

## Risk factors for the progression of chronic kidney disease after acute kidney injury

Fatores de risco para a progressão da doença renal crônica após a lesão renal aguda

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### ABSTRACT

**Introduction:** The incidence of chronic kidney disease (CKD) is increasing with the increasing age of the population and the increasing number of elderly survivors of acute kidney injury (AKI). The risk factors for the progression of CKD after AKI are unclear. **Objective:** To investigate the association between AKI and its progression to CKD and the risk factors involved. **Methods:** An observational, retrospective study of AKI patients followed from 2009 to 2012 was carried out. We evaluated the etiology of AKI, the use of vasoactive drugs and mechanical ventilation, the need for dialysis, the presence of comorbidities, the glomerular filtration rate (GFR), the length of stay and the progression of CKD. Statistical analyses, including the Chi-square test and Pearson's correlation, were performed using SPSS. **Results:** The 207 patients analyzed had a mean age of  $70.1 \pm 13.1$ , and 84.6% of the male patients exhibited decreased renal function and CKD (*vs.* 60.4% of the female patients). The progression of AKI to CKD was more frequent in patients admitted to wards (63.8%), cancer patients (74.19%), patients with sepsis (67.18%) and patients with obstruction (91.66%). Dialyses were performed in 16.4% of the patients, but this was not correlated with the progression of CKD. **Conclusions:** Being an elderly male patient with AKI due to sepsis and obstruction was correlated with progression to CKD following discharge.

**Keywords:** acute kidney injury; kidney diseases; kidney failure, chronic; renal dialysis; dialysis.

### RESUMO

**Introdução:** A incidência da doença renal crônica (DRC) está aumentando com o aumento da idade da população e o número crescente de idosos sobreviventes da lesão renal aguda (LRA). Os fatores de risco para a progressão da DRC após a lesão renal aguda (LRA) não são claros. **Objetivos:** Investigar a associação entre a LRA e sua progressão para a DRC e os fatores de risco envolvidos. **Métodos:** Foi realizado estudo observacional, retrospectivo de pacientes com LRA acompanhados de 2009 a 2012. Foram avaliados a etiologia da LRA, o uso de drogas vasoativas, ventilação mecânica, necessidade de diálise, presença de morbidades associadas, ritmo de filtração glomerular estimado (eGFR), duração da internação e a progressão da DRC. As análises estatísticas incluíram o teste Qui-quadrado e a correlação de Pearson utilizando o programa do SPSS. **Resultados:** Os 207 pacientes analisados apresentaram idade de  $70,1 \pm 13,1$  anos, 84,6% eram do sexo masculino e que apresentaram redução da função renal e DRC (*vs.* 60,4% dos pacientes do sexo feminino). A progressão da LRA para DRC foi mais frequente em pacientes internados em enfermarias (63,8%), pacientes com câncer (74,19%), com sepse (67,18%) e com obstrução do trato urinário (91,66%). As dialises foram realizadas em 16,4% dos pacientes, mas isso não foi correlacionado com a progressão da DRC. **Conclusões:** Pacientes idosos com LRA devido à sepse e obstrução do trato urinário foram correlacionados com a progressão para DRC após a alta.

**Palavras-chave:** Lesão renal aguda; nefropatias; falência renal crônica; diálise renal; diálise.

## INTRODUCTION

Acute kidney injury (AKI) is one of the most significant complications in critically ill patients, contributes to more than half of mortalities,<sup>1-5</sup> increases patients' length of stay (LOS) at the hospital and the risk of death and is associated with the need for renal replacement therapy (RRT).<sup>1,2,6-11</sup>

Individuals who survive one episode of AKI are at risk for the development chronic kidney disease (CKD) and can progress into more advanced stages of CKD.<sup>2,3,6-9,12-15</sup> A meta-analysis published by Coca *et al.*<sup>14</sup> showed that AKI is an independent risk factor for the development of end-stage renal disease (ESRD) morbidity and mortality by cardiovascular disease.

Relevant risk factors for the progression of AKI to CKD include the need for RRT, AKI severity, old age and diabetes.<sup>16-22</sup> However, the mechanism by which AKI leads to progressive CKD is not fully understood, pre-clinical studies point to possible mechanisms, such as acute endothelial injury, nephron loss and the degree of tubulointerstitial fibrosis is the best predictor of ESRD.<sup>1,7,17,23</sup>

Clinical studies conducted to obtain better information about the progression of AKI to CKD represent a significant contribution to the understanding the relationship between AKI and CKD.<sup>7,21,22</sup> In this paper, our objective was to investigate the association between AKI and CKD and the risk factors involved in CKD development.

## CASE SERIES AND METHODS

AKI patients followed by the Nephrology Division of the Hospital do Servidor Público Estadual (HSPE) of São Paulo, Brazil from 2009 to 2012 were retrospectively assessed. A total of 1,200 patients were evaluated based on the records referral forms; patients who died during the follow-up period and patients with stage 5 CKD were excluded. The following data were evaluated: etiology of AKI, use of vasoactive drugs, mechanical ventilation for more than 48 hours, need for RRT and the presence of comorbidities.

The glomerular filtration rates (GFRs) were estimated using the Chronic Kidney Disease-Epidemiology Collaboration Equation (CKD-EPI) in patients who had basal creatinine levels taken at admission, discharge and as outpatients; the need for dialysis, the duration of AKI and LOS were also

recorded. The assessed outcomes were death and progression to CKD. In the patients with GFR < 60 ml/min, the CKD stage was classified according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria<sup>24</sup> and the progression to later stages of CKD was assessed following discharge from the hospital.

This study was approved by the Research Ethics Committee.

For the statistical analyses, the qualitative variables were summarized as absolute (n) and relative (%) frequencies and the quantitative variables as the means, standard deviations (SD), medians and minimum and maximum values. The associations between clinical outcomes (discharge or death) and the variables of interest were investigated using Pearson's Chi-square Test or the Likelihood Ratio. The significance level was set to 0.05 for all of the tests; the analyses were performed using SPSS version 15.0 for Windows (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA.)

## RESULTS

A total of 1,200 follow-up forms from 2009 to 2012 that were available at the Nephrology Division of the HSPE were assessed; 993 cases were excluded because they met the exclusion criteria. A total of 207 patients were included in the analysis. The average age was  $70.1 \pm 13.1$  years, and 53.6% of the patients were male. The median duration of AKI was 10 days; the average LOS at the hospital was 21 days; the time until a follow-up by a nephrologist was 6 days; and the length of survival after discharge was 103 days. These data are described in Table 1.

The serum creatinine (SCr) level before follow-up by the Nephrology Division was  $1.27 \pm 0.41$  mg/dl (GFR =  $56.3 \pm 4.7$  ml/min). The SCr levels at admission ( $2.89 \pm 2.68$  mg/dl), at discharge ( $1.66 \pm 0.85$  mg/dl) and after discharge ( $1.84 \pm 1.25$  mg/dl) are presented in Table 2.

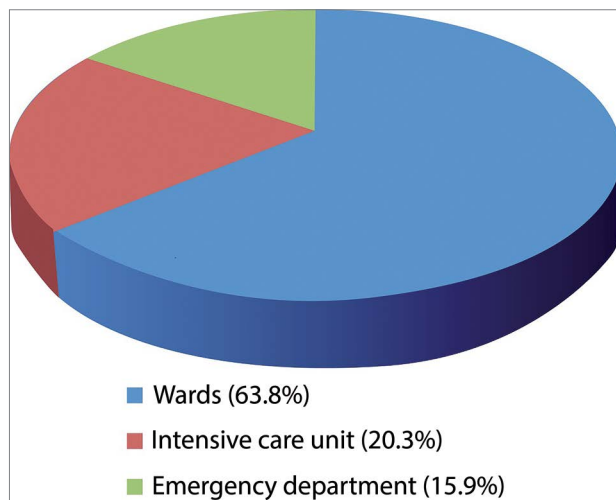
**TABLE 1** CLINICAL CHARACTERISTIC OF PATIENTS WITH AKI DURING HOSPITALIZATION (N = 207)

Age (years)	70.15 ± 13.15
Male (n = 111)	53.6%
AKI duration (days)	10 (1-219)
Length of stay (days)	21 (1-369)
Follow-up by nephrologist (days)	6 (1-93)
Survival after discharge (days)	103 (7-1416)

**TABLE 2** CREATININE LEVELS AND eGFR DURING THE FOLLOW-UP OF PATIENTS WITH AKI (N = 207)

	SCr (mg/dl)	CKD-EPI (ml/min)
Basal	1.27 ± 0.41	56.3 ± 4.7
Admission	2.89 ± 2.68	23.2 ± 5.3
Discharge	1.66 ± 0.85	44.2 ± 16.1
After discharge	1.84 ± 1.25	46.5 ± 10.1

Progression to CKD of AKI patients after discharge occurred, in order of decreasing frequency, in patients admitted to hospital wards (63.8%), patients admitted to the ICU (20.3%) and patients admitted to the emergency department (15.9%) (Figure 1).

**Figure 1.** Progression to CKD of AKI patients after discharge and the hospitalization setting of AKI patients.

During their hospital stay, 34 patients (16.4%) required dialysis. The mortality after discharge was 53%, 63% and 70.58% in patients who needed RRT, patients with mechanical ventilation and patients with septic shock, respectively. There was a significant correlation between mortality and more than one episode of AKI upon hospital admission (Table 3).

**TABLE 3** CORRELATION BETWEEN CLINICAL COMPLICATIONS OF AKI PATIENTS DURING THEIR HOSPITAL STAY AND MORTALITY AFTER DISCHARGE

Complications	N	%	p
Dialysis	18	(53.00)	0.92
Vasoactive drugs	25	(62.50)	0.14
Ventilation for more than 48 hours	19	(63.33)	0.18
Septic shock	24	(70.58)	0.19
More than one AKI episode upon admission	2	(20.00)	0.037

The use of vasoactive drugs, the need for mechanical ventilation for more than 48 hours, septic shock and the need for dialysis had no correlation with the progression of CKD in these patients (Table 4).

**TABLE 4** CORRELATION BETWEEN CLINICAL COMPLICATIONS DURING HOSPITAL STAY AND PROGRESSION TO CKD BASED ON THE LAST ESTIMATED GFR

Complications	Total n = 2017 (%)	CKD-EPI (ml/min) n = 152 (%)	p
Vasoactive drugs	40 (19.00)	26 (65.00)	0.066
Ventilation for more than 48 hours	30 (14.50)	20 (66.67)	0.36
Septic shock	34 (16.42)	23 (67.64)	0.45
Need for dialysis	34 (16.42)	26 (76.47)	0.28

The progression of AKI to CKD was more frequent in 84.68% male patients, admitted to wards (63.8%), cancer patients (74.19%), patients with sepsis (67.18%) and patients with obstruction (91.66%) (Table 5).

Death occurred in 55.3% of the patients admitted to wards ( $p = 0.06$ ) and 57.35% of patients whose AKI was caused by sepsis ( $p = 0.06$ ). Vascular disease (70.58%), cancer (70.96%) and nephrolithiasis (8.33%) were factors that were significantly associated with this outcome ( $p = 0.01$ ,  $p = 0.02$  and  $p = 0.02$ , respectively) (Table 6).

Among the 142 patients whose AKI progressed to CKD, changes between CKD stages during the hospital stay were assessed at discharge based on the last recorded SCr. The results showed that CKD advanced by two stages and one stage in 11.3% and 19% of the patients, respectively. The disease status did not change, regressed by one stage and regressed by two stages in 23.2%, 10.6% and 4.9% of the patients, respectively (Figure 2).

Shifts in the CKD stage that occurred after discharge from the hospital, based on the last SCr recorded before death, showed that the disease advanced by two stages, advanced by one stage, did not change in status, regressed by one stage and regressed by two stages in 14.1%, 14.1%, 18.3%, 19.7% and 2.8% of the patients, respectively (Figure 3).

## DISCUSSION

There are few data on the long-term progression of CKD in hospitalized patients who survived an episode

**TABLE 5** CORRELATION BETWEEN CLINICAL CHARACTERISTICS AND PROGRESSION TO CKD OF AKI PATIENTS, ACCORDING TO LAST RECORDED CKD-EPI

	All patients		CKD-EPI < 60 ml/min		<i>p</i>
	N = 207	%	N = 152	%	
<b>Gender</b>					
Female	96	(46.37)	58	(60.41)	
Male	111	(53.63)	94	(84.68)	0.01*
<b>Comorbidities</b>					
Hypertension	132	(64.10)	97	(73.48)	0.57
Diabetes	57	(27.70)	47	(82.45)	0.06
Vascular disease	34	(16.40)	22	(64.70)	0.17
Heart failure	37	(17.90)	28	(75.67)	0.20
Cancer	31	(15.00)	23	(74.19)	0.01*
Cirrhosis	15	(7.20)	13	(86.66)	0.06
Nephrolithiasis	12	(5.80)	10	(83.33)	0.28
Other causes	18	(8.70)	15	(83.33)	0.32
<b>Hospital settings</b>					
Wards	132	(63.80)	105	(79.54)	< 0.04*
ICU	41	(20.30)	25	(59.52)	
Emergency department	33	(15.90)	22	(66.55)	
<b>Cause of acute kidney injury</b>					
Nephrotoxicity	23	(11.10)	18	(78.26)	0.54
Pre-renal	88	(42.51)	66	(75.00)	0.49
Obstructive	24	(11.60)	22	(91.66)	0.3*
Sepsis	68	(32.85)	43	(67.18)	0.01*
Urinary tract infection	25	(12.10)	19	(76.00)	0.35
Acute interstitial nephritis	7	(3.50)	4	(57.14)	0.30
Ischemia	5	(2.40)	3	(60.00)	0.16
Other causes	23	(11.10)	18	(78.26)	0.40

\**p* < 0.05.

of AKI and did not undergo acute dialysis.<sup>18</sup> Several studies included patients admitted to the ICU, whereas other studies only included patients with severe AKI or individuals requiring RRT.<sup>25</sup>

The average age of the population analyzed in the present study was 70.15 ± 13.15 years, which is similar to ages reported by other authors.<sup>18,25-28</sup> In addition, elderly patients have a poorer quality of life and reduced their functional status following AKI, which are factors that contribute to adverse outcomes.<sup>29,30</sup> AKI was due to obstruction in 11.6% of patients in the present study and was associated with progression to CKD in 91.66% of patients.<sup>31</sup>

In our study, the median duration of AKI was 10 days, and it varied between 1 and 219 days. These findings agree with other reports in the literature, which also describe longer durations because the condition occurs in elderly patients with several

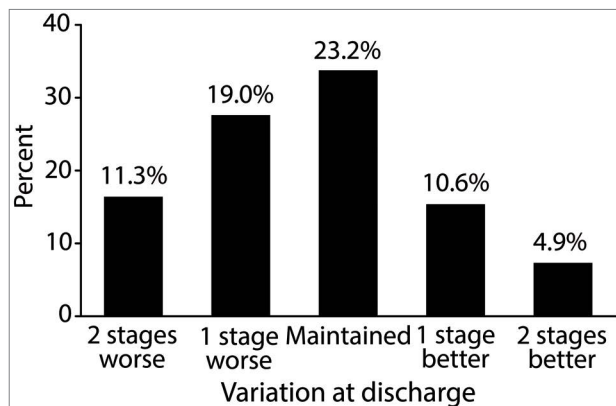
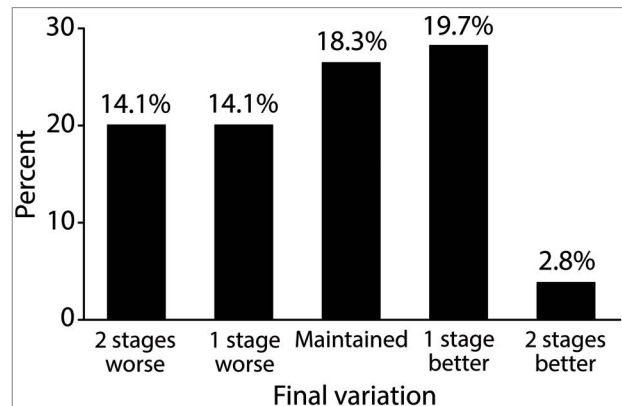
comorbidities and clinical complications during the course of AKI.<sup>32-35</sup>

Among the AKI survivors, the median length of time to a follow-up by nephrologists was 6 days; this value might be considered low compared with the LOS (21 days), but it is in agreement with the average duration of AKI (10 days). These findings suggest that AKI did not occur early during hospitalization. The follow-up after discharge by nephrologists has a significant impact on the duration of AKI and on patient mortality.<sup>25</sup>

Evidence from epidemiological studies suggests that old age increases the odds that basal renal function will not recover after an episode of AKI at the time of discharge.<sup>22</sup> In our study, we found that the SCr was elevated before discharge compared with the SCr before admission, in accordance with several authors that have observed that aging reduces the capacity for kidney recovery after AKI.<sup>30,36-38</sup>

**TABLE 6** CORRELATION BETWEEN CLINICAL CHARACTERISTICS AND MORTALITY IN AKI PATIENTS (N = 207)

	All patients		Deaths		<i>p</i>
	N = 207	%	N = 108	%	
Gender					
Female	96	(46.37)	58	(47.20)	
Male	111	(53.63)	57	(52.80)	0.76
Comorbidities					
Hypertension	132	(64.10)	66	(50.00)	0.45
Diabetes	57	(27.70)	28	(49.12)	0.61
Vascular disease	34	(16.40)	24	(70.58)	0.01*
Heart failure	37	(17.90)	21	(56.75)	0.53
Cancer	31	(15.00)	22	(70.96)	0.02*
Cirrhosis	15	(7.20)	10	(66.67)	0.24
Nephrolithiasis	12	(5.80)	1	(8.33)	0.02*
Other causes	18	(8.70)	8	(50.00)	0.84
Hospital settings					
Wards	132	(63.80)	73	(55.30)	0.06
ICU	41	(20.30)	26	(63.41)	
Emergency department	33	(15.90)	9	(0.27)	
Cause of acute kidney injury					
Nephrotoxicity	23	(11.10)	10	(43.48)	0.65
Pre-renal	88	(42.51)	45	(51.00)	0.79
Obstructive	24	(11.60)	15	(62.50)	0.28
Sepsis	68	(32.85)	39	(57.35)	0.06
Urinary tract infection	25	(12.10)	11	(44.00)	0.38
Acute interstitial nephritis	7	(3.50)	3	(42.85)	0.61
Ischemia	5	(2.40)	3	(20.00)	0.14
Other causes	23	(11.10)	11	(47.80)	0.65

\**p* < 0.05.**Figure 2.** Shifts between CKD stages of AKI patients at discharge (n = 142).**Figure 3.** Shifts between CKD stages of AKI patients after discharge (n = 142).

Because our study assessed AKI survivors, the population admitted to hospital wards was the most representative and was significantly associated with CKD progression ( $p < 0.04$ ); this population also tended to have a higher mortality after discharge ( $p = 0.06$ ). Most of the patients analyzed

were not severely ill, and few patients required admission to the ICU. The lack of illness severity could be why these patients were discharged and therefore developed CKD or exhibited worsening kidney function, as reported in other studies that followed up critical AKI patients.<sup>39-41</sup>

Post-renal AKI caused by obstruction of the urinary tract is generally observed in elderly patients.<sup>27</sup> In our study, obstructive AKI was significantly associated with CKD progression, in accordance with urinary tract obstruction being a significant cause of AKI. When the obstruction is complete, kidney injury occurs within 12 to 24 hours; however, the repercussions of the permanent damage and recovery of kidney function depend on the duration and degree of obstruction, the previous kidney function status and the presence of comorbidities or infection.<sup>27,42</sup> This data is also compatible as described in models of renal fibrosis after ureteral obstruction.<sup>43,44</sup>

Sepsis-induced AKI is a common occurrence in the ICU and in our study, the incidence of sepsis was 32.85% and was associated with 57.35% of mortality after discharge ( $p = 0.06$ ) and with progression to CKD in 67.18% of the cases ( $p = 0.01$ ).<sup>45,46</sup>

Despite the relatively large number of individuals monitored after discharge, our study had several limitations. This was a retrospective observational study conducted at a single center. In addition, it only included patients with available records of SCr who had survived an episode of AKI without considering its degree of severity.

## CONCLUSIONS

The occurrence of AKI was associated with the development of CKD or progression to more advanced stages of renal disease among patients with GFR < 60 ml/min before AKI, patients with cancer, with sepsis-induced or obstructive AKI and patients who had been admitted to hospital wards. Patients with neoplasms or vascular disease exhibited the lowest survival rates after discharge. Prospective randomized clinical trials are needed to more thoroughly investigate the impacts of single or multiple interventions before and after AKI on the need for chronic dialysis and mortality.

## CONFLICT OF INTEREST

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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