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The urine albumin creatinine ratio is one of the predictors of acute kidney injury in hepatitis C-related cirrhotic hepatic encephalopathy

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Abstract

Background/objective: Hepatic encephalopathy (HE) is a main manifestation of acute decompensation in liver cirrhosis. Recently, systemic inflammation was proposed as a key mechanism in the development of acute kidney injury (AKI) in cirrhotic patients. The urine albumin creatinine ratio (UACR) is considered a marker of systemic inflammation in a variety of clinical settings. Here, we aimed to evaluate the role of the urine albumin creatinine ratio in the early prediction of AKI in HE.

Patients and methods: Sixty-seven consecutive patients presented with cirrhotic HE, and 59 age- and sex-matched cirrhotic patients with no history of HE served as controls. HE was defined and graded by the West Haven criteria. The severity of liver cirrhosis was evaluated by the Child-Turcotte-Pugh (CTP) score, and model for end-stage liver disease (MELD) score. The incidence of AKI that developed during hospital admission and the in-hospital mortality rate was estimated among HE patients. In addition, predictors of AKI were analyzed.

Results: The mean age of HE patients was 58.09±12.26 years; 36 (53.7%) were males, and 31 (46.3%) were females. Among HE patients, 16 (23.9%) developed AKI during hospital admission. The in-hospital mortality rate among HE patients was 22 (32.8%), the in-hospital mortality among HE-AKI patients was 81.3% (n=13/16), and UACR levels > 91.5 mg/g identified HE-AKI with 81.25% sensitivity (AUC = 0.85, $P \leq 0.001$).

Conclusions: Patients with cirrhotic HE are at high risk of AKI. HE-AKI patients had a high rate of in-hospital mortality. Estimation of UACR at hospital admission is suggested for the early detection of patients with HE-AKI.

Keywords: Acute kidney injury, Albuminuria, Hepatic encephalopathy, Hospital mortality, Incidence, Liver cirrhosis

Introduction

Cirrhosis is the leading cause of liver-related death worldwide. In 2017, cirrhosis caused more than 1.32 million deaths globally [1]. Egypt has a high liver cirrhosis burden [2]. Indeed, it was reported that Egypt had the highest age-standardized death rate due to cirrhosis from 1990 to 2017 [1]. Overt hepatic encephalopathy (OHE) occurs in 30–40% of patients with cirrhosis during the natural course of their disease [3]. Once depicted, the course of decompensated cirrhosis is characterized by repeated episodes of HE. The in-hospital mortality rate of patients with HE ranges from 33 to 75% [4–6]. This high in-hospital mortality rate is largely dependent on the

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grade of HE and associated comorbidities. Acute kidney injury (AKI) is a common comorbidity in patients with decompensated cirrhosis, occurring in 20% of hospitalized patients and resulting in high mortality [7].

The prediction of AKI and early therapeutic intervention in decompensated cirrhosis can decrease in-hospital mortality. Accurate assessment of renal function by serum creatinine is difficult in patients with cirrhosis, due to an enlarged volume of fluid distribution, low protein intake, and decreased creatinine production secondary to muscle atrophy. Alternative urinary markers (e.g., cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and urinary IL-18) are not widely available [8]. A urine albumin creatinine ratio (UACR) ≥30 mg/g is associated with more severe liver disease and a lower glomerular filtration rate (GFR) in patients with decompensated cirrhosis [9]. It was reported that albuminuria predicted AKI in liver cirrhosis [7] and mortality in HE [10].

The occurrence of albuminuria in patients with HE-related AKI (HE-AKI) may be explained by the associated systemic inflammation. The relationship between microalbuminuria and inflammation has been reported in a variety of clinical settings [11]. On the other hand, recent large-scale European observational studies have shown that systemic inflammation is a hallmark of kidney injury in cirrhotic patients. Indeed, systemic inflammation induces nitric oxide-mediated accentuation of the preexisting splanchnic vasodilation, resulting in the overactivation of the endogenous vasoconstrictor systems, which elicits intense vasoconstriction and hypoperfusion in certain vascular beds, in particular the renal circulation, and subsequently acute kidney injury (AKI) [12].

Data on the prediction of HE-AKI are limited. Here, we attempted to evaluate the role of the UACR in the early prediction of AKI among hospitalized cirrhotic HE patients.

Patients and methods

This prospective case-control study included 126 cirrhotic patients. Sixty-seven (53.2%) consecutive patients presented with hepatic encephalopathy (HE), and 59 (46.8%) age- and sex-matched cirrhotic patients had no history of HE and served as controls. All included patients were admitted to the Department of Internal Medicine, El Hussein University Hospital, Cairo, Egypt, during the period from September 2019 to September 2020. Patients with severe cardiopulmonary disease, history of renal disease, previous liver transplantation, nephrotoxic drugs, and nonsteroidal anti-inflammatory drug (NSAID) use in the last 4 weeks or diabetes mellitus were excluded.

Cirrhosis was diagnosed by liver biopsy, endoscopic signs of portal hypertension, radiological evidence of liver nodularity, or clinical evidence of hepatic decompensation (including ascites, HE, and acute variceal bleeding) in patients with chronic liver disease. Overt ascites was diagnosed by clinical examination and confirmed by ultrasonography. Patients with fibrosis-4 (Fib-4) scores ≥ 3.5 in the absence of liver decompensation and liver biopsy were categorized as compensated liver cirrhosis [13]. HE was defined and graded by the West Haven criteria. The severity of liver cirrhosis was evaluated by the -Turcotte-Pugh (CTP) score and the model for end-stage liver disease (MELD) score. Serum creatinine was measured for all included patients on he first day of hospital admission (considered the baseline serum creatinine) and daily durin the hospital stay to detect patients who developed AKI.

Acute kidney injury (AKI) was defined as an acute increase in serum creatinine (S. Cr) 0.3 mg/dl or more above the baseline serum creatinine in less than 48 h [14]. Diagnosis of hepatorenal syndrome-AKI was based on the criteria previously reported [15]. Prerenal AKI was defined as elevated serum creatinine 0.3 mg/dl or more above the baseline serum creatinine, with a subsequent decrease in S. Cr to ≤1.5 mg/dl within 48 h of treatment with diuretic withdrawal and intravenous hydration [15]. Acute elevation in serum creatinine 0.3 mg/dL or more above the baseline serum creatinine, not responding with 48 h of volume resuscitation and not meeting the criteria for HRS [15] were categorized as intrinsic AKI.

To assess the value of the urine albumin creatinine ratio (UACR) in the prediction of AKI in HE patients, UACR was measured for all included patients (n=126) on the first day of hospital admission.

Detection of UACR

A solid-phase fluorescence immunoassay was used to measure urinary albumin, with a sensitivity level of 0.05 mg/dl. The coefficient of variation for urinary albumin measurement varied from 4.8 to 16.1%. Urine creatinine was measured with the Jaffé rate reaction (Beckman Astra, Brea, CA), and the coefficient of variation ranged from 1.5 to 7.7% (National Center for Health Statistics, 1996).

Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables that were normally distributed were expressed as the mean values ± standard deviation (SD), and non-normally distributed were expressed as the median values with interquartile range (IQR). Categorical data are expressed as the frequencies and percentages. An independent samples t test was used when comparing two means (for normally distributed

data), the Mann-Whitney *U* test was used when comparing two medians of non normally distributed data, the chi-square test was used when comparing categorical data, and multivariate logistic regression analysis was used to identify the independent factors significantly associated with AKI. The area under a receiver operating characteristic curve (AUROC) was used to detect the cut-off point, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). A *P* value < 0.05 was considered significant.

Results

Among 126 patients with liver cirrhosis, the mean age was 57.9 ± 12.8 years, including 75 (59.5%) men and 51 (40.5%) women. HCV (114 patients, 90.5%) was the most common aetiology of liver cirrhosis. Twenty-three (18.3%), 55 (43.7%), and 48 (38%) patients had child classes A, B, and C, respectively. The mean MELD score was 15.01± 5.8, the median (IQR) UACR was 51.5 (88.6) mg/g, and the hospital stay was ≤ 7 days in the majority of patients (*n*=106; 84.1%). The incidence of AKI in the included cirrhotic patients who developed AKI during hospital admission was 18.3% (*n*=23). In addition, the in-hospital mortality rate among the included cirrhotic patients was 17.5% (*n*=22) (Table 1).

Table 1 Baseline characteristics of the included cirrhotic patients

Age, mean ± SD *(years)*	57.9 ± 12.8
Sex	
Male, *n (%)*	75 (59.5)
Females, *n (%)*	51 (40.5)
Hepatic encephalopathy,*n (%)*	
Yes	67 (53.2)
No	59 (46.8)
Grade I	1 (1.5)
Grade II	11 (16.4)
Grade III	38 (56.7)
Grade IV	17 (25.4)
ALT, mean ±SD (U/L)	33.1±28.6
AST, mean ±SD (U/L)	62.1±67
Serum albumin, mean ±SD (g/dl)	2.9 ± 0.9
Total bilirubin, mean ±SD (mg/dl)	3.0±3.5
INR mean ± SD	1.7±0.6
Hb, mean ±SD (g/dl)	10.0±2.4
WBCs ±SD	9.0±7.5
Platelets, mean ±SD	101.3±65.8
Baseline serum creatinine , mean ±SD (mg/dl)	0.91±0.2
CTP score mean ±SD	8.5±2.2
CTP class,*n (%)*	
A	23 (18.3)
B	55 (43.7)
C	48 (38.0)
MELD score, mean ±SD	15.01± 5.8
UACR, median (IQR) (mg/g)	51.5 (88.6)
AKI,*n (%)*	
Yes	23 (18.3)
No	103 (81.7)
Causes of AKI,*n (%)*	
Pre-renal	20 (87)
HRS	2 (8.7)
Intrinsic renal	1 (4.3)
Length of Hospital stays,*n (%)*	
≤ 7 days	106 (84.1)
8–14 days	20 (15.9)
Mortality,*n (%)*	
Yes	22 (17.5)
No	104 (82.5)

SD standard deviation, *HCV* hepatitis C virus, *HBV* hepatitis B virus, *NASH* non-alcoholic steatohepatitis, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *INR* international normalized ratio, *Hb* hemoglobin, *WBCs* white blood cell count, *CTP* Child Turcotte Pugh, *MELD* model for end-stage liver disease, *UACR* urine albumin creatinine ratio, *AKI* acute kidney injury, *HRS* hepatorenal syndrome

Characteristics of cirrhotic-HE patients

Among the 67 patients with cirrhotic HE, the mean age was 58.09±12.26 years; 36 (53.7%) were males and 31 (46.3%) were females. Patients with HE had significantly lower levels of serum albumin (2.35±0.58 g/dl). In addition, they had significantly higher levels of serum bilirubin (3.68±3.86 mg/dl) and international normalized ratio (INR) (1.87±0.64). Although HE patients had normal mean serum creatinine levels (1.0±0.45 mg/dl) at baseline, they were significantly higher than cirrhotic patients without HE (0.87±0.18 mg/dl). However, the mean estimated glomerular filtration rate (eGFR) (77.76±26.91 mL/min/1.73 m^2) was significantly lower among cirrhotic HE patients. The mean MELD (17.21± 5.54) and child's (9.65±1.70) scores were significantly higher among HE patients. There was no significant difference among cirrhotic patients with and without HE regarding UACR levels at hospital admission (Table 2). The incidence of AKI among cirrhotic patients with and without HE was 23.9% and 11.86%, respectively. The in-hospital mortality rate among cirrhotic HE patients was 32.8 %; however, no mortality was detected among cirrhotic patients without HE (Table 2).

Hepatic encephalopathy-associated AKI

Among 67 patients with HE, 16 (23.9%) developed AKI during hospital admission. The median (IQR) age for AKI patients was 60.5 (9) years, including 12 (75%) males and 4 (25%) females. Patients with HE-AKI had significantly increased serum bilirubin, higher Child-Turcotte-Pugh (CTP) scores, elevated basal serum creatinine, increased UACR, increased length of hospital stay, and higher in-hospital mortality rates (Table 3). The median (IQR) serum bilirubin, CTP score, admission serum creatinine,

Table 2 Baseline characteristics of patients with no-HE versus those with HE

Variables	Cirrhotic without HE (*n*=59)	Cirrhotic with HE (*n*=67)	
Age *(mean ± SD)*	57.712 ±13.3985	58.09 ±12.26	0.869
Sex			0.158
Male	39 (52.0%)	36 (53.7 %)	
Females	20 (39.2%)	31 (46.3 %)	
Hb *(mean ± SD)*	10.298±2.3775	9.690±2.3086	0.148
PLT *(mean ± SD)*	102.797±67.5512	99.940±64.6658	0.809
TLC *(mean ± SD)*	6.425±3.7393	11.337±9.0936	0.000
AST *(mean ± SD)*	45.000±31.0383	77.133±84.6291	0.007
ALT *(mean ± SD)*	27.686±25.5294	37.925±30.4044	0.044
Serum albumin *(mean ± SD)*	3.5036±.67822	2.35 ± 0.58	0.000
Total bilirubin *(mean ± SD)*	2.2361±2.75812	3.68±3.86	0.019
INR *(mean ± SD)*	1.4692±.48824	1.87±0.64	0.000
Baseline serum creatinine *(mean ± SD)*	0.87±0.18	1.00±0.45	0.044
eGFR at admission *(mean ± SD)*	91.051±24.5135	77.76±26.91	0.005
UACR *median (IQR)*	53 (81)	51 (96.6)	0.324
MELD score at admission *(mean ± SD)*	15.52±5.04	17.21± 5.54	0.000
CTP score *(mean ± SD)*	7.271±1.9985	9.65±1.70	0.000
AKI *n* (%)	7 (11.86 %)	16 (23.9 %)	0.08
Mortality *n* (%)			
Yes	0 (0 %)	22 (32.8 %)	0.00

SD standard deviation, *Hb* hemoglobin, *PLT* platelet, *TLC* total leucocytic count, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *eGFR* estimated glomerular filtration rate, *UACR* urine albumin creatinine ratio, *MELD* model of end-stage liver disease, *CTP* Child-Turcotte-Pugh, *AKI* acute kidney injury

Table 3 Baseline characteristics of patients with HE without AKI versus those with AKI

Variables	HE with no AKI *n*=51	HE-AKI *n*=16	*P value*
Age, years			
Median (IQR)	59 (16)	60.5 (9)	0.139
Sex, *n* (%)			
Males	24 (47.1%)	12 (75%)	
Females	27 (52.9%)	4 (25%)	0.051
AS T, median (IQR)	48 (38)	64.5 (132)	0.112
ALT, median (IQR)	32 (28)	34 (32.4)	0.546
Serum albumin, median (IQR)	2.3 (0.9)	2.25 (0.58)	0.680
Total bilirubin, median (IQR)	1.8 (3.3)	4.6 (3.9)	0.005
INR, median (IQR)	1.66 (0.7)	2 (0.7)	0.078
CTP score, median (IQR)	9 (3)	11 (1.75)	< 0.001
CTP class, *n* (%)			
B	28 (54.9%)	0 (0%)	< 0.001
C	23 (45.1%)	16 (100%)	
MELD score, mean (SD)	16 (5.4)	20.9 (4.1)	0.313
Baseline serum creatinine, median (IQR)	0.9 (0.4)	1.15 (0.38)	0.004
UACR, median (IQR)	39 (46.6)	249 (256.6)	< 0.001
Hospital length of stay, n (%)			
≤ 7 days	47 (92.2%)	9 (56.3%)	0.001
8–14 days	4 (7.8%)	7 (43.8%)	
Mortality, *n* (%)	9 (17.6%)	13 (81.3%)	< 0.001

HE hepatic encephalopathy, *n* number, *AKI* acute kidney injury, *IQR* interquartile range, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *CTP* Child-Turcotte-Pugh, *MELD* model of end-stage liver disease, *UACR* urine albumin creatinine ratio

and UACR were 4.6 (3.9) mg/dl, 11 (1.75), 1.15 (0.38) mg/dl, and 249 (256.6) mg/g, respectively. All HE patients with AKI had child's class C liver cirrhosis. Seven (43.8%) HE patients with AKI had hospital stays of more than 7 days, and the in-hospital mortality rate among HE patients with AKI was 81.3% (n=13) (Table 3).

Predictors of AKI in HE patients

Increased serum total bilirubin, elevated basal serum creatinine, elevated UACR, higher CTP score, and increased length of hospital stay were identified as independent risk factors for HE-AKI by multivariate analysis (Table 4).

ROC curve analysis

Prolonged length of hospital stay identified HE-AKI at a cut-off level of > 5.5 days, with 75% sensitivity, 82.4% specificity, 81% PPV, and 76.7% NPV (AUC = 0.83, $P \leq 0.001$). Total serum bilirubin identified HE-AKI at a cut-off level of > 3.1 mg/dl, with 68.75% sensitivity, 66.7% specificity, 67.4% PPV, and 68.1% NPV (AUC = 0.73, $P \leq 0.005$). Basal serum creatinine identified HE-AKI at a cut-off level of > 1.05 mg/dl, with 62.5% sensitivity, 66.7% specificity, 65.2% PPV, and 64% NPV (AUC = 0.74, $P = 0.005$). UACR levels > 91.5 mg/g, identified HE-AKI with 81.25% sensitivity, 82.4% specificity, 82.2% PPV, and 81.5% NPV (AUC = 0.85, $P \leq 0.001$). The CTP score could be used to discriminate between HE-AKI and HE patients without AKI at a cut-off level of > 11.5, with 35.3% sensitivity, 90% specificity, 77.9% PPV, and 58.2% NPV (AUC = 0.78, $P \leq 0.001$) (Table 5 and Fig. 1).

Table 4 Multi-variate logistic regression analysis for factors predictive of HE-AKI

Variables	*P* value	OR	95% CI
Age	0.094	1.05	0.99–1.1
Sex	0.058	0.29	0.08–1.04
Serum total bilirubin	0.037	1.16	1.01–1.34
Baseline serum creatinine	0.008	38.7	2.6–567.9
UACR	0.001	1.01	1.003–1.01
CTP	0.001	2.78	1.52–5.07
Length of hospital stays	0.002	9.1	2.2–37.8

HE-AKI hepatic encephalopathy-associated acute kidney injury, *OR* odds ratio, *UACR* urine albumin creatinine ratio, *CTP* Child-Turcotte-Pugh, *CI* confidence interval

Discussion

In the current study, we found that cirrhotic patients with HE had a higher incidence of AKI. Moreover, the occurrence of AKI in HE markedly increased in-hospital mortality. Increased serum total bilirubin, elevated serum creatinine, elevated UACR, higher CTP score at admission, and increased length of hospital stay predicted the development of AKI in hospitalized cirrhotic patients with HE.

Data on the incidence of HE-AKI are limited. In the current study, patients with HE had a 2-fold increase in AKI incidence compared with cirrhotic patients without HE. Based on a single study, renal function impairment (RFI) was an important prognostic factor for mortality in cirrhotic HE. Interestingly, the impact of HRS and acute renal failure (ARF) on the long-term mortality of cirrhotic HE was more deleterious than that of chronic kidney disease and end-stage kidney disease [16].

Among chronic liver disease-related hospitalizations, the crude in-hospital mortality rate is 7.4% [17]. The concurrent cirrhosis-related complications are associated with increasing in-hospital mortality rates [17]. For instance, HRS was associated with higher odds of in-hospital mortality in cirrhotic HE [17]. Based on these results, a higher in-hospital mortality rate was detected among cirrhotic HE-AKI patients in the current study. This impact of AKI on HE patients may be attributed to poor clearance of bloodstream ammonia that increases the susceptibility to brain edema in cirrhotic HE [18]. Taken together, these data suggest early diagnosis and intervention to avoid the grave outcome of AKI on cirrhotic HE.

A urine albumin/creatinine ratio ≥30 mg/g is associated with more severe liver disease, lower GFR, and worse liver transplantation-free survival in patients with decompensated cirrhosis [9]. Indeed, it was reported that albuminuria is associated with AKI in cirrhotic

Table 5 Diagnostic performance of factors predictive of HE-AKI

Risk factors	Cut-off point	AUC	Sensitivity	Specificity	PPV	NPV	*P* value
Hospital stays	> 5.5	0.83	75 %	82.4 %	81 %	76.7 %	< 0.001
Total bilirubin	> 3.1	0.73	68.75 %	66.7 %	67.4 %	68.1 %	0.005
Admission serum creatinine	> 1.05	0.74	62.5 %	66.7 %	65.2 %	64 %	0.005
UACR	> 91.5	0.85	81.25 %	82.4 %	82.2 %	81.5 %	< 0.001
CTP	> 11.5	0.78	35.3 %	90 %	77.9 %	58.2 %	0.0006

PPV positive predictive value, *AUC* the area under receiver curve, *NPV* negative predictive value

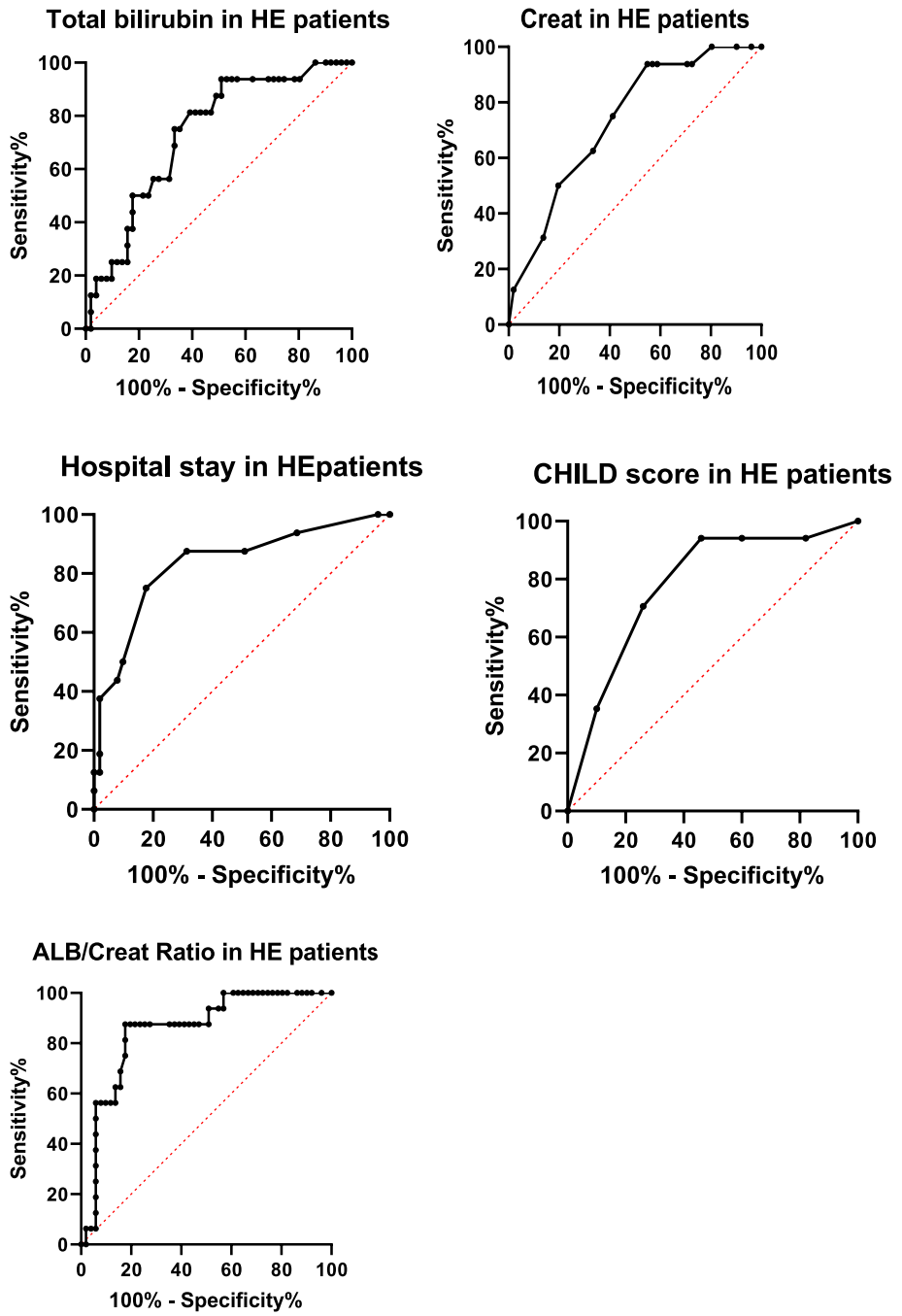

Fig. 1 Area under the receiver operating characteristic curve for predictors of HE-AKI

patients [7]. Considering this result, we first showed that UACR levels > 91.5 mg/g identified HE-AKI with reasonable sensitivity (81.25% sensitivity; AUC = 0.85, $P \leq 0.001$). Elevated UACR is associated with systemic inflammation, and recent large-scale European observational studies have shown that systemic inflammation is a hallmark of kidney injury in cirrhotic patients [19]. Indeed, it was shown that patients with HRS-AKI have marked systemic inflammation with an altered cytokine profile compared to patients with decompensated cirrhosis without AKI. Interestingly, the intensity of the inflammatory response is correlated with a lack of resolution of AKI and mortality [20]. Taken togethe, these data lent support to the speculation that the higher

UACR levels in HE-AKI may reflect greater systemic inflammation.

In pooled analysis, the MELD score and CTP stage class C were associated with an elevated risk of developing AKI, in cirrhotic patients [21–24]. Although renal function is an important component of the MELD score, and the basal MELD score was significantly higher among HE patients, it could not predict HE-AKI in our cohort. Based on our results, the severity of liver disease in HE may be underestimated by the MELD score [25, 26]. In contrast to the MELD score, HE is a component of the CTP scoring system. Indeed, HE is one of the most important complications of liver cirrhosis, and it has been related to a worse prognosis [26]. This relationship was recently confirmed in patients with acute-on-chronic liver failure [27]. Interestingly, CTP independently predicted HE-AKI in our study. Taken together, these data suggest that CTP reflects the severity of underlying liver disease in HE patients, more so than the MELD score and hence predicts HE-AKI more accurately.

Admitted cirrhotic patients with higher baseline S. Cr are at higher risk for in-hospital development of AKI and are more likely to have AKI progression with reduced survival [28]. Higher S. Cr is independently associated with AKI development [7, 29]. Interestingly, serum creatinine at admission identified HE-AKI at a cut-off level (> 1.05 mg/dl) below the upper limit of the normal laboratory reference range. It was reported that the risk for persistent kidney injury is elevated in cirrhotic patients with basal creatinine within the normal reference range (0.70 mg/dL) [30]. These data support the need for a lower clinical threshold to initiate monitoring of renal function and implementation of kidney-protective strategies in cirrhotic patients.

The limitation of our study may be related to the relatively small number of patients, and patients with AKI were not categorized according to different AKI stages.

Conclusions

Patients with cirrhotic HE are at high risk of AKI and increased in-hospital mortality. UACR estimation at hospital admission is suggested for the early prediction of HE-AKI.

Authors' contributions

A. Elbahrawy and S. Mostafa designed the work, HS and OMO collected the data , A. Mohamed , MSH, A. Alashkar, A. Alaboudy and A. Eliwa did technical support and discussion , M.S-E.R did the laboratory work , and HH supervised the work. The author(s) read and approved the final manuscript.

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Availability of data and materials

All authors have access to the entirety of the data underlying this manuscript. Access to the data can be granted at any time upon reasonable request.

Declarations

Ethics approval and consent to participate

The protocol for the research project has been approved by medical ethics committee of Al-Azhar Faculty of Medicine, and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from patients or their next of kin for being included in the study.

Competing interests

Hossam Shahbah, Osman Mohamed Osman,Sadek Mostafa, Abdelgawad Saied Mohamed, Ahmed Alashkar, Mohamed Saad-Eldeen Radwan, Mohammed Salah Hussein, Alshimaa Alaboudy, Ahmed Eliwa, Ashraf Elbahrawy Hafez Abdelhafeez declare that they have no conflict of interest.

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