Renal Doppler ultrasound and serum Cystatin C level as predictors of hepatorenal syndrome in patients with advanced liver cirrhosis and normal serum creatinine level

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Background and objectives
Patients with advanced of liver cirrhosis are liable to many serious complications as hepatorenal syndrome (HRS). This study was performed to evaluate renal resistance index (RRI) and Cystatin C (Cyst C) as predictors of HRS.

Patients and methods
The included 100 adult patients with liver cirrhosis and ascites were divided into three groups; group I with HRS (30 patients), group II with normal serum creatinine and increased RRI (40 patients), and group III with normal serum creatinine and normal RRI (30 patients). International normalized ratio, total bilirubin, albumin, creatinine, and Cyst C were measured in all enrolled candidates. Also, abdominal ultrasound was done with duplex Doppler examination of the kidneys and RRI was calculated. Group II was randomly divided into subgroups IIA and IIB where group IIA were received prophylactic therapy against HRS and group IIB did not. Both subgroups were followed for 6 months to assess their outcome and possibility to develop HRS.

Results
Serum Cyst C and RRI were significantly higher in those with HRS in comparison with other enrolled patients. There were significant correlation between serum Cyst C with RRI and estimated glomerular filtration rate. Progression to HRS and death was frequently higher in those patients who did not receive prophylactic therapy against HRS. With multivariate regression analysis; low serum albumin, increased RRI, and increased Cyst C are independent risk factors for progression to HRS while prophylactic therapy is protective against HRS in patients advanced liver cirrhosis.

Conclusion
Cyst C and RRI may be used as predictors for HRS in patients with advanced liver cirrhosis while prophylactic therapy may protect against HRS.

Keywords:
hepatorenal syndrome, resistance index, serum Cystatin CL

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Introduction

Once hepatorenal syndrome (HRS) develops in patients with advanced liver cirrhosis the outcome will be deteriorated with poor prognosis. Recent therapy includes intravenous glypressin and salt free albumin shows improvement in only 40% patients. So, accurate assessment of renal function in these patients is mandatory to determine perfect intervention and evaluate the outcome and prognosis [1,2].

The most commonly used marker to assess the glomerular filtration rate (GFR) and estimate renal function is serum creatinine. In patients with advanced liver cirrhosis, GFR will be overestimated secondary to reduced muscular mass, elevated bilirubin level may interfere with creatinine level, and reduced synthesis of creatine which is the source of creatinine [3].

Other accurate methods to estimate glomerular filtration rate (eGFR) as inulin or radioisotopes markers like ^{125}Iothalamate or ^{99}Tc-diethylene triamine pentacetic acid but these methods had many limitations as time consuming and cannot be used in daily clinical practice. Importantly, use of serum creatinine to diagnose renal dysfunction in patients with advanced liver cirrhosis may delay early diagnosis and appropriate early treatment [4].

Secondary to inaccuracy of serum creatinine level and limitations of other accurate methods, many recent studied were done to assess newer methods that might better estimate GFR as Cystatin C (Cyst C) based equation, plasma clearance of iohexol, Modified Diet in Renal Disease-4, Modified Diet in Renal

Disease-6, and Chronic Kidney Disease Epidemiology Collaboration equations [5].

Cyst C based equations have many advantages over the other methods to determine GFR as Cyst C is produced at constant rate by all nucleated cells, is filtrated completely by renal glomeruli and can be measured at serum or urine. Although Cyst C had many limitations as lacks the standard reference value, is affected by sepsis and inflammation, sex, smoking, and is produced by extrarenal sources but Cyst C based equation is considered superior to other equations for estimating GFR in patients with advanced liver cirrhosis [6].

Patients with liver cirrhosis had splanchnic arterial vasodilatation but at the same show increased renal arterial tone with decreased renal perfusion. This may be attributed to activation of the sympathetic nervous system, renin–angiotensin–aldosterone system, and antidiuretic hormone secondary to peripheral vasodilatation [7].

Renal resistance index (RRI) is used to estimate intrarenal resistance and measured by intrarenal duplex ultrasound. Patients with liver cirrhosis had higher RRI than healthy participants and those with ascites had higher value in comparison with those with liver cirrhosis only [8].

Gotzberger *et al.*[9] reported that elevated RRI predicts progression of the liver disease before occurrence of laboratory changes. Thus RRI may identify high-risk patients that need close monitoring and follow up.

The current study was designed to assess the value of serum Cyst C and RRI as predictors of HRS and role of prophylactic therapy in prevention of HRS in patients with advanced liver cirrhosis and normal serum creatinine level.

Patients and methods

Patients

This prospective study included 100 adult patients of 18–60 years old, 53 (53%) males and 47 (47%) females with liver cirrhosis and ascites admitted to Tropical Medicine and Gastroenterology Department of Al-Rajhi Liver Hospital in the period between January 2016 and December 2016 were enrolled. Diagnosis of liver cirrhosis was established by combination of clinical, laboratory, and ultrasonographic data [10].

Any patient with condition that affects such as RRI as diabetes mellitus, hypertension, spontaneous bacterial peritonitis, and gastrointestinal bleeding or condition that may affect serum Cyst C level as corticosteroid therapy were excluded. The local ethics committee approved the study. A written informed consent was obtained from all participating patients before inclusion in the study.

Methods

All enrolled patients underwent full history taking, thorough medical examination, abdominal ultrasonography, and baseline laboratory data [liver function tests, blood urea nitrogen, serum creatinine, international normalized ratio (INR), and complete blood picture]. Baseline serum Cyst C level that was measured using enzyme-linked immunosorbent assay kits by a double antibody sandwich enzyme-linked immunosorbent technique (human Cyst C, Cyst C enzyme-linked immunosorbent assay kit, catalog number: KN1364Hu; Kono Biotech Co. Ltd, Siemens; No. 205 Shijia North Road, Zhejiang, China).

Patients were examined – after 8 h fasting – by abdominal ultrasonography using ultrasound equipment with color Doppler capability using convex linear (2.5–5 MHz) (Siemens XML 300 pro, Siemens German multi-frequency curvy-linear). RRI was automatically calculated and mean RRI was calculated for each participant (mean of both kidneys) where RRI more than 0.7 was considered high [11].

To assess severity of liver disease in all patients model for end-stage liver disease (MELD) score and Child–Pugh classification were calculated. MELD score was calculated by the following formulae: MELD = 9.57 $\log_e$ [creatinine (mg/dl)]+3.78 $\log_e$ [bilirubin (mg/dl)]+11.2 $\log_e$ [INR]+6.43 (14) (Kamath *et al.*, 2001). [12,13] Also Child–Pugh classification was calculated based on patients' clinical and laboratory data (ascites, hepatic encephalopathy, serum albumin, serum bilirubin, and INR) [14].

eGFR was estimated Cockcroft–Gault formula [15]:

Based on baseline creatinine level and RRI, patients were divided into three groups:

(1) Group I: 30 patients with HRS. The diagnosis of HRS was defined according to the diagnostic criteria of New International Ascites Club [16].
(2) Group II: 40 patients with normal serum creatinine-increased renal resistance index (NC-IRRI).
(3) Group III: 30 patients with normal serum creatinine-normal renal resistance index (NC-NRRI) as a control group.

Nearly half of patients with group II (NC-IRRI) were randomly received prophylactic therapies against HRS. So, patients in this group were further subdivided into:

(1) Group IIA: 19 patients received prophylactic therapies against HRS (in form of intravenous 1 mg glypressin/6 h with salt free albumin in dose 1 g/kg/day) for 2 weeks [17].
(2) Group IIB: 21 patients did not receive prophylactic therapy for HRS.

Both subgroups were followed for 6 months from the start of the study. They were evaluated clinically, laboratory (serum creatinine), and radiologically (by Doppler ultrasound) to assess their clinical course and the possibility to progress to HRS.

Statistical analysis

Data were analyzed using SPSS, version 20 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± SD (in case of normally distributed data and compared with Student *t* test and analysis of variance) or median and range (in case of not normally distributed data and compared with Wilcoxon, Mann–Whitney, and Kruskal–Wallis tests) while nominal data was expressed in form of frequencies (percentage) and compared by χ^2 test.

Spearman's correlation coefficient and receiver operating characteristic curve with calculation of area under receiver operating characteristic curve and cutoff value with best accuracy were determined. Survival curves were evaluated and compared using the Kaplan–Meier method. Multivariate regression analysis was used to determine the independent risk factors for prediction of HRS in high-risk patients (patients with NC-IRRI). *P* value was significant if less than 0.05.

Results

Baseline demographic and clinical data

Baseline demographic and clinical data of all enrolled patients are shown in Table 1. All studied groups had predominance of males. Majority of enrolled were admitted secondary to suspicious of spontaneous bacterial peritonitis. No significant differences presented between the studied groups as regarding baseline demographic and clinical data ($P > 0.05$).

Table 1 Baseline demographic and clinical data of the studied groups of cirrhotic patients

Variables	Group I (*n*=30) (HRS)	Group II (*n*=40) (NC-IRRI)	Group III (*n*=30) (NC-NRRI)	*P*
Age (years)	55.67±6.17	55.08±4.81	54.23±4.84	0.57
Sex				
Male	16 (53.3)	21 (52.5)	20 (66.7)	0.44
Female	14 (46.7)	19 (47.5)	10 (33.3)	
Suspected SBP	20 (66.67)	20 (50)	19 (63.33)	0.33
Liver function tests				
ALT (U/l)	88 (26-177)	75 (27-177)	75 (19-167)	0.39
AST (U/l)	81 (13-88)	77 (10-95)	755 (14-78)	0.14
Total protein (g/l)	69 (60-80.7)	70 (44-87)	77 (66-88)	**0.00**
Serum albumin (g/l)	19 (16.57-29)	23.44 (13-32)	25 (18-32)	**0.02**
Total bilirubin (mmol/l)	50.49 (20-501)	41.5 (16-321)	28.5 (12-88)	**0.00**
Direct bilirubin (mmol/l)	36.35 (11-267)	23.5 (7-281)	18.5 (6-49)	**0.01**
Coagulation profile				
PT (s)	24.89 (15.5-34)	17.95 (11.7-25)	16.68 (13-23.81)	**0.00**
PC (%)	34.45 (13-54)	48.5 (28-89)	52 (33-67)	**0.00**
INR	1.6 (1.2-2.4)	1.4 (1.3-2.1)	1.3 (1.2-1.9)	**0.00**
Baseline KFTs				
Creatinine (mmol/l)	230 (145-600)	85 (37-111)	81 (37-110)	**0.00**
Urea (mmol/l)	9 (4-19)	7 (5-13)	8 (6-13)	**0.00**
eGFR (ml/min)	78.2 (66.1-101)	99.8 (90.1-112)	123 (120-134.1)	**0.01**
Child-Pugh classification				
B	0	19 (47.5)	30 (100)	**0.04**
C	30 (100)	21 (52.5)	0	
Score	9±2	8±1	6±1	**0.01**
MELD score	21 (18-26)	16 (14-19)	13 (10-14)	**0.00**

Data were expressed in form of *n* (%), mean and SD or median (range) as appropriate value was significant if<0.05. ALT, alanine aminotransferase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; HRS, hepatorenal syndrome; INR, international normalized ratio; KFTs, kidney function tests; MELD, model for end-stage liver disease; NC-IRRI, normal creatinine-increased renal resistance index; NC-NRRI, normal creatinine-normal renal resistance index; PC, prothrombin concentration; PT, prothrombin time; SBP, spontaneous bacterial peritonitis, Bold values are just to indicate that variables of these values are of significant differences between studied groups.

Baseline laboratory data

Table 1 showed baseline laboratory data of all patients. Regarding liver function tests, patients with HRS had significantly higher serum bilirubin than other two groups included in the study ($P < 0.05$). Total protein and serum albumin were significantly higher in those patients either with NC-IRRI (group II) or NC-NRRI (group III) in comparison with those with HRS ($P < 0.05$).

Prothrombin time and INR were significantly prolonged in patients with HRS (group I) while patients with NC-NRRI (group III) or NC-IRRI (group II) had higher prothrombin concentration. Renal impairment was noticed more in those patients with HRS (group I) where urea and creatinine were significantly increased while eGFR was significantly lower in those patients in comparison with other patients included in the study ($P < 0.05$). Other data were of no significant difference ($P > 0.05$).

Child score had significant difference between the three groups ($P = 0.04$) where all patients with HRS were class C, patients with NC-NRRI (group III) were class B while 19 (47.5%) and 21 (52.5%) patients in those with NC-IRRI (group II) were class B and C, respectively. MELD score was significantly higher in those patients with HRS in comparison with other patients included in the study ($P = 0.00$).

Baseline renal resistance index and serum Cystatin C

Patients either with HRS or NC-IRRI had significantly higher serum Cyst C and RRI in comparison with other patients with NC-NRRI ($P < 0.05$) (Table 2).

Serum Cyst C had significant moderate positive correlation with RRI ($P = 0.00$, $r = 0.60$) and significant strong negative correlation with eGFR ($P = 0.01$, $r=-0.70$) while a significant strong negative correlation was found between RRI and eGFR ($P = 0.01$, $r=-0.72$) (Figs. 1, 2).

Both subgroups (IIA and IIB) were followed for 6 months by RRI and serum creatinine to assess their clinical course and possibility to progress to HRS. Both subgroups were matched as regard baseline demographic, clinical, and laboratory data including serum Cyst C and RRI.

Percentage of change in serum creatinine and renal resistance index after 6 months of follow up in subgroups (group IIA and group IIB) of group II (normal serum creatinine-increased renal resistance index)

Percentage of change after 6 months of follow up in serum creatinine, and RRI in group IIA (those patients who received prophylactic therapy against HRS) was significantly lower than group IIB (those patients who did not receive prophylactic therapy against HRS) (Table 3). Group IIB had significantly higher frequency of hospital admission, death, and development of HRS in comparison with group IIA. It was noticed that HRS developed in 6/19 (31.5%) and 16/19 (76.2%) patients of group IIA and group IIB, respectively (Table 4).

It was noticed that at a cutoff point more than 0.78 mg/dl, serum Cyst C had 84.6% sensitivity, 100% specificity for detection of HRS with area under the curve was 0.91 (Fig. 3).

Survival analysis of subgroups (group IIA and group IIB) of group II (normal serum creatinine-increased renal resistance index)

It was noticed that mean disease (HRS) free survival during duration of follow up (180 days) was 135 and 111.43 days for those received therapy (group IIA) and those who did not receive therapy (group IIB), respectively, with significant ($P = 0.01$). Hazard ratio was 0.4 that means patients who were received prophylactic therapy against HRS (group IIA) had an estimated risk of development of HRS 0.4 less than those who did not receive prophylactic therapy (group IIB).

Table 2 Serum Cystatin C and renal resistance index of the studied groups of cirrhotic patients

Variables	Group I (*n*=30) (HRS)	Group II (*n*=40) (NC-IRRI)	Group III (*n*=30) (NC-NRRI)	*P*
Renal resistance index	1.22 (0.86-2.56)	1.03 (0.85-1.29)	0.59 (0.27-0.68)	0.00
Serum Cyst C (mg/dl)	0.76 (0.60-0.86)	0.74 (0.71-0.91)	0.64 (0.6-0.64)	0.00

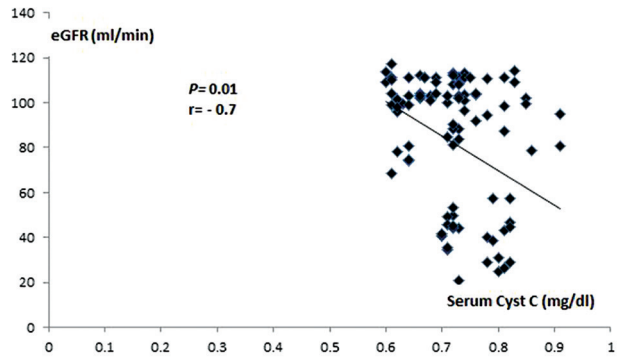
Data were not normally distributed and expressed in form of median (range). Cyst C, Cystatin C; HRS, hepatorenal syndrome; NC-IRRI, normal creatinine-increased renal resistance index; NC-NRRI, normal creatinine-normal renal resistance index; RRI, renal resistance index. $P<0.05$.

Table 3 Percentages of changes of serum creatinine and renal resistance index after 6 months of follow up in both subgroups (group IIA and group IIB) of group II (normal serum creatinine-increased renal resistance index)

Variables	Group IIA (*n*=19)			Group IIB (*n*=21)		
	Baseline	After 6 month	% of change	Baseline	After 6 month	% of change
Cr (mmol/l)	88	99	11	91	134	32
RRI	0.92	1.01	9	0.87	1.23	29

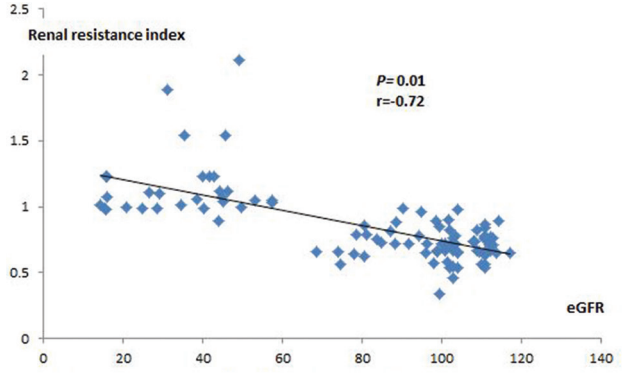
Group IIA, received prophylactic therapy; group IIB, did not receive prophylactic therapy. Cr, creatinine; NC-IRRI, normal creatinine-increased renal resistance index; RRI, renal resistance index.

Figure 1



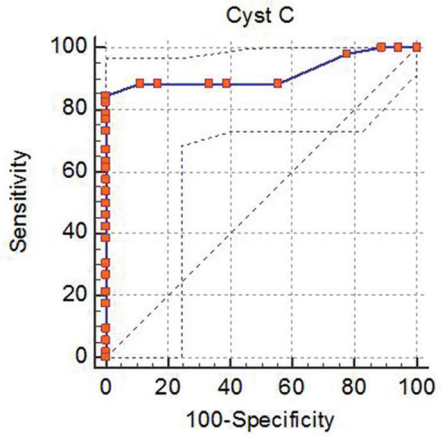
Correlation between serum Cyst C level and eGFR. Cyst C, Cystatin C; eGFR, estimated glomerular filtration rate.

Figure 2



Correlation between eGFR and renal resistance index. eGFR, estimated glomerular filtration rate.

Figure 3



ROC analysis for diagnostic indices of Cyst C for prediction of HRS. Cyst C, Cystatin C; HRS, hepatorenal syndrome; ROC, receiver operating characteristic.

The current study revealed that patients who received prophylactic therapy against HRS (group IIA) had significantly more mean of survival in comparison with those patient did not receive prophylactic therapy (group IIB) (156 vs. 122 day; $P = 0.00$). Hazard ratio (odd's ratio) was 0.7 that means patients who were received prophylactic therapy against HRS (group IIA) had an estimated risk of death 0.7 less than those who did not receive prophylactic therapy (group IIB).

Table 4 The outcome of patients of both studied subgroups (group IIA and group IIB) of group II (normal serum creatinine-increased renal resistance index)

Variables	Group IIA (*n*=19)	Group IIB (*n*=21)	*P*
Frequency of hospital admission	6 (3-9)	9 (5-12)	0.00
Development of HRS	6 (31.5)	16 (76.2)	0.01
Outcome			
Alive	12 (63)	9 (43)	0.03
Dead	7 (47)	12 (67)	

Data were not normally distributed and expressed in form of median (range) or *n* (%). Group IIA, received prophylactic therapy; group IIB, did not receive prophylactic therapy. HRS, hepatorenal syndrome; NC-IRRI, normal creatinine-increased renal resistance index. $P<0.05$.

Multivariate regression analysis for prediction development of hepatorenal syndrome in patients with normal serum creatinine-increased renal resistance index

Multivariate regression analysis showed that the independent risk factors for development of HRS in the studied group with NC-IRRI were:

(1) Low serum albumin [95% confidence interval (CI)=1.99–4.88; $P = 0.01$].
(2) Raised serum Cyst C (95% CI = 3.1–3.4; $P = 0.00$).
(3) Raised renal artery resistance index (95% CI = 2.34–3.33; $P = 0.02$).

But receiving prophylactic therapy against HRS in those patients was found to be protective factor against development of HRS in those patients with NC-IRRI (95% CI = 0.45–0.67; $P = 0.00$) (Table 5).

Discussion

HRS is one of the most serious complications that occur in patients with advanced liver cirrhosis. Usual assessment of renal impairment in those patients with serum creatinine had many drawbacks where it could be affected by BMI and bilirubin level. So, early detection of renal impairment in those patients may help in early appropriate care [3].

The current study confirms results of many previous studies about role the Cyst C early detection of renal impairment among patients with advanced liver cirrhosis [18,19]. Cyst C was significantly elevated in those patients with HRS than other patients who were enrolled in the current study.

Table 5 Multivariate regression analysis for predictors of hepatorenal syndrome

Variables	OR	95% CI	*P*
Prophylactic therapy	0.4	0.45-0.67	0.00
Low serum albumin	1.34	1.99-4.88	0.01
Raised serum Cyst C	1.99	3.1-3.4	0.00
Raised renal RI	1.67	2.34-3.33	0.02

CI, confidence interval; Cyst C, Cystatin C; OR, odd's ration; RI, renal resistance. *P*<0.05.

There was a strong significant correlation between Cyst C and eGFR (r=–07, P = 0.01). This result was consistent with other many previous studies that reported significant negative correlation between Cyst C and eGFR[20] (Mahmoud *et al.*, 2015).

Based on these findings, serum Cyst C could be on the top of markers that can be easily used for early detection of HRS in such patients. At a cutoff point more than 0.78 mg/dl, serum Cyst C had 84.6% sensitivity, 100% specificity for detection of HRS with area under the curve was 0.91. Mahmoud *et al.* (2015) reported serum Cyst C at a cutoff value of 1.2 mg/l had 89.6% sensitivity and 63.6% specificity for detection of HRS.

In the current study renal function was evaluated based on eGFR that have many limitations where it affected by age, sex, and weight, in contrast to other studies that used CrCl which is more accurate [21].

Patients with advanced liver cirrhosis had IRRI and many studies proved that patients with IRRI at baseline with normal creatinine at higher risk for development of HRS [22]. Our study showed positive strong significant correlation between serum Cyst C and RRI (r = 0.06, P = 0.00).

Consistently with Koda *et al.* [23], Cazzaniga *et al.* [24], Fouad *et al.* [25], Ustundag *et al.* [26], Popov *et al.*[27] RRI was increased with severity of liver disease where patients with HRS had higher RRI than other enrolled patients in the current study.

There are no previously reported studies about the use of intravenous glypressin and salt free albumin as a prophylaxis for HRS in cirrhotic patients with normal creatinine levels and raised RRI, perhaps due to the absence of accurate and accepted theory for the pathophysiology of HRS in addition to the lack of studies described the role of RRI in the pathophysiology of HRS.

The majority of patients who received treatment (13/19, 68.4%) did not develop HRS and majority of patients (16/21, 76.2%) who did not receive the prophylactic therapy developed HRS after 6 months follow up, prophylactic therapy (intravenous glypressin and salt free albumin) for HRS in patients with normal Cr level and IRRI may be beneficial and protect against HRS but further studies are needed. Also, mean survival and outcome were better in those patients who received prophylactic therapy.

In conclusion, findings of this study prove the great value of RRI and Cyst C in patients with advanced liver cirrhosis as predictors of HRS in such patients. Also, this study showed that prophylactic therapy of HRS may improve survival and outcome of patients with liver cirrhosis and raised RRI but further studies are needed.

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Conflicts of interest
There are no conflicts of interest.

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