Original Paper

Evaluation of Absolute Serum Creatinine Changes in Staging of Cirrhosis-Induced Acute Renal Injury and its Association with Long-term Outcomes

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Key Words

Acute kidney injury • Cirrhosis • Classification • Creatinine • Mortality

Abstract

Background/Aims: To assess the prognostic accuracy of absolute serum creatinine (sCr) changes ('Delta-sCr') on the long-term outcomes in cirrhotic patients, and evaluate the performance of the 'Delta-sCr' approach to stage acute kidney injury (AKI), compared with the Kidney Disease Improving Global Outcomes (KDIGO) criteria. **Methods:** We conducted a retrospective analysis of 333 hospitalized patients. We classified AKI stages using two methods: 1) KDIGO AKI criteria; 2) 'Delta-sCr' system, defined by the difference between the baseline and the peak sCr value during the hospitalization. The end point was the hazard of 1-year death. **Results:** The prevalence of AKI in cirrhotic patients was 18.01% by the KDIGO criteria, and 25.22% by the 'Delta-sCr' system. On multivariable Cox hazard analysis, both of the two methods were independent predictive factors of death ('Delta-sCr' system: OR=2.911, $p<0.001$), (KDIGO criteria: OR=2.065, $p<0.001$). However, the 'Delta-sCr' system provided a modest improvement in classification over the KDIGO criteria with a net reclassification improvement (NRI) of 28.7% ($p<0.001$) and integrated discrimination improvement (IDI) of 7.5% ($p=0.03$). And the predictive value of the 'Delta-sCr' system could be significantly improved ($p=0.006$), when combined with age and MELD score. **Conclusion:** The Delta-sCr is associated with the 1-year mortality. And the 'Delta-sCr' system may optimize the discrimination of risk prediction.

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Introduction

Acute kidney injury (AKI) is a common complication in cirrhotic patients and is associated with a poor prognosis independently [1, 2]. Approximately 20% of hospitalized patients with cirrhosis develop renal failure [3]. And a meta-analysis showed AKI predicting a 7-fold increased risk of death in cirrhotic patients [4]. With the improved understanding of renal failure in cirrhosis, the definition of renal failure has been challenged. Recently, a working group composed of members of the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative (ADQI) reached the final proposal for the diagnosis of cirrhosis-AKI, named IAC-AKI, which is defined that any patients with cirrhosis and an increase in serum creatinine (sCr) by either 26.5 $\mu\text{mol/L}$ within 48 h or by 50% from baseline within 7 days, would be classified as having AKI, abandoning the threshold of sCr $\geq 133 \mu\text{mol/L}$ in the traditional criteria [5].

However, as to the classification system specific to cirrhosis-AKI, there is still an area of great controversy so far [6]. Several prospective studies have demonstrated that the risk of cirrhotic, patient mortality was directly related to the patients severity of AKI [7-9]. Hence, an exact AKI staging system, rather than a simple binary descriptor, is more crucial to help the physicians to predict the clinical outcome and decide on the intensity of monitoring and consequently, the most appropriate treatments for patients with cirrhosis. Existing widely used AKI staging systems in nephrology include the RIFLE (Risk-Injury-Failure-Loss-End stage renal disease) criteria, the AKIN (Acute Kidney Injury Network) criteria, and now the KDIGO (Kidney Disease Improving Global Outcomes) criteria, which are all based on the relative changes in sCr. Recently, some studies proposed to stage AKI using absolute increases in sCr, which indicated a promising alternative to the KDIGO criteria for characterizing the severity of AKI [10-12]. Those studies were mostly validated amongst general hospitalized patients, but its application specific to cirrhotic patients is less certain.

Our study was performed to access the prognostic accuracy of absolute sCr changes ("Delta-sCr") on the long-term outcomes (1-year mortality) in patients with cirrhosis, and evaluate the performance of the "Delta-sCr" approach to stage AKI, compared with the KDIGO criteria, using the relative increases in sCr.

Materials and Methods

Study Design and Patients

The study was conducted retrospectively, including cirrhotic patients admitted to the Department of Liver Diseases of Ningbo NO.2 Hospital, a 2000-bed, tertiary care and university affiliated hospital, between January 2013 and December 2014. Inclusion criteria included (1) patients age ≥ 18 years with diagnosis of liver cirrhosis of any etiology. And the diagnosis of cirrhosis was established by clinical, biochemical, ultrasonographic and endoscopic findings; (2) patients with at least one outpatient sCr measurement within 1 year before hospitalization, or >1 measurement during the hospitalization. The criteria for exclusion included (1) previous liver or kidney transplantation; (2) hepatocellular carcinoma outside Milan criteria or advanced non-hepatic neoplasia; (3) advanced chronic kidney disease (baseline sCr $>353.6 \mu\text{mol/L}$) acute or chronic renal replacement therapy before admission; (4) patients who had incomplete sCr data. Patients' electronic medical records were reviewed including basic data such as demographics, laboratory results, and comorbidities at the time of admission were collected. Only Data from the initial admission was analyzed exclusively for patients with multiple admissions. MELD and Child-Pugh score were also calculated from the time of admission.

Baseline sCr was defined as the most recent and lowest value during the 7 days to 1 year preceding hospitalization (in 232/333 patients, 69.67%) or the sCr value at admission (in 101/333 patients, 30.33%), if the former was not available. And the peak sCr was defined as the highest sCr value reached during hospitalization.

We classified AKI stages using two methods: 1) KDIGO AKI staging criteria (KDIGO criteria) [13], defined at the time of first fulfillment: Stage 1: increase in sCr $\geq 26.5 \mu\text{mol/L}$ within 48 hours or sCr increase ≥ 1.5 -1.9times baseline within 7days; Stage 2: sCr increase 2-2.9times baseline; Stage 3: sCr increase ≥ 3 times baseline. In the criteria, the use of urine output as one of the criteria has been removed since it is inaccurate for diagnosis in patients with cirrhosis; 2) the 'Delta-sCr' system, which was defined by the difference between the baseline and the peak sCr value. Cut-offs were determined based upon the Kaplan-Meier survival analysis to optimally differentiate survival function for each stage [12]: Stage 1, Delta-sCr: 26.5 - $132.6 \mu\text{mol/l}$ (0.3 - 1.5mg/dl), Stage 2, Delta-sCr: 132.7 - $221.0 \mu\text{mol/l}$ (1.5 - 2.5mg/dl) and Stage3, Delta-sCr $> 221.0 \mu\text{mol/l}$ (2.5mg/dl).

Patients were followed up at an outpatient clinic or via telephone contact (records were collected in the electronic medical system). The end point (for 1 year) was the hazard of death. For those patients whose lengths of follow-up were more than 1 year, the survival time was censored at 365 days after admission.

The study protocol was approved by the Ethics Committee of Ningbo NO.2 Hospital according to Institutional guidelines. Given the retrospective nature of the study, we were granted a waiver of informed consent.

Data Analysis

Continuous variables were reported as mean and standard deviation or median, minimum and maximum. Categorical variables were reported as count and percentage in each category. Univariate logistic analyses were conducted to identify potential predictors of end point. Multivariate, logistic, and Cox regression models were performed by a backward elimination technique to explore the independent prognostic value of predictors. To prevent multicollinearity, we created other models for multivariate analysis, excluding those variables that are computed from other variables, such as MELD score or Child-Pugh score. Since the factors peak sCr, and Delta sCr were highly correlated with AKI stages, we did not put them into the same model. Moreover, multivariate analysis was repeated with either of the AKI staging method to avoid multicollinearity.

1-year survival probability curves of different stages of AKI were calculated with the Kaplan-Meier method and compared with log-rank test. The prognostic values of the two methods were demonstrated by using the area under ROC curve (AUC) evaluation metric. DeLong's method was used for ROC curve comparison. The predictive values for 1-year mortality of "Delta-sCr" system was compared with KDIGO criteria using the net reclassification improvement (NRI) and integrated discrimination improvement (IDI). The confidence interval was accepted as 95% and p values equal or smaller than 0.05 were accepted as statistically significant. SPSS Version 22.0 (SPSS, Inc, an IBM Company, Chicago, Illinois, USA) and R i386 3.3.0 software (for the calculation of NRI and IDI) were used for statistical analysis.

Results

Demographic Characteristics and Clinical Features

A total of 333 cirrhotic patients were enrolled in the present study. The median age was 55.68 ± 12.56 years, and 63.06% (n=210) of the patients were male. The most common etiology of cirrhosis was HBV infection (n=232, 69.7%), followed by Miscellaneous (n=40, 12%), Alcohol (n=30, 9%), Cholestasis (n=17, 5.1%), and Autoimmune (n=14, 4.2%). Mean MELD and Child-Pugh scores on admission were 11.58 and 9, respectively. The prevalence of AKI was found to be 18.01%, defining by KDIGO criteria, and 25.22% by the "Delta-sCr" system. 24 patients with mild renal injury were detected by the "Delta-sCr" system, whose sCr increase $\geq 26.5 \mu\text{mol/l}$ beyond a 48h time period, but < 1.5 folds in 7 days, without reaching the KDIGO criteria. Among them, three patients (12.5%) died in the follow-up.

After 1-year follow-up, 303 patients were alive and 31 dead. No patient was lost to follow-up. The cohort was divided into two groups based on the 1-year mortality rate of all the patients. The patients of the 'non-survivor group' were older, with higher severity of cirrhosis, higher rates of complications of infection and chronic kidney disease (CKD). AKI was developed much more in the 'non-survivor group'. (Table 1)

Table 1. Baseline characteristics and Univariate analysis for factors associated with 1-year mortality

	Total (n=333)	Survivor (n=302)	Non-survivor (n=31)	Survivor VS. Non-survi vor <i>p</i>	1-year mortality Univariate <i>p</i>
Age, yr	55.68±12.56	54.87±0.72	63.80±1.75	<0.001	<0.001
Sex, Male	210(63.06%)	188(62.05%)	22(73.33%)	0.325	0.411
Etiology				0.175	0.327
HBV	232(69.7)	210(69.3)	20(66.7)		
Alcohol	30(9.0)	23(7.6)	7(23.3)		
Autoimmune	14(4.2)	13(4.3)	1(3.3)		
Cholestasis	17(5.1)	17(5.6)	0(0)		
Miscellaneous	40(12)	38(12.5)	2(6.7)		
Child-Pugh Score	9[5,15]	9[5,15]	12[6,15]	<0.001	<0.001
MELD Score	11.58[1.75, 35.02]	10.67[1.75, 28.26]	16.82[7.71, 35.02]	<0.001	<0.001
MAP, mmHg	92.66[82, 100]	93.33[53.33, 128.67]	87.33[54, 134.67]	0.066	0.055
WBC count, ×10 ⁹ /L	4.10[0.90, 27.90]	4[0.90, 27.60]	5.90[1.50, 24.50]	<0.001	<0.001
Platelet count, ×10 ⁹ /L	74[3, 358]	74[16, 358]	75[3, 168]	0.673	0.690
INR	1.39[0.80, 4.53]	1.37[0.80, 2.90]	1.50[1.18, 4.53]	<0.001	<0.001
Tbil, μmol/L	36.30[2.60, 523.60]	32.30[2.60, 523.60]	60.10[13.40, 444]	0.031	0.021
Alb, g/L	29.10±6.10	29.11±0.34	27.86±1.34	0.224	0.285
ALT, g/L	34[3, 758]	35[3, 758]	31[3, 446]	0.075	0.089
TBA, μmol/L	55.90[0.20, 390.10]	53[0.20, 348.80]	80[7.70, 390.10]		0.155
Serum Sodium, mmol/L	138.43±5.75	138.92±0.29	133.51±1.59	<0.001	<0.001
CRP, mg/L	5.76[0.03, 324.16]	5.24[0.03, 324.16]	12.93[0.28, 203.80]	0.001	<0.001
SBP	53(15.91)	45(14.85)	8(26.67)	0.195	0.092
Other Bacterial Infection	75(22.52)	60(19.80)	15(50.00)	0.001	<0.001
DM	60(18.02)	52(17.16%)	8(26.67)	0.307	0.197
Hypertension	47(14.11)	40(13.20%)	7(23.33)	0.244	0.129
Baseline sCr, μmol/L	70.9[20.30, 240.10]	68.10[20.30, 240.10]	88.74[64.50, 152.10]	<0.001	<0.001
Peak sCr, μmol/L	76.60[42.60, 639.80]	74.70[42.60, 409.70]	228.40[71.80, 639.80]	<0.001	<0.001
Delta-sCr, μmol/L	7.2[0.10, 543]	5.80[0.10, 291.60]	54.80[5.30, 543]	<0.001	<0.001
CKD	24(7.20)	21(6.93)	3(10.00)	0.041	0.049
KDIGO criteria				<0.001	<0.001
Stage 0	273(81.98)	264(87.41)	9(29.03)		
Stage 1	32(9.60)	23(7.62)	9(29.03)		
Stage 2	16(4.80)	10(3.31)	6(19.35)		
Stage 3	12(3.60)	5(1.66)	7(22.58)		
Delta-sCr system				<0.001	<0.001
Stage 0	249(74.77)	243(80.46)	6(19.35)		
Stage I	60(18.02)	50(16.56)	10(32.26)		
Stage II	14(4.20)	8(2.65)	6(19.35)		
Stage III	10(3.00)	1(0.33)	9(29.03)		

Values are given as numbers(n), percentage(%), means±SD. or median [min,max]. HBV, Hepatitis B virus; MELD, Model for End Stage Liver Disease; MAP, Mean arterial pressure; WBC, White blood cell; INR, International normalized ratio; Tbil, Total bilirubin; Alb, Serum Albumin; ALT, Alanine aminotransferase; TBA, Total bile acid; CRP, C-reactive protein; SBP, Spontaneous bacterial peritonitis; DM, Diabetes mellitus; sCr, serum creatinine; CKD, Chronic Kidney Disease; KDIGO, Kidney Disease Improving Global Outcomes.

The End Point

At the end of the 1-year follow-up period, a total of 31 patients (9.31%) had died. 8 patients died during hospitalization whereas 23 patients died after the discharge from the hospital. A univariate analysis of survival demonstrated that variables related with age ($p<0.001$), Child-Pugh score ($p<0.001$), MELD score ($p<0.001$), WBC count ($p<0.001$), INR ($p<0.001$), Tbil ($p=0.021$), Serum Sodium ($p<0.001$), CRP ($p<0.001$), all the renal parameters including sCr (Baseline sCr ($p<0.001$), Peak sCr ($p<0.001$), and Delta sCr ($p<0.001$)), AKI stages according to KDIGO criteria ($p<0.001$) or 'Delta-sCr' system ($p<0.001$) and CKD ($p=0.049$), as well as Other Bacterial Infection ($p<0.001$) were associated with mortality.

Several multivariate Cox regression models were performed to exclude multicollinearity. In Model 1 including individual variables and excluding liver scores and AKI classification, the independent predictive factors of survival were: Age, WBC count, and INR. When liver scores were included in the analysis (Model 2), the independent predictive factors were: age and MELD score. And either of the two staging methods of AKI was independent predictive factor of survival (KDIGO:

OR=2.065, $p<0.001$) and 'Delta-sCr': OR=2.911, $p<0.001$), when included respectively in Model 2, Model 3 and 4).

ROC curve analysis was performed to evaluate the four models in predicting 1-year mortality. As shown in Table 2, the areas under the curve (AUC) for Model 1-4 were respectively 0.827, 0.873, 0.896 and 0.920. The results indicated that Model 4 including Age, MELD score and 'Delta-sCr' system had a better predictive value for 1-year mortality in cirrhotic patients ($p=0.01$, $p=0.04$, $p=0.16$) in comparison with Model 1, 2 or 3 respectively.

Comparison of the prognostic value of KDIGO criteria vs 'Delta-sCr' system

Kaplan-Meier analysis and log-rank test were constructed to determine the differences in survival situation of AKI stages according to the two methods. Significant differences were found among the survival curves according to the 'Delta-sCr' system ($p=0.023$, $p<0.001$, $p=0.016$, resp.). However, with the KDIGO criteria, the difference was only significant between AKI stages 1 and 3 ($p=0.032$), not between AKI stage 1 and 3 and between stage 2 and 3 ($p=0.639$ and $p=0.113$, resp.) (Fig. 1).

Compared with the original classification by the KDIGO criteria, the 'Delta-sCr' system reclassified 34 of 333 patients (10.21%) to higher AKI stages, and 16 patients (4.80%) to lower AKI stages. The total reclassification was hence 15.02% (50/333). The 'Delta-sCr' system incorrectly downreclassified 3 of 31 deaths (9.68%), and incorrectly up-reclassified 25 of 302 survivors (8.28%). Though not very statistically significant in AUC comparison ($p=0.106$), the 'Delta-sCr' system provided a modest improvement in classification over the KDIGO criteria with an NRI of 28.7% (95% CI 12.1-42.5%, $p<0.001$) and IDI of 7.5% (95% CI 0.7-16%, $p=0.03$), suggesting that the risk levels for individuals reclassified by 'Delta-sCr' system might be more accurate to predict long-term risk mortality (Table 3).

The two methods classifying AKI according to KDIGO criteria and 'Delta-sCr' system were also assessed by calculating sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for 1-year mortality as an outcome. The 'Delta-sCr' system delivered both increased specificity and LR+ at a cost of sensitivity or LR-, when classifying AKI stage 2 and 3. Whereas classifying AKI stage 1, the 'Delta-sCr' system exhibited improved sensitivity, with some loss of specificity (Table 4).

Table 2. Independent predictors of 1-year mortality in patients with cirrhosis using cox regression model

	OR (95% CI)	p
MODEL1: AUC (95% CI): 0.827 (0.748-0.905)		
Age	1.096 (1.058-1.135)	<0.001
WBC count	1.126 (1.054-1.202)	<0.001
INR	5.890 (2.852-12.164)	<0.001
MODEL2: AUC (95% CI): 0.873 (0.817-0.930)		
Age	1.069 (1.038-1.103)	<0.001
MELD Score	1.190 (1.118-1.267)	<0.001
MODEL3: AUC (95% CI): 0.896 (0.843-0.948)		
Age	1.064 (1.030-1.098)	<0.001
MELD Score	1.157 (1.086-1.233)	<0.001
KDIGO criteria	2.065 (1.410-3.023)	<0.001
MODEL4: AUC (95% CI): 0.920 (0.881-0.958)		
Age	1.045 (1.011-1.079)	0.009
MELD Score	1.156 (1.087-1.230)	<0.001
Delta-sCr system	2.911 (2.007-4.223)	<0.001
OR, Odds Ratio; 95%CI, 95% confidence intervals; WBC, White blood cell; DM, Diabetes mellitus; MELD, Model for End Stage Liver Disease; sCr, serum creatinine; INR, International normalized ratio; KDIGO, Kidney Disease Improving Global Outcomes; AUC, area under ROC curve		

Discussion

The present study was conducted to investigate the performance of the 'Delta-sCr' approach to stage AKI for predicting long-term outcomes, compared with the KDIGO criteria. To the best of our knowledge, this is the first study using the new approach to classification of AKI in cirrhotic patients. The diagnosis of ARF in cirrhosis is traditionally made by a 50% increase in sCr with setting a fixed sCr threshold of ≥ 1.5 mg/dl [14]. However, final consensus has not been reached yet on classification of cirrhosis-AKI. In the last decade, several attempts have been made. In 2002, the ADQI Working Group developed RIFLE criteria for AKI. Subsequent evidence that even small increase in sCr (as small as 0.3 mg/dl) also has a negative impact on survival led to a modification of the RIFLE criteria called AKIN [3]. More recently, the KDIGO criteria have been developed to reach a consensus drawing consolidating elements of both RIFLE and AKIN on staging AKI [15]. Whether these criteria improve the traditional criterion (a final threshold value for sCr of 1.5 mg/dl) in terms of a better prediction of mortality is still a matter of debate [16]. Piano et al. reported that the traditional criterion was more accurate than the AKIN criteria in the prediction of in-hospital mortality in patients with cirrhosis and ascites [17]. Furthermore, Fagundes et al. developed a 'new classification' that combined the AKIN criteria and traditional criterion in cirrhosis [9] (i) stage 1 with a final sCr of ≤ 1.5 mg/dl; (ii) stage 1 with a final sCr of > 1.5 mg/dl, and (iii) combined stages 2 and 3, providing a better prognostic stratification than AKIN criteria alone. Whereas, it has recently been challenged that even

Table 3. Log-rank tests refer to statistically significant differences between stages stratified by KDIGO and Delta-sCr system

KDIGO criteria	AKI staging	Log Rank-p		
		0	1/I	2/II
	0	-	-	-
	1	<0.001	-	-
	2	<0.001	0.639	-
	3	<0.001	0.032	0.113
Delta-sCr system	0	-	-	-
	I	<0.001	-	-
	II	<0.001	0.023	-
	III	<0.001	<0.001	0.016

AKI, Acute Kidney Injury; KDIGO, Kidney Disease Improving Global Outcomes; sCr, serum creatinine

Fig. 1. Kaplan-Meier graphs for 1-year survival stratified by KDIGO criteria (Figure 1A) and Delta-sCr system (Figure 1B) of AKI.

Table 4. Accuracy of KDIGO criteria and Delta-sCr system in prediction of 1-year mortality

	AKI staging	Sensitivity (%)	Specificity (%)	LR+	LR-	AUC (95%CI)	<i>p</i>	IDI(%) (95%CI)	<i>p</i>	NRI(%) (95%CI)	<i>p</i>
KDIGO criteria	1	29.03	92.38	3.81	0.77	0.803 (0.756-0.844)	0.108	7.5 (0.7-16.0)	0.03	28.7 (12.1-42.5)	<0.001
	2	19.35	96.67	5.85	0.83						
	3	54.84	95.70	12.74	0.47						
Delta-sCr system	I	32.26	83.44	1.95	0.81	0.844 (0.801-0.882)					
	II	19.35	97.35	7.30	0.83						
	III	29.03	99.67	87.68	0.71						

AKI, Acute Kidney Injury; KDIGO, Kidney Disease Improving Global Outcomes; sCr, serum creatinine; LR+, positive likelihood ratio; LR-, negative likelihood ratio; AUC, area under ROC curve; NRI, net reclassification improvement; IDI, integrated discrimination improvement; 95%CI, 95% confidence intervals

“mild” AKI in cirrhotic patients whose peak sCr remained below 1.5mg/dl had a surprisingly higher mortality rate compared to those without AKI, indicating that the ‘new classification’ proposed by Fagundes et al. did not improve the prognostic assessment of patients with cirrhosis [18, 19]. Therefore, it seems all of these various criteria are not that perfect, still requiring further refinement. At present, a number of studies have reported the absolute changes in sCr appear to be more accurate for estimating prognosis of AKI than the relative changes in sCr, on which the cut-offs of AKIN or KDIGO criteria are mainly based. Those studies performed in general hospitalized patients and patients with acute myocardial infarction, however, the information on cirrhosis is lacking.

In our study, both staging methods (KDIGO criteria and ‘Delta-sCr’ system) were independent risk factors for mortality, however, compared to the ‘Delta-sCr’ system, the KDIGO criteria revealed lower OR or AUC value. And the KDIGO criteria showed no significant difference between AKI stage 1 and 3 and between stage 2 and 3. The new approach of ‘Delta-sCr’ system modestly improved the classification accuracy by IDI and NRI analysis, superior to the KDIGO criteria in cirrhosis. Further analysis showed that when classifying stage I, the ‘Delta-sCr’ system showed higher sensitivity to small sCr increases, which did not yet achieved the KDIGO criteria but might still yield a poor prognosis, providing a wider therapeutic window. This approach could be important in the early detection of mild renal injury for the potential to improve management, more closely monitoring, halting the process of renal injury. Also, the new expanded diagnostic criteria could help to identify AKI, which would be missed by KDIGO criteria for delayed sCr repeated assay, and sustained progressive kidney injury, which had an increase in sCr that was less rapid than what the KDIGO criteria required [20]. While classifying AKI stage II and III, the ‘Delta-sCr’ system showed higher specificity and LR+, avoiding undue changes in management. In our study, AKI were classified when they first fulfilled KDIGO criteria, but reclassified by ‘Delta-sCr’ in a dynamic context, especially when progressing to more severe one. It is reported that patient survival is not only impacted by the stage of renal dysfunction but also by the progression of renal dysfunction on follow-up [21]. Taking into account that, it may be logical this new approach could be a more sensitive, accurate and simple way for prognostic assessment and targeted interventions.

Besides the new staging approach we proposed, there are several strengths to this study. First, we use of a relatively non-selected cirrhotic patient population with ascites or not, and a wide range of comorbidities, except cancer and ESRD, providing the potential generalization of the new staging approach. Second, in previous studies, the admission sCr were commonly used as the baseline value, which would have obscured the presence or severity of AKI, and the mortality risk associated with various stages of AKI [15]. IAC and ADQI defined baseline sCr as the stable sCr value within the last 3 months before admission [5]. However, in clinical practice, this timeframe seems unfeasible in most cases. So we had prolonged the timeframe to 1 year, which considered to be most closely approximating nephrologist-adjudicated basal sCr values [22, 23]. In our study, most of the patients (69.67%) used the pre-hospitalized sCr. And the admission sCr were only used in those (30.33%) without the pre-hospitalized sCr. Third, the studied population was from China. There are obvious differences in the etiology

of cirrhosis between the East and West. In Western societies, alcohol is the main etiology of cirrhotic patients. In contrast, in the Asia-Pacific region, the majority of cirrhosis is caused by HBV [24]. Therefore, it was interesting to investigate whether the current KDIGO AKI staging also applies in the Asia-Pacific region.

Limitations

Our study also has some limitations that should be acknowledged. First, it was a single-centre retrospective study. Being observational in nature, we did not have daily sCr values for all patients, which might predispose to bias and residual confounding. In fact, in daily routine, there is less attention to the renal function paid by the hepatologists. Repeated measures of sCr were not always available, especially within 48 hours for defining AKI by KDIGO criteria. A multicenter prospective study capturing real-time laboratory and clinical characteristics are needed for further verification. Second, although the new AKI staging approach of 'Delta-sCr' system herein did well in long-term risk prediction in cirrhosis, the cut-offs we selected for each 'Delta-sCr' stage were retrospective data derived. So, it is very important to evaluate the 'Delta-sCr' system and its cut-offs with larger, external validation data set. Third, sCr is no doubt an inexpensive and the most practical biomarker of renal function. However, it is well recognized that sCr is a neither sensitive nor specific marker of kidney injury for cirrhotic patients [25]. As a consequence, GFR is also inaccurate in cirrhosis, since it is calculated based on sCr measurement [26]. Recently, many novel biomarkers have been explored for early diagnosis of AKI, including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1), and Toll-like receptor 4 (TLR4) [27-31]. Moreover, it is not likely that AKI alone is adequate for risk stratification in patients with cirrhosis [32-34]. Our study also revealed that age and MELD score predicted survival in cirrhosis as well. Thus, the two prognostic factors were combined in the final model (Model 4), leading to the incremental value of the 'Delta-sCr' system in prediction of mortality (Model 4: AUC=0.920, 'Delta-sCr': AUC=0.844, $p=0.006$).

Conclusion

In summary, the 'Delta-sCr' system, based on absolute increases in sCr, appeared to better stratify cirrhosis-AKI and predict long-term mortality risk than the current KDIGO criteria. However, optimization of the cut points for the new 'Delta-sCr' system still needs to be prospectively validated. Moreover, novel biomarkers and other prognostic factors related to cirrhosis should be considered to combine with AKI classification for improved predictive ability.

Disclosure Statement

There are no conflicts of interest associated with this work.

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