A Pilot Study to Evaluate Renal Hemodynamics in Cirrhosis by Simultaneous Glomerular Filtration Rate, Renal Plasma Flow, Renal Resistive Indices and Biomarkers Measurements


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Key Words
End-stage liver disease · Glomerular filtration rate · Renal plasma flow · Renal resistive index · Cystatin C · β-Trace protein · β₂-Microglobulin · Kidney injury molecule-1 · Neutrophil gelatinase-associated lipoprotein

Abstract
Background: Renal hemodynamic measurements are complicated to perform in patients with cirrhosis, yet they provide the best measure of risk to predict hepatorenal syndrome (HRS). Currently, there are no established biomarkers of altered renal hemodynamics in cirrhosis validated by measured renal hemodynamics. Methods: In this pilot study, simultaneous measurements of glomerular filtration rate (GFR), renal plasma flow (RPF), renal resistive indices and biomarkers were performed to evaluate renal hemodynamic alterations in 10 patients with cirrhosis (3 patients without ascites, 5 with diuretic-sensitive and 2 diuretic-refractory ascites). Results: Patients with diuretic-refractory ascites had the lowest mean GFR (36.5 ml/min/1.73 m²) and RPF (133.6 ml/min/1.73 m²) when compared to those without ascites (GFR 82.9 ml/min/1.73 m², RPF 229.9 ml/min/1.73 m²) and with diuretic-sensitive ascites (GFR 82.3 ml/min/1.73 m², RPF 344.1 ml/min/1.73 m²). A higher mean filtration fraction (FF) (GFR/RPF 0.36) was noted among those without ascites compared to those with ascites. Higher FF in patients without ascites is most likely secondary to the vasoconstriction in the efferent glomerular arterioles (normal FF ∼0.20). In general, renal resistive indices were inversely related to FF. While patients with ascites had lower FF and higher right kidney main and arcuate artery resistive indices, those without ascites had higher FF and lower right kidney main and arcuate artery resistive indices. While cystatin C and β₂-microglobulin performed better compared to Cr in estimating RPF, β-trace protein, β₂-microglobulin, and SDMA, and (SDMA+ADMA) performed better in estimating right kidney arcuate artery resistive index. Conclusion: The results of this pilot study showed that identification of non-invasive biomarkers of reduced RPF and increased renal resistive indices...
Introduction

The estimated prevalence of acute and chronic kidney diseases (CKD) among hospitalized patients with cirrhosis is reported to be 20% [1]. Acute kidney injury (AKI) in cirrhosis is associated with high morbidity and mortality [2–4]. In particular, hepatorenal syndrome (HRS), a specific cause of AKI [5] due to severe reduction of renal blood flow [1, 4, 6–9], may lead to consequent acute tubular necrosis (ATN) requiring renal replacement therapy. Without liver and possibly simultaneous liver-kidney transplantation, HRS is frequently fatal [1, 4, 6]. Based on Organ Procurement and Transplantation Network data as of February 21, 2014, 8% of all adult liver transplants performed in 2012 were simultaneous liver-kidney transplants (excluding simultaneous liver-kidney-heart, liver-kidney-intestine, liver-kidney-pancreas, liver-kidney-pancreas-intestine) [10].

Current treatments of HRS include splanchnic vasoconstrictors (octreotide, terlipressin), α-agonists and albumin. These treatments are effective in fewer than 50% of patients with cirrhosis [3, 4]. The lack of efficacy in the treatment of HRS is likely due to delays in the administration of splanchnic vasoconstrictors caused by the limitation of the current diagnostic criteria of HRS [11]. There is no gold standard method to diagnose HRS; it is largely a diagnosis of exclusion. It can also be superimposed on anatomical kidney diseases, or functional changes in renal function such as prerenal azotemia due to gastrointestinal bleeding, further complicating the diagnosis. Existing methods to identify reduced renal blood flow in cirrhosis that are clinically practical have limited accuracy [11]. First, serum creatinine (Cr) is not a sufficiently accurate marker of kidney function in cirrhosis [12], yet current diagnostic criteria for HRS is based on serum Cr [5]. Furthermore, reduction in renal blood flow, particularly renal cortical blood flow, is a key phenomenon in the development of HRS and may precede the increase in Cr and decline in glomerular filtration rate (GFR) [13]. Second, current criteria [14] are inadequate to diagnose HRS in subjects with cirrhosis and underlying CKD who already have elevated Cr levels [5, 11]. Third, these criteria traditionally require 2 days of albumin administration to differentiate hypovolemia-induced prerenal azotemia from HRS [14]. Waiting for 2 days to determine the effects of albumin infusion can cause substantial delays in initiation of vasoconstrictor treatment in HRS and reduce the efficacy of existing treatments [11]. Differentiation of prerenal azotemia from HRS may not be the best strategy, as cirrhotics can have combined HRS and hypovolemia-induced azotemia [11].

Currently, there are no established biomarkers of altered renal hemodynamics in cirrhosis validated by measured GFR and renal plasma flow (RPF) measurements. The primary objective of this pilot study was to assess renal hemodynamic levels in different stages of cirrhosis using a gold standard invasive assessment and determine whether novel non-invasive biomarkers including cystatin C, β-trace protein, β2-microglobulin and dimethylarginines were more accurate estimators of altered renal hemodynamics compared to Cr in patients with cirrhosis.

Methods

Study Participants

Between September and December 2013, patients with cirrhosis were recruited from the University of Maryland Medical Center. Inclusion criteria were having cirrhosis based on either liver histopathology or clinical, laboratory and radiological results, and being 18 years of age or older at the time of enrollment. Exclusion criteria included inability to give informed consent and cognitive impairment; being pregnant or breastfeeding; allergy to iothalamate, iodine, iodine-containing radiographic contrast media or p-aminohippurate (PAH); untreated active hyperthyroidism, thyroid autonomy, multinodular goiter, or ongoing treatment with radioactive iodine limitations for voiding or collecting urine; renal failure treated with dialysis or estimated GFR <15 ml/min/1.73 m²; treatment with corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) except any daily dose of aspirin <325 mg daily within 1 week of enrollment; any change in the dose of diuretics, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers or new onset of diuretic, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers use within 1 week of enrollment; acute onset of infection, hospitalization due to exacerbation of encephalopathy, acute gastrointestinal bleeding, AKI within 1 week of enrollment; acute cardiovascular or cerebrovascular disease diagnosed within 3 weeks of enrollment; history of transjugular intrahepatic portosystemic shunt placement, and previous kidney or liver transplantation.

The study was approved by the Institutional Review Board of the University of Maryland, Baltimore, and all study subjects provided written informed consent.

Study Visits and Procedures

The study included a screening visit that was conducted either at the University of Maryland Medical Center clinics or General Clinical Research Center (GCRC) and a procedure visit that was...
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Conducted at the GCRC. During screening visit, subjects were enrolled in the study and had a complete history and physical examination taken. They were instructed to have an overnight fast prior to the procedure day except they were allowed to take water and medications. If they were diabetic, they were asked to fast only for 2 h.

The 6-hour procedure visit was scheduled in GCRC within 1–3 weeks of screening visit. On the procedure date, after consuming 500 ml of water, subjects underwent simultaneous measurements of RPF, GFR, renal resistive indices and biomarkers. The procedures and methods were as follows:

**RPF Measurement.** RPF was measured by PAH clearance as described in Wang et al. [15]. After an IV loading dose of 200 mg (1 ml), subjects received a constant infusion to achieve steady-state PAH plasma concentration of 20 mg/l. All subjects received PAH infusion at 60 ml/h. The desired maintenance doses were based on the subjects’ screening GFR estimated by Modification of Diet in Renal Disease (MDRD) Study equation [16]. A 5-ml blood sample was collected in heparinized tubes before and at 5, 15, 30, 45, 60, 120, 180, 240 and 360 min after the initiation of PAH administration. Following a pre-PAH urine collection, spontaneous urine collections were obtained at 0–60, 60–120, 120–180, and 180–360 min after starting the PAH infusion and urine volume collected at each time point was measured and 3 ml was transferred into a test tube. Plasma and urine samples were harvested by centrifugation, and aliquots stored at −20°C until analysis. Plasma and urine PAH concentrations were determined using high performance liquid chromatography (HPLC) assay method [17]. RPF was calculated as the average renal clearance of PAH during the 360-min urine collection period: Renal PAH clearance = (Amount of PAH excreted) / (Area under the plasma PAH concentration vs. time curve) x–y, where x–y was the time interval of the urine collection period.

**GFR Measurement.** GFR was measured by non-radiolabeled iothalamate plasma clearance as described in Mindikoglu et al. [18]. The same blood samples as collected for RPF measurements were used for the GFR measurements. Plasma concentrations of iothalamate were determined by reversed-phase HPLC with ultraviolet detection as described by Dowling et al. [17]. Plasma iothalamate concentration versus time curve was modeled based on a two-compartment model [19] applying iterative least-square method using WinNonlin® version 5.1 (Certara LP (Pharsight), St. Louis, Mo., USA).

**Measurement of Renal Resistive Indices.** Duplex Doppler ultrasonography of both kidneys was performed using the Philips Healthcare iU22 Ultrasound System with C5-1 convex transducer. Duplex waveforms of the main, segmental, interlobar and arcuate arteries were assessed in the upper, mid and lower poles in both kidneys and peak systolic velocity, end-diastolic velocity and resistive indices were measured simultaneously with GFR and RPF measurements. Renal resistive index was calculated as [(peak systolic velocity – end-diastolic velocity)/peak systolic velocity] [20]. Two repeated measurements were taken from each renal artery; renal resistive index of each artery was reported as the mean value of these two measurements. Final resistive index was reported as the mean value of the mean resistive indices of the upper, mid and lower segmental, interlobar and arcuate arteries (e.g. arcuate artery resistive index reported in the analysis was equal to the mean value of the mean resistive indices of the upper, mid and lower arcuate arteries). Duplex Doppler ultrasonography of all patients was performed by the same sonographer.

**Measurement of Systemic Hemodynamics.** Subjects’ intravascular volume status was assessed by measuring inferior vena cava (IVC) diameter during expiration using ultrasonography simultaneously with GFR and RPF measurements. Three measurements were taken from the IVC; IVC diameter was reported as the mean value of these three measurements.

**Renal Hemodynamic Biomarkers.** Pre-RPF/GFR blood samples were collected for symmetric (SDMA) and asymmetric dimethylarginine (ADMA), l-arginine, renin and aldosterone levels, SDMA, ADMA, l-arginine were measured using a Diagnostika® standard ELISA method [21, 22], renin using a Renin Human ELISA method (BioVendor Research and Diagnostic Products) [23] and aldosterone using an ELISA method (BioVendor Research and Diagnostic Products) [24].

**Filteration Markers.** Pre-RPF/GFR blood samples were collected for Cr, cystatin C, β-trace protein, β2-microglobulin measurements. Cr, cystatin C and β2-microglobulin concentrations were measured using Siemens Dimension Vista® System Flex® reagent cartridge (Siemens Healthcare Diagnostics, Inc., Newark, Del., USA) [25–27]. β-Trace protein was measured using N Latex βTP assay using Siemens ProSpec® nephelometer (Siemens Healthcare Diagnostics, Inc.) [28] at the University of Minnesota Advanced Research and Diagnostic Laboratory.

**Other Laboratory Tests.** Pre-RPF/GFR blood samples were collected for basic metabolic panel, complete blood count with differential, hepatic panel consisting of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and direct bilirubin, alkaline phosphatase (ALP), albumin, globulin, and total protein; prothrombin time (PT)/international normalized ratio (INR) and C-reactive protein.

**Urine Tests.** Pre-RPF/GFR urine samples were collected for microscopic analysis, Cr and protein to calculate spot urine protein to Cr ratio, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipoprotein (NGAL). NGAL was measured using Quantikine® ELISA Human Lipocalin-2/NGAL Immunoassay (RD Systems, Inc.) [29] and KIM-1 using Human KIM-1 ELISA Kit (Aviscera Bioscience, Inc.) [30].

**Statistical Analysis**

For statistical analyses, we used SAS Version 9.2 (SAS, Cary, N.C., USA) [31] and Minitab (Minitab, Inc., State College, Pa., USA) [32] statistical software. Linear regression analysis was performed to assess the performance of renal biomarkers to predict RPF and renal arcuate artery resistive index.

**Results**

**Study Participants**

A total of 14 subjects with cirrhosis were enrolled in the study; 10 out of 14 (7 men and 3 women; age ranging from 45 to 69) completed all study procedures. Table 1 shows clinical and laboratory characteristics of 10 patients with cirrhosis. Seven patients had hepatitis C cirrhosis and 3 alcohol cirrhosis. Three patients had no as-

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cites, 5 diuretic-sensitive ascites and 2 diuretic-refractory ascites. While the lowest Model for End-Stage Liver Disease (MELD) score was 8, the highest was 19. All patients except 1 (spot urine protein to Cr ratio 0.25) had a spot urine protein to Cr ratio <0.2, suggesting no evidence for clinically significant glomerular disease. No patient’s urine KIM-1 and NGAL level was greater than the optimal cut points of KIM-1 (15.4 ng/ml = 15,400 pg/ml) and NGAL (365 ng/ml) that differentiates ATN from non-ATN as described by Belcher et al. [33].

**Renal Hemodynamics**

Table 2 shows GFR and RPF measured simultaneously with renal resistive indices of main, segmental, interlobar and arcuate arteries of both kidneys. No subjects had evidence of volume depletion or overload; mean IVC diameter was 1.61 cm, ranging from 1.07 to 2.19 cm. In general, filtration fraction (FF) (GFR/RPF) was lower and renal resistive indices were higher in patients with ascites compared to those without ascites (table 3). A higher mean FF (0.36) was noted among those without ascites.
compared to those with ascites (table 3). Patients with diuretic-refractory ascites had the lowest mean GFR (36.5 ml/min/1.73 m²) and mean RPF (133.6 ml/min/1.73 m²) when compared to those without ascites (GFR 82.9 ml/min/1.73 m², RPF 229.9 ml/min/1.73 m²) and with diuretic-sensitive ascites (82.3 and 344.1 ml/min/1.73 m²) (table 3).

### Renal Resistive Indices

As shown in table 3, mean renal resistive indices were higher in cirrhotics with ascites compared to those without ascites. In general, renal resistive indices, particularly right kidney arcuate artery resistive indices, showed medium level negative correlation with FF (Pearson correlation coefficient $r = -0.44$, $p = 0.20$) (fig. 1); while patients with ascites had lower FF and higher right kidney main and arcuate artery resistive indices, those without ascites had higher FF and lower right kidney main and arcuate artery resistive indices (fig. 2–4). We observed similar findings with left kidney main and arcuate artery resistive indices.

### Biomarkers

Additionally, we measured renal biomarkers including serum Cr, cystatin C, β-trace protein, β₂-microglobulin, SDMA, ADMA and L-arginine simultaneously with GFR, RPF and renal resistive indices.

In terms of estimating RPF, the linear regression fit was better for cystatin C ($R^2 = 0.43$, $p = 0.038$), β-trace protein ($R^2 = 0.35$, $p = 0.073$) and β₂-microglobulin ($R^2 = 0.46$, $p = 0.030$) compared to Cr ($R^2 = 0.31$, $p = 0.094$), SDMA ($R^2 = 0.27$, $p = 0.124$), the sum of SDMA and ADMA (SDMA + ADMA) ($R^2 = 0.24, 0.155$), L-arginine ($R^2 = 0.03$, $p = 0.643$), ADMA ($R^2 = 0.15, p = 0.267$) and L-arginine/SDMA ratio ($R^2 = 0.20, p = 0.199$) (fig. 5). We obtained similar results when we controlled for age, sex and race.

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Table 3. Mean GFR, RPF, FF and renal resistive indices stratified by type of ascites in patients with cirrhosis

<table>
<thead>
<tr>
<th>Right kidney</th>
<th>Left kidney</th>
<th>Mean renal resistive index</th>
<th>Mean GFR¹</th>
<th>Mean RPF²</th>
<th>Mean FF²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ascites</td>
<td>main renal artery 0.670</td>
<td>main renal artery 0.677</td>
<td>82.894</td>
<td>229.857</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>segmental artery 0.641</td>
<td>segmental artery 0.647</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>interlobar artery 0.636</td>
<td>interlobar artery 0.628</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arcuate artery 0.616</td>
<td>arcuate artery 0.640</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic-sensitive ascites</td>
<td>main renal artery 0.715</td>
<td>main renal artery 0.753</td>
<td>82.336</td>
<td>344.141</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>segmental artery 0.706</td>
<td>segmental artery 0.702</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>interlobar artery 0.680</td>
<td>interlobar artery 0.694</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arcuate artery 0.676</td>
<td>arcuate artery 0.658</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic-refractory ascites</td>
<td>main renal artery 0.818</td>
<td>main renal artery 0.790</td>
<td>36.506</td>
<td>133.606</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>segmental artery 0.761</td>
<td>segmental artery 0.763</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>interlobar artery 0.734</td>
<td>interlobar artery 0.759</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>arcuate artery 0.753</td>
<td>arcuate artery 0.699</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ GFR and RPF were reported in ml/min/1.73 m². ² FF = GFR/RPF.
While all biomarkers appeared to perform better compared to serum Cr ($R^2 = 0.20$, $p = 0.198$) in estimating renal cortical blood flow assessed by right kidney arcuate artery resistive index; the β-trace protein ($R^2 = 0.52$, $p = 0.018$), β2-microglobulin ($R^2 = 0.42$, $p = 0.043$), SDMA ($R^2 = 0.44$, $p = 0.038$) (SDMA+ADMA) ($R^2 = 0.42$, $p = 0.044$) performed the best (fig. 6). The performance of L-arginine ($R^2 = 0.04$, $p = 0.585$), ADMA ($R^2 = 0.31$, $p = 0.092$) and L-arginine/SDMA ratio ($R^2 = 0.05$, $p = 0.537$) was poor.

Discussion

In this pilot study, we performed simultaneous measurements of GFR, RPF, renal resistive indices and biomarkers to evaluate patterns of change in different stages of cirrhosis. To our knowledge, our study is the first to measure renal resistive indices simultaneously with direct RPF and GFR measurements in cirrhotics. Our results suggest that in different stages of cirrhosis assessed by the type of ascites (no ascites, diuretic-sensitive and -refractory ascites), there are distinct patterns of glomerular hemodynamics and resistive indices.

We observed a higher mean FF (GFR/RPF 0.36) among those without ascites compared to those with ascites (table 3). Higher FF in patients without ascites is most likely secondary to the vasoconstriction in the efferent glomerular arterioles (normal FF $\sim 0.20$). Among those with diuretic-refractory ascites, we observed the lowest GFR and RPF consistent with the results of our recent study [18]. Among those with ascites, FF was near normal and renal resistive indices were higher. In general, renal resistive indices were inversely related to FF.
Fig. 5. Candidate biomarkers were measured simultaneously with RPF (adjusted for body surface area) and their performances compared to serum Cr.

Fig. 6. Candidate biomarkers were measured simultaneously with right kidney arcuate artery resistive indices and their performances compared to serum Cr.
arteries that supply the renal cortex and medulla and give rise to interlobular arteries (fig. 1). Arcuate arteries are located at the junction of renal cortex and medulla and give rise to interlobular arteries (fig. 2–4). These findings suggest that in late stages of cirrhosis, reduced RPF is associated with increase in renal arterial resistive indices as there is no compensatory increase in FF. According to Poiseuille’s law [34], resistance to flow is inversely related to volume flow rate. As renal vascular resistance is positively and significantly correlated with renal resistive indices [35], our findings of reduced RPF with increased renal resistive indices suggest that our findings are in line with Poiseuille’s law. While cystatin C and beta-2 microglobulin performed better compared to Cr in estimating RPF (fig. 5); beta-trace protein, beta-2 microglobulin, SDMA, and (SDMA+ADMA) performed better in estimating right kidney arcuate artery resistive index (fig. 6).

In our recent review, we emphasized the importance of simultaneous evaluation of GFR, RPF and FF in cirrhosis and proposed a dynamic classification system that takes both GFR and RPF into account in evaluating kidney dysfunction in cirrhosis [11]. In 1951, Leslie et al. [36] evaluated renal hemodynamics in 17 patients with cirrhosis and showed the importance of FF (simultaneous GFR and RPF measurements) in cirrhosis. In patients without ascites, mean FF was elevated, whereas in those with ascites, mean FF was normal [36]. The elevation in FF most likely resulted from the vasoconstrictive effect of angiotensin II on efferent glomerular arterioles [11, 36, 37]. On the other hand, simultaneous reductions in mean GFR and RPF resulted in normal/subnormal levels of FF in parallel to the severity of ascites. The results of our study are in line with these findings (table 3).

Additionally, we showed that normal FF (FF ∼0.20) was associated with reductions in renal cortical blood flow that was assessed by renal arcuate artery resistive indices (fig. 1). Arcuate arteries are located at the junction of renal cortex and medulla and give rise to interlobular arteries that supply the renal cortex [38]. Measurement of interlobular artery resistive indices by Duplex Doppler ultrasound is technically challenging and poorly reproducible in patients with cirrhosis and ascites given the size of the arteries [39, 40]. Therefore, we elected to measure resistive indices in the arcuate arteries to assess the renal cortical blood flow. The increase in resistive indices in the right kidney in patients with decompensated cirrhosis, particularly in those with diuretic-refractory ascites was previously shown by Rivolta et al. [41]. However, the authors did not validate increases in renal resistive indices by simultaneous RPF measurements; rather they compared alterations in renal resistive indices with Cr clearance which is not an accurate measure of GFR in cirrhosis [41]. In this study, we confirmed the increases in renal resistive indices by the decrease in RPF measured by PAH clearance.

Our study suggests that both normal FF (∼0.20) and an increase in renal resistive indices can be associated with severe reductions in renal blood flow in cirrhosis. Development of spontaneous bacterial peritonitis, sepsis, aggressive diuresis and frequent paracenteses at this stage may increase risk of patients with cirrhosis to develop ATN in the setting of already severely reduced renal blood flow. Therefore, early identification of this stage by non-invasive biomarkers may facilitate early management in patients with cirrhosis including holding diuretics, infusion of albumin, and administration of vasoconstrictor drugs before waiting for increases in Cr.

Our study was limited to only 10 patients with cirrhosis which precluded formal statistical inference testing of between-group differences and correlations of RPF with the circulating biomarkers. Additionally, our study population was limited to only Caucasian and African-American participants. Our results are preliminary and a larger study is needed to assess the performance of these biomarkers. Despite the small study, our results are consistent and encouraging. These biomarkers may have significant specificity and sensitivity to assist management in patients with cirrhosis.

In conclusion, this pilot study suggests that normal FF (∼0.20) with reduced RPF and GFR and increased renal arterial resistance were the key alterations in renal hemodynamics of decompensated stages of cirrhosis. As direct measurement of GFR, RPF and renal resistive indices would be impractical and costly in a clinical setting: identification of non-invasive biomarkers more accurate than Cr which are predictive of these hemodynamic changes may lead to modifications in treatment by identifying cirrhotics at risk for HRS at a stage more amenable to therapeutic intervention. Ultimately, such early identification could perhaps decrease the need for simultaneous kidney transplantation in cirrhotics awaiting liver transplantation, and reduce mortality from kidney failure in cirrhosis.

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31 SAS software: http://www.sas.com/. The data analysis for this paper was generated using SAS software, version 9.2 of the SAS System for Windows. Copyright 2002–2008 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, USA.

Disclosure Statement
The authors have no conflicts of interest to disclose.


