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Royal Free Hospital-estimated glomerular filtration rate for prognostic stratification of first acute kidney injury in cirrhosis

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Abbreviations: AKI, Acute Kidney Injury; ATN, Acute Tubular Necrosis; ArLD, Alcohol-related liver disease; AUROC, area under the receiver operating characteristic; BMI, Body mass index; CKD, Chronic kidney disease; CKD-EPI, Chronic kidney disease-epidemiology; CI, Confidence Interval; EASL, European Association for the Study of the Liver; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HCC, hepatocellular carcinoma; HRS, Hepatorenal Syndrome; INR, International normalized ratio; IQR, interquartile range; KDIGO, Kidney Disease Improving Global Guidelines; MDRD, modified diet renal disease; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NS, not significant; OLT, orthotopic liver transplant; OR, odds ratio; RRT, Renal Replacement Therapy; RFH, Royal Free Hospital; sCr, serum creatinine;

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Abstract

Background & Aims: Renal function is a major determinant of prognosis in patients with cirrhosis. Current guidelines only contemplate serum creatinine (sCr) to assess kidney injury. However, there are formulas to estimate glomerular filtration rate (eGFR) which better measure renal function in patients listed for liver transplantation. There is no data available on whether these formulas predict prognosis in patients with acute kidney injury (AKI).

Methods: In 143 patients presenting with a first episode of AKI, we compared the prognostic value of renal function estimated using sCr or eGFR assessed with Modification of Diet in Renal Disease (MDRD-6), chronic kidney disease epidemiology (CKD-EPI) and Royal Free Hospital (RFH) for renal replacement therapy (RRT) within 30 days of AKI, and 30- and 90-day transplant-free survival.

Results: eGFR was calculated on values obtained before and at admission, at presentation of AKI (D0) and 48 hours after AKI (D2).15% of patients (more commonly in alcohol+metabolic etiology; p=0.049 vs. other) required RRT. Transplant-free survival at 30-and 90-day were 77% and 63%. Among sCr, MDRD-6, CKD-EPI and RFH-eGFR, the latter predicted best RRT (HR .937 95% CI .893-.982, p=0.007), 30-d (HR .936 95% CI .901-.972, p=0.001) and 90-d (HR .934 95% CI .908-.972, p<0.001) mortality/OLT.

Conclusions: Renal function estimated using the RFH-eGFR calculated at D2 after AKI diagnosis is a strong predictor of RRT and of 30-d and 90-d transplant-free survival. Results suggest that in cirrhosis, RFH-eGFR may be a better indicator of prognosis in AKI than sCr.

Keywords: hepatorenal syndrome; chronic kidney disease; advanced chronic liver disease

Lay summary:

- The prognostic value of different eGFR formulas and sCr in AKI in cirrhosis is unknown.
- Renal function estimated using the RFH-eGFR calculated at D2 after AKI diagnosis is a strong predictor of RRT and of 30-d and 90-d transplant-free survival, and may be better than sCr and other formulas for eGFR.
- RFH-eGFR eliminated gender-based differences in sCr levels.

Introduction

Renal injury in cirrhosis represents one of the most important predictors of major morbidity and mortality; therefore, accurately assessing renal function is paramount.(1, 2) Serum creatinine (sCr) is widely used for the current definitions of acute kidney injury (AKI) and chronic kidney disease (CKD). However, factors such as gender, age, nutritional status, and/or underlying structural kidney disease may significantly influence serum creatinine levels and lead to an underestimation of the severity of renal dysfunction. (3) Other options to evaluate renal function in cirrhosis such as several equations for estimating the glomerular filtration rate (eGFR) that have been validated against measured GFR (mGFR). Among these are the modified diet in renal disease (MDRD) with 6 variables (MDRD-6), chronic kidney disease-epidemiology (CKD-EPI) and, more recently, the Royal Free Hospital Cirrhosis GFR (RFH-eGFR), a formula developed and validated specifically in cirrhosis.(4-7)

It has been recently shown that by using these formulas instead of sCr for renal function estimation, MELD score would be significantly higher in almost 40% of patients on the waiting list for OLT, hence improving risk stratification in this setting.(5) However, no data exist on whether in the setting of AKI these formulas outperform sCr for prognostication.

Further additional prognostic value in patients with AKI could be achieved by the use of changes in renal function over time; this concept is well proven in patients with chronic kidney disease (CKD) without liver disease. (8) Indeed, the most recent European Association for the Study of the Liver (EASL) guidelines on cirrhosis adopted the AKI Kidney Disease Improving Global Guidelines (KDIGO) definition (9, 10), which shifted from a static definition to one based on change in creatinine levels from baseline for all types of AKI (Supplementary Table 1).(11)

Thus, the main aim was to compare different existing formulas to estimate renal function (eGFR) (Supplementary Table 2): Modification of Diet in Renal Disease (MDRD-6), chronic kidney disease epidemiology (CKD-EPI) and Royal Free Hospital (RFH) and sCr, in the setting of AKI, for the prediction of renal replacement therapy (RRT) within the first 30 days of AKI, and 30- and 90-day transplant-free survival. As a secondary aim, we assessed the time-dependent use of these formulas and other predictors of outcomes.

Methods

Population selection and design

We retrospectively studied hospitalized patients with cirrhosis (defined by histology or by a combination of biochemical, radiological, and endoscopic findings) presenting with a first AKI episode at our center.

AKI was defined by the revised consensus recommendations of the International Club of Ascites: an increase in sCr ≥0.3 mg/dl (26.5 µmol/L) or an increase in sCr ≥1.5-fold to 2-fold from preadmission (one value of sCr within the previous 3 months, the value closest to the admission time to the hospital was used as baseline/preadmission) which was known, or presumed, to have occurred within the prior 7 days.(9) In case there was no preadmission sCr available, sCr at admission was used as preadmission value. All the remaining values (at day 0, 2 and 7 of AKI) were available in all cases, with no missing value. If the patient presented a second AKI episode during hospitalization, only the first was considered for the analysis. The severity of AKI and its evolution (resolution, partial regression and no improvement or progression) were classified according to EASL guidelines (grades 1a to 3).(11)

Liver cirrhosis OR Cirrhosis AND Hepatorenal syndrome OR Acute kidney injury OR Renal failure were searched in the electronic hospital database. From the period between February 2012 and February 2018, among 1181 episodes of kidney injury in hospitalized patients with liver disease, 143 patients with (1) liver cirrhosis, (2) first known episode of AKI, and (3) preadmission information available were included in this study (Supplementary Figure 1). Exclusion criteria were: RRT before or on first day of hospital admission, hepatocellular carcinoma (HCC) outside Milan criteria at baseline or other advanced non-hepatic cancer, and previous kidney or liver transplantation at admission. As the majority of patients (96.5%) had previous outpatient and/or inpatient follow-up at our center, this greatly facilitated an accurate selection of the first episode of AKI. The local Research Ethics Committee approved this study (KEK 2018-00487). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and an informed consent was not requested for this retrospective study.

Data collection and outcomes

Clinical data recorded included the etiology and severity of liver disease, presence of metabolic syndrome (body mass index to define overweight or obesity, diabetes mellitus/insulin resistance, arterial hypertension and dyslipidemia), presence of CKD, and medications known to influence renal function.

CKD was defined as an eGFR (using CKD-EPI, used routinely in our center) of <60 mL/min per 1.73 m^2 for >3 months), according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Guidelines.(12)

Alcohol-related liver disease (ArLD) was considered the cause or a co-factor for liver disease in men and women consuming over 30 and 20 grams of alcohol per day, respectively.

Renal function was assessed at different time-points: before admission (outpatient information only within the last 3 months before first AKI episode, when available), at admission, at presentation of AKI (D0), and 48 hours after AKI (D2). Renal function parameters 7 days after AKI (D7) were also analyzed in the subset of patients with HRS-AKI, to factor the potential impact of response to therapy.

CKD-EPI and MDRD-6 eGFRs were obtained from online medical calculator sites widely available. RFH-eGFR was calculated using the formula available on the online calculator at www.rfh-cirrhosis-gfr.ucl.ac.uk.

All patients were evaluated to identify the cause of AKI according to international guidelines. The causes of AKI were divided as: 1) *Pre-renal*: hypovolemia, if related with diuretic overuse, bleeding or diarrhea, in the absence of other causes of kidney injury; (2) *Renal*: Hepatorenal syndrome if meeting the current criteria (11), with or without infection, vs. acute tubular necrosis (ATN) or nephrotoxicity in cases with history of a potentially nephrotoxic agent and development of AKI; (3) *Post-renal* when an obstruction in the urinary tract below the kidneys causes renal injury.

As the study period spans from February 2012 to February 2018, the majority of patients received therapy for AKI according to previous EASL guidelines indications that defined

recent renal injury in patients with cirrhosis as a percentage increase in sCr ≥50% to a final value ≥1.5 mg/dl (133 μmol/L).(13) AKI treatment included withdrawal of diuretics or known nephrotoxins and/or administration of albumin of 1 g/kg of body weight daily up to 100 g for at least 2 days, and/or treatment of infection if present, and/or the use of I.V. terlipressin (bolus or continuous infusion) and/or RRT according to the type and severity of AKI. (13)

All subjects received either intermittent hemodialysis or continuous veno-venous hemofiltration as their modality of RRT. The indication to start renal replacement therapy at our center was discussed interdisciplinarily in every patient with the attending nephrologist and determined by the presence of refractory fluid overload, signs of uremia, severe hyperkalemia (>6.5 mEq/L) or rapidly rising potassium levels and severe metabolic acidosis (pH <7.1) according to the standard operating procedures. Patients were followed until date of last contact after discharge, death or OLT. RRT within first 30 days of AKI, and 30 and 90-day transplant-free survival were assessed.

Statistical analysis

Continuous variables with normal distribution are expressed as mean±standard deviation and non-normal as medians and inter-quartile ranges. Categorical data are presented as percentages and counts. Group comparisons for categorical variables were done using the $\chi 2$-test with the corresponding degrees of freedom while those for continuous variables were done with either a two-sample, independent t-test or a one-way analysis of variance if more than three groups were compared. Group comparisons for continuous variables were done using a non-parametric Mann–Whitney U-test for two groups or the Kruskal–Wallis for > 2 groups. Variables associated with outcomes on univariate Cox regression analysis were entered into a multivariate Cox logistic regression. A backward stepwise procedure (variable entry/drop criteria, $p < 0.05$) was applied to select factors significantly contributing to the model fit. Hosmer–Lemeshow test was used to confirm goodness-of-fit of the model. Since sCr, MDRD-6, CKD-EPI and RFH-eGFR are highly collinear (all assess renal function), as a first step the four were entered into a multivariate analysis to assess which best predicted each outcome for each time point. Similarly, INR, total bilirubin, albumin and Child Pugh score were considered highly

collinear variables associated with liver function and if any of them and Child Pugh score were associated with outcomes in univariate analysis only Child Pugh score was included in the multivariate analysis. MELD-Na score was not used since kidney function is an integral part of the calculation.

In the following steps, the best renal parameter (sCr, MDRD-6, CKD-EPI and RFH-eGFR) and its respective time point (preadmission, D0, D2), was entered into a multivariate analysis together with liver function to identify factors independently associated with each outcome.

We additionally used a competing events framework to assess the cumulative incidence of death (considering transplant as a competing event) and to assess the cumulative incidence of RRT (with death or transplant without RRT as competing event). We used Fine and Gray's regression to assess the association of RFH-eGFR with survival. These analyses were performed with the cmprsk package in R version 3.3.3 (http://www.r-project.org).

All other statistical analyses were performed using IBM SPSS Version 25.0 (Chicago, IL, United States) software. For all analyses, a P-value of <0.05 was considered to be statistically significant.

Results

Demographic and preadmission clinical characteristics

The preadmission characteristics of patients are summarized in Table 1. The cohort was primarily composed of patients with alcohol-related liver disease, nonalcoholic fatty liver disease (NAFLD) or a combination of ArLD and metabolic syndrome. As expected, most patients had ascites and with a mean MELD-Na score of 16 points. As for renal function, 56 patients (38.5%) met the criteria of CKD.

Presentation of AKI

The AKI was pre-renal in 37%, renal in 62% and post-renal in 1%. Infection was diagnosed in 90 patients (63%), either at admission or during hospitalization, and in 75 (52%) was present at the onset of AKI. The site of infection is shown in Supplementary Figure 2.

The degree was grade 1a in 23 (16%), 1b in 58 (41%), grade 2 in 32 (22%), and grade 3 in 30 (21%). Patients with preadmission CKD did not present more severe AKI (p=0.12). At presentation of AKI (D0), men had higher creatinine values (p=0.046), but similar eGFR by any formula as compared to women (Figure 1A-D). In addition, eGFR values using the RFH formula were consistently lower compared to the other formulas (Figure 1A-D). Regarding cirrhosis etiology, alcohol associated with metabolic syndrome was more frequently associated with severe AKI than other etiologies (p=0.049).

Seventy-six patients (53%) fulfilled criteria for HRS-AKI.

Outcomes

The median hospital admission period was 17 days (IQR 10-28). Seventy patients with HRS-AKI received terlipressin and albumin for a median of six days (IQR 4-9) (Supplementary Table 3). Terlipressin was started after a median of two days (IQR 1-4).

In the remaining six patients, either RRT was started within 48 hours or terlipressin was not administered due to contraindications.

The evolution of AKI during and after hospitalization is shown in Figure 2. Resolution was achieved in 66 cases (46%), partial regression in 44 (31%) and no improvement or progression in 33 (23%).

Twenty-two patients (15%) required RRT within the first 30 days of AKI (of them, only three completely recovered to preadmission renal function). Cumulative incidence of need for RRT within 30 days was 15% considering transplant and death (without RRT) as competing events (Supplementary figure 3).

Transplant-free survival was 77% at 30 day and 63% at 90 days. 23 patients (16%) died or were transplanted within the hospitalization. Four and 11 patients were transplanted within 30 and 90 days, respectively. Supplementary figure 4 shows the cumulative incidence of death and transplant up to day 90.

Factors associated with need for renal replacement therapy (RRT) within first 30 days of AKI

Of the 22 patients requiring RRT, 18 had HRS-AKI (see detailed characteristics on Supplementary Table 4). The median period between AKI diagnosis and start of RRT was 8 days (IQR 3-17). Bacterial or fungal infection was present in 82% of patients submitted to RRT.

Table 2 displays the univariate analysis of factors associated with RRT within the first month of AKI. There was a trend for infection during the hospital admission to be associated with RRT during the first month after AKI (HR 2.60, 95%CI 0.881-7.69, p=0.08). Patients with ArLD and metabolic syndrome were more commonly submitted to RRT in comparison to other etiologies.

The RFH-eGFR on day 2 best predicted the need for RRT within the first month of AKI and independently predicted RRT in a model with Child Pugh at D0 (adjusted HR .949, 95%CI .907-.993, p=0.025; adjusted sHR from Fine and Gray model: .912, 95% CI: .830-1.096; p=0.057). Changes in eGFR vs. preadmission eGFR did not perform better in

predicting the need of RRT than the absolute value of eGFR at D2, by any of the tested formulas.

Factors associated with 30- and 90-day mortality or OLT

In univariate and multivariate Cox regression, the significant predictive factors for 30-day and 90-day mortality/OLT are shown on Tables 3 and 4, respectively. In Cox multivariate regression, including Child Pugh score at presentation (D0) and RFH-eGFR at D2, both remained independently associated with 30- (Child Pugh D0 HR 1.59 95%CI 1.27-1.99, p<0.001 and RFH-eGFR at D2 HR .962 95%CI .930-.995, p=0.025) and 90-day mortality/OLT (Child Pugh D0 HR 1.44 95%CI 1.21-1.71, p <0.001 and RFH-eGFR D2 HR .957 95%CI (.930-.987, p=0.001). This was also the case when assessing the risk of death considering transplant as a competing event (Child Pugh D0 sHR 1.34 95% CI: 1.11-1.63, p=0.003 and RFH-eGFR D2 sHR 0.95 95%CI 0.92-0.98, p=0.001).

Patients with HRS and nephrotoxicity had a higher 90-day mortality/OLT rate (43% vs. 25%, p=0.03). Patients with HRS-AKI stage 3 presented a higher rate of 30-day (HR 3.42 95%CI 1.71-6.83, p<0.001) and 90-day mortality (HR 2.38 95%CI 1.33-4.25, p=0.003) compared to other AKI grades. In the subset of patients with HRS-AKI treated with terlipressin (see detailed characteristics on Supplementary Table 2), multivariate analysis showed that D7 RFH-eGFR was the strongest predictor of 30-day (HR .958, 95%CI .933-.987 p=0.02) and 90-day mortality (HR .969, 95%CI .943-.996 p=0.026).

Discussion

The results of the study show that in the AKI setting using eGFR with a formula derived specifically from patients with liver cirrhosis at the Royal Free Hospital may be better for prognostic stratification than serum creatinine. According to our findings, RFH-eGFR may be superior to serum creatinine, MDRD-6 and CKD-EPI - eGFRs in predicting need of RRT and 30 and 90-day mortality. Furthermore, in most patients of this cohort, day 2 of AKI was the crucial time point to determine outcomes. However, for patients with HRS-AKI treated with terlipressin and albumin, day 7 was the most informative, which is not surprising because this time point adequately reflects the positive impact of treatment (or the lack of effect) on the course of HRS-AKI. This finding underlines the importance of using predictive factors reliant on response to therapy.

Since the RFH eGFR formula was specifically derived from and tested on patients with end-stage liver disease, it factors important prognostic components such as INR, urea, moderate/severe ascites and serum sodium, possibly justifying its prognostic capability when used together with the Child-Pugh score. In fact, a recent multicenter study showed that a model incorporating creatinine, blood urea nitrogen, age, gender, race, and albumin outperformed CKD-EPI and MDRD-6 in estimating GFR in patients with low (<30 ml/min) GFRs before and after OLT.(14)

The eGFR formulas compared in our cohort incorporate creatinine as the major determinant of GFR, and serum creatinine has known drawbacks in cirrhosis (gender related; muscle mass related, etc.). Indeed, men had significantly higher serum creatinine values at all time points in our study, but these differences decreased considerably when the CKD-EPI and MDRD-6 eGFR formulas were applied, and disappeared using the RFH eGFR formula. This suggests that the use of RFH eGFR in the context of AKI might allow a better understanding of the severity of renal function independent of gender, potentially leading to a prompter start of therapy (e.g. albumin and terlipressin), with better outcomes. This would confirm previous data showing that integrating RFH eGFR in the corrected MELD score would allow a more objective assessment of renal function with improved access to transplantation waiting list and organ allocation (5), potentially reducing known gender disparities. (15)

Although we found that patients with an initial grade of AKI of 3 had higher 30 and 90-day mortality compared to other grades, we preferred to use an objective, continuous and quantitative parameter, such as eGFR, over semi-quantitative, categorical scales, in order to avoid loss of information due to categorization of renal function.

We highlight that our study population is composed of a contemporary cohort of predominantly alcohol-related and non-alcoholic fatty liver disease related liver cirrhosis patients. (16) Around 75% of patients had either alcohol-related cirrhosis, nonalcoholic fatty liver disease related cirrhosis or alcohol-related cirrhosis associated with metabolic syndrome. This is in marked contrast with previous studies evaluating kidney function in cirrhosis and AKI with many viral hepatitis-associated cirrhosis.(17-19) Indeed, in our study patients with alcohol etiology and added metabolic component of cirrhosis had more severe AKI, requiring RRT more frequently, suggesting that these patients might be especially susceptible to AKI.

Interestingly, perhaps due to the high number of patients with metabolic syndrome, 38% of our patients met the criteria of CKD at baseline, a clearly higher proportion than in previous cohorts evaluating AKI in cirrhosis, which report between 9-23% of CKD.(17, 19) Although the number of patients submitted to RRT was slightly higher in the CKD group (18% vs. 14%; p=NS), these patients did not present worse outcomes in terms of mortality.

Our study has some limitations. It is a retrospective single-center study, with the risk of inadvertent selection bias that limits the extrapolation of data. However, we included all patients hospitalized at our center with a diagnosis of AKI during the study period using a well-defined, pre-specified diagnostic protocol, which is likely to diminish the risk of selection bias. Nevertheless, it is not possible to be certain that it was the first episode of AKI. In addition, serum cystatin C, which has been suggested as an alternative to creatinine-based formulas, (20) (21) is not routinely used in our center we cannot provide data comparing its performance to eGFR-based formulas. Furthermore, we do not have information regarding the exact indication for RRT, although each case was discussed with a nephrologist from our center.

In conclusion, our study shows that RFH-eGFR calculated on the second day after AKI diagnosis is a strong predictor of need for RRT and of 30-d and 90-d transplant free survival. Gender disparities inherent to creatinine use, are not observed using RFH-eGFR. Altogether, our results strongly suggest that in patients with liver cirrhosis, RFH-eGFR may be a better indicator of prognosis in AKI and in HRS, than serum creatinine.

Figure legends

Figure 1. Differences in renal function parameters according to gender at different time points. D0 indicates onset of AKI. D2 indicates 48 hours of AKI onset. Panel A. Serum creatinine. Panel B. CKD-EPI-eGFR. Panel C. MDRD-6-eGFR. Panel D. RFH-eGFR.

Figure 2. Outcome of patients included in the study.

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Table 1. Preadmission Characteristics of the Study Population. * available in 138 patients.

Age – years, mean±SD	59±11
Gender – male, n (%)	88 (61.5%)
Black race, n (%)	4 (3.0%)
BMI, Kg/m^2 mean±SD	27.3±5.8
Obesity, n (%)	45 (31.0)
Overweight, n (%)	93 (65.0)
Etiology, n (%)	
Alcohol	42 (29.4)
Alcohol and metabolic syndrome	35 (24.5)
Viral	18 (12.6)
Non-alcoholic fatty liver disease	30 (21.0)
Cholestatic	9 (6.3)
Autoimmune	6 (4.2)
Other	3 (2.0)
Diabetes mellitus, n (%)	47 (33.0)
Arterial hypertension, n (%)	59 (41.0)
Chronic kidney disease, n (%)	55 (38.5)
HCC within Milan criteria, n (%)	19 (13.0)
History of ascites, n (%)	119 (83.2)
History of hepatic encephalopathy, n (%)	58 (40.6)
Beta-blockers, n (%)	81 (56.6)
Diuretics, n (%)	114 (79.7)
MELD-Na score*, mean±SD	16.5±6.2
Child-Pugh score*, mean±SD	9±2
Serum creatinine* (µmol/L), median (IQR)	92 (75-118)
CKD-EPI-eGFR* (ml/min/1.73m^2), median (IQR)	72.0 (50.0-88.0)
MDRD-6-eGFR* (ml/min/1.73m^2), median (IQR)	61.7 (43.5-79.4)

RFH-eGFR* (ml/min/1.73m^2), median (IQR)	49.6 (35.3-64.2)

BMI, body mass index; HCC, hepatocellular carcinoma; CKD-EPI, Chronic kidney disease-epidemiology; eGFR, estimated glomerular filtration rate; MDRD-6, modified diet renal disease-6; RFH, Royal Free Hospital

Table 2. Univariate logistic regression for predicting need of renal replacement therapy during the first month after first episode of AKI

Variable	Univariate OR (95%CI)	*P* value
Age	.995 (.956-1.03)	0.79
Gender male	1.10 (.463-2.63)	0.83
BMI	1.03 (0.964-1.11)	0.37
Obesity (BMI≥30 kg/m^2)	1.27 (0.497-3.25)	0.62
Overweight (BMI≥25 kg/m^2)	3.67 (1.09-12.4)	**0.04**
Etiology ArLD + metabolic synd. *vs*. only ArLD/NAFLD	2.63 (1.04-8.26)	**0.048**
Diabetes mellitus	1.18 (.495-2.82)	0.71
Arterial hypertension	1.48 (.642-3.42)	0.36
Chronic kidney disease*	1.29 (.559-2.99)	0.55
Beta-blocker	.724 (.304-1.73)	0.47
HCC	1.56 (.365-6.69)	0.55
Infection during admission	2.60 (.881-7.69)	0.08
Preadmission MELD-Na score	1.06 (.993-1.14)	0.08
Preadmission Child-Pugh score	1.15 (.922-1.42)	0.21
Preadmission sCr	1.007 (1.003-1.011)	**<0.001**
Preadmission CKD-EPI-eGFR	.985 (.968-1.003)	0.10
Preadmission MDRD-6-eGFR	.994 (.977-1.01)	0.46
Preadmission RFH-eGFR	.983 (.959-1.007)	0.16
D0 AKI Total Bilirubin	1.003 (1.001-1.005)	**0.007**
D0 AKI Serum Albumin	.936 (.865-1.01)	**0.10**
D0 AKI INR	4.68 (2.41-9.08)	**<0.001**
D0 AKI MELD-Na score	1.16 (1.08-1.24)	**<0.001**
D0 AKI Child-Pugh score	1.45 (1.13-1.86)	**0.003**
D0 AKI Creatinine	1.006 (1.002-1.01)	**0.005**
D0 AKI CKD-EPI-eGFR	.965 (.933-.998)	**0.04**
D0 AKI MDRD-6-eGFR	.979 (.944-1.02)	0.26
D0 AKI RFH-eGFR	.963 (.918-1.01)	0.12
D2 AKI Creatinine	1.008 (1.004-1.011)	**<0.001**
D2 AKI CKD-EPI-eGFR	.961 (.933-.990)	**0.008**
D2 AKI MDRD-6-eGFR	.965 (.935-.996)	**0.03**
D2 AKI RFH-eGFR	.940 (.899-.983)	**0.007**
D7 AKI Creatinine	1.008 (1.005-1.012)	**<0.001**
D7 AKI CKD-EPI-eGFR	.945(.919-.972)	**<0.001**
D7 AKI MDRD-6-eGFR	.948 (.920-.977)	**<0.001**

D7 AKI RFH-eGFR	.933 (.897-.969)	**<0.001**

BMI, body mass index; ArLD, alcohol related liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; sCr, serum creatinine; CKD-EPI, Chronic kidney disease-epidemiology; eGFR, estimated glomerular filtration rate; MDRD-6, modified diet renal disease-6; RFH, Royal Free Hospital

*eGFR<60 ml/min/1.73m^2

Table 3. Univariate Cox regression for predicting 30-day mortality/OLT after first episode of AKI

Variable	Univariate HR (95%CI)	*P* value
Preadmission data		
Age	1.01 (.98-1.05)	0.47
Gender male	1.76 (.82-3.79)	0.15
BMI	1.03 (.966-1.09)	0.42
Obesity (BMI≥30 kg/m^2)	1.51 (.75-3.04)	0.24
Overweight (BMI≥25 kg/m^2)	1.07 (.528-2.18)	0.85
Etiology ArLD + metabolic synd. *vs*. only ArLD/NAFLD	1.21 (.562-2.60)	0.63
Diabetes mellitus	1.57 (.71-3.49)	0.27
Arterial hypertension	1.25 (.627-2.47)	0.53
Chronic kidney disease*	1.79 (.833-3.86)	0.14
Beta-blocker	0.68 (.335-1.39)	0.29
HCC	1.17 (.453-3.04)	0.88
Preadmission MELD-Na score	1.06 (1.01-1.11)	**0.02**
Preadmission Child-Pugh score	1.44 (1.20-1.73)	**<0.001**
Preadmission sCr	1.001 (.995-1.006)	0.84
Preadmission CKD-EPI-eGFR	1.009 (.995-1.02)	0.20
Preadmission MDRD-6-eGFR	1.008 (.999-1.018)	0.09
Preadmission RFH-eGFR	1.008 (.994-1.022)	0.24
Data at AKI diagnosis		
D0 AKI Total Bilirubin	1.004 (1.002-1.006)	**<0.001**
D0 AKI Serum Albumin	0.931 (.837-.993)	**0.03**
D0 AKI INR	1.87 (1.09-3.21)	**0.02**
D0 AKI MELD-Na score	1.11 (1.06-1.17)	**<0.001**
D0 AKI Child-Pugh score	1.64 (1.31-2.04)	**<0.001**
D0 AKI sCr	1.002 (.999-1.005)	0.15
D0 AKI CKD-EPI-eGFR	.974 (.949-.999)	**0.049**
D0 AKI MDRD-6-eGFR	.974 (.945-.1.004)	0.08
D0 AKI RFH-eGFR	.947 (.910-.986)	**0.009**
D0 AKI stage	1.64 (.791-3.40)	0.183
Data 2 days after AKI		
D2 AKI sCr	1.003 (1.001-1.006)	**0.02**

D2 AKI CKD-EPI-eGFR	.978 (.958-.999)	**0.04**
D2 AKI MDRD-6-eGFR	.984 (.963-1.005)	0.13
D2 AKI RFH-eGFR	.952 (.921-.984)	**0.004**

OLT, orthotopic liver transplantation; HR, hazards ratio; AKI, acute kidney injury; BMI, body mass index; ArLD, alcohol related liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; sCr, serum creatinine; CKD-EPI, Chronic kidney disease-epidemiology; eGFR, estimated glomerular filtration rate; MDRD-6, modified diet renal disease-6; RFH, Royal Free Hospital

*(eGFR<60 ml/min/1.73m^2)

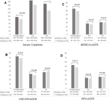
Table 4. Univariate Cox regression for predicting 90-day mortality/OLT after first episode of AKI

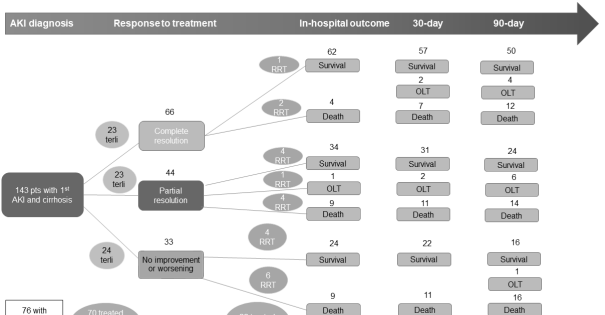
Variable	Univariate HR (95%CI)	*P* value
Preadmission data		
Age	1.02 (.992-1.04)	0.17
Gender male	1.23 (.69-2.018)	0.47
BMI	1.003 (.96-1.05)	0.89
Obesity (BMI≥30 kg/m^2)	1.38 (.79-2.343)	0.26
Overweight (BMI≥25 kg/m^2)	1.29 (.74-2.25)	0.36
Etiology ALD + metabolic synd. *vs*. only ALD/NAFLD	1.31 (.72-2.38)	0.38
Diabetes mellitus	1.31 (.75-2.29)	0.34
Arterial hypertension	1.21 (.70-2.1)	0.49
Chronic kidney disease*	1.31 (.75-2.27)	0.34
Beta-blocker	.712 (.40-1.25)	0.24
HCC	1.66 (.83-3.130)	0.15
Preadmission MELD-Na score	1.07 (1.04-1.12)	**<0.001**
Preadmission Child-Pugh score	1.45 (1.25-1.68)	**<0.001**
Preadmission sCr	1.001 (.998-1.005)	0.42
Preadmission CKD-EPI-eGFR	.997 (.987-1.008)	0.62
Preadmission MDRD-6-eGFR	1.008 (.999-1.02)	0.09
Preadmission RFH-eGFR	.995 (.981-1.009)	0.37
Data at AKI diagnosis		
D0 AKI Total Bilirubin	1.004 (1.002-1.006)	**<0.001**
D0 AKI Serum Albumin	.944 (.897-.993)	**0.03**
D0 AKI INR	1.59 (.988-2.55)	0.06
D0 AKI MELD-Na score	1.10 (1.06-1.14)	**<0.001**
D0 AKI Child-Pugh score	1.49 (1.26-1.76)	**<0.001**
D0 AKI sCr	1.002 (1.001-1.005)	0.06
D0 AKI CKD-EPI-eGFR	.972(.952-.993)	**0.008**
D0 AKI MDRD-6-eGFR	.965 (.941-.9819)	**0.004**
D0 AKI RFH-eGFR	.944 (.914-.974)	**<0.001**
D0 AKI stage	1.35 (.731-2.50)	0.34
Data 2 days after AKI		
D2 AKI sCr	1.003 (1.001-1.005)	**0.01**

D2 AKI CKD-EPI-eGFR	.977 (.961-.993)	**0.004**
D2 AKI MDRD-6-eGFR	.975 (.957-.993)	**0.007**
D2 AKI RFH-eGFR	.950 (.925-.975)	**<0.001**

OLT, orthotopic liver transplantation; HR, hazards ratio; AKI, acute kidney injury; BMI, body mass index; ArLD, alcohol related liver disease; NAFLD, nonalcoholic fatty liver disease; HCC, hepatocellular carcinoma; sCr, serum creatinine; CKD-EPI, Chronic kidney disease-epidemiology; eGFR, estimated glomerular filtration rate; MDRD-6, modified diet renal disease-6; RFH, Royal Free Hospital

*(eGFR<60 ml/min/1.73m^2)


A
P=0.95
P=0.63
P=0.006
Preadmission
D0
D2
Serum Creatinine
C
P=0.37
P=0.37
P=0.91
MDRD-6-eGFR
B
P=0.21
P=0.38
P=0.52
CKD-EPI-eGFR
D
P=0.17
P=0.78
P=0.99
RFH-eGFR


AKI diagnosis
Response to treatment
In-hospital outcome
30-day
90-day
143 pts with 1st AKI and cirrhosis
23 terli
23 terli
24 terli
66
Complete resolution
44
Partial resolution
33
No improvement or worsening
1 RRT
2 RRT
4 RRT
1 RRT
4 RRT
4 RRT
6 RRT
62
Survival
4
Death
34
Survival
1
OLT
9
Death
24
Survival
9
Death
57
Survival
2
OLT
7
Death
31
Survival
2
OLT
11
Death
22
Survival
11
Death
50
Survival
4
OLT
12
Death
24
Survival
6
OLT
14
Death
16
Survival
1
OLT
16
Death
76 with hepatorenal syndrome
70 treated with terlipressin
22 treated with RRT