the identification of AKI patients more prone to the progression toward CKD at hospital discharge remains challenging both for clinical and organizational problems. For these reasons, AKI patients should enter a program of specialized follow-up aimed at evaluating renal function and the development of comorbidities such as cardiovascular, neuromuscular, pulmonary, gastrointestinal, immunologic and metabolic complications[37].

# Aim of the study

The aim of the present study is to analyze in-hospital AKI incidence by using a standardized model of epidemiologic data analysis to lead to the improvement of AKI recognition, diagnosis and hopefully paving the way to the development of an outpatient clinic and biomarker discovery studies to limit CKD progression.

# PATIENTS AND METHODS

## Study design and population

We performed a retrospective observational study on the hospitalized population admitted to Policlinico Universitario San Martino, Genova, Italy and Azienda Ospedaliera Universitaria Maggiore della Carità, Novara, Italy. We collected data on adult patients (age≥18 years) admitted from January 1, 2016, to December 31, 2019. All patients were included at the time of first hospital admission.

Inclusion criteria were:

- Adult age (age≥18 years)
- First hospital admission from January 1, 2016, to December 31, 2019
- At least two values of sCr collected during hospitalization.

The only criterium of exclusion was the presence of chronic kidney disease (CKD) stages 4-5 or identified by the ICD-9-CM (International Classification of Disease, 9th Revision, Clinical Modification) diagnosis codes reported on the Hospital Discharge Form (HDF).

The institutional review boards approved the study protocol (Genova: N. Registro CER Liguria: 515/2020; Novara: Protocollo 530/CE, Studio n. CE 220/19 NOV-AKI Study) and waived the need for informed consent. The study was performed in accordance with the Helsinki Declaration.

## Data collection

All data were extracted from the hospital electronic database. We exported the following demographic, clinical and laboratory data: age, sex, comorbidities, serum creatinine (sCr), admission ward, length of hospital stay (LOS), death, and outcomes. We considered these comorbid conditions: diabetes mellitus (DM), heart failure (HF), kidney transplantation, CKD, and sepsis, which were identified using ICD-9-CM codes (https://www.salute.gov.it/portale/documentazione/p6_2_2_1.jsp?lingua=italiano&id=2251).

The sCr levels were collected at admission, at discharge, and at the lowest and peak levels during hospitalization. Only patients with at least two sCr determinations were included in the study.

When available in the healthcare database, we also collected sCr measured from 7 to 180 days before the hospitalization.

# Definitions

For the main purposes of the study, AKI incidence was calculated by changes in sCr, dividing the peak sCr by the lowest sCr during hospitalization (peak sCr / lowest sCr) under the assumption that the lowest sCr would represent baseline kidney function[38].

We defined AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline, based only on sCr changes 10. We reported each stage according to the KDIGO guidelines framework as stages 1, 2, and 3. These correspond to 1.5 to 1.9 times their baseline creatinine, 2 to 2.9 times their baseline creatinine, and 3 or more times their baseline creatinine or newly required dialysis (figure 1)[1].

Urine output was not considered due to the retrospective nature of the study and to the limited collected data.

In addition, in the subgroup of patients with availability of at least one sCr measurement between 7 to 180 days before the hospitalization, we calculated estimated GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration creatinine-based equation, and CKD was defined as eGFR <60 ml/min/1.73m$^2$.

Then, we differentiated and compared patients with pure AKI defined as AKI occurring without preexisting CKD, and AKI on CKD defined as AKI that developed in patients with preexisting CKD.

We identified patients developing AKI and its recognition by investigating administrative data reported on Home Discharge Form HDF (code 584.5-584.9).

Moreover, among all the patients meeting KDIGO criteria for AKI diagnosis, we further distinguished between patients presented peak sCr within 48h from hospital admission (Adm-AKI) and those presenting peak sCr later (in-hospital AKI- IH-AKI).

Renal recovery was calculated in AKI patients alive at the hospital discharge dividing the sCr at the discharge by the lowest sCr during hospitalization (discharge sCr/lowest sCr). Patients were considered recovering when they did not meet KDIGO criteria for AKI (ratio <1.5). Conversely, patients with a ratio of 1.5 or higher were classified as having persistent AKI.

# Outcomes

The primary and secondary outcomes were incident in-hospital AKI and its variation due to sex and age differences. Moreover, we considered outcomes: overall mortality, length of staying (LOS), the type of discharge and kidney function at the discharge in AKI patients.

# Statistical analysis

Normally distributed variables are presented as mean ± 1SD and compared using an independent or paired t-test as appropriate. Logarithmically transformed values of skewed variables were used for the statistical analysis. Comparisons between groups were made by analysis of variance. Comparisons of proportions were made using the $\chi 2$-test or Fisher's exact test when appropriate. The incidence rate of AKI was calculated.

Univariate and multivariate logistic regression analyses were used to describe the relationship between all available clinical variables of biological relevance and the presence of AKI. We investigated as comorbid condition: DM, HF, sepsis and as factor associated to hospitalization: length of stay (LOS) and admission to intensive care unit (ICU). Odds ratios and 95% confidence intervals were calculated by exponentiation of logistic regression coefficients.

Time-to-event analyses were performed using: (i) the Kaplan-Meier method for survival curves estimation and log-rank test to compare them; (ii) univariate and multivariate Cox regression models: risk was reported as hazard ratios (HR) along with their 95% confidence intervals (CI). The time variable was defined as the interval time between the baseline date and the date of endpoint occurrence during hospitalization.

We used Kaplan Meier analyses to assess difference in mortality between AKI and no-AKI patients, stages of AKI and pure-AKI and AKI on CKD patients and differences between AKI development on the basis of age and sex.

We used Cox regression to assess mortality risks, we examine as covariates: DM, HF, sepsis, ICU admission, LOS, CKD or sCr ad admission and the presence of AKI.

Power analysis showed that the number of individuals in the database (n = 87,087) represented a sample largely sufficient to avoid b error also after stratification by AKI. Statistical calculations were performed by STATA package, version 14.2 (Stata Corp, 4905 Lakeway Drive, College Station, Texas 77845 USA). The null hypothesis was rejected for values of $P < 0.05$.

# RESULTS

## Patient general characteristics

We collected data on 87,087 patients, with an average age of 69.2±17.7 years of whom 43467 (49.9%) were male. Among them, there were 848 (0.97%) kidney transplanted patients.

As reported on the HDF 8,455 (9.7%) patients were diabetic, 7,767 (8.9%) had heart failure (HF) and 5924 (6.8%) had CKD. Sepsis occurred in 3,361 (3.9%) of the total patients. At the admission, the mean sCr was 1.12±0.98 mg/dl, corresponding to an eGFR of 90.1±16 ml/min. Most of the patients were admitted to Medical Wards and 3,147 (3.6%) to ICU (Table 1).

| | **All** | **Non-AKI** | **AKI** | **P (Non AKI vs AKI)** |
|---|---|---|---|---|
| **N,** | 87087 | 69141 (79.4) | 17946 (20.6) | |
| **Age (years)** | 69.2±17.7 | 66.7±18.1 | 74.8±14.7 | <0.001 |
| **Gender M%** | 43467 (49.9) | 34869 (50.4) | 8598 (47.9) | <0.001 |
| **Comorbidities, %** | | | | |
| **Diabetes** | 8455 (9.7) | 6446 (9.3) | 2009 (11.2) | <0.001 |
| **Heart failure** | 7767 (8.9) | 5122 (7.4) | 2645 (14.7) | <0.001 |
| **Sepsis** | 3361 (3.9) | 1448 (2.1) | 1913 (10.7) | <0.001 |
| **CKD** | 5924 (6.8) | 4220 (6.1) | 1704 (9) | <0.001 |
| **Kidney Tx** | 848 (0.97) | 596 (0.86) | 252 (1.4) | < 0.001 |
| **sCr at admission (mg/dl)** | 1.12± 0.98 | 1±1 | 1.55 ± 1.53 | <0.001 |
| **eGFR at admission (ml/min)** | 90.1 ±16 | 91±15 | 81.6 ±16 | <0.001 |
| **Hospital Ward** | | | | **AKI incidence(%)** |
| **Medicine** | 37902 (43.5) | 30951 (44.7) | 6951 (38.7) | 10.4 |
| **Surgery** | 22569 (25.9) | 18949 (27.4) | 3620 (20.2) | 16 |
| **ICU** | 3147 (3.6) | 1666 (2.4) | 1481 (8.2) | 47 |
| **Emergency medicine** | 23467 (26.9) | 17574 (25.4) | 5893 (32.8) | 25.1 |

Abbreviations: CKD chronic kidney disease, Tx transplantation, sCr serum creatinine, ICU intensive care unit, AKI acute kidney injury.

**Table 1. Main clinical characteristics of patients hospitalized in the studied period (Jan 2016-Dec 2019), distinguished according to the AKI development.**

# Incidence and risk factors for AKI

In the enrolled patients, AKI developed in 17,946 (20.6%). In respect to the non-AKI population, patients with AKI were significantly older, with a higher prevalence of females.

Moreover, AKI patients presented a higher prevalence of all the recorded comorbidities, including CKD (9 vs 6.1% of the non-AKI group, $p<0.001$). Diabetes (11.2 vs 9.3%, $p<0.001$), heart failure (14.7 vs 7.4%, $p<0.001$) and sepsis (10.7 vs 2.1%, $p<0.001$) were also significantly higher in the AKI vs non-AKI group, respectively (Table 1). Furthermore, among the AKI group, there was also a significantly higher number of kidney transplanted patients (1.4 vs 0.86% of the non-AKI group, $p<0.001$). Looking at the admission data, we found that patients experiencing AKI had significantly higher sCr levels (1.55±1.53 vs 1±1 mg/dl, $p<0.001$) and lower eGFR (81.6±16 vs 91±15 ml/min, $p<0.001$) when compared with the non-AKI group.

AKI incidence was significantly higher in patients admitted to ICU (47%) and emergency medicine wards (25%) compared with general medicine and surgery.

Subsequently, clinical determinants of AKI were analyzed in the entire patient cohort through both univariate and multivariate logistic regression analyses (Table 2). For the latter, two independent models were generated as CKD and admission serum creatinine levels, as reported in the Hospital Discharge Form (HDF), were found to be intercorrelated during preliminary analysis. The results of logistic regressions demonstrated that in both univariate and multivariate analyses, demographic characteristics (age, female sex), length of hospital stay, ICU admission, main comorbidities (except for diabetes), and admission serum creatinine levels were significantly associated with the risk of AKI development (Table 2).

| | Univariate | | | Multivariate Model 1 | | | Multivariate Model 2 | | |
|---|---|---|---|---|---|---|---|---|---|
| **RISK FACTORS** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| **Gender (female)** | 1.11 | 1.07 – 1.14 | <0.0001 | 1.08 | 1.04 – 1.12 | <0.0001 | 1.23 | 1.18 – 1.27 | <0.0001 |
| **Age** | 1.03 | 1.02 – 1.03 | <0.0001 | 1.03 | 1.02 – 1.03 | <0.0001 | 1.02 | 1.02 – 1.02 | <0.0001 |
| **Comorbidities** | | | | | | | | | |
| **Diabetes** | 1.23 | 1.16-1.29 | <0.0001 | 1.05 | 0.99-1.11 | 0.08 | 1.02 | 0.96-1.08 | 0.58 |
| **HF** | 2.16 | 2.05-2.27 | <0.0001 | 1.51 | 1.43 – 1.6 | <0.0001 | 1.43 | 1.35– 1.51 | <0.0001 |
| **Sepsis** | 5.58 | 5.2 – 5.9 | <0.0001 | 3.61 | 3.35 – 3.9 | <0.0001 | 3.2 | 2.96-3.4 | <0.0001 |
| **CKD** | 1.61 | 1.52-1.71 | <0.0001 | 1.38 | 1.28 – 1.47 | <0.0001 | - | - | - |
| **Admission sCr** | 1.67 | 1.64-1.70 | <0.0001 | - | - | - | 1.55 | 1.53 -1.58 | <0.0001 |
| **Medical ward** | Ref | | | | | | | | |
| **ICU stay** | 4.38 | 4.11 – 4.67 | <0.0001 | 4.65 | 4.33 – 4.9 | <0.0001 | 4.73 | 4.4– 5.1 | <0.0001 |
| **LOS (day)** | 1.21 | 1.17 – 1.36 | <0.0001 | 1.05 | 1.05 – 1.06 | <0.0001 | 1.05 | 1.05– 1.06 | <0.0001 |

Abbreviations: OR odds ratio, CI confidence interval, HF heart failure, CKD chronic kidney disease, sCr serum creatinine, ICU intensive care unit, LOS length of stay

**Table 2. Logistic models for the development of acute kidney injury in hospitalized patients**

# Correlation of outcomes with AKI development

The in-hospital mortality rate was significantly higher in the AKI group compared to the non-AKI group (Table 3). Additionally, we observed that a greater number of AKI patients were admitted to the ICU compared to low- and medium-intensity care settings. These patients also experienced a significantly longer LOS compared to non-AKI patients. Upon hospital discharge, AKI patients still exhibited elevated sCr levels and required a significantly higher percentage of protected follow-up to ensure continuity of care and assistance.

| | All | Non-AKI | AKI | P (Non AKI vs AKI) |
|---|---|---|---|---|
| **N** | 87087 | 69141 | 17946 | |
| **In-hospital outcomes** | | | | |
| **Mortality rate, %** | 6156 (7.07) | 2984 (4.3) | 3172 (17.7) | <0.0001 |
| **ICU admission, %** | 3147 (3.6) | 1666 (2.4) | 1481 (8.2) | <0.0001 |
| **LOS (days)** | 11.1±13 | 8.9±11.12 | 19.2±16 | <0.0001 |
| **Discharge status- alive** | | | | |
| **Discharge at home, %** | 63666 (73.1) | 54284 (78.5) | 8382 (52.8) | <0.0001 |
| **Protected discharge, %** | 17265 (19.8) | 11873 (17.7) | 5392 (30.05) | <0.0001 |
| **sCr (mg/dl)** | 1.05 ± 1 | 1.00 ±0.7 | 1.27 ± 1.1 | <0.0001 |
| **eGFR ml/min** | 90.89 ±16 | 92.46 ± 15.7 | 84.86 ±15.9 | <0.0001 |

Abbreviations: sCr serum creatinine, ICU intensive care unit, LOS length of stay.

**Table 3. Clinical outcomes of all the population of hospitalized patients (2016-2029) based on AKI development.**

Mortality risk factors were further investigated in the study population through both univariate and multivariate Cox analyses. Univariate analysis revealed that age, male sex, ICU admission, sCr level at admission, and the occurrence of AKI were all significantly associated with mortality. In the multivariate analysis, the development of AKI remained a significant and independent predictor of mortality risk (HR 1.23; 95% CI 1.16-1.30) (Table 4). This finding was further confirmed by Kaplan-Meier survival analysis (Figure 7).

| | Univariate | | | Multivariate Model | | |
|---|---|---|---|---|---|---|
| ***RISK FACTORS*** | **HR** | **95% CI** | **p** | **HR** | **95% CI** | **p** |
| ***Gender (male)*** | 1.06 | 1.01 – 1.12 | 0.013 | 1.11 | 1.06 – 1.17 | <0.0001 |
| ***Age*** | 1.05 | 1.05 – 1.05 | <0.0001 | 1.06 | 1.05 – 1.06 | <0.0001 |
| ***Basal sCr*** | 1.18 | 1.17-1.2 | <0.0001 | 1.15 | 1.13 -1.17 | <0.0001 |
| ***Medical ward*** | Ref | | | | | |
| ***ICU stay*** | 3.16 | 2.96 – 3.38 | <0.0001 | 3.86 | 3.61 – 4.13 | <0.0001 |
| ***AKI*** | 1.9 | 1.8-2 | <0.0001 | 1.23 | 1.16 – 1.30 | <0.0001 |

Abbreviations: sCr serum creatinine, ICU intensive care unit.

**Table 4. Univariate and multivariate Cox regression analyses for intra-hospital mortality in hospitalized patients between 2016 and 2029**

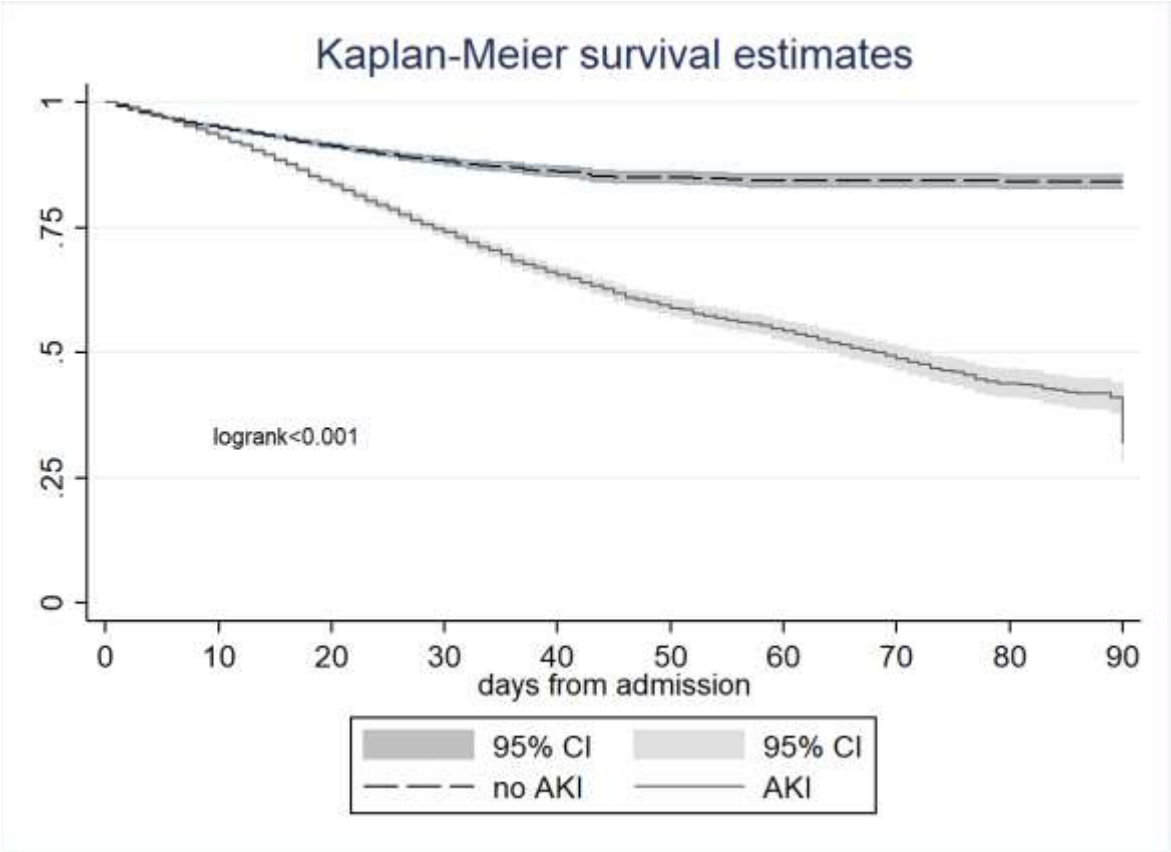


**Figure 7. Kaplan-Meier curves of overall survival at 90-day from the admission of all the population of hospitalized patients (2016-2020) based on the presence of AKI**

# Comparison of outcomes according to AKI severity

The following step was to evaluate the impact of AKI severity (graded following the KDIGO 2012 criteria) on patients' outcomes.

We observed that out of 17,946 patients, 10,679 (59.5%) developed stage 1 AKI, 4,611 (25.7%) stage 2, and 2,656 (14%) stage 3, respectively (Table 5).

| | All AKI | AKI-1 | AKI-2 | AKI-3 | p (AKI stages) |
|---|---|---|---|---|---|
| **N,** | 17946 | 10679 (59.5) | 4611 (25.7) | 2656 (14) | |
| **Age (years)** | 74.8±14.7 | 74.8±15 | 75.9±14 | 73±14.4 | <0.0001 |
| **Gender. M%** | 8598 (47.9) | 5065 (47.4) | 2181 (47.3) | 1352 (50.9) | 0.004 |
| **Comorbidities on HDR, %** | | | | | |
| **Diabetes** | 2009 (11.2) | 1271 (11.9) | 480 (10.4) | 258 (9.7) | 0.001 |
| **HF** | 2645 (14.7) | 1582 (14.8) | 733 (15.9) | 330 (12.4) | <0.0001 |
| **Sepsis** | 1913 (10.7) | 787 (7.4) | 677 (14.7) | 449 (16.9) | <0.0001 |
| **CKD** | 1704 (9) | 878 (8.2) | 451 (9.8) | 375 (14.1) | <0.0001 |
| **Kidney Tx, n (%)** | 252 | 56 (22,3) | 32 (12,7) | 164 (65) | <0.0001 |
| **sCr at admission (mg/dl)** | 1.55 ± 1.53 | 1.27± 0.96 | 1.61±1.29 | 2.6 ± 2.5 | <0.0001 |
| **eGFR at admission (ml/min)** | 81.6 ±16 | 84 ±15 | 79.5±15.6 | 74.6 ±18 | <0.0001 |
| **Hospital Ward** | | | | | **AKI 3 (%)** |
| **Medicine** | 6951 (38.7) | 4215 (39.4) | 1673 (36.3) | 1063 (40) | 15.3 |
| **Surgery** | 3620 (20.2) | 2371 (22.2) | 824 (17.8) | 425 (16) | 11.7 |
| **ICU** | 1481 (8.2) | 731 (6.8) | 444 (9.7) | 306 (11.5) | 20.6 |
| **Emergency Medicine** | 5893 (32.8) | 3361 (31.5) | 1670 (36.2) | 862 (32.4) | 14.6 |

Abbreviations: HF heart failure, CKD chronic kidney disease, Tx transplantation, sCR serum creatinine, ICU intensive care unit, LOS length of stay.

**Table 5. Main clinical characteristics of patients hospitalized in the studied period (Jan 2016-Dec 2019), distinguished according to the AKI severity (KDIGO stages).**

Notably, the average age was lower in the stage 3 AKI group.

Comorbidities exhibited different distributions among AKI stages. Patients with stage 3 AKI, as compared to stages 1 and 2, showed a lower prevalence of diabetes and cardiac diseases and a concomitant higher prevalence of sepsis and CKD. Remarkably, among the 252 kidney-transplanted patients developing AKI, stage 3 was the most commonly found (164/252 patients, 65%). Moreover, ICU patients exhibited a higher prevalence of stage 3 AKI compared to stages 1 and 2. Conversely, patients hospitalized in low- and medium-intensity care settings (Internal Medicine and Surgery wards) showed a higher prevalence of stage 1 AKI (Table 5).

Stratifying age into quartiles revealed an increased incidence of overall AKI in patients in the higher quartiles (i.e., >73 and >83 years, respectively) with different distribution of AKI stages (Figure 8).

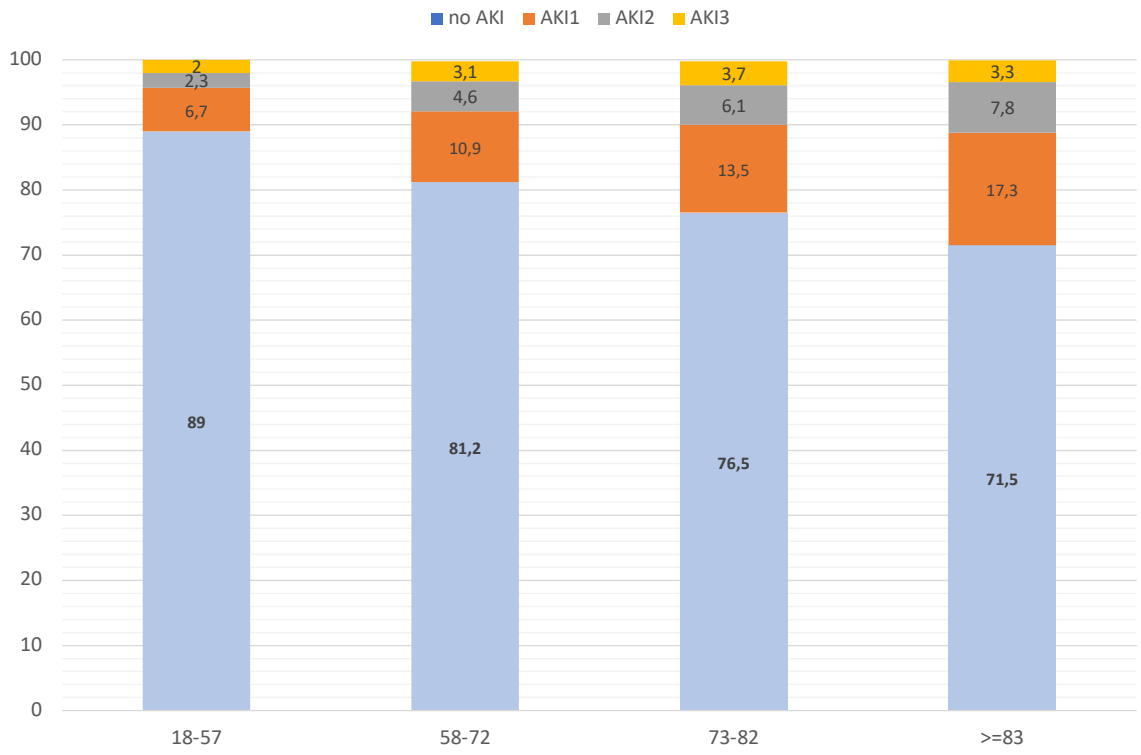


**Figure 8. Distribution of AKI stages divided for age's quartiles.**

The in-hospital mortality rate was significantly higher in stage 3 AKI patients (Table 6). A 90-day Kaplan-Meier survival analysis confirmed a progressive increase in mortality with the severity of AKI (Figure 9). Additionally, stage 3 AKI patients were more commonly admitted to the ICU and had a longer LOS.

Finally, among patients alive at discharge, those developing AKI stage 3 presented a lower rate of renal recovery, a worse kidney function and more frequently required protected discharge (Table 6).

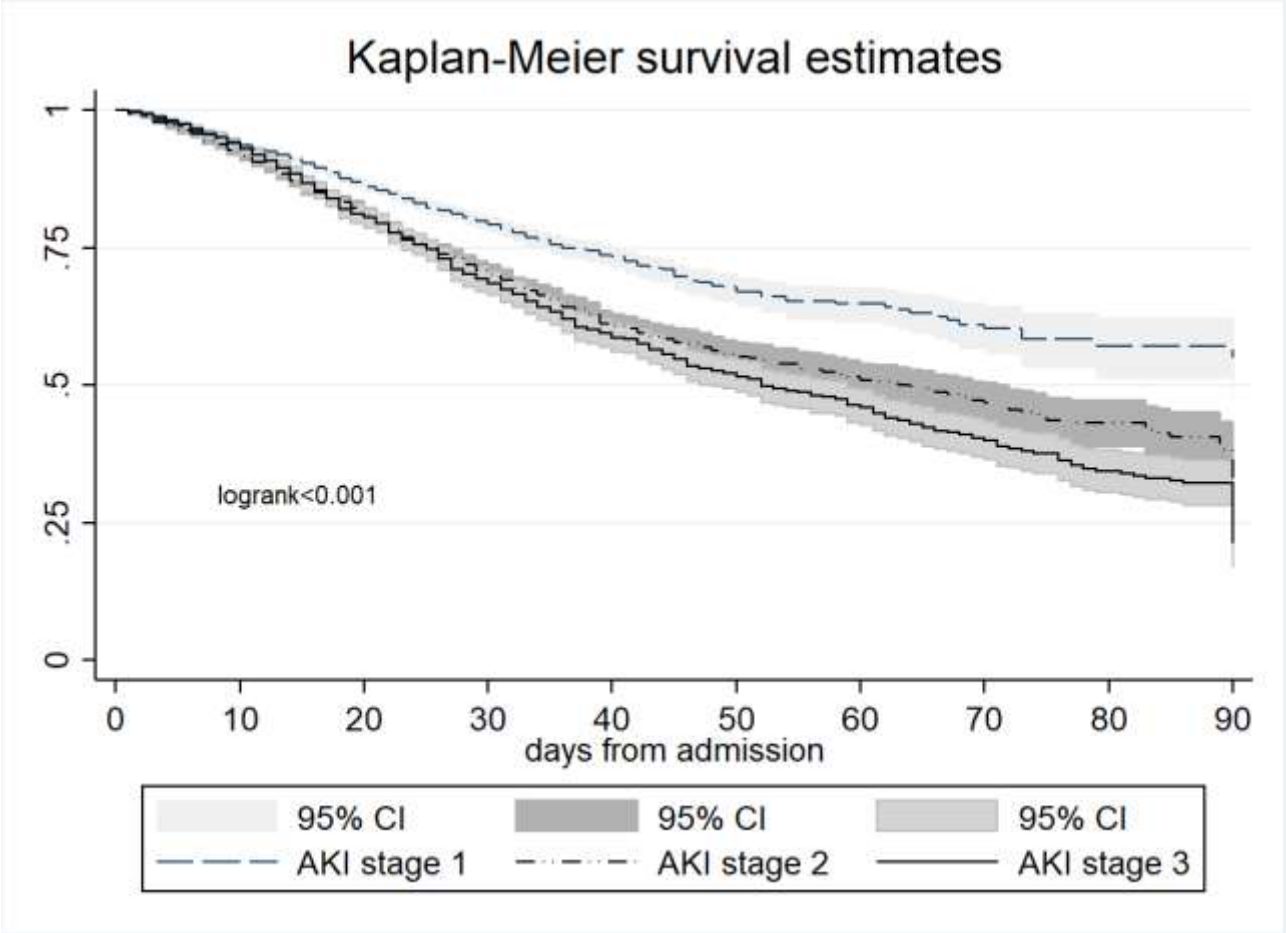


**Figure 9. Kaplan-Meier curves of overall survival at 90-day from the admission of all the population of hospitalized patients (2016-2020) based on AKI stage.**

Finally, among patients alive at discharge, those developing AKI stage 3 presented significantly higher serum creatinine levels and more frequently required protected discharge (Table 6).

| | All AKI | AKI1 | AKI2 | AKI3 | p (AKI stages) |
|---|---|---|---|---|---|
| **N,** | 17946 | 10679 (59.5) | 4611 (25.7) | 2656 (14) | |
| **In-hospital outcomes** | | | | | |
| **Mortality rate, %** | 3172 (17.7) | 1245 (11.6) | 1078 (23.4) | 849 (32) | <0.001 |
| **ICU admission, %** | 1481 (8.2) | 731 (6.8) | 444 (9.7) | 306 (11.5) | <0.001 |
| **LOS (days)** | 19.2±16 | 16.3±13.3 | 21.6±17.9 | 27.1±22.8 | <0.001 |
| **Discharge status- alive** | 14774 | 9434 | 3533 | 1807 | |
| **Discharge at home, %** | 9382 (52.3) | 6226 (66) | 2091 (59) | 1065 (59) | <0.001 |
| **Protected discharge, %** | 5302 (30.05) | 3208 (34) | 1442 (40) | 742 (41) | |
| **Renal recovery** | 12175 (82.4) | 8045 (85.3) | 2754 (78) | 1376 (76.2) | <0.001 |
| **sCr (mg/dl)** | 1.27 ± 1.09 | 1.15 ±0.92 | 1.33 ±1.09 | 1.67 ±1.51 | <0.001 |
| **eGFR ml/min** | 84.86 ±15.9 | 86.28±.15.3 | 83.36 ± 15.9 | 81.75 ± 17.7 | <0.001 |

Abbreviations: sCr serum creatinine, ICU intensive care unit, LOS length of stay.

**Table 6. Clinical outcomes of all the population of hospitalized patients (2016-2029) according to the AKI staging.**

# Comparison of outcomes in the pure AKI vs AKIonCKD

Pre-hospitalization sCr levels were available in 34,285 patients, constituting 39% of the total cohort. Among them, 9697 patients (28.2%) presented with CKD before hospital admission, with a mean eGFR of 40.2±14.1 ml/min.

Pure AKI occurred in 4263 patients out of the 33,460 without previous CKD (12.7%), while 2795 patients (31.1% of patients with previous CKD) developed AKIonCKD (p<0.001).

AKIonCKD patients were characterized by advanced age, a higher prevalence of males (Table 7), and a higher prevalence of HF, while the prevalence of diabetes and sepsis did not differ between the two groups. Notably, more transplanted patients were included in the AKIonCKD group.

| | AKIonCKD | Pure AKI | P |
|---|---|---|---|
| **N,** | 2795 | 4263 | |
| **Age (years)** | 79.0 ± 11.3 | 70.7 ± 14.7 | <0.0001 |
| **Gender M%** | 1328 (47.5) | 2192 (51.4) | 0.001 |
| **Comorbidities, %** | | | |
| **Diabetes** | 430 (15.4) | 434 (10.2) | <0.0001 |
| **HF** | 611 (21.9) | 478 (11.2) | <0.0001 |
| **Sepsis** | 335 (12.0) | 489 (11.5) | 0.510 |
| **CKD** | 691 (24.7) | 119 (2.8) | <0.0001 |
| **Kidney Tx** | 108 (3.86) | 16 (0.38) | |
| **sCr at admission (mg/dl)** | 2.45 ± 1.9 | 1.12 ± 0.88 | <0.0001 |
| **eGFR at admission (ml/min)** | 34.3 ± 28.8 | 74.8 ± 17.0 | <0.0001 |
| **AKI stage** | | | <0.0001 |
| **1** | 1562 (55.9) | 2660 (62.4) | |
| **2** | 798 (28.6) | 1010 (23.7) | |
| **3** | 435 (15.6) | 593 (13.9) | |

Abbreviations: HF heart failure, CKD chronic kidney disease, sCr serum creatinine, Tx transplantation.

**Table 7. Main clinical characteristics of AKI patients hospitalized in the studied period (Jan 2016-Dec 2019), distinguished according to the diagnosis of previous CKD.**

AKIonCKD patients presented higher sCr levels at admission and developed more severe AKI during hospitalization. The in-hospital mortality rate was significantly higher in AKIonCKD patients (Table 8). A A 90-day Kaplan-Meier survival analysis confirmed increased mortality in this group (Figure 10). Finally, AKIonCKD patients had significantly higher sCr levels at discharge.

However, at the hospital discharge, AKIonCKD patients presented a significantly higher rate of renal recovery, despite having higher sCr levels.

| | AKIonCKD | Pure AKI | p |
|---|---|---|---|
| **N,** | 2795 | 4263 | |
| **In-hospital outcomes** | | | |
| **Mortality rate, %** | 550 (19.7) | 758 (17.8) | 0.045 |
| **ICU admission, %** | 160 (5.7) | 285 (6.7) | 0.104 |
| **LOS (days)** | 19.2 ±15.3 | 19.7±17.8 | 0.232 |
| **Discharge status- alive** | 2245 (80.3) | 3505 (82.2) | |
| **Discharge at home, %** | 1624 (58.1) | 2476 (58.1) | 0.165 |
| **Protected discharge, %** | 621 (27.7) | 1029 (29.4) | |
| **Renal recovery** | 1912 (85.2) | 2838 (81) | <0.001 |
| **sCr (mg/dl)** | 1.9±1.41 | 0.99±0.79 | <0.001 |

Abbreviations: sCr serum creatinine, ICU intensive care unit, LOS length of stay.

**Table 8. Clinical outcomes of all the population of hospitalized patients (2016-2029) according to the diagnosis of previous CKD**

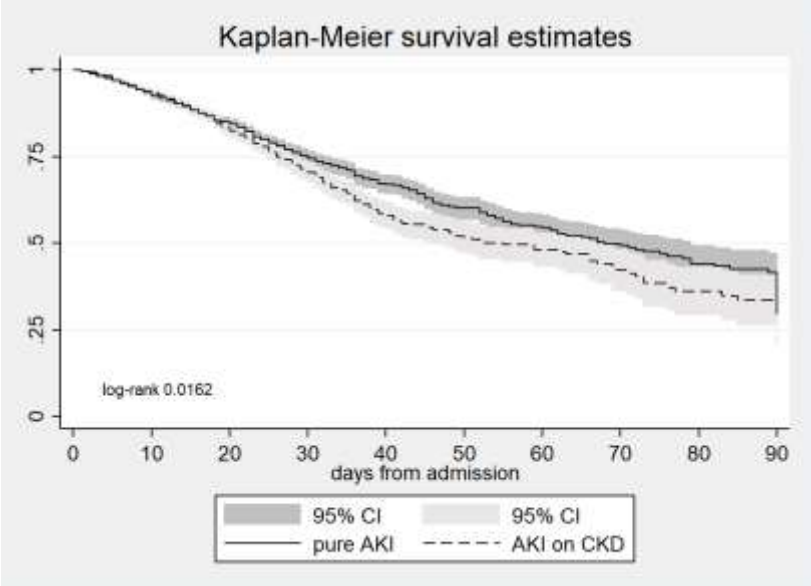


**Figure 10. Kaplan-Meier curves of overall survival at 90-day from the admission of all the population of hospitalized patients (2016-2020) based on AKI stage.**

# Comparison of AKI incidence and outcomes stratified by age and sex

Examining AKI distribution by sex, we noted that most AKI patients were female: overall, 17,946 patients (20.6%) developed H-AKI, females were 21.4% vs. 19.8% of males, p=0.000.

Considering the differences for sex in AKI patients, we observed that females were older than males (69.9±16.5 vs 68.5±18.9 years, p<0.001) and more affected by HF, while males by CKD, and acute myocardial ischemia and sepsis. Admission eGFR was lower in females than males, 82.6 (54.5-99.1) vs 84.2 (57.8-99.0) ml/min, p<0.001 (Table 9). All other characteristics are shown in Table 9.

| | **All H-AKI patients N= 17946** | **Males N=8598** | **Females N=9348** | **P values Males vs Females** |
|---|---|---|---|---|
| **Age** | 74.8 ± 14.7 | 72.5 ± 14.6 | 76.9 ± 14.6 | 0.000 |
| **Comorbidities** | | | | |
| **Diabetes mellitus type 2** | 2009 (11.2) | 994 (11.6) | 1015 (10.9) | 0.136 |
| **Heart failure** | 2645 (14.7) | 1197 (13.9) | 1448 (15.5) | 0.003 |
| **Chronic kidney disease** | 1704 (9.5) | 880 (10.2) | 824 (8.8) | 0.001 |
| **Acute myocardial ischemia** | 1014 (5.6) | 527 (6.1) | 487 (5.2) | 0.008 |
| **Sepsis** | 1913 (10.7) | 979 (11.4) | 934 (10.0) | 0.002 |
| **Data on kidney function** | | | | |
| **Serum creatinine at admission** | 1.55 ± 1.47 | 1.73 ± 1.7 | 1.38 ± 1.36 | 0.000 |
| **eGFR at admission** | 60.9 ± 31.8<br>59.5 (34.4-87.9) | 62.6 ± 32.4<br>61.7 (35.7-90.0) | 59.3 ± 31.1<br>57.6 (33.3-86.3) | 0.000 |
| **Data on Hospital-AKI** | | | | |
| **H-AKI KDIGO stages:**<br>**Stage 1**<br>**Stage 2**<br>**Stage 3** | <br>10679 (59.5)<br>4611 (25.7)<br>2656 (14.8) | <br>5065 (58.9)<br>2181 (25.4)<br>1352 (15.7) | <br>5614 (60.1)<br>2430 (26.0)<br>1304 (14.0) | 0.004 |
| **Diagnosed AKI on HDF** | | 1897 (4.4) | 1668 (3.8) | <0.0001 |

**Table 9. Description of the AKI population based on sex.**

The male/female ratio varied across AKI severity, with stage 3 AKI more frequent in males. Moreover, when we stratified our cohort according to the age quartiles, we observed that for each AKI stage in the 1st age quartile H-AKI incidence was higher in males, in the second quartile there was no difference between male and female patients, while in the last quartiles, AKI incidence was higher in females (Fig. 11).

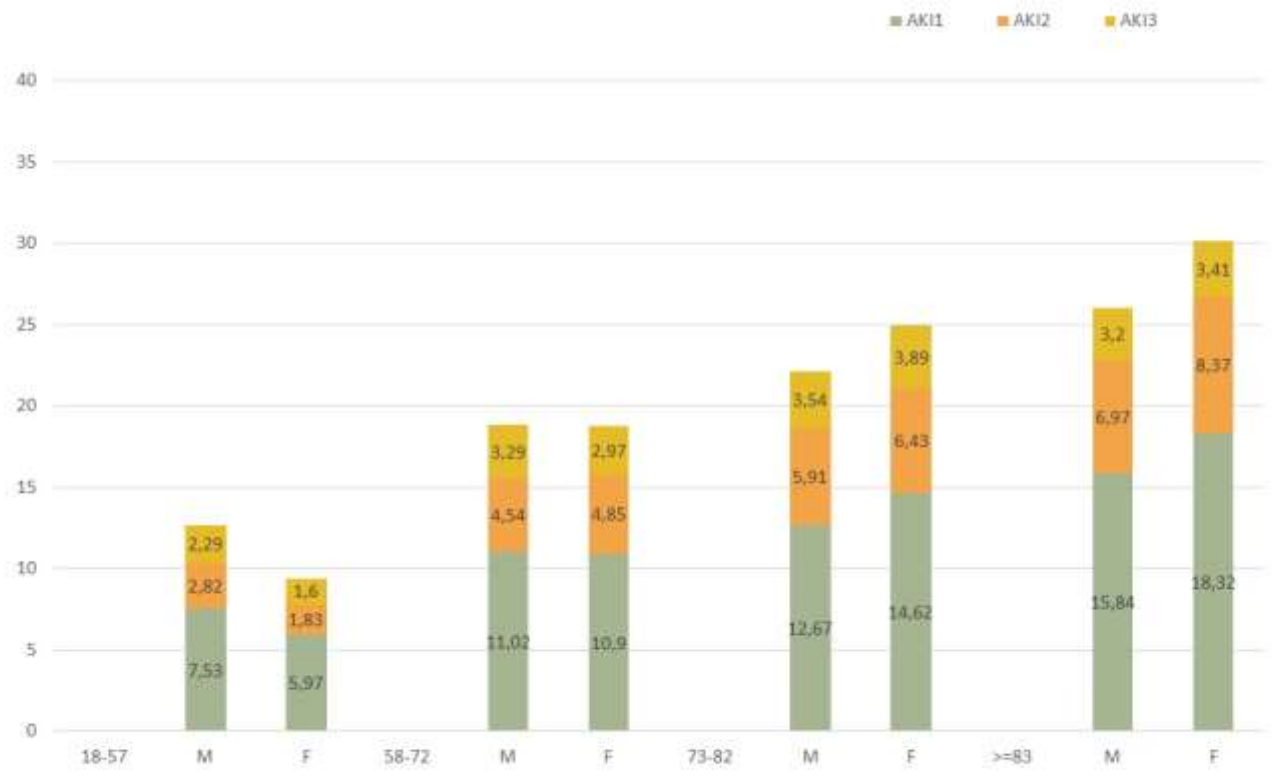


**Figure 11. Distribution of AKI stages based on age quartiles and sex.**

Further stratification for sex and age in all the study population revealed that AKI incidence increased with age, particularly in female patients. Thus, female patients in the higher age quartile were the most represented group for each AKI stage (Table 9).

In the first age quartile AKI was more incident in males (1463, 13.1% vs 1167, 10%, p 0.000), in the second there were no differences (2390, 19,1% vs 1705, 19.6%, p 0.373), while in the higher quartiles, women developed more AKI, respectively 2801, 25.2% vs 2738, 22.6% (p0.000) and

3675, 30.4% vs 2007, 26% (p=0-000) (Table 10). This tendency was also confirmed by Kaplan Meier analysis (Figure 12). However, when we separately analyzed the risk of developing AKI in the different age quartiles with multivariate logistic regression analysis we found that while in the youngest quartiles the risk of developing AKI was not correlated with sex, in the elderly, female sex was an independent risk factor for developing AKI (3rd quartile OR 1.30, IC 1.21-1.39; 4th quartile OR 1.46 IC 1.38-1.59, adjusted for age, DM, HF, CKD, admission to ICU, sCr, LOS). There were no differences between the incidences of pure AKI and AKI on CKD.

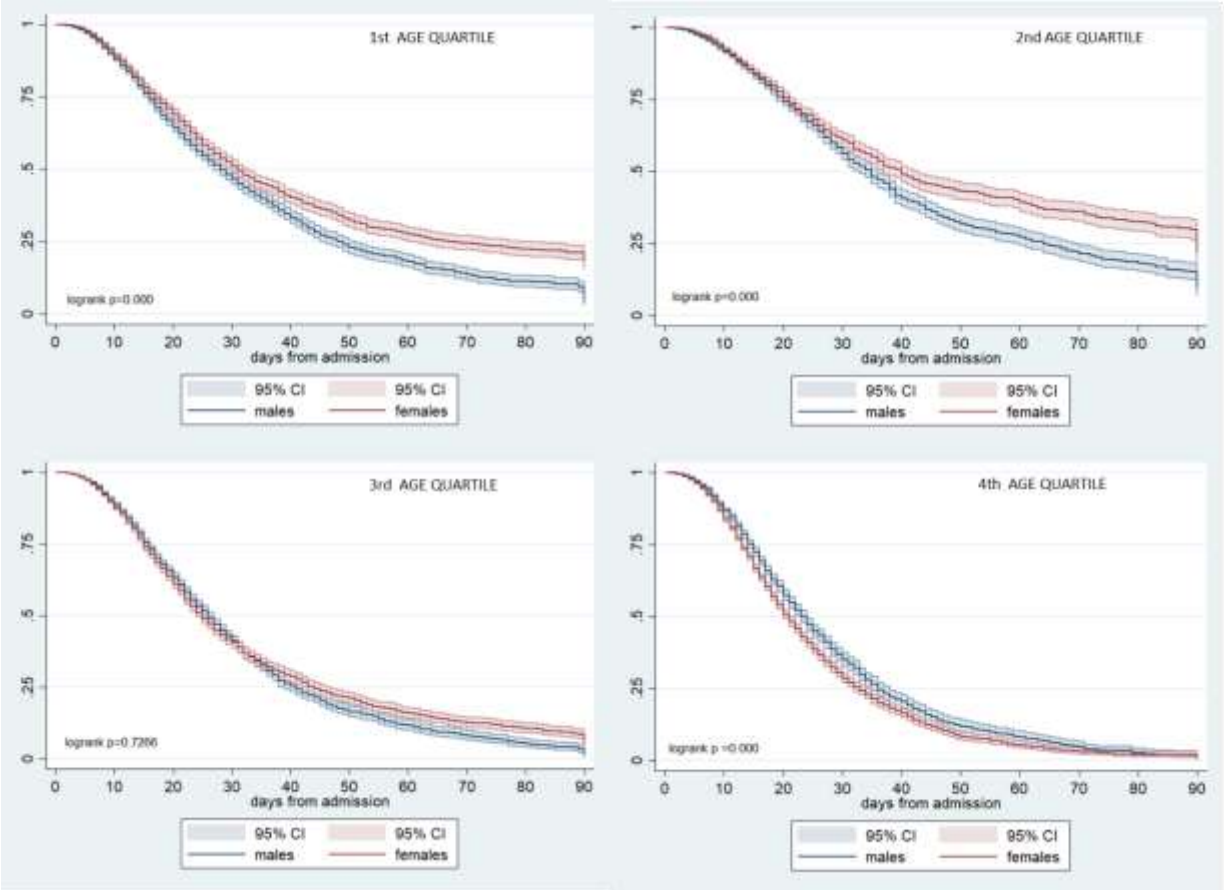


**Figure 12. Kaplan Meier analysis for development on AKI divided by sex in the four quartiles.**

| AGE'S QUARTILES | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st | | | 2nd | | | 3rd | | | 4th | | |
| | **M 11199** | **F 11719** | ***p*** | **M 12527** | **F 8713** | ***p*** | **M 12118** | **F 11163** | ***p*** | **M 7734** | **F 12161** | ***p*** |
| **Age** | 45.6 ± 11.2 | 43.3 ± 11.3 | *0.000* | 67.1 ± 4.0 | 67.3 ± 4.0 | *0.0004* | 78.6 ± 2.8 | 78.9 ± 2.8 | *0.000* | 88.0 ± 3.3 | 88.9 ± 3.8 | *0.000* |
| **H-AKI** | 1463 (13.1) | 1167 (10.0) | *0.000* | 2390 (19.1) | 1705 (19.6) | *0.373* | 2738 (22.6) | 2801 (25.2) | *0.000* | 2007 (26.0) | 3675 (30.4) | *0.000* |
| **H-AKI on CKD** | 89 (16.4) | 83 (16.7) | *0.903* | 292 (28.5) | 223 (28.5) | *1.0* | 493 (42.0) | 506 (44.9) | *0.155* | 454 (58.2) | 655 (57.8) | *0.864* |
| **H-AKI on normal renal function** | 413 (83.3) | 83 (16.7) | *0.903* | 732 (71.5) | 559 (71.5) | *1.0* | 682 (58.0) | 621 (55.1) | *0.155* | 326 (41.8) | 478 (42.2) | *0.864* |
| **H-AKI KDIGO stages**<br>**Stage 1**<br>**Stage 2**<br>**Stage 3** | 877 (60.0)<br>325 (22.2)<br>261 (17.8) | 732 (62.7)<br>240 (20.6)<br>195 (16.7) | *0.346* | 1392 (58.2)<br>586 (24.5)<br>412 (17.2) | 990 (58.1)<br>437 (25.6)<br>278 (16.3) | *0.603* | 1575 (57.5)<br>728 (26.6)<br>435 (15.9) | 1641 (58.6)<br>745 (26.6)<br>415 (14.8) | *0.521* | 1221 (60.8)<br>542 (27.0)<br>244 (12.2) | 2251 (61.2)<br>1008 (27.4)<br>416 (11.3) | *0.636* |
| **Serum creatinine at admission** | 1.0 ± 1.0 | 0.76 ± 0.75 | *0.000* | 1.2 ± 1.08 | 0.93 ± 0.90 | *0.000* | 1.34 ± 1.12 | 1.04 ± 0.79 | *0.000* | 1.51 ± 1.11 | 1.20 ± 0.84 | *0.000* |
| **eGFR at admission** | 100.5 ± 25.4 | 105.1 ± 23.5 | *0.000* | 80.2 ± 25.1 | 80.7 ± 24.6 | *0.231* | 67.9 ± 24.4 | 67.1 ± 24.1 | *0.319* | 57.1 ± 23.4 | 56.0 ± 23.4 | *0.009* |
| **CKD** | 328 (8.9) | 298 (6.3) | *0.000* | 1109 (20.6) | 703 (18.1) | *0.004* | 1861 (34.7) | 1672 (38.0) | *0.001* | 1664 (54.6) | 2062 (54.5) | *0.939* |
| **ICU admission** | 742 (6.6) | 342 (2.9) | *0.000* | 762 (6.1) | 426 (4.9) | *0.000* | 661 (5.4) | 504 (4.5) | *0.001* | 249 (3.2) | 292 (2.4) | *0.001* |
| **Length of stay> 15 days** | 1842 (16.4) | 1662 (14.2) | *0.000* | 2299 (18.3) | 1874 (21.5) | *0.000* | 2632 (21.7) | 2578 (23.1) | *0.01* | 1701 (22.0) | 2636 (21.7) | *0.596* |
| **Protected discharge** | 1858 (16.9) | 1134 (9.8) | *0.000* | 2324 (19.6) | 1556 (18.8) | *0.132* | 2501 (22.5) | 2721 (26.4) | *0.000* | 1771 (27.1) | 3474 (33.0) | *0.000* |
| **Death** | 229 (2.0) | 179 (1.5) | *0.003* | 679 (5.4) | 421 (4.8) | *0.057* | 1015 (8.4) | 849 (7.6) | *0.030* | 1198 (15.5) | 1624 (13.3) | *0.000* |

**Table 10. Description of the study population based on sex and age quartiles.**

In the youngest quartile males have the worst outcomes. In actual fact, we observed that young males developing AKI have more ICU admission (24.4 vs 15.8%) and protected discharge (32.2% vs 21.2%, p=0.000) (Table 11).

In the second quartile there were no differences between sexes.

In the eldest quartiles males have longer hospitalization's length, higher mortality rate (20% vs 17% and 27% vs 20%, respectively 3rd and 4th quartile) and more admission rate to ICU (12% vs 9% and 5% vs 3,5%, respectively 3rd and 4th quartile) (Table 11).

There were no differences for renal recovery (Table 11).

| | AGE'S QUARTILES | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st | | | 2nd | | | 3rd | | | 4th | | |
| | M 1463 | F 1167 | *p* | M 2390 | F 1705 | *p* | M 2738 | F 2801 | *p* | M 2007 | F 3675 | *p* |
| **LOS** | 21.9± 20.6 | 22.0±23.8 | 0.863 | 20.0±19.0 | 20.5±17.1 | 0.412 | 19.6 15.8 | 19.4±16.3 | 0.550 | 18.0±17.4 | 16.5±16.1 | 0.000 |
| **LOS> 15 days** | 744 (50.8) | 571 (48.9) | 0.326 | 1104 (46.2) | 828 (48.6) | 0.134 | 1324 (48.4) | 1302 (46.5) | 0.163 | 908 (45.2) | 1490 (40.5) | 0.001 |
| **ICU admission** | 357 (24.4) | 184 (15.8) | 0.000 | 392 (16.4) | 259 (15.2) | 0.296 | 336 (12.3) | 264 (9.4) | 0.001 | 98 (4.9) | 129 (3.5) | 0.012 |
| **Protected discharge** | 427 (32.3) | 227 (21.2) | 0.000 | 666 (33.3) | 504 (34.7) | 0.409 | 835 (38.1) | 920 (39.4) | 0.368 | 584 (40.0) | 1229 (41.7) | 0.295 |
| **Death** | 143 (9.8) | 97 (8.3) | 0.196 | 391 (16.4) | 251 (14.7) | 0.155 | 548 (20.0) | 468 (16.7) | 0.001 | 548 (27.3) | 726 (19.8) | 0.000 |
| **Renal recovery** | 1083 (82) | 853 (80) | 0.149 | 1608 (80) | 1165 (80) | 0.772 | 1800 (82) | 1902 (82) | 0.562 | 1252 (86) | 2512 (85) | 0.559 |

**Table 11. Outcomes of AKI population based on sex and age quartiles.**

# Determinants and outcomes of Renal recovery and Persistent AKI

Finally, in the cohort of 14,774 AKI patients who survived hospitalization, we evaluated the incidence and determinants of renal recovery versus persistent AKI at discharge.

Overall, 12,175 (82.4%) patients experienced renal recovery, whereas 2,599 (17.6%) had persistent AKI, still meeting the diagnostic criteria for AKI at discharge (Table 12).

There was no significant difference in sex distribution between the two groups. However, patients with persistent AKI were slightly but significantly younger, had a higher prevalence of HF, and a lower prevalence of CKD compared to those who recovered.

Interestingly, the majority of kidney transplant recipients (225/249, 90%) regained kidney function by discharge.

At admission, patients who eventually recovered from AKI had significantly higher sCr) levels compared to those with persistent AKI. Additionally, AKI severity differed between the groups, with a higher incidence of stages 2-3 AKI in the persistent AKI group.

Multivariate logistic regression analysis indicated that the probability of renal recovery was significantly and positively associated with older age and a diagnosis of CKD (as reported in administrative records) (Table 13). Conversely, renal recovery was negatively associated with LOS, a history of HF, and ICU admission.

Furthermore, clinical outcome analysis revealed that patients with persistent AKI were more frequently admitted to the ICU, had longer hospitalizations, and more often required protected discharge arrangements (Table 14).

| | Recovery | Persistent AKI | P |
|---|---|---|---|
| **N,** | 12175 (82.4) | 2599 (17.6) | |
| **Age (years)** | 74.2 ± 15 | 73.8 ± 14.9 | <0.0001 |
| **Gender M%** | 5743 (47.2) | 1222 (47) | 0.9 |
| **Comorbidities, %** | | | |
| **Diabetes** | 1456 (12) | 314 (12.1) | 0.8 |
| **HF** | 1462 (12) | 500 (19.3) | <0.0001 |
| **Sepsis** | 965 (8) | 189 (7) | 0.2 |
| **CKD** | 1242 (10.2) | 230 (8.9) | 0.039 |
| **Kidney Tx** | 225 (1.8) | 24 (0.92) | <0.001 |
| **sCr at admission (mg/dl)** | 1.63 ± 1.6 | 1.16 ± 0.88 | <0.0001 |
| **eGFR at admission (ml/min)** | 59 ± 32 | 75 ± 31 | <0.0001 |
| **AKI stage** | | | <0.0001 |
| **1** | 8045 (66) | 1388 (53.5) | |
| **2** | 2754 (22.6) | 777 (29.9) | |
| **3** | 1376 (11.3) | 434 (16.6) | |

**Table 12. Main clinical characteristics of AKI patients based on recovery status at the discharge**

Abbreviations: CKD chronic kidney disease, HF hearth failure, Tx transplantation, sCr serum creatinine, ICU intensive care unit, AKI acute kidney injury

| | Univariate | | | Multivariate Model | | |
|---|---|---|---|---|---|---|
| **RISK FACTORS** | **OR** | **95% CI** | **p** | **OR** | **95% CI** | **p** |
| **Age** | 1.006 | 1.004 – 1.009 | <0.0001 | 1.007 | 1.004 – 1.01 | <0.001 |
| **Comorbidities** | | | | | | |
| **Diabetes** | 0.98 | 0.87-1.12 | 0.84 | 1 | 0.87-1.14 | 0.9 |
| **HF** | 0.57 | 0.51-0.64 | <0.0001 | 0.52 | 0.46 – 0.59 | <0.0001 |
| **CKD** | 1.17 | 1.01-1.35 | 0.039 | 1.38 | 1.28 – 1.47 | <0.0001 |
| **AKI stage** | 0.71 | 0.67-0-76 | <0.0001 | 0.74 | 0.7-0.78 | <0.0001 |
| **ICU stay** | 0.75 | 0.65 – 0.86 | <0.0001 | 0.89 | 0.77 – 1.03 | 0.1 |
| **LOS (day)** | 0.99 | 0.98 – 0.99 | <0.0001 | 0.99 | 0.99 – 0.99 | <0.0001 |

**Table 13. Logistic models for the recovery after acute kidney injury in hospitalized patients**

Abbreviations: OR odds ratio, CI confidence interval, HF heart failure, CKD chronic kidney disease, sCr serum creatinine, ICU intensive care unit, LOS length of stay.

| | Recovery | Persistent AKI | p |
|---|---|---|---|
| **N,** | 12175 (82.4) | 2599 (17.6) | |
| **ICU admission, %** | 975 (8) | 271 (10.4) | <0.001 |
| **LOS (days)** | 18.5 ±15.2 | 22.4±22.1 | <0.001 |
| **Discharge at home, %** | 7786 (64) | 1596 (61.5) | 0.019 |
| **Protected discharge, %** | 4389 (36) | 999 (38.5) | |
| **sCr (mg/dl)** | 1.01±0.69 | 1.56±1.32 | <0.001 |

**Table 14. Clinical outcomes of AKI distinguished according to recovery status at the discharge**

# DISCUSSION

This study aimed to analyze AKI epidemiology in a large cohort of patients admitted to two hospitals in Italy to define the clinical characteristics and outcomes associated with this condition.

First, we observed an AKI incidence of approximately 21% among the total hospitalized patients, closely aligning with global AKI epidemiology studies following KDIGO guidelines in our geographical region (South-West Europe)[1]. This finding indirectly supports the reliability of our extended and simplified AKI definition based solely on sCr changes. Moreover, as expected and consistently with previous reports, AKI stage 1 emerged as the most prevalent form, accounting for approximately 60% of cases[39]. Investigating deeper into the AKI population, we identified demographic and clinical characteristics, such as age, sex, and comorbidities, as independent contributors to the risk of AKI development. Specifically, AKI patients were older with a higher comorbidity burden compared to non-AKI patients.

The impact of sex on AKI risk warrants special consideration[40]. There is an open debate surrounding the influence of sex on AKI development, in fact, while KDIGO defined female sex as a risk factor for AKI[1] other data showed a different epidemiology[32].

Indeed, despite a higher prevalence of females among AKI patients, we observed that female patients developed less severe forms of AKI and the incidence varied according to age; moreover, the male/female ratio across AKI staging was variable. So notably, in females, AKI incidence increased significantly with age in each AKI stage, suggesting a non-linear relationship between sex, age, and AKI risk, probably due to the modifications of health status occurring during female lifetime. Several studies now showed how sexual dysmorphism and different hormonal condition change the renal response to acute damage. Unfortunately, we do not have information on the cause of AKI, in fact it seems that in cardiac surgery, aminoglycoside nephrotoxicity, rhabdomyolysis and radio-contrast administration females have a higher risk for kidney damage, so we cannot further investigate in which contests sex differences have more impact. Anyway, the setting and the pathogenesis seem to be relevant in different AKI incidence and outcome based on sex. Finally, women undergo hormonal changes during lifetime, in our cohort females were older, and the incidence of AKI was higher in the eldest period of their life. In the young population, male had more incidence of AKI and severe damage needing ICU access.

Examining in-hospital distribution, we found that while AKI presented a higher incidence in ICU patients, it also developed in up to 20% of patients in low- and medium-intensity care settings. This observation underscores the need for expanded studies on AKI epidemiology and outcomes in non-critically ill patients, an area currently lacking in research. Furthermore, our study confirmed the independent and significant impact of AKI on clinical outcomes, rising with its severity. This was valid for short time intrahospital outcomes, such as mortality and LOS, but also for discharge conditions. So, we highlighted that AKI patients, especially if experiencing AKI 2-3, at the discharge had higher serum creatinine levels and required more protected discharge compared to patients without AKI. These factors may imply a higher social and economic cost for the long-term management of these patients but also constitute the basis for the transition to AKD and CKD. Early diagnosis and treatment of AKI could, sometimes, have some benefit, but the precocious recognition of kidney damage is quite hard. Some tools as alert have been tested but with debating results.[41] Moreover, the nephrologists' burden of work to evaluate all AKI cases in hospital could be unaffordable for our Health System.

Regrettably, it is hard to identify early the patients with higher risk to progress toward CKD, in fact some studies tried to observe the use of clinical multivariant models as well as novel biomarkers, as proinflammatory cytokines, urinary epidermal growth factor (EGF), kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) .[42] Additionally, a post-AKI clinic could be an instrument to patients' follow up, both for clinical and research purposes.

However, the relationship between AKI and CKD is bidirectional, and conversely, CKD constitutes a known risk factor for AKI development. To ascertain this issue in our cohort, we compared clinical characteristics and outcomes of patients developing pure AKI with patients developing AKI on previous CKD. Our findings confirmed the higher incidence of AKI among patients with previous CKD, highlighting their older age, higher comorbidity prevalence, and elevated sCr at admission. Notably, these patients developed more severe forms of AKI with worse clinical outcomes, emphasizing the role of even mild CKD as an additional risk factor for AKI and its complications.

To address this peculiar aspect and avoid potential bias from arbitrary definitions of preadmission renal function often used in epidemiological studies, in this analysis we included only patients with known preadmission serum creatinine levels. These patients represented more than 30% of our study population.

Our findings confirmed the higher incidence of AKI among patients with previous CKD, highlighting their older age, higher comorbidity prevalence, and elevated sCr at admission. Notably, these patients developed more severe forms of AKI with worse clinical outcomes, emphasizing the role of even mild CKD as an additional risk factor for AKI and its complications.

Finally, given the emerging importance of post-AKI care and long-term sequelae management, we evaluated the renal recovery status in AKI patients who survived until hospital discharge.

Our analysis revealed that while most AKI patients recovered their baseline kidney function, a significant proportion (16.7%) still had persistent AKI at discharge.

Patients who experienced renal recovery were older and had a higher prevalence of CKD. They also presented with worse kidney function at admission but developed less severe forms of AKI during hospitalization. A possible interpretation of this finding, which might seem contrary to the established relationship between CKD and AKI risk, is that these patients likely developed AKI outside the hospital, fitting the definition of community-acquired AKI (CA-AKI). This hypothesis aligns with our findings, as it is well-known that CA-AKI has better outcomes compared to in-hospital AKI and is more often associated with reversible functional causes of AKI.

Conversely, persistent AKI was more prevalent among younger patients who developed more severe in-hospital AKI and required longer hospital stays with more intensive care. These patients also had worse conditions at discharge, necessitating a higher percentage of protected discharges.

This finding is of utmost importance, as one of the goals of post-discharge AKI management is to identify high-risk patient groups. Targeted monitoring and prevention programs for long-term complications should be directed towards these patients to improve their outcomes.

# Strengths and limitations

This study is one of the few Italian ones exploring the hospital incidence of AKI. The points of strength are the multi-center approach, which reduced eventual inclusion biases, the large number of patients included and the possibility to analyze comorbid condition, kind of discharge and the type of department.

Our study has several limitations. Firstly, its retrospective, observational design may restrict the generalizability of findings due to potential variations in AKI incidence, mortality rates, and procedures across different hospitals, regions, and countries[43].

Furthermore, although our results are consistent with those reported in large epidemiological studies, the pragmatic method used for calculating AKI, while reflective of real-world clinical practices, introduces a potential source of variability. Specifically, the choice of baseline serum creatinine, and notably, the absence of data on urine output, may significantly impact the accuracy of AKI incidence assessments and recognition[44].

In particular, the lack of evaluation of urine output, which is common in many large studies, represents a significant limitation not only of our study but also of much of the current literature on AKI epidemiology[45].

Additionally, we have no data on specific causes for hospitalization, such as for AKI etiology, which could influence disease presentation and outcomes.

Moreover, we analyzed only differences based on biological sex, not more complete based on gender.

Lastly, comorbidities were identified using administrative codes entered in the hospital database, introducing the possibility of information bias.

# CONCLUSIONS

AKI in hospitalized patients is a frequent and complex complication, it shares common pathophysiological pathways for kidney damage that have differences secondary to age, sex, comorbidities, previous CKD. In all the subgroups AKI patients have the worst outcomes, correlating to AKI stages.

Prompt nephrology consultation can improve the outcome of these patients[46] but a simple and valuable method to screen hospitalized patients or to identified promptly AKI patients is still lacking. Different biomarkers and alert systems[41,47] have been used but strong evidence is still lacking.

Understanding the population with increased risk, less renal recovery ca be useful to stratify hospitalized patients and try to increase the nephrologist attention on who needs more consideration and can benefit from nephrologist care and probably also a post-AKI follow up.

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