



ORIGINAL RESEARCH ARTICLE

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# Role of renal Duplex ultrasonography in evaluation of hepatorenal syndrome

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## Abstract

**Background:** Hepatorenal syndrome is a potentially fatal complication of advanced liver disease. Markers for early diagnosis and identification of high-risk patients are lacking. Our aim was to evaluate the role of renal Duplex ultrasonography in the diagnosis and early prediction of hepatorenal syndrome. This study included 50 patients. Clinical assessment, liver function tests, hepatitis C virus antibody, kidney function tests, and abdominal and renal color Duplex ultrasound were done to all subjects.

**Results:** Univariate regression analysis for hepatorenal syndrome showed a statistically significant positive correlation with the Model For End-Stage Liver Disease score ( $p$ -value  $< 0.0001$ ) and renal artery hilum resistivity index ( $p$ -value = 0.0017). Logistic multivariable regression analysis proved that the renal artery hilum resistivity index was an independent predictor of hepatorenal syndrome. Renal artery hilum resistivity index can be used as a predictor of hepatorenal syndrome with 100% sensitivity and 66.7% specificity with a cut-off value  $> 0.77$ .

**Conclusion:** The renal resistive index could be a good predictor of hepatorenal syndrome.

**Keywords:** Liver cirrhosis, Renal Duplex ultrasonography, Renal resistive index

## Background

Hepatorenal syndrome (HRS) is historically viewed as a functional form of acute kidney injury (AKI) that commonly affects patients with advanced liver disease [1]. Intrarenal vasoconstriction is described to compromise glomerular filtration rate with a secondary retention of sodium and water [2]; various factors are implicated in such pathology. Peripheral vasodilatation present in advanced liver disease triggers a myriad of compensatory hormonal and neurohormonal vasoconstrictors which reduce effective renal blood flow [3]. Nevertheless, renal imaging and histology remain essentially normal [4].

Progression of AKI in this setting is an ominous sign of high mortality risk. Classic renal function tests are inconsistent in providing a measure for actual GFR in hepatic

patients [5]. Creatine and creatinine production is decreased in chronic liver disease. This renders serum creatinine falsely “low” in such patients with subsequent falsely “low” estimated GFR by any equation. Liver failure, malnutrition, aging, and decreasing muscle mass all are causes that can affect the serum level of creatinine; hence, it cannot be used as a good marker for assessment of renal impairment, especially in cirrhotic patients [6].

Diagnosis of HRS based on ICA-AKI criteria is as follows [7]: (1) diagnosis of cirrhosis and ascites, (2) diagnosis of AKI according to ICA-AKI criteria, (3) no response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g/kg of body weight), (4) absence of shock, (5) no current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.), and (6) no macroscopic signs of structural kidney injury, defined as the absence of proteinuria ( $> 500$  mg/day), absence of microhematuria ( $> 50$  red blood cells per high power field), and normal findings on renal ultrasonography.

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**Table 1** Gender distribution among patients

Gender	Patients
	Number (%)
Male	27 (54%)
Female	23 (46%)
Total	50 (100%)

Thus, diagnosis of HRS by classic methods is usually late, which prevents early intervention to improve survival. Researches into novel techniques that can diagnose early functional intrarenal hemodynamic changes are underway. Elevated renal resistive index (RRI) due to renal vascular constriction has been described in cirrhotic patients. The RRI is proposed to be a sensitive marker of intrarenal hemodynamics, and it has been reported to increase even in non-azotemic patients with cirrhosis. Thus, it can be an early marker of the functional renal impairment in such patients [8].

## Methods

### Study design and aims

This single tertiary referral center cohort prospective study aimed to evaluate the role of renal Duplex ultrasonography as a possible method in early diagnosis and prediction of HRS in patients with liver cirrhosis.

### Patients and recruitment

The study included 50 patients, aged 18 years or above, with Child C liver cirrhosis with documented normal baseline serum creatinine within 1 year prior to AKI. The patients were randomly selected among a group of patients presenting to the emergency room unit and admitted to the Department of Internal Medicine in Kasr Al Ainy Hospital during the period from January 2018 to July 2019.

Patients with confirmed pregnancy, prior kidney or liver transplant, known hypertensive patients, or other known causes of renal insufficiency such as advanced chronic kidney disease (CKD): baseline creatinine > 4.0 mg/dl, acute or chronic renal replacement therapy, diabetic nephropathy, glomerulonephritis, urinary tract obstruction, and urinary tract infection were excluded from the study.

We diagnosed HRS based on ICA-AKI criteria as mentioned before [7].

**Table 2** Age distribution among patients

Age	Mean	SD	95% confidence interval for mean	
			Lower bound	Upper bound
Patients	59.72	8.1	57.4	62.02

**Table 3** Child-Turcotte-Pugh and MELD scores of the patients

Variables	Median	IQR
Child score	10	2
MELD	19	7

## Methods

Patients with liver cirrhosis were randomly selected irrespective of the presenting symptom, hepatic status, and presence of complications. All these patients were subjected to thorough history taking and clinical examination including age, gender, comorbid diseases (diabetes, hypertension, and dyslipidemia), concomitant medications (renin-angiotensin-aldosterone system (RAAS) blockade and diuretics), and symptoms and signs of hepatic decompensation. Patients were evaluated using the Child-Pugh score and Model for End-Stage Liver Disease (MELD) score.

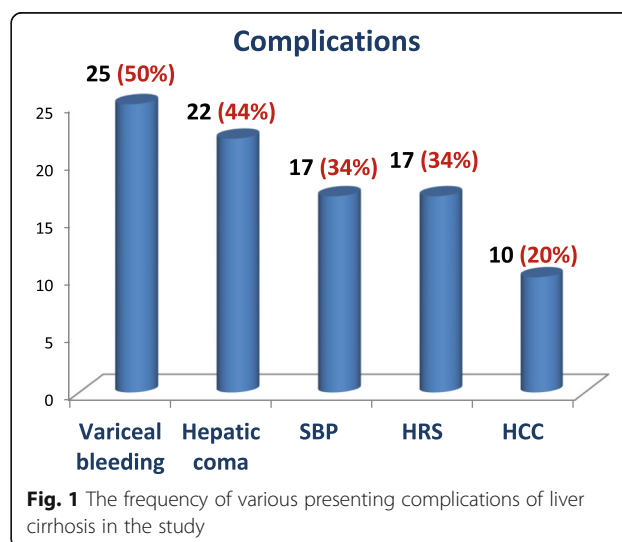
### Laboratory investigations

Patients' preparation: diuretics were stopped in all patients, at least 24 h before laboratory testing. Patients were advised to adopt a low sodium diet (less than 40 mmol/day).

A fresh 10-ml blood sample was collected daily. Laboratory tests were performed in Kasr Al Ainy Chemical Pathology Central Lab and included liver function tests, HCV antibody, and kidney function tests.

Creatinine was measured from samples collected as part of routine clinical care in our institution inpatients. Laboratory measurements were performed by personnel blinded to patient information.

Creatinine clearance (CLCr) was calculated by CrCl Cockcroft Gault equation  $C_{Cr} = \{[(140 - \text{age}) \times \text{weight}] / (72 \times S_{Cr})\} \times 0.85$  (if female). eGFR was calculated by the MDRD formula [9].



**Table 4** Ultrasonographic features of the patients included

		Number	Percent, %
PVT	No	44	88%
	Yes	6	12%
Ascites	No	4	8%
	Mild	3	6%
	Moderate	3	6%
	Severe	17	34%
	Marked	23	46%
Ascites echoes	No	33	66%
	Yes	17	34%
Echogenicity	No	41	82%
	Yes	9	18%
Number of focal lesions	0	40	80%
	1	8	16%
	3	2	4%

PVT portal vein thrombosis

Abdominal ultrasound (US) and Duplex renal ultrasound were done using IU 22, Philips machine. A convex probe (C5-1 Hz) was used and US was done to all patients to confirm the presence of cirrhosis; to assess portal vein, hepatic artery and vein diameter, the presence or absence of portal vein thrombosis, and splenic size; to confirm the presence or absence of ascites and its degree; to confirm the presence of focal lesions of the liver and spleen; and to assess kidney size, volume, and echogenicity.

Duplex renal ultrasonography was also done to all patients by direct visualization of the renal arteries from the origin up to the interlobar arteries.

The renal resistive index (RRI) was evaluated along renal arteries up to interlobar arteries. RRI was calculated automatically by the machine as we measured the peak systolic and end-diastolic velocities of the different arteries.

We also determined the renal aortic ratio (RAR) which is the ratio of the PSV in the renal artery at the origin to the PSV in the aorta (at renal artery level) to exclude a diagnosis of renal artery stenosis.

**Table 5** Kidney function tests of the included patients

Variables	Median	IQR
Serum creatinine (mg/dl)	1.28	0.85
Blood urea (mg/dl)	57.9	50.5
Serum Na (mEq/l)	136	11
Serum K (mEq/l)	4	1
eGFR (ml/min/1.73m <sup>2</sup> )	56.01	44.8
Cr clearance (ml/min)	58.76	37.13

Na sodium, K potassium, eGFR estimated glomerular filtration rate, Cr clearance creatinine clearance

**Table 6** Correlation of hepatorenal syndrome and patients' variables

HRS	Correlation coefficient	p-value
MELD	0.605	<0.0001
HCC	0.274	0.054
Focal lesions	0.269	0.059
CREAT (mg/dl)	0.8	<0.0001
UREA (mg/dl)	0.62	<0.0001
eGFR (ml/min/1.73m <sup>2</sup> )	-0.756	<0.0001
Cr Clearance(ml/min)	-0.755	<0.0001
PO4 (mg/dl)	0.368	0.001
Mg (mg/dl)	0.48	0.001
UA (mg/dl)	0.422	0.002
PVT	0.385	0.006
K long D (mm)	-0.474	0.001
K volume (mm)	-0.537	<0.0001

p value is considered significant when its value < 0.05

The patients were followed up for 1 month by clinical evaluation of any deteriorating symptoms or lab profile.

### Statistical methodology

The analysis of our data was performed using IBM computer exploiting SPSS (Statistical Program for Social Science version 12) as follows: description of quantitative variables as mean, SD, and range. Description of qualitative variables was done as number and percentage. A chi-square test was used to compare qualitative variables between groups. An unpaired *t*-test was used to compare quantitative variables, in parametric data (SD<50% mean). The Mann-Whitney-Willcoxon *U* test was used in nonparametric data instead of an unpaired *t*-test. One-way ANOVA (analysis of variance) was used to compare more than two groups as regard quantitative variable. The Kruskal-Wallis test was used instead of the ANOVA test in non-parametric data SD>50% mean. Spearman correlation test was used to rank variables versus each other positively or inversely. Logistic regression analysis was used to find out the significant independent predictors of the dependent variable using the

**Table 7** Correlation of hepatorenal syndrome with Duplex findings

HRS	Correlation coefficient	p-value
PSV(O) cm/s	-0.271	0.012
PSV(H) cm/s	-0.149	0.175
RI (H)	0.514	0.000
RI (interlobar)	0.201	0.065

p value is considered significant when its value < 0.05

RAV O renal artery at the origin, RAV H renal artery at the hilum, PSV peak systolic velocity, RI resistivity index

**Table 8** Univariate regression analysis for hepatorenal syndrome

HRS	Coefficient	Odds ratio	95% CI	p-value
MELD	0.328	1.38	1.14–1.7	<0.0001
PSV(O) cm/s	−0.018	0.934	0.95–1.01	0.229
PSV(H) cm/s	−0.0005	0.99	0.97–1.06	0.6234
RI (H)	18.37	95.2	49–181	0.0017
RI (interlobar)	−8.8	0.000	0–0.04	0.0005

p value is considered significant when its value < 0.05

backward likelihood ratio technique. In this context,  $p$ -value > 0.05 was considered as insignificant,  $p$  < 0.05 as significant, and  $p$  < 0.01 as highly significant.

### Ethical consideration

The study was approved by the institution ethical committee and form review board of Kasr Al Ainy Hospital. Oral and written informed consents were obtained from all subjects or from their eligible relatives.

The medical record profession has its own code of ethics which applies to all medical record practitioners. Confidentiality of data, safe data storage, and privacy rights are respected by all who handle patient information. Data was coded and patient names or identity was not appearing in any of data collection forms or during statistical analysis.

### Results

The study cohort included 27 males (54%) and 23 females (46%) (Table 1), their age ranged from 41 to 86 years (mean = 59.72) (Table 2), the Child score ranged from 10 to 14, and the MELD score ranges from 11 to 38 (Table 3). Seventeen of them were diagnosed with HRS based on ICA-AKI criteria.

The frequency of various presenting complications of liver cirrhosis is shown in Fig. 1.

Abdominal ultrasound revealed portal vein thrombosis in 6 patients (12%) and ascites in 46 patients (92%) (Table 4).

The total number of patients who completed the study till the end was 48 patients while 2 female patients dropped out due to mortality. Both patients presented with HRS and hepatic encephalopathy, with Child scores 11 and 14 and MELD 29 and 38, respectively.

Kidney function tests of the patients in the study cohort are shown in Table 5.

**Table 9** Logistic multivariable regression analysis for hepatorenal syndrome

Independent variables	Coefficient	Odds	p-value
RI (H)	58.8	35.4	0.0337

There was no statistically significant difference in the ultrasonographic data of patients as regards kidney diameters, volume, and echogenicity. All were within the normal range.

There were a positive correlation of HRS, MELD, HCC, focal lesions, creatinine, urea, PO<sub>4</sub>, Mg, UA, and PVT and a negative correlation with others using Spearman's rho test as shown in Table 6.

When correlating HRS with Duplex findings, it showed a positive correlation with the resistive index (RI) at the hilum of the kidney (RAH) and interlobar artery (RI) and a negative correlation with renal artery peak systolic velocity at the origin PSV(O) and hilum PSV(H) using Spearman's rho test (Table 7). Univariate regression analysis showed a statistically significant association between HRS on one side and each of MELD, RAH (RI), and interlobar artery (RI) on the other. There were no significant associations as regards other variables (Table 8).

Multivariable regression analysis proved that RI (H) was an independent predictor of HRS (Table 9).

When comparing HRS with the non-HRS group, we found that there was a statistically significant difference as regards MELD and RI (H) (RI).

Diagnostic accuracy of RI (H) for predicting HRS showed 64.6% positive predictive value with 45.05–80.36 for 95% CI as illustrated in Table 10.

Receiver operating characteristic (ROC) curves for the assessment of sensitivity, specificity, and optimum cut-off values for RI (H) as a predictor of HRS are shown in Table 11 and Fig. 2 that showed that renal artery RI can be used as a predictor of HRS with 100% sensitivity and 66.7% specificity (cut-off value >0.77).

### Discussion

Our study showed that HRS has a statistically significant positive correlation with MELD and RI (H) by univariate regression. Renal RI is therefore linked to the progression of liver disease. This association is a reflection of the aforementioned pathological mechanisms that are closely associated to advancing liver disease.

The present study also showed that renal artery RI can be used as a predictor of HRS with 100% sensitivity and 66.7% specificity (cut-off value >0.77). Renal artery (hilum) RI has got a higher positive predictive value reaching 64%. Duplex renal ultrasonography of two of our studied hepatorenal patients showed a high RRI as in Figs. 3 and 4.

This data is very promising in the context of prediction, early diagnosis, and early management of HRS.

**Table 10** Predictive values for HRS

Variables	PPV	95% CI	NPV	95% CI
RI (H)	64.6%	45.05–80.36	81.8%	69.85–89.73

PPV positive predictive value, NPV negative predictive value

**Table 11** Cut-off values, sensitivity, specificity, and AUC for hepatorenal syndrome

Variables	Criterion	Sensitivity	Specificity	AUC	p-value
RI (H)	>0.77	64.7%	81.8%	0.76	0.0007

AUC area under the curve

Renal RI may appear to be a simple, efficient, and non-invasive tool to use at the patient bedside. The feasibility of the measure is good, even in the settings of critically ill patients. However, a well-trained competent sonographer must perform the renal Duplex as it is very difficult to assess in irritable ascitic patients.

It was also demonstrated by Sameh et al. [10] in a study that included 120 patients with HCV liver cirrhosis and showed that RRI was correlated with liver cirrhosis severity and had a comparable prognostic value to the MELD score. Götzberger et al. [11] have also shown that the RRI had comparable sensitivity and specificity to the MELD score. The study also demonstrated a link of elevated renal RI to poor survival. El-Shazly et al. [12] reported that RRI was significantly higher in Child-Pugh C patients than in Child-Pugh B or A patients.

The optimum cut-off value for RA RI defined in this study is similar to a few similar studies done close to that field. Kastelan et al. [13] found that the average value of the interlobar arterial resistive index in patients with hepatorenal syndrome ( $0.74 \pm 0.01$ ) was statistically significantly higher than the interlobar arterial resistance index values measured in liver cirrhosis patients without the signs of azotemia ( $0.65 \pm 0.03$ ) or in those with liver

cirrhosis and kidney dysfunction, but without hepatorenal syndrome ( $0.67 \pm 0.01$ ). In all patients with hepatorenal syndrome, the value of the interlobar arterial resistance index was over 0.70.

Goyal et al. [11] showed that RI was significantly higher in cirrhotic patients than in healthy controls ( $0.62$  vs.  $0.52$ ,  $p < 0.01$ ). It was also higher in patients with ascites than in those without ( $0.70$  vs.  $0.62$ ,  $p < 0.01$ ). His cut-off value was RI  $> 0.70$  as a significant independent predictor of subsequent HRS development ( $p = 0.006$ ).

More importantly, this study included ten patients with normal kidney function tests that were classified as Child C with a high renal RI. This number represented around 32% of cirrhotic patients with normal kidney functions and “no” HRS. They also represent 37% of patients with elevated RI in this study cohort (the rest developed HRS). They define the most important subgroup of patients to be targeted via this study. We believe they are a “high risk” category to develop HRS. Early changes in intrarenal hemodynamics were detected by renal RI before HRS sets in, so elevated RRI can be a predictor for early renal impairment before laboratory affection.

This is in agreement with Platt et al. [14] who concluded that normal serum creatinine levels may be associated with a significantly decreased glomerular filtration rate and that more than 50% of patients with end-stage liver disease and increased renal RI have normal serum creatinine levels. Also, Corradi et al. [15] had suggested that cortical blood flow redistribution and an increase in renal vascular resistance may be early sensitive signs of an impending hemodynamic deterioration, even in apparently stable patients.

The identification of this “high-risk” subgroup of patients with normal kidney function tests would enable practitioners to employ preventive strategies and closer follow-up as well as prompt management of HRS. This will ultimately lead to a better outcome.

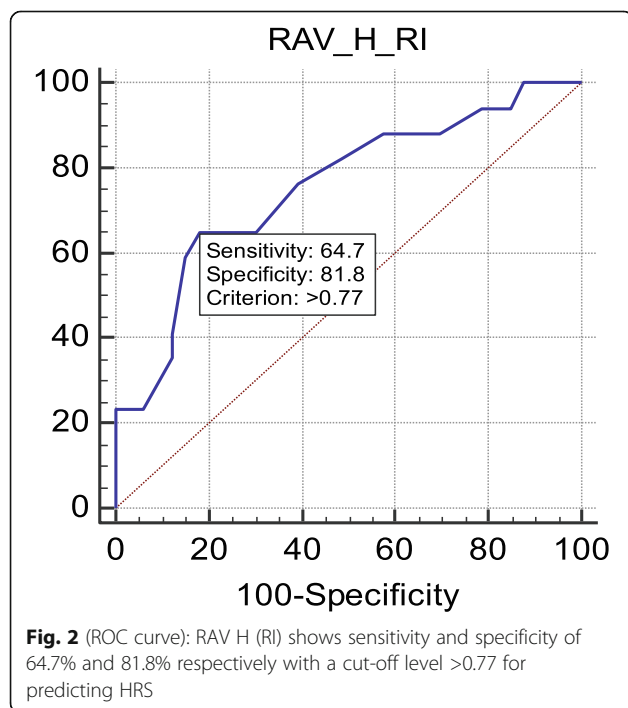
### Further investigations

The subgroup of non-HRS patients with RRI beyond cut-off values are to be put under close follow-up and regarded as a high-risk group for HRS development.

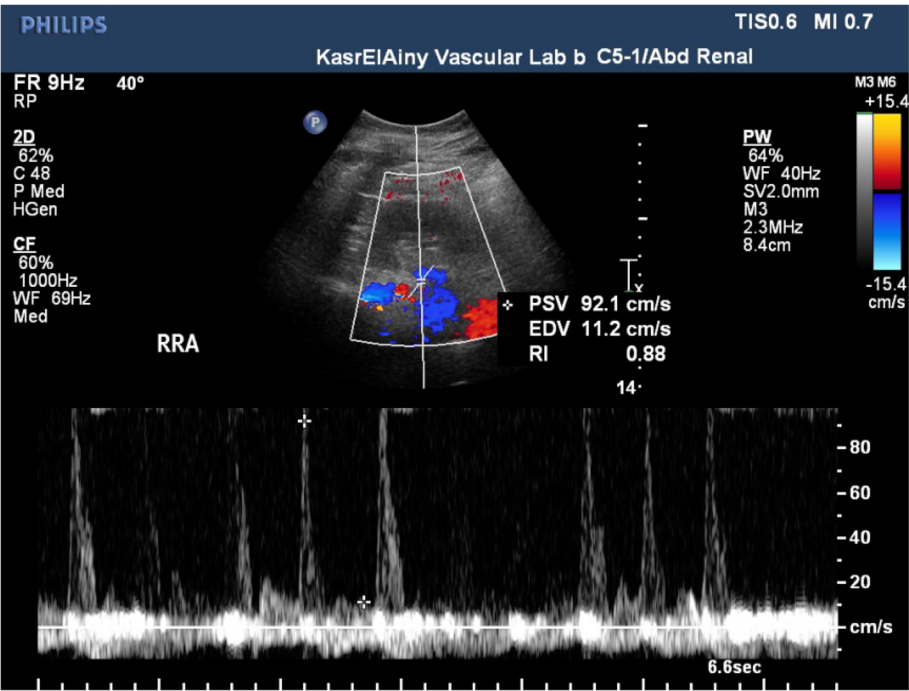
The value of renal RI as a predictor of HRS occurrence and progression needs to be verified in multiple cohorts. Future studies are suggested to add the assessment of HRS patient outcomes and analyze their association to renal resistivity index.

### Conclusions

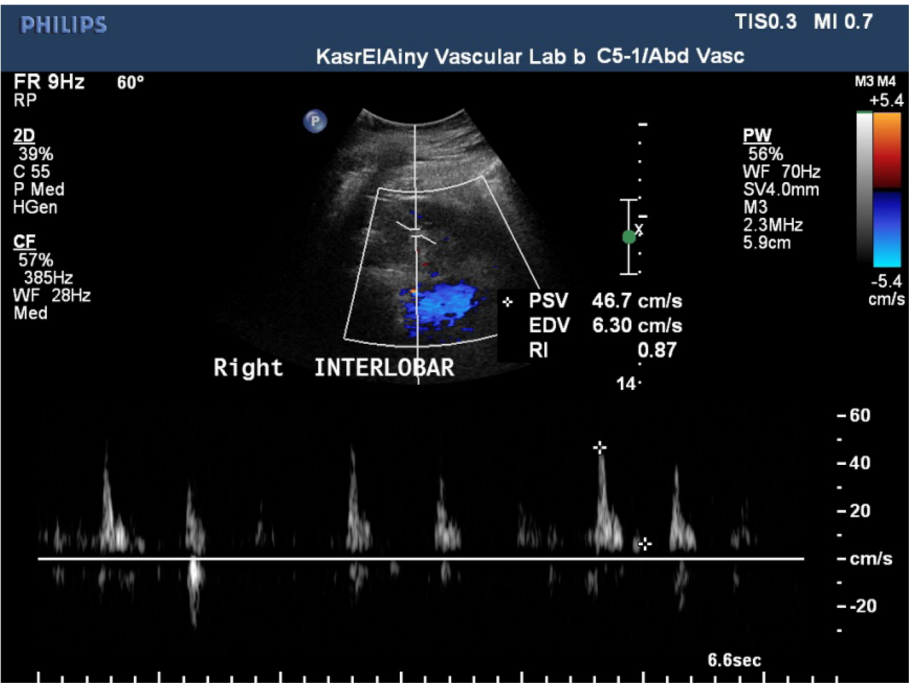
We conclude that Duplex ultrasound of renal arteries is a simple, effective, and non-invasive method which enables the early detection of renal hemodynamic disturbances in patients with liver cirrhosis even before renal dysfunction becomes clinically evident. It also makes







**Fig. 3** Color Doppler renal ultrasonography of a patient with HRS with high RI at the hilum



**Fig. 4** Color Doppler renal ultrasonography of a patient with HRS with high RI at the right interlobar artery

possible the identification of a subgroup of patients with liver cirrhosis who are at higher risk for developing hepatorenal syndrome.

We suggest that renal Duplex can be used as a simple and non-invasive tool to predict HRS.

## Recommendations

Renal Duplex ultrasound can be used as a screening tool in Child C liver cirrhosis patients for early detection of HRS to improve prognosis. However, more studies are recommended for the development of new markers aiming at improving the ability of early detection of HRS in patients with liver cirrhosis.

## Abbreviations

AKI: Acute kidney injury; CKD: Chronic kidney disease; CLCr: Creatinine clearance; GFR: Glomerular filtration rate; HRS: Hepatorenal syndrome; MELD: Model for End-Stage Liver Disease; PSV: Peak systolic velocity; RAAS: Renin-angiotensin-aldosterone system; RAR: Renal aortic ratio; ROC: Receiver operating characteristic; RRI: Renal resistive index; US: Abdominal ultrasound

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## Authors' contributions

MS analyzed and interpreted the patients' data and general supervision of the research group. SA analyzed and interpreted the patients' data and performed the Doppler examination. SM participated in the interpretation of the data of the patients. SE analyzed and interpreted the patients' data and statistical analysis. NE participated in the interpretation of the data of the patients. UM analyzed and interpreted the data of the patients and helped in writing the manuscript. AA was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

Not applicable

## Declarations

### Ethics approval and consent to participate

The study was approved by the institution ethical committee and form review board of Kasr Al Ainy Hospital. Oral and written informed consents were obtained from the patient or from his eligible relatives. The ethical approval number and date are not available.

### Consent for publication

Oral and written informed consents were obtained from the patient or from his eligible relatives.

### Competing interests

The authors declare that they have no competing interests.

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