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Early mortality risk factors at the beginning of continuous renal replacement therapy for acute kidney injury

Camilo Alberto Gonzalez[1]*, Jessica Liliana Pinto[1], Viviana Orozco[1], Kateir Contreras[1], Paola Garcia[1], Patricia Rodriguez[1], Juan Patiño[1] and Jorge Echeverri[2]

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*Corresponding author: Camilo Alberto Gonzalez, Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogota 111134, Colombia
E-mail: cagonzalez@husi.org.co

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Abstract: *Introduction:* Acute kidney injury (AKI) occurs in more than 50% of critically ill patients, 23% need renal replacement therapy. The aim of our study is to identify early mortality risk factors at the beginning of continuous renal replacement therapy (CRRT) for AKI. *Methods*: A cohort study was performed in adult patients with AKI who required CRRT in the intensive care unit of a university hospital. We did a bivariate and multivariate analysis for early death, defined as death within 24 h of onset of CRRT. *Results:* 214 AKI patient required CRRT, The mean age was 61.5 years (± 15.47), 57.73% men. The most frequent cause of AKI was sepsis in 30.9% of cases. A total of 774 CRRT days were conducted with a median of 3 days per patient (1–19). Mean Charlson comorbidity index was 5.22 (± 2.85), APACHE II score 29.65 (± 6.66), total non-renal SOFA had a median of 11 (range 6–18) at the time of starting therapy. The hospital mortality was 68.4% and early mortality was 19.07%. In multivariate analysis for early death: lactate levels ($p = 0.007$), glucose ($p = 0.01$) and age ($p = 0.02$) were independent risk factors with AUC of 0.73. *Conclusions*: Patients with AKI on CRRT have high mortality. Age, Low glucose and high lactate at onset of CRRT are independent risk factors of early death. We need an external validation.

Subjects: Nephrology; Dialysis; Critical Care Medicine

Keywords: Acute kidney injury; renal replacement therapy; mortality; critical illness; renal insufficiency

1. Background

The incidence of acute kidney injury (AKI) in the intensive care unit (ICU) is increasing. In a recent study by Hoste et al. (2015) More than 50% of ICU patients developed AKI according to Kidney disease, improving global outcomes (KDIGO) definition (2012) and Kellum and Lameire (2013), and at least 23% of them needed renal replacement therapy (RRT), choosing continuous mode as the

ABOUT THE AUTHOR

The author is internist and nephrologist; he practice since 2012 in Bogotá, Colombia. He is currently working in two university hospitals and his main focus is on the patient with acute kidney injury and critical nephrology. He is very interested in improving the practice and timely use of resources and technologies in my institution, and in clinical research.

PUBLIC INTEREST STATEMENT

The incidence of acute kidney injury is high; up to 23% of cases usually require renal replacement therapy. Continuous renal replacement therapy is the most used, however the mortality continues in these cases being very high. Some factors associated with critical illness are markers of mortality in the first 24 hours of the start of CRRT, factors that may be modifiable to select the best time to start therapy; to identify these factors is the main objective of this study.

preferred one (Hoste et al., 2015). However, in the real life the mortality is too high as 64% (Uchino et al., 2007) All the new research focuses on de right time to continuous renal replacement therapy (CRRT) initiation by renal dysfunction characteristics. But, AKI is a systemic disease, so we need to consider systemic markers. Many studies had evaluated the strategy of early initiation of RRT; recently two clinical trails had demonstrated the history of that inconsistency, both only considering early or delayed initiation based on renal dysfunction characteristics in all the etiologic spectrum of AKI (Gaudry et al., 2016; Zarbock et al., 2016)

Kawarazaki et al. (2013) show us; how serum lactate, serum albumin, vasopressor use and neurological disease were associated with increased death at 48 h after CRRT initiation (Ronco et al., 2015). And those factors were considered as poor prognosis. The aim of our study is to determine which factors (systemic markers) at the beginning of CRRT are associated with early mortality, defined as death within 24 h of the onset of the therapy. Those variables could be markers of poor prognosis that can be considered individually as late biomarkers to start CRRT or conditions where CRRT could be an inadequate therapy and we would need to wait a better condition to start it. However, without leading to ethical discussions, in some patients we will consider those factors as futility markers, since approximately 8% of patients in the Mehta cohort did not received renal replacement therapy related with futility (Villa, Ricci, & Ronco, 2015).

2. Methods

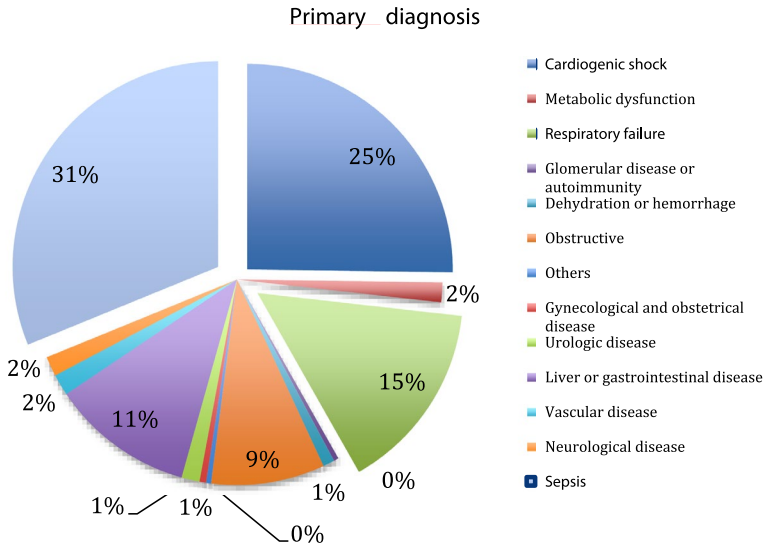
We design a retrospective cohort study were we included all the patients over 18 years old with AKI by KDIGO criteria that required CRRT as the first RRT modality in the ICU of a teaching hospital in Bogota, Colombia between 2009 and 2014. We excluded patients with end stage renal disease, kidney transplant, non-renal indications of CRRT, metastatic cancer and severe dementia. The CRRT was provided with Aquarius® Edwards® technology, polyethersulfone membrane of 1.2 and 1.4 m^2 (Aquamax®) and replacement fluids with lactate as buffer (Premixed®). Decision to start and the prescription was made according to the nephrologist criteria, based on 2012 AKI-KDIGO guideline (KDIGO, 2012). We define modality of RRT as the type of therapy between continuous or intermittent, cardiogenic shock as symptomatic hypotension or hyperlactatemia caused by cardiac dysfunction; and respiratory insufficiency as a failure to adequately provide oxygen to cells of the body and to remove carbon dioxide excess from them, and severe cases who need mechanical ventilation as respiratory failure.

Initially we calculate a sample size of 10 cases per dichotomy variable related with early death (Older age, sex, high comorbidity score, high severe illness score, high serum lactate levels, etc.) However, the sample cohort were insufficient and we included patients requiring CRRT during the study period. We did a description of demographic and clinical variables. Bivariate analysis was described with dependent variable as early death defined as death within 24 h of onset of CRRT, and finally we proceed to perform a multivariate logistic regression analysis with Stata® 12.0 for Mac® for early death as dependent variable. The appropriate selection of the final model were do by *stepwise* command for $p < 0.2$. The area under the receiver operating characteristic curve was use to assessed model calibration. And the model fit was assessed by Hosmer-Lemeshow goodness of fit test. We considered statistically significant a p value < 0.05.

3. Results

A total of 214 patients required CRRT during the period, 20 (9.34%) patients were excluded; 7 patients with age less than 18 years old, 3 with incomplete data and 10 with previous end stage renal disease. A total of 194 patients were analyzed, 2 patients had non-dialysis advanced chronic kidney disease (stage 4). The mean age was 61.5 years (± 15.47), 57.73% were men. The most frequent cause of AKI was sepsis in 30.9%, follow by cardiogenic shock in 20.6% (Figure 1). A total of 774 CRRT days were prescribed with a median of 3 days per patient (range 1–19), the most frequent prescription was continuous veno-venous hemofiltration (CVVH) with 100% pre-filter substitution in 73.7% of patients and the rest with continuous veno-venous hemodialysis (CVVHD). The given dose at first day of CRRT was 24 mL/k per day with a blood flow (QB) of 194.5 mL/min. The population had much

Figure 1. Primary diagnosis in ICU.



comorbidity calculated by Charlson comorbidity score and a high score of critical illness by APACHE II score. The mean sequential organ failure assessment (SOFA) without renal score was 10.3 (±2.7) with the highest cutoff in cardiovascular SOFA score median and mode of 4. We summarize demographic and clinical variables on Table 1 and labs data at CRRT initiation on Table 2. In-hospital mortality was 68.4% and early mortality was 19.07%.

Table 1. Clinical and demographic data

Variable	Early death (37)	Controls (Non-early death = 157)	All (194)
Female (%)	40.5%	42.7%	42.27%
Age (years)	66.1(±14.2)	60.5 (±15.6)	51.5(±15.4)
Pre-existing CKD* (%)	21.6%	26.1%	25.2%
Contrast exposure (%)	18.9%	15.4%	16.1%
Sepsis(%)	78.3%	71.7%	72.7%
Charlson score	5.58(±2.4)	5.13(±2.94)	5.2 (2.8)
BMI* (k/m^2)	25.7(±5.2)	24.9(±5.34)	25.1(±5.3)
Baseline eGFR CKD-EPI*	39.3(±26.1)	40.4(±28.8)	40.2(±28.2)
Noradrenaline (%)	86.4%	79.6%	80.9%
Noradrenaline and vasopressin use (%)	32.4%	27.4%	38.3%
APACHE II score	20.48(±5.6)	29.4(±6.8)	29.6(±6.6)
Mean Non-renal SOFA score	11.8(±2.7)	10.6(±2.8)	10.3(±2.7)
Urine outflow (mL per day)	813(±957)	595(±622)	637(±701)
MAP* (mmHg)	52.5(±12.6)	61.9(±11.4)	60.1(±12.2)
Fluid balance (mL)	3607(±3553)	3224(±5891)	3297 (±5514)
CRRT prescribed dose (ml/kg/h)	34.8(±9.5)	33.8(±7.9)	34(±8.2)
ICU Admission to CRRT initiation (days)	9.37(±9.95)	10(±12.6)	9.98(±12.1)
AKI to CRRT initiation (hours)	29(±42)	67.5(±112)	62.1(±103)

Legends: BMI: body mass index, eGFR CKD-EPI: estimated glomerular filtration rate in ml/min/1.73 m^2 (Basal) MAP: mean arterial pressure.

*CKD: chronic kidney disease.

Table 2. Labs value previous to start CRRT

Variable	Cases: Early death (37)	Controls (Non -early death= 157)	All (194)
Serum creatinine (mg/dL)	3.04(±1.24)	3.63(±1.84)	3.5(±1.7)
Urea nitrogen (mg/dL)	54.6(±27)	61.35(±28.5)	60.05(±2.04)
pH	7.23(0±.1)	7.26(±0.15)	7.25(±0.15)
HCO3- (mEq/L)	15.8(±5.9)	16.8(±5.6)	16.6(±5.6)
BE effect*	−10(±9.1)	−7.38(±13.8)	−7.92(±13.5)
Sodium (mEq/L)	142(±7)	140(±6.5)	140.4(6.65)
Potassium (mEq/L)	5.1(±1.25)	4.8(±0.9)	4.89(±1.02)
Chlorine (mEq/L)	110.8(±7.7)	109(±6.7)	110.1(±6.9)
Phosphorus (mg/dL)	6.3(±2.5)	5.57(±2.2)	5.71(±2.29)
Hemoglobin (g/dL)	9.23(±2.5)	10.1(±2.7)	9.96(±2.74)
Glucose (mg/dL)	108(±45)	138(±49)	132(±50)
Albumin (g/dL)	1.66(±0.8)	2.05(±0.8)	1.99(±0.8)
Total bilirubin (mg/dL)	3.96(±3.5)	2.4(±3.5)	2.71(±4.3)
Lactate (meq/L)	4.7(±3.5)	3.21(±2.6)	3.49(±2.86)

Legend: *BE effect: Base excess. *p*-value early death (cases) and controls (non early death).

In the bivariate analysis for early death vs. non-early death as a dependent variable: mean arterial pressure (MAP) at the beginning of CRRT was less in early death patients (52.5 ± 0.9 vs. 61.9 ± 2 mm Hg with $p = 0.00001$), like as serum glucose ($p = 0.002$), serum albumin ($p = 0.0048$), serum lactate ($p = 0.01$) and age ($p = 0.04$). All other variables: sex ($p = 0.8$), chronic kidney disease CKD ($p = 0.57$), chronic obstructive pulmonary disease (COPD) ($p = 0.58$), non metastatic neoplasm ($p = 0.053$), coronary heart disease ($p = 0.54$), contrast medium exposure ($p = 0.59$), sepsis ($p = 0.38$), noradrenaline use ($p = 0.34$), and combination of noradrenaline and vasopressin ($p = 0.54$), fluids balance 24 previous to CRRT initiation ($p = 0.27$), clearance dose of CRRT in ml/kg/h ($p = 0.41$) urea blood nitrogen ($p = 0.22$), serum creatinine ($p = 0.15$), pH ($p = 0.12$), bicarbonate ($p = 0.22$), effective base excess ($p = 0.22$), hemoglobin ($p = 0.06$), total bilirubin ($p = 0.5$), basal glomerular filtration rate estimated by CKD-EPI equation ($p = 0.85$), Charlson comorbid score adjusted to age ($p = 0.39$), urinary output 24 h before initiation of CRRT ($p = 0.52$), time between ICU admission to CRRT initiation ($p = 0.95$), APACHE II score ($p = 0.39$) and non-renal SOFA score ($p = 0.38$); was no statistically significant.

In multivariate analysis we performed a full model including: age, sex, APACHE II score, SOFA score, Charlson comorbidity score, body mass index BMI, baseline estimated glomerular filtration rate (eGFR), use of noradrenaline, use of noradrenaline and vasopressin, urine outflow, MAP, fluid balance 24 h before CRRT initiation, dose of CRRT at first day of therapy, ICU admission to CRRT initiation time in days, AKI diagnosis to CRRT initiation in hours, urea nitrogen, serum creatinine, HCO3−, sodium, potassium, chloride, phosphorus, hemoglobin, glucose, serum albumin and lactate for early death as a dependent variable. By stepwise multivariate logistic regression analysis, serum lactate levels (OR = 1.19 [IC95% 1.049–1.35] $p = 0.007$), glucose (OR = 0.98 [IC95% 0.98–0-99] $p = 0.01$) and age (OR = 1.03 [IC95% 1.004–1.06 $p = 0.02$) were independent risk factors associated with early death, with an AUC ROC of 0.73.

4. Discussion

Acute kidney injury is a big silent problem in ICU patient (Kellum & Lameire, 2013) mortality risk increase exponentially in relation with KDIGO classification, (Hoste et al., 2015) but in most severe cases like required RRT, the mortality is as high as 50–70% (Uchino et al., 2007; Villa et al., 2015). We usually select CRRT modality based on hemodynamic state or according specific therapeutic goal (slow clearance, slow ultrafiltration, etc.) (KDIGO, 2012; Ronco et al., 2015) however, we usually choose CRRT modality in severe score of critical illness patients, and this selection bias explain higher

mortality in the real life. In our cohort we had an in-hospital mortality of 68%, near to 63.8% of the multinational B.E.S.T study cohort of CRRT (Uchino et al., 2007). We know the high cost of critical illness and of the therapies in the ICU like CRRT. So, it is important for us to have adequate selection of patient. To determine prognostic factors for early death is the most important aim in this study. Those factors could be modify before to start CRRT, or could be markers of condition to consider delay CRRT initiation, waiting for a better clinical condition of the patient; or at worst to selected some patients who do not benefit from CRRT by futility, to discuses at institutional Ethical Committee, because it could be a sort of "critical care failure to thrive syndrome".

A study in 14 Japanese ICUs in 12 tertiary hospitals, show some factors associated with mortality after 48 h of CRRT initiation. Serum lactate (OR: 1.19, 95% CI: 1.11–1.28), albumin (g/dL) (OR: 0.52, 95% CI: 0.28–0.92), vasopressor use (OR: 3.68, 95% CI: 1.37–12.16), and neurological disease (OR: 9.64, 96% CI: 1.22–92.95) were related to early death. Also serum lactate had an AUC ROC of 0.83 to predict death within 48 h after CRRT initiation (Kawarazaki et al., 2013). Similarly, in a Canadian study by Prasad, Urbanski, Ferguson, Karreman, and Tangri (2016) Vasopressor use and hypoxia were independently factors associated with adverse short-term survival, however they did not included serum lactate in the analysis.

In our study serum lactate levels, glucose and age were independent risk factors, with an area under the curve of 0.73. All the patient with low glucose levels had received dextrose, others corticosteroids, and others nutritional support; and all the patient with high serum lactate received hemodynamic support, fluid resuscitation, mechanical ventilation, AKI ethiology control, etc. before CRRT initiation. So we consider that the real problem is the persistence of high levels of serum lactate and hypoglycemia despite treatment at the onset of CRRT.

In the literature as in our study, critical illness score, did not predict early death on CRRT, probably by collinearity of the model with all other included variables, and because APACHE score for example was developed to predict in hospital mortality in general ICU population.

The most important limitation of our study is the small sample size in a single center; we will provide in the future an external validation and a prospective multicenter large sample size.

5. Conclusions

Serum lactate levels, glucose and age were independent risk factors, with an area under the curve of 0.73. The most important limitation of our study is the small sample size in a single center.

List of abbreviations

AKI	Acute kidney injury
APACHE II	acute physiologic and chronic health disease classification system II
AUC ROC	area under the receiver operating characteristic curve
BMI	Body mass index
CRRT	continuous renal replacement therapy
CVVH	continuous veno-venous hemofiltration
CVVHD	continuous veno-venous hemodialysis
COPD	chronic obstructive pulmonary disease
CKD-EPI	equation to estimated glomerular filtration rate in ml/min/1.73 m^2
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
HCO3	Serum bicarbonate
ICU	intensive care unit

KDIGO	Kidney disease, improving global outcomes
RRT	area under the receiver operating characteristic curve
SOFA	sequential organ failure assessment
MAP	mean arterial pressure
OR	Odds ratio
QB	Blood flow

Authors' contributions
CG supervises recruitment, built the methods, analyzed and interpreted the patient data, and edit manuscript, JP worked in protocol development and recruit patient data, VO help in protocol development and recruited patient data, KC contributed to study's design and to edit manuscript, PG help in manuscript edition, PR contributed in protocol design, JP recruited patient data, JE built the database and helped draft and revised the manuscript.

Declarations
Ethics approval and consent to participate: The study protocol was presented to ethical committee of the "Hospital Universitario San Ignacio" from Bogota, Colombia and was approved to patient recruitment with register code number 50-2015. Because we take the data from a secondary source we didn't need a written informed consent for the research subjects.

Consent to publish: Not applicable

Availability of data and materials: The datasets generated during the current study are not publicly available due to "Hospital Universitario San Ignacio" internal principles for research, but are available from the corresponding author on reasonable request on e-mail: cagonzalez@husi.org.co.

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Competing interests
The authors declare no competing interest.

Author details
Camilo Alberto Gonzalez[1]
E-mail: cagonzalez@husi.org.co
ORCID ID: http://orcid.org/0000-0001-8213-4595
Jessica Liliana Pinto[1]
E-mail: jessicalilianapintoramirez@gmail.com
Viviana Orozco[1]
E-mail: Vivioro05@hotmail.com
Kateir Contreras[1]
E-mail: kcontreras@husi.org.co
ORCID ID: http://orcid.org/0000-0002-8892-9652
Paola Garcia[1]
E-mail: pkgarcia@husi.org.co
ORCID ID: http://orcid.org/0000-0001-9852-749X
Patricia Rodriguez[1]
E-mail: mprodriguez@husi.org.co
Juan Patiño[1]
E-mail: Juan.patino@javeriana.edu.co
Jorge Echeverri[2]
E-mail: Je.echeverri.s@gmail.com
[1] Hospital Universitario San Ignacio, Pontificia Universidad Javeriana, Bogota 111134, Colombia.
[2] Hospital Militar Central, Universidad Nueva, Bogota, Colombia.

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