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Acute renal failure as an independent risk factor for developing chronic kidney disease. A single-center observational study.

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Abstract

Introduction: The incidence of acute renal failure (AKI) in noncritical hospital areas ranges from 0.5% to 13%. This rate varies from 25% to over 45% in intensive care units. This study aims to determine the prevalence of acute kidney injury and understand its association with the development of chronic kidney disease (CKD) in a public reference center in Mexico City.

Methods: This observational longitudinal study was conducted at Hospital Juárez de México from 2017 to 2018, involving hospitalized adult patients with at least two serum creatinine measurements. Patients diagnosed with AKI were identified, and those with CKD within 90 days were noted. The relationship between AKI and the development of CKD was examined using logistic regression. The prevalence of AKI and the prevalence of CKD among patients diagnosed with AKI were calculated.

Results: A total of 160 patients were enrolled in the study. The prevalence of acute kidney injury (AKI) was 58%, while the prevalence of chronic kidney disease (CKD) among patients presenting with AKI was 55%. A significant association was found between AKI and the subsequent development of CKD at 90 days (glomerular filtration rate (GFR) <60 ml/min x 1.72 m^2), with an odds ratio (OR) of 16.62 (95% confidence interval (CI) 5.34 - 34.54) and a P value of <0.001. Other factors that may impact AKI, such as type 2 diabetes mellitus (T2DM), age, systemic arterial hypertension (SAH), sepsis, sex, and intensive care unit (ICU) stay were assessed through multivariate analysis; however, no significant association was observed.

Conclusion: This study demonstrates a significant association between an episode of AKI and the risk of developing CKD within 90 days.

Keywords:

Acute kidney failure, Chronic kidney disease, risk factor.

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A Kidney injury (AKI) is a clinical syndrome characterized by a rapid decline in renal excretory function over hours to days, resulting in the accumulation of nitrogen metabolism products such as creatinine, urea, and other unmeasured waste products. [1].

It encompasses various etiologies, including specific renal diseases (acute interstitial nephritis, acute glomerular diseases, and vasculitis), nonspecific conditions such as ischemia and toxins, and extrarenal pathologies (prerenal azotemia and acute obstructive nephropathy) [2].

The incidence of acute kidney injury is increasing in noncritical hospital areas, ranging from 0.5% to 13%. In intensive care units, the incidence fluctuates from 25% to over 45%. A study involving 50 patients at Juarez Hospital in Mexico revealed a prevalence of 60% among patients in noncritical areas.

Mortality rates due to acute kidney injury remain high, particularly among critically ill patients, where mortality can reach as high as 53% [2]. Previous observational studies and meta-analyses have documented the association between an episode of acute kidney injury and the development of subsequent chronic kidney disease. For example, a meta-analysis with a total of 3000 patients from 13 studies revealed an HR of 8.8 (95% CI 3.1–25.5) for developing CKD after an episode of AKI and 3.1 (95% CI 1.9–5.0) for end-stage CKD (stage V). The greater the severity of AKI was, the greater the risk of CKD, with an HR of 2.0 for mild AKI, an HR of 3.3 for moderate AKI, and an HR of 28.2 for severe AKI. The risk of end-stage CKD (requiring a TSFR) also increased progressively with AKI severity: HR 2.3 for mild AKI (95% CI: 1.7–3.3), HR 5.0 for moderate AKI (95% CI: 2.69.8), and HR 8.0 for severe AKI (95% CI: 1.3–48.6) [4].

AKI of greater severity increases the risk of death and the need for a TSFR. After an AKI episode resolves, there is an increased long-term risk of cardiovascular disease, mortality, and up to 30% for CKD [2].

Factors associated with the development of CKD after AKI include the severity of AKI, underlying CKD, multiple AKI episodes, advanced age (above 76 years), mixed-etiology ATN, type 2 diabetes mellitus (DM2), decreased albumin levels, and cardiac surgery [5]. Previous CKD is a significantly associated factor, as the risk of CKD progression increases 49-fold with an episode of AKI (CI 95% 34.6–49.1) [6].

An episode of AKI can be considered an independent risk factor for CKD, as indicated by a meta-analysis involving 3,476 children aged 1 month to 18 years with hemolytic uremic syndrome (HUS) associated with diarrhea who did not present other risk factors, such as chronic degenerative diseases. Eight percent of AKI survivors maintained a TFR of 5–59 ml/min after resolution[7].

The recovery pattern is also identified as a significant factor, as patients with rapid recovery tend to have a better prognosis and a lower risk of CKD than those with slow recovery, who face a greater risk of CKD. Specifically, the risk for CKD was HR 1.43 (95% CI, 1.39–1.48) for rapid recovery (at 2 days), HR 2.00 (95% CI, 1.88–2.12) for intermediate recovery (3–10 days), and HR 2.65 (95% CI, 2.51–2.80) for slow recovery (after 10 days). Another associated factor is a high Charlson comorbidity (HR 1.10; 95% CI 1.05–1.15) and arterial hypertension (HR 1.82; 95% CI 1.28–2.58)[8].

Repeated renal injury and aberrant repair lead to CKD due to a maladaptive response in which tubular epithelial cells are arrested in the G2/M phase of the cell cycle. This process is accompanied by an increase in transforming growth factor B and the activation of JNK (c-jun NH2-terminal kinase) signaling, which results in glomerulointerstitial fibrosis. Moreover, pericytes differentiate into myofibroblasts, causing fibrosis and microvascular rarefaction. Autophagic failure of dendritic cells and renin–angiotensin–aldosterone system (RAAS) activation are also observed. Fibrogenic cells likely do not return to their quiescent state, and some of these processes are exacerbated by high-sodium and high-protein diets [10].

With the hypothesis that patients with AKI are more likely to develop CKD, this longitudinal observational study was conducted.

Materials and methods

Study design

This was a longitudinal observational study. The source is ambispective.

Scenery

The study was conducted at Juarez Hospital in Mexico from August 1, 2017, to January 31, 2018.

Participants

Records of patients older than 17 years who were hospitalized with acute renal failure and had at least two serum creatinine measurements recorded during their hospitalization were included. From the selected cases, controls hospitalized during the same period were matched by age at a rate of 1.4 cases per control.

Variables

The variables included age, sex, comorbidities, progression to chronic kidney disease, primary diagnosis at hospitalization, previous diagnosis of chronic kidney disease, hemodialysis treatment, and admission to intensive care.

Data sources/measurements

The source was indirect; an electronic form was completed on the basis of institutional medical records.

Biases

The application of the participant selection criteria helped to avoid observation and selection bias. To prevent potential interviewer, information, and memory biases, the principal investigator consistently

maintained the data via a guide and records approved in the research protocol. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was established and verified.

Study size

An alpha value of 5%, a power of 80%, and a prevalence of acute kidney injury of 14% were assumed (from previous studies). We obtained one hundred sixty patients by substituting these values into the proportion formula.

Quantitative variables

Descriptive statistics were utilized. The results are presented as frequencies and percentages. The categorical variables were not converted into quantitative variables.

Statistical analysis

Qualitative variables were analyzed using frequencies and percentages. A 95% confidence interval is provided for the proportion of the relevant prevalence. Depending on the outcome, two groups are examined: patients who developed chronic kidney disease and those who did not. Logistic regression was conducted with the variables pertinent to the development of chronic kidney disease. An odds ratio and a 95% confidence interval are presented. The statistical package used was IBM Corp., released in 2017: IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM.

Results

Participants

A total of 160 patients were included in the study.

Characteristics of the study groups

The prevalence of CKD in patients who presented with AKI was 55% in a population of 160 patients. Among the 94 patients diagnosed with AKI, 41 (43%) were women, and 53 (57%) were men. The average age was 50.26 years (1892 years), and the average hospital stay was 10 days, as shown in the Table 1 of the general characteristics.

Table 1. Characteristics of patients with AKI according to development of CKD (< 60 ml/min) at 90 days.

Variable	AKIN Group N=94	Group Without AKIN N=66
Age (Years)	50.3	50.2
IMC (kg/m ²)	26.6	27.13
Sex woman	41 (43%)	17 (40%)
Days of hospitalization	10.7	11.95
Septicemia	35 (37.23%)	15 (35.71%)
Respiratory Disease	14 (14.89%)	5 (11.90%)
Abdominal surgery	23 (24.46%)	12 (28.57%)
Cardiovascular Disease	14 (14.89%)	7 (16.66%)
Gastrointestinal/Liver Disease	18 (19.14%)	7 (16.66%)
Neurological Disease	6 (6.38%)	4 (9.52%)
Cancer	17 (18.05%)	7 (16.66%)
Trauma	3 (3.19%)	2 (4.76%)
Poisoning	3 (3.19%)	1 (2.38%)
Obstructive Uropathy	14 (14.89%)	6 (14.28%)
Rhabdomyolysis	4 (4.25%)	2 (4.76%)
Glomerulonephritis	5 (5.31%)	2 (4.76%)
Shock	19 (12.76%)	10 (23.80%)
Obesity	12 (12.76%)	18 (19.04%)
Heart failure	11 (11.70%)	6 (14.28%)
High blood pressure	38 (40.42%)	14 (33.33%)
Type 2 Diabetes Mellitus	27 (28.72%)	7 (16.66%)
Kidney stones	5 (5.31%)	3 (7.14%)
Use of nephrotoxic agents	11 (11.70%)	7 (16.66%)
AKIN 1	13 (13.80%)	-
AKIN 2	12 (12.76%)	-
AKIN 3	69 (73%)	-
Renal function replacement therapy	42 (44%)	-
Hemodialysis	36	-
Prism	6	-
Intensive Care Unit	24	-
ERC	52 (55%)	6 (9%)

In the evaluation of comorbidities, 13% of patients were obese (BMI =/>30 kg/m2), 7.44% had a previous diagnosis of CKD, 12% had a diagnosis of heart failure, 41% had systemic arterial hypertension, and 29% had type 2 diabetes mellitus.

According to the classification of acute renal failure, 13.80% of individuals had AKIN I, 12.76% had AKIN II, and 73% had AKIN III. Twenty-five percent of patients with AKI required admission to the intensive care unit, 44% required TSFR, and 85.70% required intermittent hemodialysis. Fourteen points (28%) required continuous slow hemodiafiltration.

The principal hospitalizing diagnoses in patients with AKI were sepsis (37%), surgery (24%), shock (20%), gastrointestinal/liver disease (19%), cancer (18%), obstructive uropathy (15%), respiratory disease (15%), cardiovascular disease (14%), neurologic disease (6%), glomerulonephritis (5%), kidney stones (5%), rhabdomyolysis (4%), poisoning (3%), and trauma (3%).

Table 1 outlines the differences between patients with AKI who developed CKD and those who did not develop CKD within 90 days. The most common characteristics among the group that developed CKD included sepsis, respiratory disease, gastrointestinal/liver disease, cancer, systemic arterial hypertension (SAH), T2DM, TSFR, and admission to the intensive care unit (ICU). Patients who met the TSFR had a greater prevalence of CKD than did those without this requirement: 53% compared with 33%, respectively.

Association analysis

A significant association was found between AKI and the subsequent development of CKD at 90 days (GFR <60 ml/min × 1.72 m2), with an OR of 16.62 (95% CI; 5.34–34.54) and *P* <0.001 (Table 2). Other factors impacting AKI were assessed by multivariate analysis via logistic regression, but no significant associations were found (Table 3).

Table 2. Association of AKI with CKD.

Patients N=160	ERC	OR 95% CI	*P*
AKI (94)	52 (55%)		
Without AKI (66)	6 (9%)	16.62 (5.34 – 34.54)	<0.001

Table 3. Logistic regression.

Variable	Coefficient	Standard error	Wald	*P*
Diabetes Mellitus	0.05996	76993.2	6.06 E-13	1.0
Age	-0.0034	0.03296	0.01079	0.917
HAS	-0.0391	47311.7	6.81 E-13	1.0
Sepsis	-0.0485	65668.4	5.46 E-13	1.0
Sex	0.00605	18970.8	1.02 E-13	1.0
ICU	24.7558	18955.6	1.71 E-6	0.999
Constant	-26.1931	9818.3	7.12 E-6	0.998

HAS: arterial hypertension. HAS: systemic arterial hypertension. ICU: intensive care unit.

Discussion

The prevalence of AKI among hospitalized patients at Juarez Hospital in Mexico was 58%, which is consistent with findings from a previous study of the same population. CKD may serve as a risk factor for AKI and vice versa. This study revealed a significant association between an episode of AKI and the risk of developing CKD within 90 days, with an odds ratio of 16.62 (95% CI; 5.34–34.54), which aligns with prior research. Multiple studies indicate that AKI is a critical risk factor for CKD; for example, a meta-analysis reported an increased risk of developing CKD following AKI (OR 8.8) [11]. Although the underlying mechanisms of this association remain unclear, some animal studies have demonstrated maladaptation in the repair of tubular cells arrested in the G2/M cell cycle, induced by the production of profibrogenic cytokines, the transition of pericytes to myofibroblasts, epigenetic changes in myofibroblasts, microvascular dysfunction, chronic inflammatory infiltration, mitochondrial dysfunction, activation of the renin–angiotensin–aldosterone system, loss of tubular epithelial cells, glomerular hyperfiltration, and the development of tubulointerstitial fibrosis and glomerulosclerosis [12].

As described in the results analysis, other factors impacting AKI were evaluated; however, they were not significantly associated. These factors include DM2, HAS, age, sex, sepsis, and intensive care unit (ICU) admission. Nevertheless, other studies have documented the associations of each of these factors with AKI.

On the other hand, a higher frequency of DM2, SAH, sepsis, ICU admission, TSFR requirement, and older age was observed in patients who developed CKD. Advanced age, the presence of diabetes mellitus, and decreased previous GFR have been identified as risk factors for progression to advanced-stage CKD. Other factors associated with this progression, as noted in different studies, include the severity, frequency, and duration of AKI [13].

The most frequent diagnosis in patients with AKI was septicemia; however, no statistical significance was found regarding it as an associated factor. A review of the literature revealed that sepsis is the most common cause of AKI, affecting 50% of patients. With sepsis, which has a 60% mortality rate at three months, the need for renal function replacement therapy in cases of septic shock increases mortality from less than 40% without AKI to over 60% with AKI, along with an increased demand for dialysis [14]. The pathophysiological mechanisms include the adaptive response of the tubular epithelium, renal inflammation, and microvasculature dysfunction, leading to global renal ischemia, cellular damage, and acute tubular necrosis (ATN). Injury can occur even without hypoperfusion, and elevated levels of cytokines (IL-6 and IL-10) have been observed. Microvascular dysfunction, hypoxia, and tissue injury are correlated with the severity of AKI [15]. Another factor involved in reducing the GFR is a combination of efferent vasodilation and systemic hypotension [16].

The mean age of patients with AKI was 50 years, whereas for patients with CKD after AKI, it was 54 years. Evidence from these findings has revealed an increased incidence of AKI in older adults over the last decade. Since survivors often develop chronic kidney disease, age has been identified as a risk factor for CKD following AKI [5]. Older patients have a lower rate of recovery of renal function than younger patients do; 31.3% of older patients do not recover renal function, whereas 25% of younger patients do. Among the factors that increase susceptibility in this population group are structural, functional, and hemodynamic changes associated with aging, as well as related diseases such as DM2, SAH, atherosclerosis, and heart disease failure.17]. Older adults with AKI who require renal function replacement therapy are at up to 500 times greater risk of progression to CKD. The mechanisms involved may include acute endothelial injury, nephron loss followed by glomerular hypertrophy, and the development of fibrosis [18].

On the other hand, age is an independent factor in the development of AKI. Additionally, patients with AKI who require dialysis tend to be older than those without such requirements. A 9-year prospective study in Madrid showed that patients over 70 years old have a 3.5 times greater risk of developing AKI and experience higher mortality rates after one year [19]. Notably, 69.2% of patients older than 55 years and admitted to the ICU experienced acute kidney injury (AKI). The associated factors include the use of nephrotoxic drugs (aminoglycosides, vancomycin, and NSAIDs), a history of hypertension (OR 1.13; 95% CI, 1.02–1.25), and sepsis (OR 2.12; 95% CI,

1.68–2.67). However, with increasing age, these variables become less predictive, whereas age remains an independent variable in the development of AKI [20].

The diagnosis of DM2 was more common among patients with AKI and those who developed CKD following AKI. DM2 has been identified as an independent risk factor for AKI [21]. On the other hand, a study involving 3,679 diabetic patients revealed that an episode of AKI is associated with the development of CKD (RR= 3.56, 95% CI 2.76--4.61), and each additional episode of AKI doubles the risk [22]. Other authors mention that among diabetic patients, AKI increases the risk of advanced CKD more than three times, independent of other risk factors for progression. Other progression factors include hypertension, with a hazard ratio of 1.82 (95% CI; 1.41–2.37), and elevated baseline creatinine at 8.59 (95% CI 6.07–12.15) for each increased unit [23]. This association can be explained in these patients by their greater susceptibility to hypoxia arising from decreased renal blood flow, a lowered threshold for free radical injury and ischemia, chronic inflammation, a history of microvascular and macrovascular disease, and a diminished response to the vasodilatory effects of nitric oxide [24].

Patients who required dialysis were found to have a greater frequency of chronic kidney disease (CKD), which is consistent with other observations. In a study of ICU patients in Denmark, those diagnosed with acute kidney injury (AKI) who required therapeutic ultrasound fluid removal (TSFR) had a heightened risk of CKD within the subsequent 180 days (HR = 105.6, 95% CI 78.1–142.9). Furthermore, from 181 days to 5 years, this elevated risk persisted (HR = 6.2, 95% CI: 4.7–8.1). Another study reported a relative risk of 28.1 (95% CI 21.1--36.6) for progression to CKD following an AKI event that necessitated dialysis [23]. Other studies have reported that ICU survivors with AKI and a high TSFR range from 4.2% to 28.9% at 180 days postdischarge [24]. Among these mechanisms, renal parenchymal injury can lead to tubulointerstitial fibrosis, a reduction in the number of functional nephrons, renal damage, renal failure, permanent microvascular changes, and signaling activation for inflammation and fibrosis, which predisposes patients to an accelerated decline in the GFR [23- 25].

The hospital mortality rate observed in patients with AKI was 19%. In other studies, mortality rates have reached 35%, whereas in AKI 3 specifically, mortality has increased to 3971% [25].

According to the above findings, a significant association between AKI and the development of CKD in the study population was observed, among other variables. Therefore, patients with AKI should be approached closely, with follow-up upon discharge. Different strategies have been explored to prevent the progression of CKD, such as the use of aldosterone antagonists, statins, ACE inhibitors, ARBs, and a low-protein diet. However, randomized controlled clinical trials investigating the prevention of CKD are lacking [12]. One advantage of this study is that although a considerable number of studies related to the subject have been published at Juarez de Mexico Hospital, the impact on the renal function of these patients has not been studied. A limitation of this study is that it was an observational and ambispective study. On the other hand, a larger sample size could reveal an association with other variables. It is possible that, in a small subgroup of patients with baseline renal dysfunction, CKD status itself was a risk factor for AKI, raising the possibility of reverse causality between AKI and CKD. Finally, more robust studies (e.g., cohort studies) are needed to determine other potential factors associated with CKD following AKI.

Conclusions

AKI was significantly associated with the development of CKD. Considering this finding, individuals with acute kidney injury require a different approach. Identifying these genes that interfere with the progression of the disease is crucial. Measures such as close follow-up in the outpatient clinic, blood pressure control, and avoidance of nephrotoxic medications can be implemented. The best way to reduce the development of CKD after an AKI event is prevention.

Abbreviations

AKI: Acute renal failure.
CKD: chronic kidney disease.
HR: hazard ratio.
CI: confidence interval.
TSFR: Renal function replacement therapy.

Additional information

No supplementary materials have been declared.

Acknowledgments

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Authors' contributions

Jorge Anselmo Peña Pérez: Conceptualization, methodology, research, Writing – Original draft.
Fernando Arturo Reyes Marín: Conceptualization, project administration, supervision, validation, visualization, writing, review and editing.
All the authors read and approved the final version of the manuscript.

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Availability of data or materials

Not applicable.

Statements

Ethics Committee approval and consent to participate

The bioethics committee of Juárez Hospital in Mexico approved the study.

Consent for publication

Does not apply when specific images, X-rays, or photographs of patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Author information
Not declared.

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