Health & Research Journal

Vol 8, No 3 (2022)

Volume 8 Issue 3 July - September 2022

Renal Biomarker combinations predict early CRRT need in a mixed ICU population

Dimitrios Panagidis, Epameinondas Angelopoulos, Panagiota Tsiara, Serafim Nanas, Eleni Magira, Stelios Kokkoris

doi: 10.12681/healthresj.28926

To cite this article:

Panagidis, D., Angelopoulos, E., Tsiara, P., Nanas, S., Magira, E., & Kokkoris, S. (2022). Renal Biomarker combinations predict early CRRT need in a mixed ICU population. *Health & Research Journal*, *8*(3), 166–178. https://doi.org/10.12681/healthresj.28926

HEALTH AND RESEARCH JOURNAL
E-ISSN:2459-3192

(2022), Volume 8, Issue 3

RESEARCH ARTICLE

RENAL BIOMARKER COMBINATIONS PREDICT EARLY CRRT NEED IN A MIXED ICU POPULATION

Dimitrios Panagidis[1], Epameinondas Angelopoulos[1], Panagiota Tsiara[2], Serafim Nanas[1], Eleni Magira[1], Stelios Kokkoris[1]

1. 1st Department of Critical Care, National and Kapodistrian University of Athens, Medical School, 'Evangelismos' General Hospital, Athens, Greece
2. Biochemistry Laboratory, 'Evangelismos' General Hospital, Athens, Greece

Abstract

Background: Acute kidney injury (AKI) is associated with markedly increased morbidity and mortality in critically ill patients and often necessitates the use of continuous renal replacement therapy (CRRT).

Aim: The aim of the present study was to compare the predictive performance of urine neutrophil gelatinase (uNGAL), plasma cystatin C (pCysC), serum creatinine (sCr), and their combinations for CRRT requirement within the first 7 days post-admission in a general ICU.

Method and Material: A total of 81 consecutive ICU patients were included in the analysis. AKI was defined according to AKIN criteria. Biomarkers' predictive abilities were evaluated by the area under the receiver operating characteristics (AUC-ROC) curves.

Results: AKI occurred in 21% of patients and 14% of them needed CRRT 7 days post-admission. The two novel biomarkers, as well as sCr had moderate predictive abilities for CRRT requirement. The most efficient combinations (sCr+ uNGAL) and (sCr+uNGAL+pCysC) had better AUC-ROCs (0.845 and 0.84, respectively) than that of any individual biomarker (sCr, pCysC, uNGAL, with AUC-ROCs 0.81, 0.74 and 0.80, respectively).

Conclusions: Renal biomarker combinations had better predictive characteristics for CRRT need within one week post admission as compared to each biomarker alone.

Keywords: Acute kidney injury, continuous renal replacement therapy, NGAL, cystatine C.

Corresponding Author: Stelios Kokkoris, MD, PhD, 1st Department of Critical Care, National and Kapodistrian University of Athens, Medical School, 'Evangelismos' General Hospital, Ipsilantou 45-47, 10636, Athens, Greece, Tel: 0030-2132041928, E-mail: skokkoris2003@yahoo.gr

Cite as: Panagidis, D., Angelopoulos, E., Tsiara, P., Nanas, S., Magira, E., Kokkoris, S. (2022). Renal biomarker combinations predict early CRRT need in a mixed ICU population. Health and Research Journal,8(3),166-178. https://ejournals.epublishing.ekt.gr/index.php/HealthResJ

INTRODUCTION

Acute kidney injury (AKI) is a common complication occurring in critically ill patients admitted to intensive care units (ICU), with an incidence of 30-50%, and is associated with markedly increased morbidity and mortality in these patients.[1] Timely identification of AKI and appropriate implementation of preventive strategies are thought to be the most effective tools to improve AKI outcomes.[2]

Serum creatinine (sCr), the most common renal dysfunction biomarker in use, has poor predictive accuracy for renal injury due to its many limitations.[3] Neutrophil gelatinase-associated lipocalin (NGAL),[4-9] cystatin C (CysC),[10-12] kidney injury molecule-1,[13-15] interleukin-18,[13,16-18] L-type fatty acid-binding protein,[16,19-20] TIMP-2 and IGFBP-7,[21-24] N-acetyl-β-D-glucosaminidase[16-17]and endogenous ouabain,[25-26] are novel biomarkers that have been validated over the years for the prognostic abilities of early AKI detection and need for continuous renal replacement therapy (CRRT). The performance of each biomarker was moderate, mainly due to the complexity and multifactorial nature of AKI syndrome.

The main purpose of this study was to compare the predictive abilities of admission urine neutrophil gelatinase-associated lipocalin (uNGAL), plasma cystatine C (pCysC), (sCr), and their combinations for CRRT need within 7 days post- ICU admission.

METHODOLOGY

Patient population

This is a prospective observational study of adult patients admitted to a 30-bed general Critical Care Department of a tertiary hospital of Athens, from October 2013 to October 2018. All consecutive patients admitted to the ICU were screened for eligibility. The exclusion criteria were the following: chronic renal disease, hemodialysis, renal transplantation, brain death, expected ICU stay or imminent death in less than 48h, transfer from another ICU, age<18 years, inability to draw blood or urine (anuria) (Figure 1). The lowest value of hospital admission or ICU discharge sCr concentration was used as baseline[27]. Patients were enrolled within 12 h of ICU admission at the latest. The protocol was approved by the Institutional Ethics Committee (Scientific Committee of 'Evangelismos' General Hospital) and informed consent was obtained from all patients' next-of-kin persons. AKI was defined using the sCr and urine output criteria of the AKIN classification[2] and patients were screened daily for AKI development and AKIN staging according to the above criteria. The decision for CRRT requirement was made by the patient's attending physician. Demographics, comorbidities, admission diagnosis, outcome measures, disease severity scores, routine laboratory data, and outcome measures, such as ICU mortality, CRRT initiation, and ICU length of stay, were also recorded.

Biomarkers Measurement

Blood samples were collected within 1h of enrolment and on CRRT initiation. Arterial blood was sampled in ethylenediaminetetraacetic acid (EDTA) tubes from an arterial line and was centrifuged at 3000 rpm at 4° C for 10 min. The supernatants were stored at -70°C. Urine samples were collected within 1h after enrolment and on CRRT initiation by the urine catheter reservoir and immediately stored at -70°C. sCr levels were determined by routine methods in the biochemistry laboratory of our hospital and pCysC levels were quantified by using an MNII nephelometer (Dade Behring GmbH, Marburg, Germany). uNGAL was measured by chemiluminescent microparticle assay using the ARCHITECT platform (Abbott Diagnostics Inc., Abbott Park, IL, USA). Personnel performing the biomarkers measurement were blinded to each patient's clinical data.

Statistical Analysis

Continuous variables were expressed as mean±standard deviation (SD), if normally distributed. Categorical variables were expressed as counts with percentages (%). Comparisons were performed with Student's t-test for continuous variables and with x^2 test for categorical variables. The predictive performance of the various biomarkers was assessed by constructing their receiver operating characteristics (ROC) curves: The log-transformed values of the biomarkers at admission were entered alone and in combinations in logistic regression models with

CRRT need by day 7 as the dependent variable. The predictive performances were assessed using the area under the ROC (AUC-ROC) curves and ROC curves were compared using the method described by DeLong et al[28]. In addition, model fit was compared between nested models using the likelihood ratio-chi-square test. Potential predictor variables for CRRT need 7 days post ICU admission included age, gender, acute physiology and chronic health evaluation II (APACHE II), and sequential organ failure assessment (SOFA). All tests were two sided and significance was accepted at $p<0.05$. All statistical analyses were performed using SPSS v.21 (SPSS Inc., Chicago, IL, USA) and Microsoft Excel.

RESULTS

Patient Characteristics

The study flowchart is depicted in Figure 1. Of the 81 patients enrolled, 17 (21%) developed AKI and 11 (14%) needed CRRT within 7 days post ICU admission, while their ICU mortality rate was 32%. Among study patients, maximum AKIN classes were as follows: AKIN-STAGE I 9%, AKIN STAGE II 1% and AKIN STAGE III 11%. Patient admission characteristics, renal parameters, and outcome measures are shown in Table 1. Patients who needed CRRT had higher APACHE II and SOFA scores, higher admission renal parameters and higher mortality. Of note, the values of sCr, pCysC and uNGAL did not change significantly from the day of admission until the day CRRT was initiated (data not shown).

Predictive Abilities of Individual Biomarkers and Their Combinations for CRRT requirement within 7 Days Post-Admission

The two novel biomarkers and sCr had moderate predictive ability for CRRT need (Table 2) and none of them had significantly higher AUC-ROC over the others, as shown in Table 3. The vast majority of their combinations had higher AUC-ROCs than that of each biomarker alone, but two of these biomarker combinations (sCr+uNGAL and sCr+uNGAL+pCysC) reached statistical significance ($p<0.05$ vs. sCr) and were selected to participate in the subsequent analyses. Of note, in the multivariate logistic regression model that combined all three biomarkers, sCr and uNGAL were independently associated with CRRT need (Table 4). None biomarker had significantly higher AUC-ROC over the others, according to the U-test by DeLong et al.[28] The likelihood tests for the addition of each variable indicate that only the addition of uNGAL to sCr significantly improved its performance, having also the greatest AUC-ROC. The ROC curves of the combinations of the aforementioned three renal biomarkers are depicted in Figure 2. The AUC-ROCs comparisons of all possible biomarker combinations are shown in Table 5.

DISCUSSION

We performed a prospective observational study in a heterogeneous adult ICU population, the main finding of which was that biomarker combinations had better performance for CRRT need prediction compared with each biomarker alone. More specifically, we compared the predictive ability of three renal biomarkers (uNGAL, pCysC, sCr) and their most efficient combinations for CRRT need within 7 days post ICU admission. Most of the biomarker combinations had better AUC-ROCs than that of each biomarker alone. More specifically, the combination of sCr+uNGAL had higher AUC-ROC than the combination of sCr+pCysC, as well as the combination of the three of them altogether. Of individual biomarkers, uNGAL showed similar performance with sCr, while it had an AUC-ROC significantly higher than that of pCysC. Our data show evidence that combining sCr with uNGAL can predict the need of CRRT in the first 7 days after ICU admission.

Studies have found that NGAL levels increase after systemic diseases with absence of bacterial infection and after renal tubular injury. In the process of the last one human pNGAL levels are increased on the order of 7- to16-fold and human uNGAL levels increased by 25- to 100-fold[4]. Synthesis of NGAL protein in the distal nephron and secretion into the urine seems to be promoting cell survival and proliferation. Comparing NGAL performance with GFR, NGAL concentration (both in serum and urine) was found to have better prognostic value in AKI prediction.[4] On

the other hand, pCysC is primarily a sensitive marker of reduction in GFR,[29] whereas urinary CysC (uCysC) can reflect tubular damage and appears to be a good biomarker in the prediction of AKI[30].

Most studies so far have focused on the performance of only one of these biomarkers to detect AKI and CRRT need in critically ill patients before sCr rise. Due to the fact that the etiology of AKI is multifactorial it is speculated that a single biomarker will be insufficiently sensitive and specific and combinations (panels) of biomarkers may prove more accurate.[31]

In observational studies of adult ICU patients, AUC-ROCs for CRRT initiation were ranging from 0.73 to 0.88 for pNGAL and 0.62 to 0.89 for Ungal.[6-9] Endre et al[13] tested 6 renal biomarkers for their ability to predict AKI. His findings for uNGAL performance in predicting CRRT need were similar to ours. Nevertheless, there is no direct comparison because his purpose was to point out that the diagnostic performance of renal biomarkers depends on time of insult and baseline renal function on ICU entry. A recent study by Ralib et al.,[32] indicated that correction of uNGAL levels for urinary creatinine might result in better performance in predicting CRRT requirement than using the absolute concentration of uNGAL. Regarding the predictive ability of pCysC for CRRT requirement in the ICU setting, the AUC-ROCs range from 0.66 to 0.84.[10-12] Kiessling et al.,[33] in a study involving a homogeneous population of cardiac surgery patients, measuring pCysC values postoperatively, found that it showed good diagnostic performance. In our study, where a heterogeneous patient population was included, pCysC did not appear superior to sCr for CRRT prediction.

We acknowledge that our study has certain limitations. First of all, it is a single-center study and its findings are not as generalizable as those of a multicenter study. The small sample size could reduce the power of the study while the enrolment of 81 patients from a total of 152 patients who were initially screened could have led to a selection bias (the main reason of the exclusion was an expected ICU stay less than 48h, so the more severe ill patients might have been selected).

We analyzed our data by using absolute uNGAL. There are some pitfalls when reporting absolute concentrations of a urinary biomarker; for example, oliguria can cause an increase and polyuria a decrease, in its absolute concentration, the production and excretion rates of which are constant. Waikar et al. found that the most accurate method to quantify urine biomarkers requires the collection of timed urine specimens to estimate the actual excretion rate.[34] However, this method has got some practical difficulties e.g., many patients in the ICU are anuric, and therefore urine collection would be impossible.

In conclusion, when we evaluated the predictive ability for CRRT need by means of AUC-ROCs, none of the two biomarkers (uNGAL and pCysC) was superior to sCr, however uNGAL was superior to pCysC. However, the combination of uNGAL with sCr was superior to each biomarker alone (uNGAL, pCysC, sCr). It may be proposed that future biomarker panels could assist in the early prediction of CRRT need in the heterogeneous population of a general ICU, the clinical implications of which needs further elucidation in future studies.

ACKNOWLEDGMENTS

The authors thank the ICU staff for their assistance with samples collection and express appreciation to the patients and their families for their participation.

Declaration of non-conflict of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

REFERENCES

1. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honore PM, Joannes -Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015; 41: 1411-23.2.

2. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012; 2: 1-138.
3. Schetz M, Gunst J, Van den Berghe G. The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. Intensive Care Med 2014; 40(11):1709-17.
4. Kokkoris S, Pipili C, Grapsa E, Kyprianou T, Nanas S. Novel biomarkers of acute kidney injury in the general adult ICU: a review. Ren Fail 2013; 35(4): 579-591.
5. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, DevarajanP. Identification of neutrophil gelatinase- associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 2003; 14:2534-2543.
6. de Geus HR, Bakker J, Lesaffre EM, le Noble JL. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 2011; 183:907-914.
7. Pickering JW, Endre ZH. The clinical utility of plasma neutrophil gelatinase -associated lipocalin in acute kidney injury. Blood Purif 2013; 35(4):295-302.
8. Hjortrup PB, Haase N, Treschow F, Moller MH, Perner A. Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. Acta Anaesthesiol Scand 2015; 59(1):25-34.
9. Linko R, Pettila V, Kuitunen A, Korhonen AM, Nisula S, Alila S, Kiviniemi O, Laru-Sompa R, Varpula T, Karlsson S. Plasma neutrophil gelatinase -associated lipocalin and adverse outcome in critically ill patients with ventilatory support. Acta Anaesthesiol Scand 2013; 57(7): 855-862.
10. Nejat M, Pickering JW, Walker RJ, Endre ZH. Rapid detection of acute kidney injury by plasma cystatin C in the intensive care unit. Nephrol Dial Transplant 2010; 25:3283-3289.
11. Royakkers AA, Korevaar JC, van Suijlen JD, Hofstra LS, Kuiper MA, Spronk PE, Schultz MJ, Bouman CS. Serum and urine cystatine C are poor biomarkers for acute kidney injury and renal replacement therapy. Int Care Med 2011; 37(3):493-501.
12. Pipili C, Ioannidou S, Tripodaki ES, Parisi M, Douka E, Vasileiadis I, Joannidis M, Nanas S. Prediction of the renal replacement therapy requirement in mechanically ventilated critically ill patients by combining biomarkers for glomerular filtration and tubular damage. J Crit Care 2014; 29(4):692.
13. Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, Frampton CM, Bennett MR, Ma Q, Sabbisetti VS, Vaidya VS, Walcher AM, Shaw GM, Henderson SJ, Nejat M, SchollumJB, George PM. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int. 2011; 79(10):1119-30.
14. Nejat M, Pickering JW, Devarajan P, Bonventre JV, Edelstein CL, Walker RJ, Endre ZH. Some biomarkers of acute kidney injury are increased in pre-renal acute injury. Kidney Int.2012; 81:1254-1262.
15. Koyner JL, Vaidya VS, Bennett MR, Ma Q, Worcester E, Akhter SA, Raman J, Jeevanandam V, O΄ Connor MF, Devarajan P, Bonventre JV, Murray PT. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. Clin J Am Soc Nephrol 2010; 5:2154-2165.
16. Doi K, Negishi K, Ishizu T, Katagiri D, Fujita T, Matsubara T, Yahagi N, Sugaya T, Noiri E. Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit. Crit Care Med 2011; 39:2464-2469.
17. Doi K, Katagiri D, Negishi K, Hasegawa S, Hamasaki Y, Fujita T, Matsubara T, Ishii T, Yahagi N, Sugaya T, Noiri E. Mild elevation of urinary biomarkers in prerenal acute kidney injury. Kidney Int 2012; 82:1114-1120.
18. Nisula S, Yang R, Poukkanen M, Vaara ST, Kaukonen KM, Tallgren M, Haapio M, Tenhunen J, Korhonen AM, Pettila V. Predictive value of urine interleukin -18 in the evolution and outcome of acute kidney injury in critically adult patients. Br J Anaesth 2015; 114(3):460-468.
19. Doi K, Noiri E, Maeda-Mamiya R, Ishii T, Negishi K, Hamasaki Y, Fujita T, Yahagi N, Koide H, Sugaya T, Nakamura T. Urinary

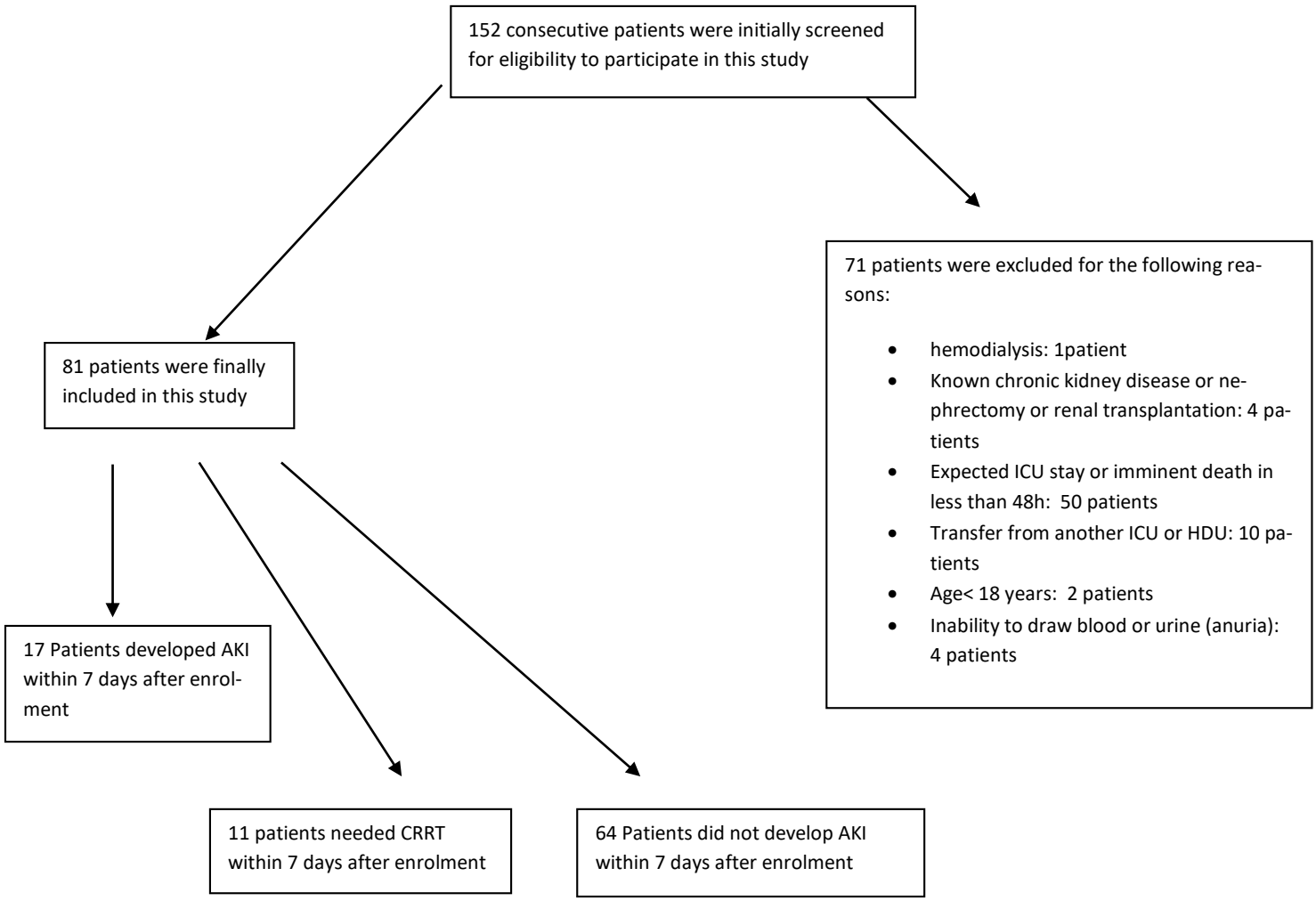
L-type fatty acid-binding protein as a new biomarker of sepsis complicated with acute kidney injury. Crit Care Med.2010; 38:2037-2042.

20. Dihazi H, Koziolek MJ, Datta RR, Wallbach M, Jung K, Heise D, Dihazi GH, Markovic I, Asif AR, Muller GA. FABP1 and FABP3 have high predictive values for Renal Replacement Therapy in patients with Acute Kidney Injury. Blood Purif. 2016; 42(3):202-213.
21. Kashani K, Al-khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmele T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharoswski K, Kellum JA. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013; 17: R25.
22. Bihorac A, Chawla LS, Shaw AD, Al-khafaji A, Davison DL, Demuth GE, Fitzgerald R, Gong MN, Graham DD, Gunnerson K, Heung M, Jortani S, Kleerup E, Koyner JL, Krell K, Letourneau J, Lissauer M, Miner J, Nguyen HB, Ortega LM, Self WH, Sellman R, Shi J, Straseski, J, Szalados JE, Wilber ST, Walker MG, Wilson J, Wunderink R, Zimmerman J, Kellum JA. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014; 189:932-939.
23. Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, Feldkamp T, Uettwiller-Geiger DL, McCarthy P, Shi j, Walker MG, Kellum JA. Derivation and validation of cutoffs for clinical use of cell cycle biomarkers. Nephrol Dial Transplant 2014; 29:2054-2061.
24. Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, Haase M, Shi J, Kellum JA. Tissue inhibitor metalloproteinase -2 (TIMP-2) IGF binding protein -7(IGFBP7) levels are associated with adverse long- term outcomes in patients with AKI. J Am Soc Nephrol 2015; 26:1747-1754.
25. Bignami E, Casamassima N, Frati E, Lanzani C, Corno L, Alfieri O, Gottlieb S, Simonini M, Shah KB, Mizzi A, Messaggio E, Zangrillo A, Ferrandi M, Ferrari P, Bianchi G, Hamlyn JM, Manunta P. Preoperative endogenous ouabain predicts acute kidney injury in cardiac surgery patients. Crit Care Med 2013; 41:744-755.
26. Simonini M, Lanzani C, Bignami E, Casamassima N, Frati E, Meroni R, Messaggio E, Alfieri O, Hamlyn J, Body SC, Collard CD, Zangrillo A, Manunta P. A new clinical multivariable model that predicts postoperative acute kidney injury: impact of endogenous ouabain. Nephrol Dial Transplant 2014; 29:1696-1701.
27. Pickering JW, Endre ZH. Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. Clin J Am Soc Nephrol 2010; S: 1165-1173.
28. DeLong ER, Delong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A non parametric approach. Biometrics.1988; 44: 837-845.
29. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. Am J Kidney Dis. 2002; 40:221-226.
30. Zhang Z, Lu B, Sheng X, JinN. Cystatin C in prediction of acute kidney injury: A systemic review and meta-analysis. Am J Kidney Dis. 2011; 58(3):356-365.
31. Kokkoris S, Parisi M, Ioannidou S, Douka E, Pipili C, Kyprianou T, Kotanidou A, Nanas S. Combination of renal biomarkerspredicts acute kidney injury in critically ill adults. Ren Fail 2012; 34: 1100-8.
32. Ralib AM, Pickering JW, Shaw GM, Devarajan P, Edelstein CL, Bonventre JV, Endre ZH. Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury. J Am Soc Nephrol 2012; 23: 322-333.
33. Kiessling AH, Dietz J, Reyher C, Stock UA, Beiras- Fernandez A, Moritz A. Early postoperative serum cystatin C predicts severe acute kidney following cardiac surgery: a post- hoc analysis of a randomized controlled trial. J Cardiothorac Surg 2014; 9:10.

34. Waikar SS, Sabbisetti VS, Bonventre JV. Normalization of urinary biomarkers to creatinine during changes in glomerular filtration rate. Kidney Int 2010; 78:486-494.

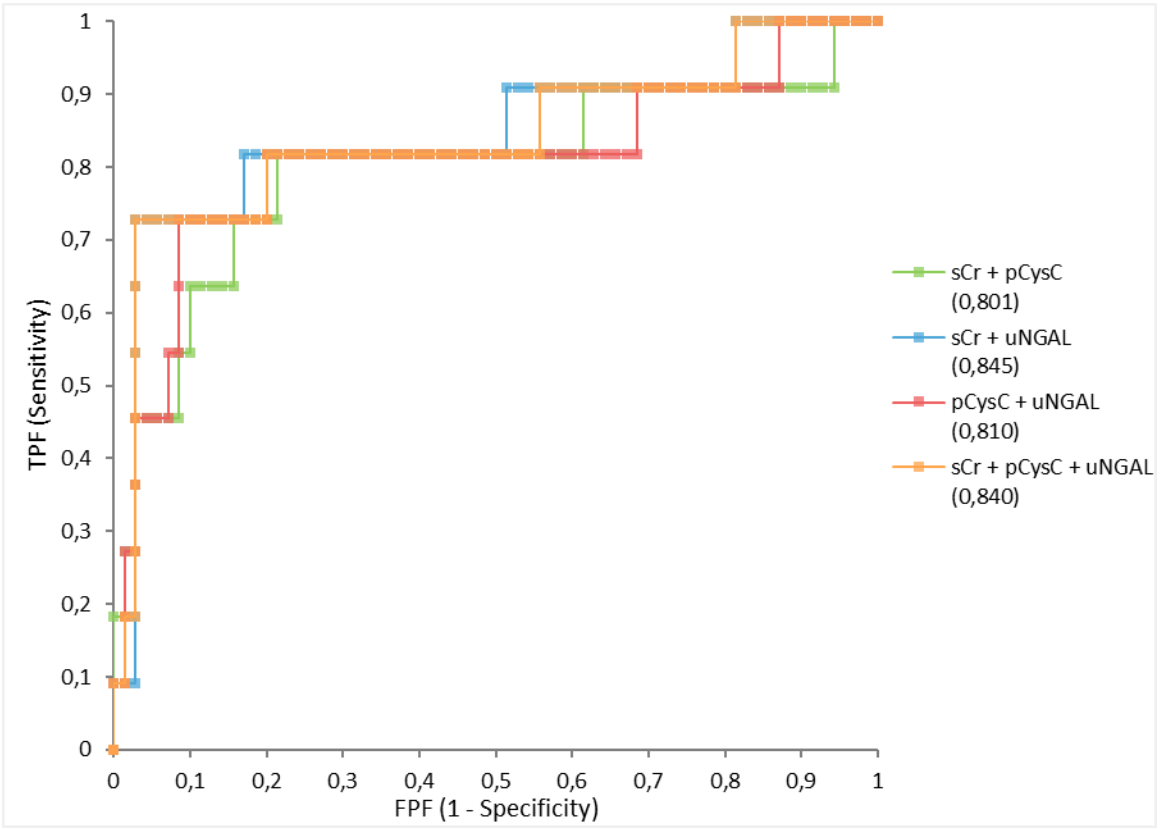
ANNEX

Figure 1. Study flowchart.



Definition of abbreviations: AKI, acute kidney injury; ICU, intensive care unit; CRRT, continuous renal replacement therapy; HDU, high dependency unit.

Figure 2. Receiver-operating characteristics curves of the biomarkers' combinations.



Definition of abbreviations: sCr, serum creatinine; pCysC, plasma cystatin; uNGAL, urine neutrophil gelatinase-associated lipocalin. Within parentheses are the AUC of each combination (AUC, area under the curve).

TABLE 1. Patient's admission characteristics, renal parameters and outcomes, according to CRRT need.

	All (n=81)	**CRRT (n=11)**	**no CRRT (n=70)**	**p-value**
Demographics				
Age, years	58±19	54±18	59±19	0.40
Female sex	37 (46)	4 (36)	33 (47)	0.74
BMI, kg/m^2	25.8±2.5	24.4±2.4	26.0±2.4	0.07
Admission parameters				
APACHE II	15±5	20±6	14±5	0.003
SOFA	8±3	10±4	8±3	0.006
Renal parameters				
pUrea (mg/dL)	58±51	113±88	49±37	0.001
sCr (mg/dL)	1.33±1.24	2.89±2.39	1.09 0,72	0.001
pCysC (mg/L)	1.47±1.32	2.16±.30	1.36±1.29	0.012
uNGAL (ng/mL)	397.0±809.1	1506.3 ±1501.4	222.7 453.3	0.001
AKIN at admission (%)				
No AKI	64 (79)	2 (18)	62 (89)	<0.001
Stage 1	7 (9)	1 (9)	6 (9)	
Stage 2	1 (1)	0 (0)	1 (1)	
Stage 3	9 (11)	8 (73)	1 (1)	
Patient type				
Emergency	72 (89)	11 (15)	61 (85)	0.349
Multiple trauma	19 (23)	0 (0)	19 (100)	0.059
Respiratory	21 (26)	4 (19)	17 (81)	0.304
Outcome				
ICU-LOS (days) *	3-19	4-10	3-19	0.85
ICU mortality (%)	26 (32)	5 (45)	21 (30)	0.32

Values are expressed as n (%) or mean±SD; Definition of abbreviations: CRRT, continuous renal replacement therapy; BMI, body mass index; APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; pUrea, plasma Urea; sCr, serum creatinine; pCysC, plasma cystatin C; uNGAL, urine neutrophil gelatinase associated lipocalin; AKI, acute kidney injury; LOS, length of stay

TABLE 2. Predictive performance of each individual biomarker for CRRT need within 7 days post-admission.

Logistic regression model	**p-value in the model**	**AUC**	**95% CI**
Univariate model			
sCr	0.001	0.817	0.654-0.980
pCysC	0.02	0.740	0.589-0.891
uNGAL	0.001	0.806	0.623-0.989
Definition of abbreviations: AUC, area under the curve; CI, confidence interval; sCr, serum creatinine; pCysC, plasma cystatin C; uNGAL, urine neutrophil gelatinase- associated lipocalin.			

TABLE 3. AUC-ROC comparisons between the biomarkers for prediction of CRRT need 7 days post-ICU admission.

Biomarkers	**ΔAUC**	**95%CI**
sCr **vs.** pCysC	0.076	0.120-0.272
uNGAL **vs.** pCysC	0.070	0.117-0.257
sCr **vs.** uNGAL	0.006	0.210-0.221

Definition of abbreviations: ROC, receiver-operating characteristics; CRRT, continuous renal replacement therapy; AUC, area under the curve; CI, confidence interval; sCr, serum creatinine; pCysC, plasma cystatin C; uNGAL, urine neutrophil gelatinase- associated lipocalin.
None biomarker had significantly higher AUC-ROC over the others, according to the DeLong test for AUCs comparison.

TABLE 4. AUC-ROC comparisons between the biomarkers for prediction of CRRT need 7 days post-ICU admission.

Logistic regression model	**p-value in the model**	**p-value (LRx^2)**	**AUC**	**95% CI**
Multivariate models				
sCr	0.006		0.801	0.631 – 0.982
+ pCysC	0.733	0.731		
sCr	0.019		0.845*	0.691 - 0.999
+ uNGAL	0.026	0.015		
uNGAL	0.009		0.810	0.637 – 0.984
+ pCysC	0.319	0.327		
sCr	0.034		0.840*	0.633 – 0.998
+ uNGAL	0.763	0.015		
+ pCysC	0.032	0.704		

Definition of abbreviations: CRRT, continuous renal replacement therapy; LR test, likelihood ratio test; AUC, area under the curve; CI, confidence interval; sCr, serum creatinine; pCysC, plasma cystatin C; uNGAL, urine neutrophil gelatinase-associated lipocalin.
*$p<0.05$ vs sCr_{AUC}, according to the test of DeLong et al. for AUCs comparison.

TABLE 5. AUC-ROC comparisons of all possible biomarkers' combinations for CRRT need prediction 7 days post ICU admission.

Biomarkers combinations	**ΔAUC**	**95% CI**
sCr+ uNGAL **vs.** sCr+pCysC	0.044	0.123-0.212
sCr+pCysC+uNGAL **vs.** sCr+pCysC	0.039	0.128-0.206
sCr+ uNGAL **vs.** pCysC+uNGAL	0.035*	0.021-0.091
sCr+pCysC+uNGAL **vs.** pCysC+uNGAL	0.030	0.027-0.087
pCysC+uNGAL **vs.** sCr+pCysC	0.009	0.204-0.223
sCr+ uNGAL **vs.** sCr+pCysC+uNGAL	0.005	0.007-0.018

Definition of abbreviations: ROC, receiver-operating characteristics; CRRT, continuous renal replacement therapy; AUC, area under the curve; CI, confidence interval; sCr, serum creatinine; pCysC, plasma cystatin C; uNGAL, urine neutrophil gelatinase- associated lipocalin.
*p<0.05, according to the test of DeLong et al. for AUCs comparison.