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ORIGINAL RESEARCH

Prediction of acute kidney injury in cirrhotic patients: a new score combining renal, liver and inflammatory markers

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Introduction: Acute kidney injury (AKI) is common in hospitalized patients with cirrhosis and is associated with poor prognosis. A risk prediction score combining values easily measured at admission could be valuable to stratify patients for prevention, monitoring and early intervention, ultimately improving patient care and outcomes. The aim of this study was to develop a risk score for AKI in a cohort of cirrhotic patients.

Patients and methods: We cross-examined the data from a retrospective analysis of 186 patients with cirrhosis admitted to the Gastroenterology and Hepatology Service of Centro Hospitalar Lisboa Norte from January 2003 to December 2005. AKI was defined as an increase in serum creatinine (SCr)≥0.3 mg/dL within 48 hours or a percentage increase in SCr≥50% from baseline. Neutrophil-to-lymphocyte ratio (NLR) was used as a marker for inflammation. A receiver operating characteristic (ROC) curve was produced to assess the discriminative ability of the variables. Cutoff values were defined as those with highest validity. The final AKI risk score model was assessed using the ROC curve.

Results: A total of 52 patients (28%) developed AKI. Higher baseline SCr ($p<0.001$), more severe liver disease as evaluated by the modified Model of End-stage Liver Disease (MELD)-Na score ($p<0.001$) and higher NLR ($p=0.028$) were independently associated with AKI. The area under the ROC (AUROC) curve for the prediction of AKI was 0.791 (95% CI 0.726–0.847) for SCr, 0.771 (95% CI 0.704–0.829) for modified MELD-Na and 0.757 (95% CI 0.689–0.817) for NLR. Cutoff values with the highest validity for predicting AKI were determined and defined as 0.9 for the SCr, 21.7 for the modified MELD-Na and 6 for the NLR. The risk score was created allowing 3 points if the SCr is higher than 0.9, 1 point if the modified MELD-Na is higher than 21.7 and 1 point if the NLR is higher than 6. The AUROC curve of the risk prediction score for AKI was 0.861. A risk score of ≥2 points predicts AKI in cirrhotic patients with a sensitivity of 88.5% and specificity of 72.4%.

Conclusion: A new score combining SCr, MELD-Na and NLR demonstrated a strong discriminative ability to predict AKI in cirrhotic patients.

Keywords: acute kidney injury, cirrhosis, risk score

Introduction

Acute kidney injury (AKI) affects between 20% and 50% of hospitalized patients with cirrhosis[1–3] and is associated with poor prognosis with mortality rates reaching as high as 90%.[4]

Considering the limitations of the traditional markers of renal function in cirrhotic patients, serum creatinine (SCr) and urinary output (UO), studies have focused on new biomarkers to increase diagnostic accuracy, but these are still far from clinical use.[5,6]

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The severity of liver disease has been associated with AKI and is an important risk factor.[7] In addition, the role of inflammation in AKI has had increasing recognition and has been reported as a prognostic factor in cirrhotic patients.[7]

Therefore, future biomarkers would have to consider markers of renal and liver function and inflammation markers. The role of the neutrophil-to-lymphocyte ratio (NLR) in predicting AKI has been reported, but it has not been studied in cirrhotic patients.[8,9]

A score combining values easily measured at admission to predict the risk of AKI could be a valuable tool to stratify patients for prevention, monitoring and early intervention and ultimately to improve patient care and outcomes.

The aim of this study was to develop a risk prediction score for AKI in cirrhotic patients, which combined renal and liver dysfunction markers as well as an inflammation marker.

Patients and methods

Study design

To investigate a potential risk score, we cross-examined the data from retrospective analysis of 186 patients with cirrhosis who were admitted to the Gastroenterology and Hepatology Service of Centro Hospitalar Lisboa Norte from January 2003 to December 2005.[10] Centro Hospitalar Lisboa Norte, Entidade Pública Empresarial (EPE), is an academic and referral center serving a population of 3,000,000 inhabitants. The study was approved by the ethical committee at the Centro Hospitalar Lisboa Norte, EPE, in agreement with institutional guidelines. Informed consent was waived by the ethical committee due to the retrospective and noninterventional nature of the study.

Participants

All patients aged 18 years or older who were admitted to the Gastroenterology and Hepatology Service of Centro Hospitalar Lisboa Norte from January 2003 to December 2005 were eligible for this study. All patients' data accessed were de-identified to preserve anonymity.

Exclusion criteria included the following: chronic kidney disease patients already on renal replacement therapy; patients who underwent renal replacement therapy the week before admission and patients who had less than two determinations of SCr during hospital stay.

Variables

All variables were collected from electronic and handwritten patient clinical records. All scores and formulas were calculated based on clinical data.

The analyzed variables included demographic characteristics (age, gender and ethnicity), etiology of liver disease, comorbidities, reason for admission, laboratory data including baseline SCr and, at admission, hemoglobin, neutrophils, leukocytes, international normalized ratio (INR), bilirubin, sodium and albumin, need for vasopressors and mechanical ventilation, AKI, mortality and length of hospital stay.

Regarding clinical characteristics, the comorbidities registered were diabetes mellitus (diagnosed according to the American Diabetes Association criteria),[11] hypertension (diagnosed according to the seventh report of the Joint National Committee),[12] cardiovascular disease (including chronic heart failure, cardiac ischemic disease and history of transient ischemic attack or stroke) and malignancy. The severity of liver disease was assessed with the model for end-stage liver disease incorporating sodium (Model of End-stage Liver Disease [MELD]-Na) and Child–Pugh scores.[13–15] A modified MELD-Na score not including SCr was calculated to exclude variable collinearity.

$$\text{Modified MELD} - \text{Na} = \text{Modified MELD} - \text{Na} - 0.025*\text{Modified MELD}*(140 - \text{Na}) + 140$$

$$\text{Modified MELD} = 0.378 \times \ln(\text{bilirubin}) + 1.120 \times \ln(\text{INR}) + 0.643$$

AKI was defined as an increase in SCr ≥0.3 mg/dL within 48 hours or percentage increase in SCr ≥50% from baseline. SCr at admission was considered baseline SCr.

Cirrhosis was diagnosed by liver biopsy or a combination of biochemical, radiological and endoscopic findings when liver biopsy was not available.

NLR was determined using neutrophil and lymphocyte counts at admission. NLR was calculated as follows: neutrophil count/lymphocyte count.

Statistical analyses

Continuous variables were presented as mean ± SD and categorical variables as the total number and percentage of cases for each category. After grouping participants according to the development of AKI, the variables of both groups were compared using Student's *t*-test for normally distributed continuous variables, Mann–Whitney *U*-test for non-normally distributed continuous variables and chi-square test for categorical variables.

Only variables that significantly differed between AKI and non-AKI groups were used in the univariate and multivariate analysis using the logistic regression method. Data were expressed as ORs with 95% CI. No sensitivity analyses were carried out.

A receiver operating characteristic (ROC) curve was produced to assess the discriminative ability of the variables for

AKI. Cutoff values were defined as those with highest validity for predicting AKI. The coefficients produced for each variable in the multivariate model were rounded to the nearest numeral to develop the risk score. By adding the variables together, the total score can range from a minimum of 0 to a maximum of 5 points. The final AKI risk score model was assessed using the area under the ROC (AUROC) curve and Hosmer–Lemeshow goodness-of-fit test.

Statistical significance was defined at a p-value of <0.05. Analyses were performed with the statistical software package SPSS 21.0 (IBM Corporation, Armonk, NY, USA) for Windows.

Results

Demographic patient variables and outcomes including comparisons between the AKI and non-AKI groups are described in Table 1. We registered no missing data.

In our cohort, 28% of patients (n=52) developed AKI (42.3% stage 1, 34.6% stage 2, and 23.1% stage 3). A total of 12 patients with AKI (23.1%) underwent renal replacement treatment. Median time to the occurrence of AKI following admission was 2 days (1–24 days). Median SCr on the day of AKI diagnosis was 2.1±1.2 mg/dL. AKI patients were more likely to require mechanical ventilation (p=0.028) and vasopressors (p=0.001). Comorbidity, etiology of liver disease and reason for admission were not associated with AKI.

A higher baseline SCr (1.8±1.2 vs 0.9±0.4, p<0.001; unadjusted OR 4.6 [95% CI 2.5–8.6], p<0.001; adjusted OR 3.4 [95% CI 1.8–6.2], p<0.001), more severe liver disease as evaluated by the modified MELD-Na score (22.8±7.4 vs 15.7±6.3, p<0.001; unadjusted OR 1.2 [95% CI 1.1–1.3], p<0.001; adjusted OR 1.15 [95% CI 1.1–1.2], p<0.001) and higher NLR (13.9±16.5 vs 5.5±4.0, p<0.001; unadjusted OR 1.2 [95% CI 1.1–1.3], p<0.001; adjusted OR 1.1 [95% CI 1.0–1.1], p=0.028) were independently associated with AKI (Table 2).

The AUROC curve for the prediction of AKI was 0.791 (95% CI 0.726–0.847) for SCr, 0.771 (95% CI 0.704–0.829) for modified MELD-Na and 0.757 (95% CI 0.689–0.817) for NLR. Cutoff values with the highest validity for predicting AKI were determined and defined as 0.9 for the SCr, 21.7 for the modified MELD-Na and 6 for the NLR (Table 3).

The risk score was created allowing 3 points if the SCr is higher than 0.9, 1 point if the modified MELD-Na is higher than 21.7 and 1 point if the NLR is higher than 6 (Table 4).

The AUROC curve of the risk prediction score for AKI was 0.861 (95% CI 0.803–0.908; Figure 1). The optimal cutoff for the diagnosis of AKI was assessed to be ≥2 points, which had a sensitivity of 88.5% and specificity of 72.4%. This cutoff identified 44.6% (n=83) of the population at risk for developing AKI, of whom 55.4% will develop AKI (n=46). In contrast, 94.2% of patients with risk score of <2 will not develop AKI (p<0.001).

Table 1 Characteristics of patients with and without AKI

Variables	AKI (n=52)	No AKI (n=134)	*p*-value
At admission			
Age (years)	57.9±10.3	55.3±12.8	0.220
Male, n (%)	45 (86.5)	93 (73.1)	0.052
Caucasian, n (%)	46 (88.5)	117 (87.3)	0.831
Comorbidity, n (%)			
Diabetes mellitus	12 (23.1)	38 (28.4)	0.729
Hypertension	19 (36.5)	37 (27.6)	0.096
Cardiovascular disease	12 (23.1)	24 (17.9)	0.250
Cancer	5 (9.6)	9 (6.7)	0.379
Etiology of liver disease, n (%)			
Alcohol consumption	31 (59.6)	84 (62.7)	0.647
Alcohol consumption plus HCV infection	5 (9.6)	24 (17.9)	0.249
Alcohol consumption plus HBV infection	1 (1.9)	4 (3)	0.763
HCV infection	2 (3.8)	11 (8.2)	0.295
HBV infection	4 (7.7)	3 (2.2)	0.054
Others	6 (11.5)	9 (6.7)	0.506
Reason for admission, n (%)			
Gastrointestinal bleeding	26 (50)	86 (64.2)	0.076
Sepsis	17 (32.7)	26 (19.4)	0.054
Liver failure	2 (3.8)	6 (4.5)	0.849
Others	5 (9.6)	16 (11.9)	0.125
Laboratory at admission			
Hemoglobin (g/L)	9.2±2.3	9.5±1.9	0.393
SCr	1.8±1.2	0.9±0.4	<0.001
NLR	13.9±16.5	5.5±4.0	<0.001
Modified MELD-Na	22.8±7.4	15.7±6.3	<0.001
Child–Pugh	34.6±5.5	33.1±7.8	0.189
During hospitalization			
MV requirement, n (%)	13 (25)	16 (11.9)	0.028
Vasopressors requirement, n (%)	18 (34.6)	17 (12.7)	0.001
Length of hospital stay (days)	18.8±12.9)	12.1±12.4	0.002
In-hospital mortality, n (%)	25 (48)	9 (6.7)	<0.0001

Abbreviations: AKI, acute kidney injury; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model of End-stage Liver Disease; MV, mechanical ventilation; NLR, neutrophil-to-lymphocyte ratio; SCr, serum creatinine.

Discussion

The high incidence of AKI in cirrhotic patients and its association with worse outcomes have raised interest in developing biomarkers to prevent AKI in patients at risk and improve diagnostic criteria.

In this study, we developed a low-cost and easily calculated risk score for the prediction of AKI in patients with cirrhosis. This is a low-cost risk score, easily calculated from

Table 2 Univariate and multivariate analysis of factors predictive of AKI

Variables	AKI			
	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Demographic characteristics				
Age	1.02 (0.99–1.05)	0.241		
Male	0.42 (0.18–1.02)	0.057		
Caucasian	1.11 (0.41–3.0)	0.831		
Parameters at admission				
Hb (g/L)	1.0 (0.9–1.3)	0.545		
SCr	4.6 (2.5–8.6)	<0.001	3.4 (1.8–6.2)	<0.001
NLR	1.2 (1.1–1.3)	<0.001	1.1 (1.0–1.18)	0.028
Modified MELD-Na	1.2 (1.1–1.3)	<0.001	1.15 (1.1–1.2)	<0.001
Child–Pugh	1.03 (0.98–1.09)	0.191		

Abbreviations: AKI, acute kidney injury; Hb, hemoglobin; MELD, Model of End-stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; SCr, serum creatinine.

Table 3 Univariate and multivariate analysis of categorical variables

Variables	AKI			
	Unadjusted OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
SCr>0.9	10.2 (4.8–21.7)	<0.001	6.9 (2.9–15.9)	<0.001
NLR>6	5.9 (2.9–11.9)	<0.001	2.4 (1.0–5.8)	0.041
Modified MELD-Na>21.7	11.7 (5.6–24.8)	<0.001	6.9 (2.9–16.3)	<0.001

Abbreviations: AKI, acute kidney injury; MELD, Model of End-stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; SCr, serum creatinine.

Table 4 Risk prediction score

Risk factor	Points
SCr>0.9	3
NLR>6	1
MELD-Na>21.7	1
Total	5
Score to predict AKI	≥2

Abbreviations: AKI, acute kidney injury; MELD, Model of End-stage Liver Disease; NLR, neutrophil-to-lymphocyte ratio; SCr, serum creatinine.

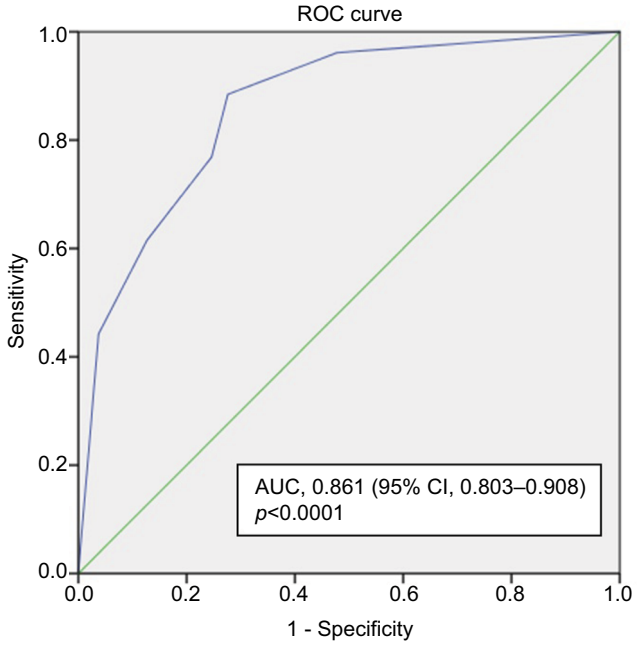

Figure 1 AUC of the risk model for the prediction of AKI in cirrhotic patients.
Abbreviations: AKI, acute kidney injury; AUC, area under the curve; ROC, receiver operating characteristic.

a complete blood count and biochemistry panel collected at hospital admission, which can reliably predict AKI with AUROC of 0.861 in cirrhotic patients at admission.

The variables used as risk factors for the prediction of AKI in this score are consistent with the previous literature.[6–8]

Although SCr is the most common renal dysfunction biomarker, its limitations in cirrhotic patients are well documented.[6,16,17] Multiple factors contribute to lower SCr values in this population, namely decreased hepatic creatine synthesis, decreased muscle mass and increased tubular creatinine secretion.[6,16,17]

The incidence of AKI in cirrhotic patients is variable depending on how baseline renal function is assessed.[18] The recent Kidney Disease Improving Global Outcome (KDIGO) classification combines the AKI definition of the risk, injury, failure, loss of kidney function and end-stage kidney disease (RIFLE) and AKI network (AKIN) classifications and its superior diagnostic accuracy and prediction of adverse outcomes has been proven in cirrhotic patients.[19–21]

The KDIGO classification accurately detects minor variations in SCr values which have been associated with poor prognosis in cirrhotic patients.[18,22,23] In addition, AKI

superimposed on previous renal dysfunction confers a higher risk for mortality.[18] Despite previous SCr thresholds being considered for clinical relevance in cirrhotic patients,[24] lesser degrees of baseline renal dysfunction can be associated with reduced survival.[18,23,25] In fact, in our cohort, the baseline SCr threshold with highest validity for predicting AKI was 0.9 mg/dL.

The MELD score is a validated prognostic marker in a wide range of severity and causes of cirrhosis, which incorporates an assessment of renal function.[13] Recent variations of this score include incorporating serum sodium (MELD-Na), which is a significant predictor of early mortality and an indirect marker of ascites.[14,26,27] In this cohort, higher MELD and MELD-Na were independently associated with AKI. To incorporate MELD-Na in our score, we separated the SCr from the MELD-Na calculation to assess the impact of the baseline SCr as a different independent variable.

Besides, Thabut et al[7] first reported that the severity of liver disease and inflammation also had an important prognostic role in patients with AKI and cirrhosis. It is well known that cirrhotic patients have a combination of systemic inflammation and immune deficiency, which has been referred as the cirrhosis-associated immune dysfunction (CAID) syndrome.[23] The pro-inflammatory status of cirrhotic patients, characterized by persistent activation of circulating immune cells and increased levels of pro-inflammatory cytokines, results in recurrent activation of circulating immune cells from damage-associated molecular patterns (DAMPs) that are released from necrotic liver cells and from pathogen-associated molecular patterns (PAMPs) that are released from the intestinal translocation.[23,28] The increased levels of pro-inflammatory cytokines induce vascular dysfunction, which worsens systemic vasodilation and renal vasoconstriction.[29] The disturbance in renal blood flow can cause oxidative stress and tubular damage and lead to AKI.[29] In addition, inflammation directly affects renal function, through the release of PAMPs and DAMPs,[29] and plays a central role in the pathogenesis of AKI.[30,31] In fact, cellular injury and its molecular products are considered important activators of inflammation after AKI.[31,32] The evidence that norfloxacin administration reduces the severity of renal dysfunction in cirrhotic patients further supports the role of inflammation in AKI.[33]

To incorporate an inflammatory marker in our risk score, we evaluated the NLR which has been recognized as an important marker for inflammation in AKI.[8,9,34,35] In fact, a higher NLR was independently associated with AKI in our study (p=0.028).

We must consider some potential limitations of our study. First, this was a single-center cohort that limited the generalization of our results. Second, the retrospective design with a relatively small cohort of patients may contribute to overlooking some potential prognostic factors. Third, we did not assess UO in our cohort to define AKI. Finally, we used SCr at admission as a baseline which can underestimate the incidence of AKI, although glomerular filtration rate-based formulas to assess baseline SCr such as the modification of diet in renal disease (MDRD) tend to overestimate glomerular filtration rate in cirrhosis.

Nevertheless, our study has many important virtues. To our knowledge, it is the first risk score to predict AKI in cirrhotic patients which incorporates renal and liver function assessment as well as inflammation. In addition, the predictive value of our ROC curve is strong, suggesting the potential confirmation of this risk score in other populations.

Conclusion

We have developed a new easily calculated risk score to predict AKI in cirrhotic patients, which combines markers of renal and liver function and inflammation and deserves further validation in large-scale studies.

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Disclosure

The authors report no conflicts of interest in this work.

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