Patient and renal prognosis after AKI – can new biomarkers help?

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Abstract

Background: Acute kidney disease (AKD) represents a critical time period during which acute-to-chronic kidney dysfunction occurs and where preventive measures could be applied so as to reduce progression to adverse outcomes. CCL14 is a new biomarker of persistent AKI. We aim to evaluate the medium-term impact of AKI on renal and patient outcomes.

Methods: We conducted a retrospective cohort study including adult patients with acute kidney injury (AKI), admitted to a Medical and Surgical Intensive Care Department from November 2017 to August 2019. AKD was defined as the persistence of AKI stage 1 or greater for more than 7 days. Mortality at 90 days, *de novo* CKD and renal recovery patterns were evaluated. CCL14 and cystatin-C were measured in persistent AKI patients. Statistics were performed in SPSS®29.0.

Results: A total of 93 ICU adult patients with AKI KDIGO stage 1 or greater were included in our study; of these, 54% (n=50) developed AKD. Male sex, renal replacement therapy and AKI stage 3 at diagnosis were associated with an odds ratio (OR) (95% CI) of 1.7 (1.0-3.1), 16 (2.1-21) and 3.2 (1.2-8.7), respectively. Survival times since AKI diagnosis were 49.3 weeks (95% CI 32.4-66.1) in AKD patients and 88.8 weeks (95% CI 75.6-102) in non-AKD patients (p<0.01). CCL14 and cystatin-C demonstrated OR (95% CI) of 1.1 (1.0-1.3) and 1.2 (1.0-1.4) and AUC-ROC (95% CI) of 0.52 (0.35-065) and 0.60 (0.46-0.75) for AKD development, respectively.

Conclusion: AKD is a prevalent adverse outcome in adult ICU patients with AKI stage 1 or greater. It is associated with a significant increased risk of adverse outcomes and reduced mean survival time. CCL14 and cystatin-C demonstrated poor performance in predicting AKD.

Keywords: acute kidney injury, acute kidney disease, chronic kidney disease, CCL14, cystatin C

Resumo

Contexto: A doença renal aguda (AKD) representa um período crítico durante o qual ocorre transição de disfunção renal aguda para crónica e no qual há possibilidade de implementar medidas preventivas no sentido de prevenir desfechos adversos. O CCL14 é um novo biomarcador de lesão renal aguda (AKI) persistente. O nosso objetivo é avaliar o impacto a médio-prazo de AKI em desfechos renais e do doente.

Métodos: Realizámos um estudo coorte retrospetivo a incluir doentes adultos com AKI admitidos numa Unidade de Cuidados Intensivos de novembro 2017 a agosto 2019. AKD definiu-se como persistência de AKI estádio 1 ou superior por mais de 7 dias. Avaliaram-se mortalidade aos 90 dias e aos 3 anos, doença renal crónica (CKD) *de novo* e padrões de recuperação da função renal. Dosearam-se as concentrações de CCL14 e cistatina C em doentes com AKI persistente. A análise estatística foi feita no SPSS®29.0.

Resultados: O estudo incluiu no total 93 doentes adultos com AKI KDIGO estádio 1 ou superior; destes, 54% (n=50) desenvolveu AKD. Sexo masculino, terapêutica de substituição renal e AKI estádio 3 associaram-se a *odds ratio* (OR) (95% CI) de 1.7 (1.0-3.1), 16 (2.1-21) e 3.2 (1.2-8.7), respetivamente. Tempos de sobrevida desde o diagnóstico de AKI foram 49.3 semanas (95% CI 32.4-66.1) nos doentes com AKD e 88.8 semanas (95% CI 75.6-102) nos doentes não-AKD (p<0.01). CCL14 e cistatina-C demonstraram OR (95% CI) de 1.1 (1.0-1.3) e 1.2 (1.0-1.4) e AUC-ROC (95% CI) de 0.52 (0.35-065) e 0.60 (0.46-0.75) para o desenvolvimento de AKD, respetivamente.

Palavras-chave: acute kidney injury, acute kidney disease, chronic kidney disease, CCL14, cystatin C

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Índice

Abreviaturas e Siglas

ADQI Acute Disease Quality Initiative

APACHEII Acute Physiology and Chronic Health Evaluation II

AKD Acute Kidney Disease

AKI Acute Kidney Injury

AUC-ROC Area Under the Curve – Receiver Operating Characteristics

CCL14 C-C Motif Chemokine Ligand 14

CI Confidence Interval

CKD Chronic Kidney Disease

eGFR estimated Glomerular Filtration Rate

ICU Intensive Care Unit

KDIGO Kidney Disease Improving Global Outcomes

MAKE Major Adverse Kidney Event

OR Odds Ratio

RRT Renal Replacement Therapy

SAPSII Simplified Acute Physiology Score II

SCr Serum Creatinine

SOFA Sequential Organ Failure Assessment

SPSS Statistical Package for the Social Sciences

Introduction

Clinical investigation in intensive care medicine has focused mainly on optimizing care within the intensive care unit (ICU) *per se*. Despite growing evidence in this sense, we remain largely unaware of chronic and long-term effects of an ICU admission in the context of critical illness.

The concept of Acute Kidney Disease (AKD) is first mentioned in the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines[1] and defined in 2017 by the Acute Disease Quality Initiative (ADQI) 16 workgroup[2]; it represents the missing piece in understanding the spectrum of acute-to-chronic kidney dysfunction transition, namely in critical care patients, in whom such acute dysfunction is frequent[3].

AKD is defined as an acute or subacute damage or loss of kidney function in which Acute Kidney Injury (AKI) stage 1 or greater, as per KDIGO criteria, is present for ≥ 7 days and < 90 days; it also encompasses the following situations: (1) not observed, but inferred AKI (such as community-acquired AKI), (2) subacute AKI which does not fulfill specific KDIGO time criteria, and (3) observed AKI, which partially improves, and then progresses after 7 days[2,4].

Similarly to AKI and CKD, AKD represents an important public health concern, particularly within critically ill patient populations[5]. A large retrospective cohort study of 62377 hospitalized patients with preserved kidney function conducted by See *et al* determined that 2.2% of these patients developed AKD[6]. In another study conducted by Yan *et al*, almost 50% of 2556 hospitalized AKI patients developed AKD, with increasing prevalences seen amongst greater AKI severities[6]. Studies further determined that patients who had AKD with AKI were more likely to develop any Major Adverse Kidney Event (MAKE) at 12 months, which included de novo CKD and kidney failure, compared to patients who had AKD without AKI or AKI alone[7-9]. Additionally, hospital readmission rates at 30 days post-hospital discharge were highest for AKD with AKI patients, representing around 16% of all readmitted patients[22,23].

Despite the epidemiological and individual importance and healthcare costs directly and indirectly associated with AKD, we remain unable to accurately predict which patients will progress to AKD and, as such, unable to elaborate personalized follow-up programs and direct therapies for prevention of adverse outcomes in these patients.

C-C Motif Chemokine Ligand 14 (CCL14) is a type of chemokine released by renal tubular epithelial cells after injury and is implicated in tissue injury and repair[15]. It has been reported as a significantly predictive biomarker of persistent severe AKI, with an AUC-ROC (95% CI) of 0.83 (0.78-0.87)[13]. Owing to its theoretical implications in renal injury and repair processes and previous study results, it seems rational to assess its role as a marker of progression to AKD.

We hereby intend to study factors associated with progression to AKD in AKI patients, and further analyze renal recovery and adverse outcomes within AKD patients. Additionally, we assess and compare the performance of CCL14 and cystatin-C as predictors of AKD and other adverse outcomes.

Methods

Study design and patient population: we conducted a single-center retrospective cohort study in a general and post-surgical ICU (UCIP and UCICRE, respectively) in Professor Doutor Fernando da Fonseca Hospital in Amadora-Sintra, Portugal. The inclusion period was from November 2017 to August 2019, during which time 1130 patients were admitted to the ICU, of which 621 were either admitted with or developed AKI stage 1 or greater during ICU stay. To these patients, we further applied the following exclusion criteria: (1) ICU stay less than 48 hours, (2) death within 7 days of AKI diagnosis, (3) AKI in the previous 3 months, (4) CKD stage G5 or RRT requirement, (5) kidney transplant, and (6) pregnancy. In the end of the selection process, an AKI cohort of 93 patients was established (figure 1). Baseline SCr was determined as the mean of two outpatient measurements in the 365 days preceding the AKI event or, in the absence of outpatient SCr measurements, backcalculated from an estimated GFR of 75 mL/min/1.73m^2.

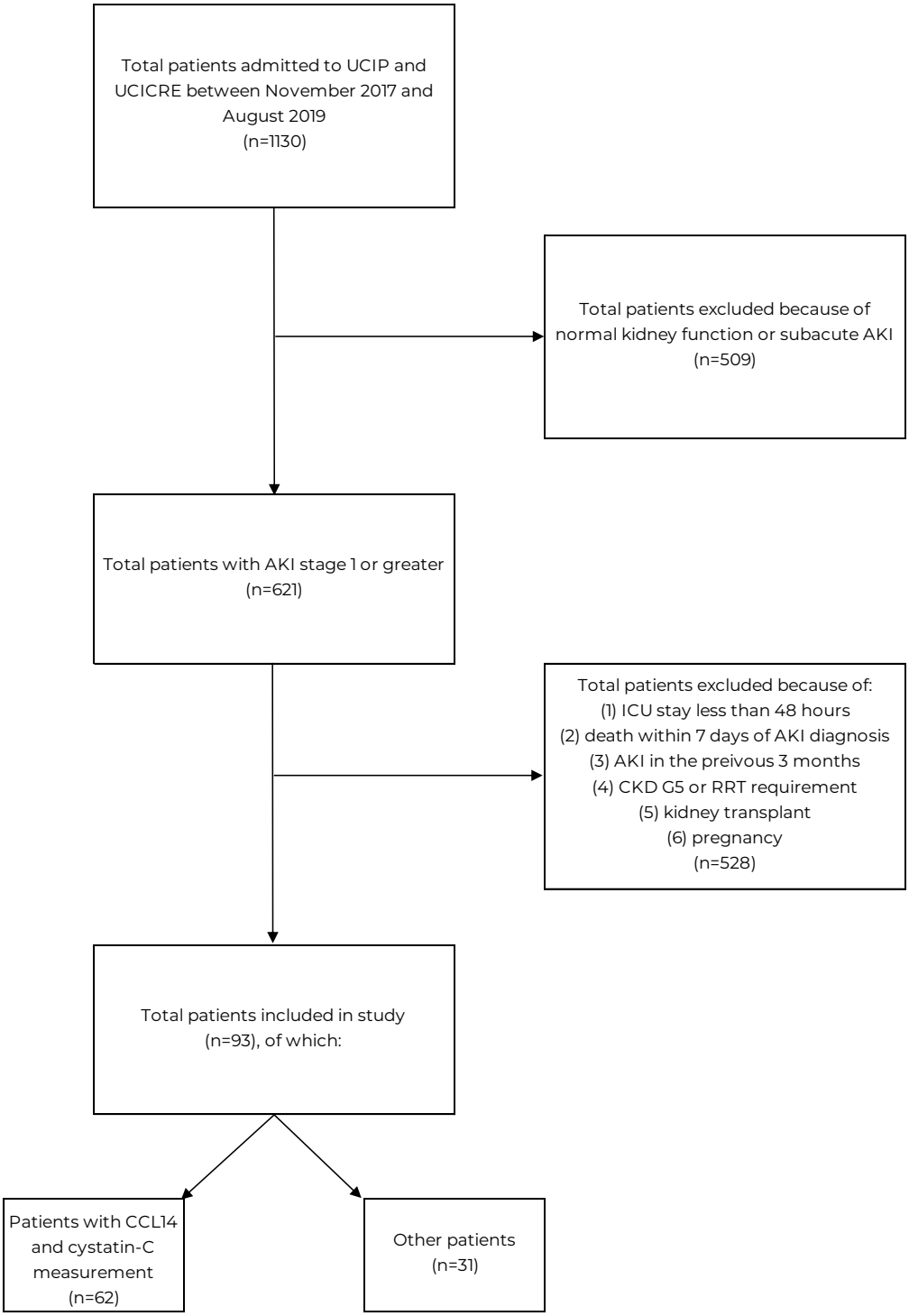

Figure 1. Flowchart for patient selection.

Definition of primary and secondary outcomes: the primary outcome was defined as the development of AKD stage 1 or greater at 7 days after AKI diagnosis (D7). Secondary outcomes were *de novo* CKD, death, and renal recovery at 90 days after AKI diagnosis (D90); patients who died before D90 were included in the *de novo* CKD category for sample enrichment purposes and in the absent recovery category. AKD was defined as the persistence of AKI stage 1 or greater for more than 7 days and for less than 90 days, as

per ADQI 16 workgroup consensus. AKI definition and staging were defined according to KDIGO 2012 criteria (supplementary table 3). Persistent AKI was defined as a duration of AKI > 48 hours. Severe AKI was defined as AKI stage 2 or 3. We defined 3 renal recovery patterns: *total recovery, partial recovery,* and *absent recovery* (see supplementary table 1 for definitions).

CCL14 and cystatin-C: In 62 of the 68 patients with persistent severe AKI (6 were excluded due to insufficient urine), cystatin C had been measured in plasma by particle-enhanced immunonephelometry (BN Systems, Dade-Behring, Marburg, Germany) with N latex Cystatin C assay. Moreover, urine samples had been centrifuged and stored at -80°C at the time of persistent AKI diagnosis. In these patients, urinary concentrations of CCL14 were measured using *the* Astute Medical NEPHROCHECK® CCL14 Test System, through an automated immunofluorescence assay. CCL14 concentrations were determined for each sample. Values smaller than the lower limit of detectability (0.20 ng/mL) were arbitrarily defined as 0.1 ng/mL, and the only value above the upper limit of measurement (30.0 ng/mL) was arbitrarily defined as 32.0 ng/mL.

Patient data collection: initial patient selection was obtained through ICU paper records screening for inclusion criteria. Patient-level data was obtained through electronic database (Soarian® Clinicals) software screening and included demographics, past medical history, ICU admission and stay information, and laboratory data, as well as primary and secondary outcome results.

Statistical analysis: SPSS®29.0. Baseline characteristics were ascertained for both AKD and non-AKD cohorts. For continuous variables, mean and standard-deviation and statistical significance of differences were obtained with the independent samples t-test. For categorical variables, frequencies and percentages were obtained with crosstabbing and statistical significance of differences was ascertained with the Pearson chi-square test. Simple descriptive statistics were used for determining primary and secondary outcomes. For primary outcome, univariate regression was used to determine significant predictors for AKD development and multivariate regression was used to determine combined prediction effect. Survival analysis at 3 years after study initiation for AKD vs non-AKD patients was conducted and further stratified by renal recovery pattern within AKD patients. Performance of CCL14 and cystatin-C was conducted with receiver operating curve (ROC) analysis and univariate regression.

Results

Patient characteristics: baseline characteristics are presented separately for AKD and non-AKD cohorts in table 1. *p*-values refer to statistical significance of intercohort differences and are considered significant if $p < 0.05$.

Characteristics		Cohort, (n=93) of AKI patients		
		AKD (n=50)	No AKD (n=43)	*p*-value
Demographics				
Age (years), $\bar{x}$ (±σ)		69 (±15)	71 (±12)	0.002
Gender	Male, n (%)	31 (62%)	18 (43%)	0.067
	Female, n (%)	19 (38%)	24 (57%)	
Race	Caucasian, n (%)	43 (86%)	39 (91%)	0.484
	Black, n (%)	7 (14%)	4 (9%)	
Comorbidities, n (%)				
Chronic kidney disease		10 (20%)	13 (30%)	0.254
Diabetes mellitus type 1 or 2		11 (22%)	11 (26%)	0.685
Hypertension		27 (54%)	30 (70%)	0.120
Stroke or transient ischemic attack		12 (24%)	9 (21%)	0.724
Heart failure		15 (30%)	11 (27%)	0.636
Chronic obstructive pulmonary disease		4 (8%)	7 (16%)	0.218
Human immunodeficiency virus		1 (2%)	1 (2%)	0.912
Hepatitis B virus		2 (4%)	1 (3%)	0.655
Hepatitis C virus		4 (9%)	1 (3%)	0.221
Chronic liver failure		5 (10%)	0 (0%)	0.033

Non-hematological malignancy		9 (18%)	13 (30%)	0.183
Laboratory data				
Basal SCr[1] (mg/dL), $\bar{x}$ (±σ)		0.92 (±0.25)	0.96 (±0.24)	0.207
Basal eGFR[2] (mL/min/1.73m2), $\bar{x}$ (±σ)		78.8 (±22.4)	72.0 (±19.8)	0.064
SCr[1] AKI[3] D0 (mg/dL), $\bar{x}$ (±σ)		2.75 (±1.14)	2.64 (±0.84)	0.002
Hemoglobin[Δ] (g/dL), $\bar{x}$ (±σ)		9.8 (±2.1)	10.5 (±2.0)	0.051
Albumin[Δ] (g/dL), $\bar{x}$ (±σ)		2.34 (±0.52)	2.53 (±0.58)	0.052
Lactate[Δ] (mmol/L), $\bar{x}$ (±σ)		2.37 (±2.06)	2.13 (±2.22)	0.293
ICU admission and stay data				
Vasopressors, n (%)		27 (55%)	19 (44%)	0.296
Invasive mechanical ventilation, n (%)		33 (67%)	25 (58%)	0.361
Renal replacement therapy, n (%)		16 (32%)	1 (2%)	< 0.001
Sepsis, n (%)		30 (60%)	22 (51%)	0.392
Septic shock, n (%)		21 (42%)	14 (33%)	0.349
Infection origin	Abdominal, n (%)	20 (40%)	14 (33%)	0.359
	Pneumonia, n (%)	14 (28%)	15 (35%)	
	Other, n (%)	16 (32%)	14 (33%)	
Hospital immunosuppression, n (%)		18 (36%)	10 (23%)	0.182
AKI[3] stage at diagnosis	1, n (%)	4 (8%)	10 (24%)	0.020
	2, n (%)	30 (60%)	27 (64%)	
	3, n (%)	16 (32%)	5 (12%)	

ICU severity scores at 24 hours of admission			
APACHEII[4], $\bar{x}$ ($\pm\sigma$)	25 (±8)	23 (±6)	0.045
SAPSII[5], $\bar{x}$ ($\pm\sigma$)	56 (±16)	49 (14)	0.033
Total SOFA[6], $\bar{x}$ ($\pm\sigma$)	9 (±4)	8 (±3)	0.132

Table 1. Baseline characteristics for AKD and non-AKD cohorts and statistical significance of intercohort differences. $\bar{x}$ Mean. σ Standard deviation. [1] Serum creatinine. [2] Estimated glomerular filtration rate. [3] Acute kidney injury. [4] Acute Physiology and Chronic Health Evaluation. [5] Simplified Acute Physiology Score. [6] Sequential Organ Failure Assessment. [Δ] Measured in AKI D0.

Progression to AKD: Progression to AKD stage 1 or greater was reported in 54% (n=50) of patients; within these patients, 48% developed AKD stage 1, 28% developed AKD stage 2 and 24% developed AKD stage 3. We further stratified AKD development by AKI stage at diagnosis (see table 2). A Spearman's correlation was run to determine the relationship between increasing AKI severity at diagnosis and increasing AKD severity, which demonstrated a statistically significant positive correlation between increasing AKI severity and increasing AKD severity (*r_s=0.324, n=50, p=0.05).*

Through univariate logistic regression, we determined the following predictors of AKD development: hospital immunosuppression, persistent severe AKI, severe AKI (AKI stage 2 and 3), RRT and male sex (see Figure 1).

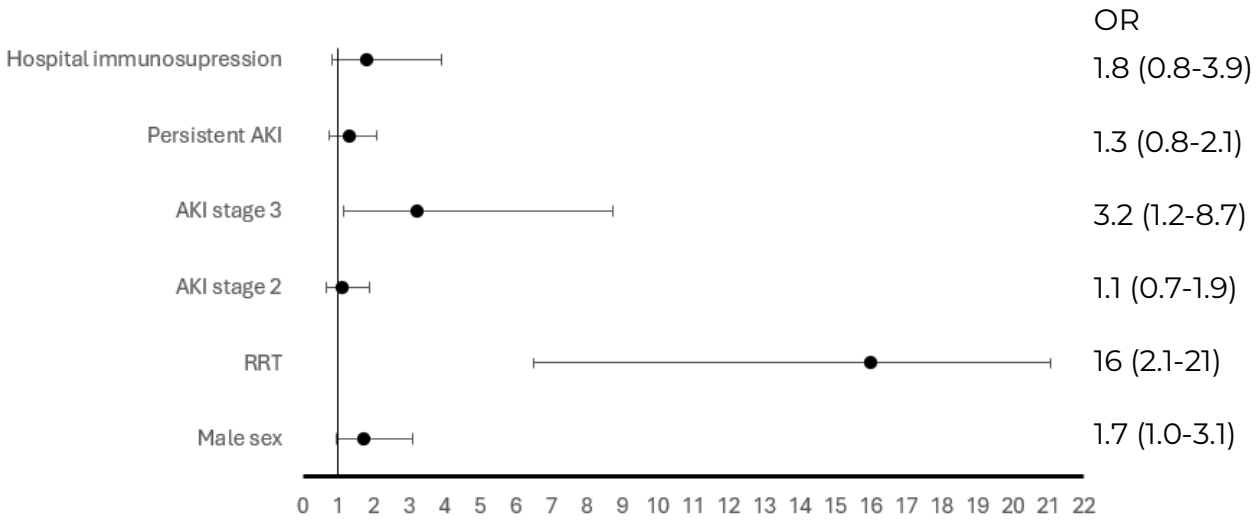

Figure 1. Forest plot for significant and deemed significant AKD development predictors.

Multivariate regression using statistically significant predictors identified through univariate regression was non-significant for every predictor.

CCL14 was associated with an OR of 1.1 (95% CI 1.0-1.3) and an AUC-ROC of 0.52 (95% CI 0.35-0.65) for AKD development, consistent with no discriminative capacity between AKD and non-AKD patients (supplementary figure 2).

Cystatin-C demonstrated an OR of 1.2 (95% CI 1.0 – 1.4) and an AUC-ROC of 0.60 (95% CI 0.46-0.75), with only slightly enhanced discriminative capacity between AKD and non-AKD patients compared to CCL14.

Renal recovery: Patients who developed AKD were more likely to present absent recovery of renal function than both total and partial recovery (supplementary figure 1).

***De novo* CKD:** *de novo* CKD was reported in 74% of AKD patients vs 56% of non-AKD patients (p=0.114).

CCL14 was associated with an OR of 1.2 (95% CI 0.9-1.6) and an AUC-ROC of 0.68 (95% CI 0.52-0.85) for progressing to *de novo* CKD.

Cystatin-C was associated with an OR of 4.1 (95% CI 1.5-11) and AUC-ROC of 0.79 (95% CI 0.65-0.93) for progressing to *de novo* CKD (figure 2).

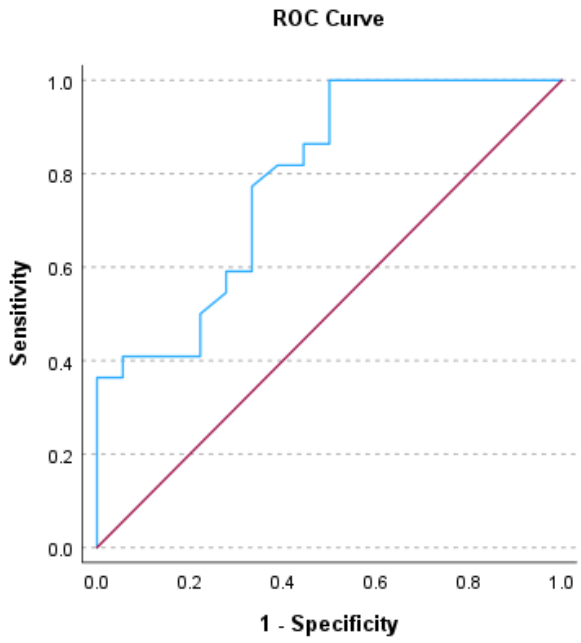

Figure 2. ROC analysis for cystatin-C in predicting de novo CKD

Death: death at D90 was reported in 61% of patients with AKD vs 39% of non-AKD patients (p=0.076).

Outcome	AKI cohort, n (%)					
	AKI stage at diagnosis			AKI duration		Total (n=93)
	1 (n=14)	2 (n=57)	3 (n=21)	Early reversal (<48h) (n=32)	Persistent (> 48h) (n=59)	
Primary outcome						
AKD development, n (%)	4 (29%)	30 (53%)	16 (76%)	15 (31%)	33 (69%)	50 (54%)

Outcome	AKI cohort		*p*-value
	AKD (n=42)	Non-AKD (n=32)	
Secondary outcome			
New CKD, n (%)	31 (74%)	18 (56%)	0,114
Death, n (%)	26 (61%)	10 (39%)	0,076

Table 2. Primary and secondary outcomes. *p*-value is for statistical significance of intercohort differences.

We further conducted a survival analysis at 3 years after study initiation for AKD vs non-AKD patients and stratified results by renal recovery status in the AKD cohort.

In the first analysis, we determined significant differences in survival distributions between AKD and non-AKD patients. AKD patients had a mean survival time since AKI diagnosis of 49.3 weeks (95% CI 32.4-66.1) compared to 88.8 weeks (95% CI 75.6-102) in non-AKD patients.

When stratified by renal recovery pattern, patients with *total recovery* (*n*=4), *partial recovery* (*n*=14) and *absent recovery* (*n*=32) had mean survival times since AKI diagnosis of 82.5 weeks (95% CI 53.2-112), 83.4 weeks (95% CI 51.2-115) and 22.8 weeks (95% CI 10.0-38.5), respectively, at a significant p=0.01 (figure 3).

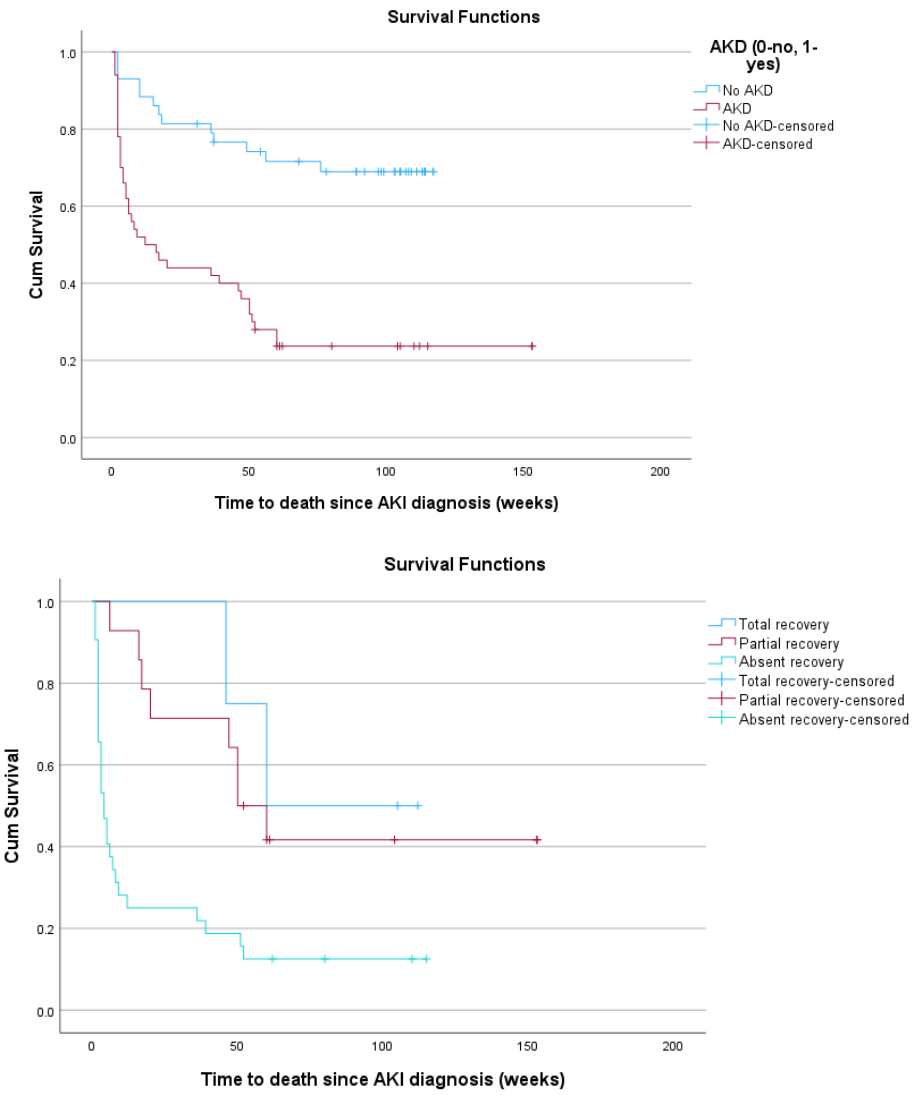

Figure 3. Kaplan-Meier curves for survival at 3 years. (a) Survival in AKD vs non-AKD patients. (b) Survival according to renal recovery status during AKD.

Discussion

The findings of the primary outcome of our study are comparable to other studies. In our study, 54% of patients with AKI stage 1 or greater developed AKD. He *et al* developed a study with 718 patients with sepsis-associated AKI admitted to the medical ICU in two general hospitals in China, in which 51% developed AKD[18]. In the aforementioned study by Yan *et al*, almost 50% of 2556 hospitalized AKI patients in China developed AKD[6]. A third study by Xiao *et al* which included 2556 hospitalized AKI patients in both general ICUs and general medicine infirmaries from three different hospitals in Beijing, China, determined AKD development in 53.17% of patients[19]. Patient baseline characteristics were similar between the studies and our study, though most patients were not admitted to the ICU; in those who were, critical illness severity was comparable to our patients. This

suggests that around half of all patients with AKI, regardless of AKI severity or duration, will progress to AKD. Additionally, He *et al* further determined that more patients with more severe AKI at diagnosis progressed to AKD, similarly to what we found in our study[18].

As for the predictors of AKD development, we identified RRT, male sex and AKI stage 3 as statistically significant. We still included hospital immunosuppression, AKI stage 2 and persistent severe AKI as they approximated statistical significance, and we found their inclusion interesting from a pathophysiological standpoint. Andonovic *et al* conducted a retrospective cohort study methodologically similar to ours in 403 AKD patients; they determined that the risk of AKD was associated with male sex, sepsis, and a lower baseline eGFR[24]. The reason for which male sex increases risk for AKD compared to female sex is probably due to differences in sex hormones. Surprisingly, our study did not find significant associations between sepsis or septic shock and severity scores (APACHEII, SAPSII and total SOFA) with AKD development; we attribute this to potential multicollinearity between these variables or reduced sample size. We found no other studies which included hospital pre-ICU admission immunosuppression or AKI duration for prediction analysis. Interestingly, in our study, hospital immunosuppression was associated with increased risk for AKD development, though at a non-significant level. We did not add a time-since-administration factor; however, considering that corticoid-induced immunosuppression can last between 2 and 4 weeks after administration[25], this effect probably still had implications at the time of AKI development. Moreover, studies have demonstrated that corticoids may preferentially suppress anti-inflammatory macrophages and regulatory B-cells[26], which are both involved in AKI immunology[27], possibly offsetting early renal anti-inflammatory and profibrotic balance. More studies are required to address this question.

Regarding outcomes, we found that AKD is associated with increased risk for *de novo* CKD development and death at 90 days. Additionally, mean survival times were significantly reduced in AKD patients compared to non-AKD patients. Gameiro *et al* conducted a study with 256 patients with septic AKI; they determined long-term mortality rate and adverse renal outcomes in AKD vs non-AKD patients of 64.8% vs 49.1% and of 77.5% vs 43.2%, respectively. To our best knowledge, no other study stratified mortality by renal recovery in AKD patients.

As for the performance of CCL14 in predicting AKD development, we found disappointing results, with an AUC-ROC just slightly above what is considered as equal to random

chance. The important role of CCL14 as a marker of persistent AKI was first reported in the RUBY study, with an AUC ROC (95% CI) of 0.83 (0.78-0.87)[12]. Since then, increasing concentrations of CCL14 have been demonstrated to be significantly associated with incidence of MAKE at 90 days, mortality at 90 days, and the composite outcome of RRT initiation or death within 90 days[13-15]. CCL14 is a chemokine released from injured renal tubular epithelial cells and plays a role in inflammatory cell chemotaxis, for which it is involved in renal injury and repair processes[14]. The inability of CCL14 to discriminate between AKD and non-AKD patients, as well as a non-significant regression analysis came as a surprising result. We think this may be due to reduced sample size, the fact the CCL14 was measured exclusively in persistent severe AKI patients which most probably would already progress to AKD, or CCL14 degradation due to aging of the urine samples.

Cystatin-C is an alternative endogenous filtration marker that is limited by a smaller number of extrarenal determinants when compared to serum creatinine[28]. It is freely filtered, catabolized within renal tubules and its metabolites reabsorbed by tubular cells, for which its measurement is done exclusively in the serum. Its role remains confirmatory in determining eGFR in patients with determinants that limit accuracy of serum creatinine[29]. In our study, its performance in predicting AKD development was only slightly superior to CCL14, achieving an AUC-ROC of 0.60, which is still considered poor. Despite this, it demonstrated an AUC-ROC of 0.79 for the development of *de novo* CKD in persistent severe AKI patients.

Our study was limited by several factors. First, its reduced sample size and retrospective nature; we consider this to have negatively impacted the significance of several of the conducted statistical tests, particularly those involving biomarker assessment. However, considering the highly specific group of patients included, we ultimately consider having obtained an adequate number of participants. As for the retrospective nature of the study, though clearly associated with specific types of biases, it is also true that a part of the patients included had previously been included in a prospectively conducted study. Secondly, determining basal serum creatinine through back-calculation from an eGFR of 75 mL/min/1.73m^2 in our cohort with a mean age of 70 years may lead to an overestimation of AKI, as there is a steady decrease in GFR with age. Thirdly, the arbitrary attribution of a value constant to CCL14 concentrations above and below inferior and superior limits of detectability leads to an underestimation of natural variability and may alter the performance of the marker in predicting certain outcomes. Lastly, considering death before day 90 as an equivalent to the development of *de novo* CKD limits

interpretability of this outcome, as well as the accuracy of biomarker prediction; however, statistical significance would not be met by only using *de novo* CKD status.

In conclusion, our study was unique in assessing the role of hospital immunosuppression and duration of AKI in predicting AKD development, as well as determining the effect of renal recovery patterns during AKD in long-term survival. Additionally, we comparatively assessed the performance of two alternative biomarkers, CCL14 and cystatin C, in determining primary and secondary outcomes.

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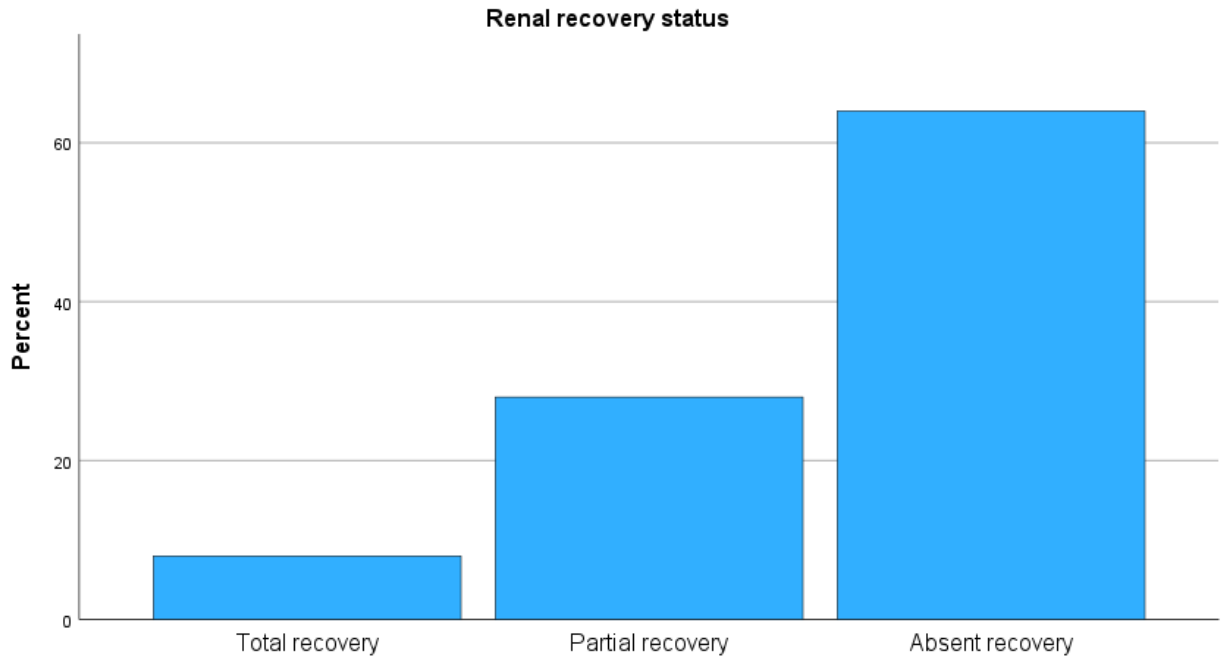
Supplementary

	Renal recovery in AKD
Pattern	**Definition**
Total recovery	AKD stage at D89 = 0
Partial recovery	0 < AKD stage at D89 < AKD stage at D7
Absent recovery	AKD stage at D89 ≥ AKD stage at D7 OR death before D89

Supplementary table 1. Definition of renal recovery patterns.



Supplementary figure 1. Proportion of renal recovery status at D89 within AKD patients.

Biomarker	AKI cohort		p-value
	AKD (n=33)	Non-AKD (n=26)	
Urinary CCL14 AKI D0			
Concentration (ng/mL), $\bar{x}$ (±σ)	3.05 (±6.23)	1.63 (±1.92)	0.113
Serum cystatin-C AKI D0			
Concentration (ng/mL), $\bar{x}$ (±σ)	3.76 (±3.53)	2.77 (±1.27)	0.108

Supplementary table 2. Concentrations of CCL14 in AKD and non-AKD patients.

Stage	*Serum creatinine*	*Urine output*
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dL increase	< 0.5 mL/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 mL/kg/h for ≥ 12 hours
3	≥ 3.0 times baseline OR Increase to serum creatinine ≥ 4 mg/dL OR Initiation of renal replacement therapy	< 0.3 mL/kg/h for ≥ 24 hours OR Anuria for ≥ 12 hours

Supplementary table 3. Staging of AKI according to KDIGO 2012 criteria.