

# A Risk Prediction Score for Renal Replacement Therapy in Critically Ill Septic – Acute Kidney Injury Patients

Filipe Marques<sup>1,\*</sup> , José Agapito Fonseca<sup>1,\*</sup> , Joana Gameiro<sup>1</sup> , João Gouveia<sup>2</sup> , José António Lopes<sup>1</sup> 

<sup>1</sup> Division of Nephrology and Renal Transplantation, Department of Medicine, Centro Hospitalar Lisboa Norte, Lisboa, Portugal.

<sup>2</sup> Division of Intensive Medicine, Department of Medicine, Centro Hospitalar Lisboa Norte, Lisboa, Portugal.

\*both authors contributed equally – joint first authors

## Contributorship Statement:

- FM, JAF and JG: Made substantial contributions to the study concept and design, analysis and interpretation of data, and were involved in drafting the manuscript, revising it critically for important intellectual content and approved the final version.
- JG: Participated in the acquisition of data, was involved in the critical revision of the manuscript and approved the final version.
- JAL: Approved the final version prior to submission.

## ABSTRACT

**Introduction:** Acute kidney injury (AKI) is a major complication in critically ill septic patients and is associated with increased morbidity and mortality. A recent study suggested a risk score based on patient's chronic comorbidities and acute events at intensive care unit (ICU) admission as a reliable tool for predicting AKI in critically ill adult population. The aim of this study was to adapt this score to septic-AKI patients and evaluate its prognostic value as predictor of the need for renal replacement therapy (RRT) at ICU admission.

**Methods:** This is a retrospective analysis of 399 septic-AKI patients admitted to the Division of Intensive Medicine of the Centro Hospitalar Universitário Lisboa Norte between January 2008 and December 2014. The Kidney Disease Improving Global Outcomes (KDIGO) classification was used to define AKI. The Renal Replacement Therapy Risk Score was adapted from the AKI risk prediction score proposed by Malhotra *et al* (Nephrol Dial Transplant. 2017;32:814-22).

**Results:** Fifty two percent of patients were KDIGO stage 3, 25.8% KDIGO stage 2 and 22.3% KDIGO stage 1. Twenty seven percent of patients required RRT. Patients requiring RRT had higher risk score than those who did not ( $6.6 \pm 2.5$  vs  $5.1 \pm 2.6$ ,  $p < 0.001$ ). An optimal cut-off value of  $\geq 6$  in this score predicted the need for RRT with sensitivity 0.630 and specificity 0.391.

**Conclusion:** The RRT risk score at ICU admission was independently associated with the requirement of RRT septic-AKI patients. The assessment of this ratio is simple and can prove useful in identifying patients at risk for need of RRT.

**Keywords:** Acute Kidney Injury; Critical Illness; Intensive Care Units; Renal Replacement Therapy; Risk Assessment; Sepsis

© 2022 Portuguese Journal of Nephrology & Hypertension. Published by Publicações Ciência & Vida  
This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## INTRODUCTION

Acute kidney injury (AKI) is life-threatening condition characterized by a rapid decrease in renal function.<sup>1</sup> AKI is frequent in hospitalized patients and its incidence is higher in critically ill patients, in whom the leading cause of AKI is sepsis, with frequent requirement for renal replacement therapy (RRT).<sup>2-4</sup> AKI has been associated with longer hospital stays, in-hospital mortality, progression to chronic kidney disease and long-term mortality.<sup>5-7</sup>

Septic-AKI patients have specific characteristics than distinguish them from non-septic AKI, that implicates more non-renal organ failure and requirement of vasopressors and mechanical ventilation. The prognosis is also worse, with prolonged length of hospital stays and higher short-term mortality.<sup>3-8</sup>

Over the past decades, a few models examined clinical risk factors for the development of AKI in the Intensive Care Unit (ICU) population, although with small populations studied. A recent multicenter study from Malhotra *et al*<sup>9</sup> prospectively analyzed a population of 1300 patients admitted in an ICU and concluded that chronic kidney disease (CKD), chronic liver disease, congestive heart failure, hypertension, atherosclerotic coronary vascular disease,  $\text{pH} < 7.3$ , nephrotoxin exposure, sepsis, mechanical ventilation and anemia were identified as independent predictors of AKI.<sup>9</sup> This study was also able to develop a risk model, based on chronic comorbidities and acute events and define an optimal cutoff value of  $\geq 5$  points as an increased risk for development of AKI (Table 1).

Although the optimal timing for the initiation of RRT in AKI is not consensual, there are no available models that can reliably predict the need for RRT once AKI is established.<sup>10-18</sup>

**Table 1**

Original Malhotra AKI risk prediction score

Risk factor	Points
Chronic kidney disease	2
Chronic liver disease	2
Congestive heart failure	2
Hypertension	2
Atherosclerotic coronary vascular disease	2
pH ≤ 7.30	3
Nephrotoxin exposure	3
Severe infection/sepsis	2
Mechanical ventilation	2
Anemia	1
Total	21
Score to predict AKI	5

Adapted from Malhotra R, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant.* 2017;32:814-22.9

**Table 2**

RRT requirement prediction score in septic-AKI patients

Risk factor	Points
Chronic kidney disease	2
Chronic hepatic disease	2
Heart failure	2
Hypertension	2
Coronary vascular disease	2
Nephrotoxin exposure	3
Acidemia	3
Mechanical ventilation	2
Anemia	1
Total	19
Score to predict RRT Requirement	6

>=6, sensitivity 0.630, specificity 0.391

Adapted from Malhotra R, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant.* 2017;32:814-22.9

We hypothesized that it was possible to adapt this risk score (Table 2), based on routinely available clinical variables, to predict the risk of requiring RRT once AKI has been established. For this purpose, we cross-examined data from a retrospective study in which we studied a cohort of critically ill patients with septic-AKI.<sup>19,20</sup>

## METHODS

This is cross-examination of a retrospective analysis, conducted in a single center, that included septic-AKI patients admitted to the Division of Intensive Medicine of the Centro Hospitalar Universitário Lisboa Norte (CHULN), Portugal, between January 2008 and December 2014. This study was approved by the Ethical Committee in agreement with institutional guidelines. Due to the retrospective and non-interventional nature of the study, informed consent was waived by the Ethical Committee.

## Participants

Eligible patients were selected as adult patients (≥18 years of age) with a diagnosis of sepsis at admission to the Division of Intensive Medicine who developed AKI within the first week of ICU hospitalization.

Exclusion criteria comprised CKD patients on renal replacement therapy, patients who underwent RRT one week prior to admission to the ICU and patients who were discharged or died less than two days after ICU admission.

## Variables and outcomes

Patient variables were collected from individual clinical records. The protocol for all patients in this ICU includes daily determination of serum creatinine (SCr) and hourly urine output (UO).

We analyzed several clinical variables including patient demographic characteristics (age, gender, ethnicity, body weight and height), comorbidities (hypertension, diabetes mellitus, coronary vascular disease, congestive heart failure, CKD, chronic hepatic disease, neoplasia), main diagnosis on admission (medical *versus* surgical nature), source of infection, laboratory values at admission (serum hemoglobin, serum albumin, SCr and pH analysis), disease severity according to the Simplified Acute Physiologic Score (SAPS) II<sup>21</sup> as determined by the worst variables documented throughout the first 24 hours of ICU admission, fluid balance during ICU admission, mechanical ventilation, vasopressor use and requirement for renal replacement therapy. The primary outcome was RRT requirement.

## Definitions

We used Kidney Disease Improving Global Outcomes (KDIGO) classification according to both SCr and UO to define AKI.<sup>21</sup> Pre-admission SCr (SCr within the previous three months) was considered as baseline value. When unavailable, baseline SCr was estimated from the MDRD equation<sup>21</sup> accepting the lower limit of a normal baseline GFR of 75 mL/min/1.73 m<sup>2</sup>.

Sepsis was diagnosed according to the third international consensus definitions as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥2 points consequent to the infection.<sup>22</sup> Diabetes mellitus was diagnosed according to the American Diabetes Association criteria<sup>23</sup> and hypertension was diagnosed according to the seventh report of the Joint National Committee.<sup>24</sup> Chronic Kidney Disease was classified according to KDIGO classification.<sup>25</sup> Anemia was defined as hemoglobin level below 12 g/dL. Acidemia was defined as a serum pH level above 7.35. Previous diagnosis of coronary vascular disease, neoplasia, chronic heart failure and chronic hepatic disease of any cause was also documented (clinical records were considered sufficient for the confirmation of these diagnosis).

The Renal Replacement Therapy Risk Score was adapted from the AKI risk prediction score proposed by Malhotra *et al.*<sup>9</sup> This Risk Score

was calculated as is discriminated on Table 2. This risk score comprises the following variables: chronic kidney disease, chronic liver disease, heart failure, hypertension, coronary vascular disease, nephrotoxin exposure, acidemia, mechanical ventilation, anemia. By adding the variables, the total score can range from a minimum of 0 to a maximum of 19 points. We excluded patients the variable “severe infection/sepsis” from the original score because the population only included septic patients.

## Statistical methods

We described categorical variables as the total number and percentage for each category, whereas continuous variables were described as the mean  $\pm$  standard deviation. Normally distributed continuous variables were compared with the Student’s t-test, non-normally distributed continuous variables were compared with the Mann–Whitney U test and categorical variables were compared with the chi-square test.

Only variables that significantly differed between RRT requirement and no need for RRT groups were used in the univariate and multivariate analysis using the logistic regression method. Univariate analysis was performed in all variables to determine statistically significant factors that may predict RRT requirement in septic-AKI patient. Only variables with a significant statistical difference were included in the multivariate analysis using the Cox logistic regression method. To prevent collinearity, variables which were part of the RRT risk score were not assessed in the multivariate analysis.

The discriminatory ability for this Risk Score to predict the need for RRT requirement in septic-AKI patients was determined using the receiver operating characteristic (ROC) curve. A cut-off value was defined as that with the highest validity.

Data were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as a  $p$ -value  $<0.05$ . Statistical analysis was performed with the statistical software package SPSS for windows (version 21.0).

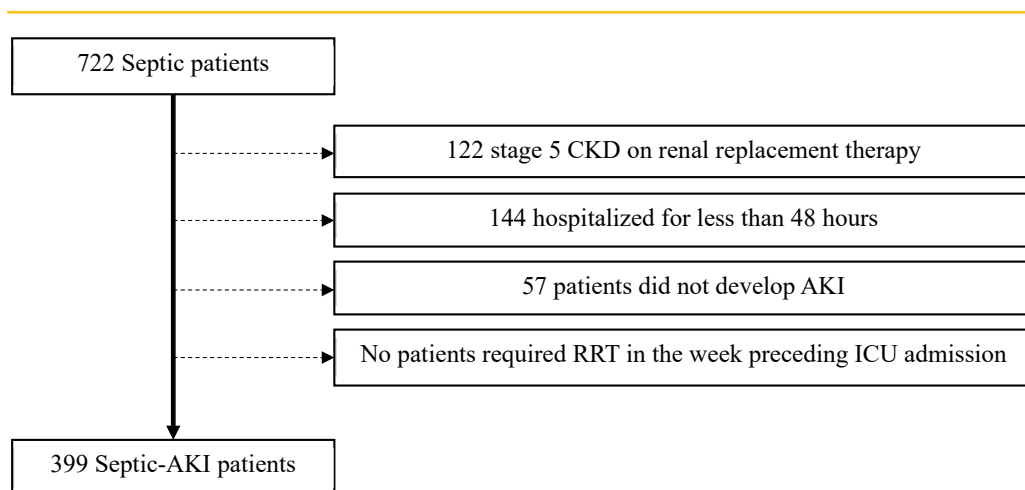
## RESULTS

We identified 722 septic patients. Of these, 323 were excluded as followed: 122 had stage 5 CKD on renal replacement therapy, 144 had been hospitalized for less than 48 hours and 57 patients did not develop AKI during ICU stay. No patients required renal replacement therapy in the week preceding ICU admission (Fig. 1). A final cohort of 399 patients was studied.

The characteristics of this population have been previously described in a study in which we assess the utility of the neutrophils, lymphocytes and platelets ratio as a predictor of mortality in septic-AKI patients.<sup>19</sup> Demographic variables, clinical and laboratory characteristics are described in Table 3.

The majority of patients were classified as KDIGO stage 3 (51.9%), 25.8% KDIGO stage 2 and 22.3% as KDIGO stage 1. During ICU admission, 77.4% patients required mechanical ventilation, 72.7% required vasopressors, 27.1% required renal replacement therapy (RRT) and required a mean fluid balance within the first 48 hours of  $4.6 \pm 5.4$  litres. Thirty percent of patients were exposed to nephrotoxin’s. These patients had a length of stay in ICU of  $10.0 \pm 10.0$  days and in hospital of  $36.7 \pm 38.6$  days. The in-hospital mortality in this cohort of septic-AKI patients was 35.8% (KDIGO stage 1 – 13.3%, KDIGO stage 2 – 16.8%, KDIGO stage 3 – 69.9%,  $p < 0.001$ ).

Septic-AKI patient who required RRT had a mean age of  $65.4 \pm 14.6$  years, mainly caucasian (98.1%), males (55.6%) and the main diagnosis at ICU admission was medical in nature (62.0%). There was no



**Figure 1**

Flow-chart of patient selection.

**Table 3**

Patients' baseline characteristics and according to renal replacement therapy (RRT) requirement

Characteristic	Septic-AKI patients 399	RRT Requirement 108	No need for RRT 291	p value
<b>Demographics</b>				
Age (year)	64.1±15.9	65.4±14.6	63.6±16.3	0.309
Gender (Male) – n (%)	229 (57.4)	60 (55.6)	169 (58.1)	0.651
Race (Caucasian) – n (%)	379 (95)	106 (98.1)	273 (93.8)	0.078
Obesity (BMI>=30) – n (%)	116 (29.1)	44 (40.7)	72 (24.7)	0.002
<b>Co-morbidities – n (%)</b>				
Hypertension	182 (45.6)	59 (54.6)	123 (42.2)	0.028
Diabetes	88 (22.1)	38 (32.4)	50 (17.2)	<0.001
Coronary vascular disease	57 (14.3)	15 (13.9)	42 (14.4)	0.890
Congestive heart failure	27 (6.8)	7 (6.5)	20 (6.9)	0.877
CKD	42 (10.5)	17 (15.7)	25 (8.6)	0.039
Chronic hepatic disease	17 (4.3)	6 (5.6)	11 (3.8)	0.435
Neoplasia	96 (24.1)	25 (23.1)	71 (24.4)	0.795
Baseline SCr (mg/dl)	1.27±0.6	1.3±0.7	1.2±0.5	0.120
Medical admission – n (%)	222 (55.6)	67 (62.0)	155 (53.3)	0.117
<b>Infection source – n (%)</b>				
Abdominal	168 (42.1)	41 (38.0)	127 (43.6)	0.307
Respiratory	122 (30.6)	29 (26.9)	93 (32.0)	0.325
Kidney	43 (10.8)	11 (10.2)	32 (11.0)	0.816
Skin	14 (3.5)	11 (10.2)	21 (7.2)	0.332
Others	20 (5.0)	8 (7.4)	12 (4.1)	0.182
Unknown	14 (3.5)	8 (7.4)	6 (2.0)	0.010
<b>At ICU admission</b>				
SAPS II	50.4±17.3	62.3±16.6	46.0±15.5	<0.001
Non-renal SOFA	7.5±6.3	7.3±3.8	7.6±7.0	0.722
Admission SCr (mg/dL)	2.44±1.6	2.6±1.6	2.4±1.5	0.365
Hemoglobin (g/dL)	10.5±2.0	10.2±2.0	10.5±2.0	0.131
Anemia – n (%)	87 (21.8)	28 (25.9)	59 (20.3)	0.225
Serum albumin (g/dL)	1.89±0.6	1.8±1.9	1.9±0.6	0.157
Acidemia (pH<7.35) – n (%)	143 (35.8)	58 (53.7)	85 (29.2)	<0.001
<b>During ICU admission</b>				
Mechanical ventilation – n (%)	309 (77.4)	97 (89.8)	212 (72.9)	<0.001
Vasopressors – n (%)	290 (72.7)	97 (89.8)	193 (66.3)	<0.001
Fluid balance first 48 hours (litres)	4.6±5.4	5.5±6.7	4.2±5.3	0.027
Nephrotoxins – n (%)	136 (34.1)	36 (33.3)	100 (34.4)	0.847
RRT Risk Score	5.5±2.7	6.6±2.5	5.1±2.6	<0.001
<b>AKI characteristics</b>				
KDIGO stage 1 – n (%)	89 (22.3)	0 (0)	89 (30.6)	
KDIGO stage 2 – n (%)	103 (25.8)	0 (0)	103 (35.4)	
KDIGO stage 3 – n (%)	207 (51.9)	108 (100)	99 (34.0)	
Persistent AKI – n (%)	256 (64.2)	105 (97.2)	151 (51.9)	<0.001
RRT – n (%)	108 (27.1)			
<b>Outcomes</b>				
LOS in hospital (days)	36.7±38.6	39.8±44.0	35.6±36.4	0.326
LOS in ICU (days)	10.0±10.0	11.4±11.4	9.5±9.4	0.096
In-hospital mortality – n (%)	143 (35.8)	65 (60.2)	78 (26.8)	<0.001

BMI – body mass index; CKD – chronic kidney disease, SCr – serum creatinine; ICU – intensive care unit; SAPS II – simplified acute physiology score II; RRT – renal replacement therapy; AKI – acute kidney injury; KDIGO – kidney disease improving global outcomes; LOS – length of stay

significantly difference in the mean age, race or gender between those who needed RRT and those who did not. There were also no significant differences on baseline creatinine (1.3±0.7 vs 1.2±0.5 mg/dL, *p*=0.120) or admission creatinine (2.6±1.6 vs 2.4±1.5 mg/dL, *p*=0.365). Septic-AKI patient who required RRT was more likely to be obese (40.7% vs 24.7%, *p*=0.002), reaching statistical significance

at the multivariable analysis (adjusted OR 2.34 (1.29-4.24), *p*=0.005) (Table 4).

Septic-AKI patients who required RRT within the hospital admission had a higher incidence of hypertension (54.6% vs 42.2%, *p*=0.028) and diabetes (32.4% vs 17.2%, *p*<0.001). At ICU admission, higher

**Table 4**

Univariate and multivariate analysis of factors predictive of RRT requirement in Septic-AKI patients

	RRT Requirement			
	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<b>Demographics</b>				
Age	1.01 (0.99-1.02)	0.309		
Male	0.90 (0.58-1.41)	0.651		
Caucasian	3.40 (0.79-14.76)	0.102		
Obesity	2.27 (1.43-3.58)	<0.001	2.34 (1.29-4.24)	0.005
<b>Co-morbidities</b>				
Hypertension	1.65 (1.05-2.57)	0.028		
Diabetes	2.62 (1.59-4.31)	<0.001		
Coronary vascular disease	0.96 (0.51-1.81)	0.890		
Congestive heart failure	0.93 (0.38-2.27)	0.877		
Chronic hepatic disease	1.50 (0.54-4.15)	0.438		
CKD	1.99 (1.03-3.85)	0.042		
Neoplasia	0.97 (0.75-1.25)	0.795		
Medical admission	1.42 (0.92-2.21)	0.118		
Baseline SCr	1.32 (0.93-1.89)	0.126		
<b>At ICU admission</b>				
SAPS II	1.06 (1.05-1.08)	<0.001	1.05 (1.03-1.07)	<0.001
Non-renal SOFA	0.99 (0.95-1.03)	0.724		
SCr	1.07 (0.93-1.23)	0.364		
Anemia	1.38 (0.82-2.31)	0.226		
Serum albumin	0.75 (0.50-1.12)	0.158		
Acidemia	2.81 (1.78-4.43)	<0.001		
<b>During ICU admission</b>				
Mechanical ventilation	3.29 (1.67-6.45)	0.001		
Vasopressors	4.48 (2.29-8.74)	<0.001	3.10 (1.45-6.63)	0.003
Fluid balance	1.00 (1.00-1.00)	0.043	1.00 (1.00-1.00)	0.214
Nephrotoxins exposure	0.96 (0.60-1.52)	0.847		
<b>AKI characteristics</b>				
Persistent AKI	32.45 (10.07-104.60)	<0.001	33.51 (9.94-112.92)	<0.001
RRT Risk Score	1.24 (1.14-1.35)	<0.001	1.14 (1.02-1.28)	0.020

CKD – chronic kidney disease, SCr – serum creatinine; ICU – intensive care unit; SAPS II – simplified acute physiology score II; RRT – renal replacement therapy

SAPS II (62.3±16.6 vs 46.0±15.5, *p*<0.001) and presence of acidemia (pH<7.35) (53.7% vs 29.2%, *p*<0.001) were associated with the requirement of RRT (Table 3).

Need for mechanical ventilation (89.8% vs 72.9%, *p*<0.001) and vasopressors (89.8% vs 66.3%, *p*<0.001) were also associated with the need of RRT (Table 3).

### Renal Replacement Therapy Risk Score

The Risk Score correlated with the requirement of RRT in septic-AKI patients (6.6±2.5 vs 5.1±2.6, *p*<0.001) (Table 4).

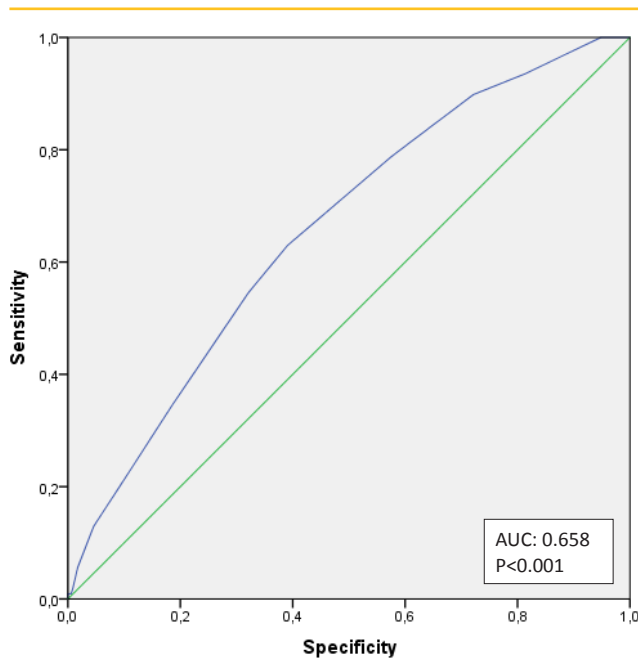
An adjusted multivariate analysis to demographic, clinical, ICU admission variables and during ICU stay factors was conducted, in which a higher RRT Risk Score remained as an independent predictor of increased risk of requirement of RRT in septic-AKI patients (6.6±2.5 vs 5.1±2.6, *p*<0.001; unadjusted OR 1.24 (95% CI 1.14-1.35), *p*<0.001; adjusted OR 1.14 (95% CI 1.02-1.28), *p*=0.020) (Table 4).

To assess the discriminative ability of this risk score for predicting RRT requirement, a ROC curve was produced. The AUC for requirement of RRT prediction in septic-AKI was of 0.658 (*p*<0.001) (Fig. 2). The optimal cut-off was assessed to be >6, which has a sensitivity of 63.0% and specificity of 39.1%.

### DISCUSSION

In this retrospective cohort, we demonstrated that a higher RRT Risk Score calculated at ICU admission was independently associated with the need of RRT in septic-AKI patients (Table 3).

AKI is a major complication in ICU patients and is associated with worse outcomes, including prolonged in-hospital stay and increased mortality.<sup>5-7</sup> Several urine and serum biomarkers of kidney injury have been identified over the past years for early detection of AKI, but they are not used in routine clinical care.<sup>26-28</sup> The most commonly used clinical (UO) and serum biomarkers (SCr and cystatin C) are unspecific and fail on the early detection of AKI. Moreover, these biomarkers fail to identify which patients will require RRT.<sup>29-32</sup>



**Figure 2**  
AUC of the risk model for the prediction of Renal Replacement Therapy requirement in septic-AKI patients.

There is no consensus about the optimal timing for the initiation of RRT. There is a controversy between those who advocate an early strategy for the initiation of RRT, without waiting for the development of AKI complication, and those more conservative who are more prone to a late strategy for the initiation of RRT, waiting for the development of acidemia, hyperkalemia, fluid overload or uremic syndrome, thus allowing for a potential renal recovery and avoiding complications associated with RRT.

Recent randomized studies failed to determine the optimal timing for the initiation of RRT, increasing the uncertainty about the optimal strategy.<sup>33-35</sup> The ELAIN trial is the only study to demonstrate a better survival in patients who started RRT earlier. In this study, patients required plasma neutrophil gelatinase-associated lipocalin level (NGAL) higher than 150 ng/mL to be included and only 9% of patients in the delayed strategy group did not require RRT start.<sup>36</sup> Interestingly, in most recent studies around 40%-50% of patients in the delayed strategy group did not require RRT start.<sup>10,37,38</sup> This highlights the need to determine which patients will, in fact, require RRT.

A recent study of Malhotra *et al*<sup>9</sup> prospectively analyzed 1300 ICU patients and successfully developed a risk score model that can identify patients at high risk to develop AKI, by integrating chronic comorbidities and acute events at ICU admission. In the multivariate model, chronic kidney disease, chronic hepatic disease, heart failure, hypertension, coronary vascular disease, nephrotoxin exposure, acidemia, mechanical ventilation and anemia were identified as independent predictors of AKI. The risk model developed based on these variables

established an optimal cutoff value of  $\geq 5$  points with 31.8% of positive predictive value and 95.4% for negative predictive value.

The aim of our study was to adapt this score and try to apply it as a predictor for RRT requirement on a population of septic-AKI patients. Our retrospective analysis studied the chronic comorbidities and acute events at ICU admission that were used in the score proposed for Malhotra *et al*<sup>9</sup> with the believe that it could also be used as tool for predicting the need of RRT.

This risk stratification could allow an early identification of patients who are more likely to need RRT and implement therapeutic strategies without waiting for severe uremic complications to develop or avoid unnecessary invasive procedures in fragile patients who might recover renal function and not require RRT.

We validated this risk score as predictor of the need for RRT in septic-AKI patients. The optimal cutoff value for the prediction of needing RRT has  $\geq 6$  points (Fig. 2). With this score value we obtain a 63.0% sensitivity and 39.1% specificity, which means that if patient's score is  $< 6$ , he is only 37% chance of requiring RRT.

The strong negative predictive value of this score could be used to justify a more conservative approach. A low score reflects a probability of requiring RRT of less than 40%, meaning we could delay RRT initiation and avoid this invasive procedure, which carries several risks including: mechanical complications associated to dialysis catheter insertion, increased infectious risk and hemodynamic and biochemical changes related to the technique which may delay renal recovery and contribute to myocardial ischemia.

Several studies reported chronic kidney disease, chronic hepatic disease, heart failure, hypertension, coronary vascular disease, nephrotoxin exposure, acidemia, mechanical ventilation and anemia as major risk factors for AKI,<sup>39-42</sup> but few addressed the risk factors for the requirement of RRT once AKI is established.

Some reports already validated several biomarkers as predictors of the need for RRT, like Inhibitor of metalloproteinase-2 (TIMP-2), insulin-like growth factor-binding protein 7 (IGFBP7), urinary neutrophil gelatinase-associated lipocalin (uNGAL) or fibroblast growth factor 23 (FGF 23).<sup>26-28</sup> Cho *et al*<sup>26</sup> prospectively studied a population of 124 patients diagnosed with AKI and demonstrated that TIMP-2 and IGFBP7 were independent predictors of renal replacement therapy at the time of AKI diagnosis (OR 5.75 and 44.98, respectively). Albeladi *et al*<sup>27</sup> prospectively analyzed a population of 75 patients, and among those 21 developed AKI and 17 required RRT. Maximum urine levels of uNGAL measured over the first and second 24 hours of an ICU admission were highly accurate predictors of the future need for RRT ( $p<0.001$ ). Fayed *et al*<sup>28</sup> studied 30 patients admitted to an ICU with acute kidney injury and showed that FGF23 levels were significantly higher in patients who needed RRT than in other participants (mean level: 529.5 vs 285.11 pg/mL,  $p=0.04$ ). Thiengo *et al*<sup>43</sup> analyzed 120 patients and found that Troponin I at admission in the ICU strongly correlated with the need of dialysis in septic shock (TnI  $> 0.42$  ng/mL - HR 3.48 [95% CI 1.69-7.18]).

Nevertheless, these studies are mainly based on biochemical markers which are not routinely used, mainly for their high associated

costs, and had small number of patients. This is the first study based on clinical variables that could successfully predict the requirement for RRT in septic-AKI patients.

Several limitations of our study must be addressed. Firstly, this was a retrospective single center analysis, which diminishes the power of the study. Another important limitation to this score; is the exclusion of criteria such as the presence of diabetes and use of vasopressors during UCI stay, which have a strong correlation with the need for RRT, but further investigation is needed to confirm this association. Finally, due to the selection of this population, these conclusions can only be applied to septic-AKI patients. Further investigation is needed to study the application of this score to other causes of AKI.

Our study has some important virtues. This is the first study to assess a valid clinical score that successfully predicts which septic-AKI patients are more likely to require RRT. This is a simple score, easily calculated at admission, derived from patients' demographics, chronic comorbidities and acute risk factors easily obtained in routine clinical practice. The study had a significant number of participants in a selected population, empowering the conclusions in this group of septic-AKI patients.

## CONCLUSION

We developed a new easily calculated risk score to predict RRT requirement in septic-AKI patients, which combines patients' demographics, chronic comorbidities and acute risk factors. This can be a valuable tool in clinical practice, helping clinicians on the decision whether to initiate or not RRT when the patient does not fulfill the classic indications (severe acidemia, hyperkalemia, fluid overload or uremic syndrome).

## References

- Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. *Nat Rev Nephrol*. 2018; 14:217-230. doi: 10.1038/nrneph.2017.184.
- Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. *Intensive Care Med*. 2015; 41:1411-23. doi: 10.1007/s00134-015-3934-7.
- Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. *Clin J Am Soc Nephrol*. 2007; 2:431-9. doi: 10.2215/CJN.03681106.
- Bouchard J, Acharya A, Cerda J, Maccariello ER, Madaraso RC, Tolwani AJ, et al. A prospective international multicenter study of AKI in the intensive care unit. *Clin J Am Soc Nephrol*. 2015; 10:1324-31. doi: 10.2215/CJN.04360514.
- Chertow G, Burdick E, Honour M, Bonventre J, Bates D. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365-70. doi: 10.1681/ASN.2004090740.
- Hoste EA, Kellum JA, Selby NM, Zarbock A, Palevsky PM, Bagshaw SM, et al. Global epidemiology and outcomes of acute kidney injury. *Nat Rev Nephrol*. 2018; 14:607-25. doi: 10.1038/s41581-018-0052-0.
- Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, et al. Risk of chronic dialysis and death following acute kidney injury. *Am J Med*. 2012; 125:585-93. doi: 10.1016/j.amjmed.2012.01.016.
- Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005; 294: 813-8. doi: 10.1001/jama.294.7.813.
- Malhotra R, Kashani KB, Macedo E, Kim J, Bouchard J, Wynn S, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant*. 2017;32:814-22. doi: 10.1093/ndt/gfx026.
- Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, et al; IDEAL-ICU Trial Investigators and the CRICS TRIGGERSEP Network. Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N Engl J Med*. 2018;379:1431-42. doi: 10.1056/NEJMoa1803213.
- Chon GR, Chang JW, Huh JW, Lim CM, Koh Y, Park SK, et al. A comparison of the time from sepsis to inception of continuous renal replacement therapy versus RIFLE criteria in patients with septic acute kidney injury. *Shock*. 2012;38:30-6. doi: 10.1097/SHK.0b013e31825adcca.
- Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vi et al; Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires. Impact of continuous venovenous hemofiltration on organ failure during the early phase of severe sepsis: a randomized controlled trial. *Crit Care Med*. 2009;37:803-10. doi: 10.1097/CCM.0b013e3181962316.
- Shum HP, Chan KC, Kwan MC, Yeung AW, Cheung EW, Yan WW. Timing for initiation of continuous renal replacement therapy in patients with septic shock and acute kidney injury. *Ther Apher Dial*. 2013;17:305-10. doi: 10.1111/1744-9987.12148.
- Baek SD, Yu H, Shin S, Park HS, Kim MS, Kim SM, et al. Early continuous renal replacement therapy in septic acute kidney injury could be defined by its initiation within 24 hours of vasopressor infusion. *J Crit Care*. 2017;39:108-114. doi: 10.1016/j.jcrc.2016.12.014.
- Oh HJ, Kim MH, Ahn JY, Ku NS, Park JT, Han SH, et al. Can early initiation of continuous renal replacement therapy improve patient survival with septic acute kidney injury when enrolled in early goal-directed therapy? *J Crit Care*. 2016;35:51-6. doi: 10.1016/j.jcrc.2016.04.032.
- Carl DE, Grossman C, Behnke M, Sessler CN, Gehr TW. Effect of timing of dialysis on mortality in critically ill, septic patients with acute renal failure. *Hemodial Int*. 2010;14:11-7.
- Chou YH, Huang TM, Wu VC, Wang CY, Shiao CC, Lai CF, et al. Impact of timing of renal replacement therapy initiation on outcome of septic acute kidney injury. *Crit Care*. 2011;15:R134. doi: 10.1186/cc10252.
- Tian H, Sun T, Hao D, Wang T, Li Z, Han S, et al. The optimal timing of continuous renal replacement therapy for patients with sepsis-induced acute kidney injury. *Int Urol Nephrol*. 2014;46:2009-14. doi: 10.1007/s11255-014-0747-5.
- Gameiro J, Fonseca JA, Jorge S, Gouveia J, Lopes JA. Neutrophil, lymphocyte and platelet ratio as a predictor of mortality in septic-acute kidney injury patients. *Nefrologia*. 2020;40:461-8.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993; 270: 2957-63.
- KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int* 2012; 2:S1-138.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:801-10. doi: 10.1001/jama.2016.0287.
- ADA. Standards of medical care in diabetes—2009. *Diabetes Care*. 2009; 32 (Suppl 1): S13–S61.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289: 2560–72.
- KDIGO Chronic Kidney Disease Evaluation and Management. *Kidney Int Suppl*. 2013;3:136–50.
- Cho WY, Lim SY, Yang JH, Oh SW, Kim MG, Jo SK. Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 as biomarkers of patients with established acute kidney injury. *Korean J Intern Med*. 2020;35:662-71. doi: 10.3904/kjim.2018.266.
- Albeladi FI, Algethamy HM. Urinary Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Acute Kidney Injury, Severe Kidney Injury, and the Need for Renal Replacement Therapy in the Intensive Care Unit. *Nephron Extra*. 2017;7:62-77.
- Fayed A, El Nokeety MM, Heikal AA, Abdulazim DO, Naguib MM, et al; Vascular Calcification Group (VCG). Fibroblast growth factor-23 is a strong predictor of insulin resistance among chronic kidney disease patients. *Ren Fail*. 2018;40:226-30. doi: 10.1080/0886022X.2018.1455594.
- Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 2004;8:R204–12.
- Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11:R31. doi: 10.1186/cc5713.
- Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int*. 1985;27:928–37.
- Royakkers AA, Korevaar JC, van Suijlen JD, Hofstra LS, Kuiper MA, Spronk PE, et al. Serum and urine cystatin C are poor biomarkers for acute kidney injury and renal replacement therapy. *Intensive Care Med*. 2011;37:493-501. doi: 10.1007/s00134-010-2087-y.
- Chen JJ, Lee CC, Kuo G, Fan PC, Lin CY, Chang SW, et al. Comparison between watchful waiting strategy and early initiation of renal replacement therapy in the critically ill acute kidney injury population: an updated systematic review and meta-analysis. *Ann Intensive Care*. 2020;10:30. doi: 10.1186/s13613-020-0641-5.
- Besen BA, Romano TG, Mendes PV, Gallo CA, Zampieri FG, Nassar AP Jr, et al. Early Versus Late Initiation of Renal Replacement Therapy in Critically Ill Patients: Systematic Review and Meta-Analysis. *J Intensive Care Med*. 2019;34:714-22. doi: 10.1177/0885066617109194.
- Li X, Liu C, Mao Z, Li Q, Zhou F. Timing of renal replacement therapy initiation for acute kidney injury in critically ill patients: a systematic review of randomized clinical trials with meta-analysis and trial sequential analysis. *Crit Care*. 2021;25:15. doi: 10.1186/s13054-020-03451-y.
- Zarbock A, Kellum JA, Schmidt C, Van Aken H, Wempe C, Pavenstädt H, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: The ELAIN Randomized Clinical Trial. *JAMA*. 2016;315:2190-9. doi: 10.1001/jama.2016.5528.
- Zhang L, Chen D, Tang X, Li P, Zhang Y, Tao Y. Timing of initiation of renal replacement therapy in acute kidney injury: an updated meta-analysis of randomized controlled trials. *Ren Fail*. 2020;42:77-88. doi: 10.1080/0886022X.2019.1705337.
- Gaudry S, Hajage D, Benichou N, Chaïbi K, Barbar S, Zarbock A, et al. Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. *Lancet*. 2020;395:1506-15. doi: 10.1016/S0140-6736(20)30531-6.
- Kane-Gill SL, Sileanu FE, Murugan R, Trietley GS, Handler SM, Kellum JA. Risk factors for acute kidney injury in older adults with critical illness: a retrospective cohort study. *Am J Kidney Dis* 2015; 65: 860–9. doi: 10.1053/j.ajkd.2014.10.018.
- Peres LA, Wandeur V, Matsuo T. Predictors of acute kidney injury and mortality in an intensive care unit. *J Bras Nefrol* 2015; 37: 38–46.

41. Chawla LS, Abell L, Mazhari R, Egan M, Kadambi N, Burke HB, et al. Identifying critically ill patients at high risk for developing acute renal failure: a pilot study. *Kidney Int* 2005; 68: 2274–80. doi: 10.1111/j.1523-1755.2005.00686.x.
42. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA. Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. *J Am Soc Nephrol* 2003; 14: 1022–30. doi: 10.1097/01.asn.0000059863.48590.e9.
43. de Almeida Thiengo D, Strogoff-de-Matos JP, Lugon JR, Graciano ML. Troponin I at admission in the intensive care unit predicts the need of dialysis in septic patients. *BMC Nephrol*. 2018;19:329. doi: 10.1186/s12882-018-1129-5.

## ■ Ethical Disclosures

**Conflicts of Interest:** The authors have no conflicts of interest to declare.

**Financing Support:** This work has not received any contribution, grant or scholarship

**Confidentiality of Data:** The authors declare that they have followed the protocols of their work center on the publication of data from patients.

**Protection of Human and Animal Subjects:** The study was approved by the Ethical Committee at the Centro Hospitalar Lisboa Norte, EPE, in agreement with institutional guidelines and in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013). Informed consent was waived by the Ethical Committee due to the retrospective and non-interventional nature of the study.

**Provenance and Peer Review:** Not commissioned; externally peer reviewed.

## Corresponding Author:

Filipe Marques 

Division of Nephrology and Renal Transplantation, Department of Medicine  
Centro Hospitalar Lisboa Norte, EPE

Av. Prof. Egas Moniz, 1649-035 Lisboa, Portugal

E-mail: filipedcmarques@campus.ul.pt