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Intrarenal Resistance Index as a Prognostic Parameter in Patients with Liver Cirrhosis Compared with Other Hepatic Scoring Systems

M. Götzberger[a] J. Singer[a] C. Kaiser[b] V. Gülberg[a]

[a]Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, and [b]Klinik für Innere Medizin 1, Klinikum Dritter Orden, München, Germany

Key Words
Liver cirrhosis · Resistance index · Hepatorenal syndrome · MELD score

Abstract
Background and Aims: Patients with advanced liver cirrhosis who develop renal dysfunction have a poor prognosis. Elevated intrarenal resistance indices (RIs) due to renal vascular constriction have been described before in cirrhotic patients. In the current study, we prospectively investigated the course of intrarenal RIs and compared their prognostic impact with those of the Model for End-Stage Liver Disease (MELD) and the Child-Pugh scores. ***Methods:*** Sixty-three patients with liver cirrhosis underwent a baseline visit which included a sonographic examination and laboratory tests. Forty-four patients were prospectively monitored. The end points were death or survival at the day of the follow-up visit. ***Results:*** In 28 patients, a follow-up visit was performed after 22 ± 8 months (group 1). Sixteen patients died during follow-up after 12 ± 8 months (group 2). Group 2 patients showed a significantly higher baseline RI (0.76 ± 0.05) than group 1 patients (RI = 0.72 ± 0.06; $p < 0.05$). As shown by receiver operating characteristic analysis, the RI and the MELD score achieved similar sensitivity and specificity [area under the curve (AUC): 0.722; 95% confidence interval (95% CI): 0.575–0.873 vs. AUC: 0.724; 95% CI: 0.575–0.873, z = 0.029, n.s.] in predicting survival and were superior to the Child-Pugh score (AUC: 0.677; 96% CI: 0.518–0.837). ***Conclusion:*** The RI is not inferior in sensitivity and specificity to the MELD score. Cirrhotic patients with elevated RIs have impaired short- and long-term survival. The RI may help identify high-risk patients that require special therapeutic care.

Introduction

Advanced liver cirrhosis is associated with a poor clinical outcome [1]. Therefore, assessment of prognosis is important in the management of these patients. The Child-Pugh score has long been the most widely used specific scoring system in liver disease [2, 3]. In 2002, the Model for End-Stage Liver Disease (MELD) was introduced for patients undergoing transjugular intrahepatic portosystemic shunt. It is currently used to predict survival in patients awaiting liver transplantation [3, 4]. The MELD seems to be superior to the Child-Pugh score in prioritizing potential liver recipients according to mortality risk [5]. However, it is only based on three laboratory variables, and thus does not take into account all prognostic factors that will impact on the survival of cirrhotic patients, notably complications due to portal hypertension [4]. There is still a need for improvement of

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Manuela Götzberger, MD
Medizinische Klinik und Poliklinik IV, Klinikum der Universität München
Ziemssenstrasse 1
DE–80336 München (Germany)
E-Mail manuela.goetzberger@med.uni-muenchen.de

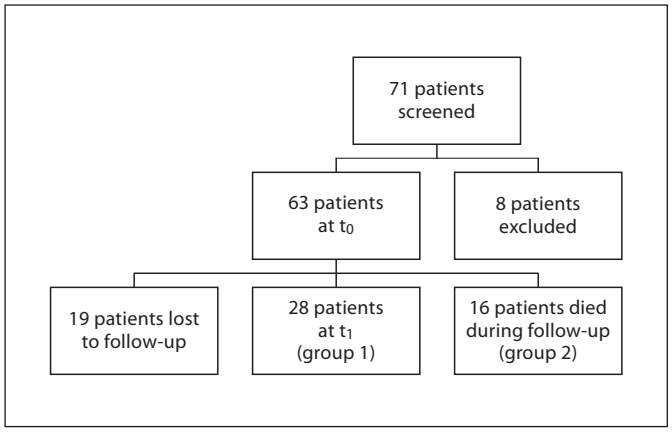

Fig. 1. Study design: 44 patients were prospectively monitored and divided in two groups. Patients of group 1 were also seen at t_1. Patients of group 2 died during the follow-up.

prognostic markers that could be easily integrated into the clinical management of these patients.

Patients with liver cirrhosis frequently develop renal dysfunction. The hepatorenal syndrome (HRS), the most serious renal complication, is associated with an extremely short survival time [6]. The HRS is characterized by renal arterial vasoconstriction, which may precede clinically manifest renal dysfunction. The intrarenal resistance index (RI) is the most frequently used parameter to assess intrarenal resistance and is calculated based on Doppler sonographic intrarenal measurements. It is routinely used to diagnose transplant rejection or renal artery stenosis [7, 8]. Increased intrarenal RIs in patients with liver cirrhosis, especially in the decompensated stage, have been described before as compared to healthy controls [9–13]. Cirrhotic patients with elevated intrarenal RIs tend to develop the HRS, leading to a poor prognosis. In the current study, we prospectively investigated the course of intrarenal RIs in patients with liver cirrhosis and compared its prognostic impact with those of the MELD and the Child-Pugh scores.

Subjects and Methods

Study Subjects

Adult patients (≥18 years old) with known liver cirrhosis, admitted to our outpatient clinic for surveillance of cirrhosis, were screened and enrolled in the study. Patients with suspected or overt malignant diseases, a history of insulin-dependent diabetes mellitus or any other nephropathy as well as patients with ongoing HRS, gastrointestinal bleeding, spontaneous bacterial peritonitis or other acute infections at the time of the baseline visit (t_0) were excluded. A follow-up of at least 6 months was required for inclusion in the study. Informed consent was obtained from all patients before their inclusion.

Study Design

At the time of the baseline visit, all patients underwent sonographic examination of the liver and kidneys, including Doppler evaluation of intrarenal resistance.

Patients were fasting 4 h prior to examination. For duplex Doppler ultrasound examination, a 3.5-MHz convex transducer was used (Hitachi EUB-8500 and Siemens Sonoline Elegra). Sonographic examinations were performed by two experienced investigators, thus precluding calculation of interobserver variation. The intraobserver coefficient of variation ranged from 3.2 to 3.4% (M.G.) and from 3.0 to 3.7% (C.K.). The RI was calculated with the following formula: RI = (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Intrarenal resistance was measured on interlobar arteries three times in different regions of each kidney. Subsequently, a mean RI was calculated for each patient (mean of both kidneys).

Laboratory tests for liver and renal function were performed on each patient and clinical parameters, such as blood pressure, heart rate and age, were measured. Hepatic encephalopathy was clinically assessed and classified according to the West Haven scale (0–4) [14]. Ascites was graded as absent, mild to moderate or severe based on sonography.

Patients were prospectively monitored. The end points were death or survival at the day of the follow-up visit (t_1). On the follow-up visit, the same parameters were investigated as on the baseline visit (t_0).

Statistical Analysis

All data were expressed as means ± standard deviations. Statistical analysis was performed using SPSS. Differences between groups were analyzed by Student's t test; $p < 0.05$ was considered significant. To discriminate the predictive value of the parameters, a receiver operating characteristic (ROC) curve was established by standard procedures [15]. Accordingly, a z-value was calculated for comparing the MELD score and the RI. Assuming a two-tailed probability, a z-value >1.96 was taken as evidence that ROC areas were different [16]. Survival curves were evaluated and compared using the Kaplan-Meier method and the log-rank test; $p < 0.05$ was considered significant.

Results

Seventy-one consecutive patients with liver cirrhosis were screened. Eight patients were excluded because of diabetes or other nephropathy in 6 cases and malignant disease in 2 cases. Sixty-three patients presented at the baseline visit (t_0), but 19 patients were lost to follow-up. Finally, 44 patients were enrolled in the follow-up study. Twenty-eight patients underwent a follow-up visit (t_1) after 22 ± 8 months (group 1). Sixteen patients (36%) died after 12 ± 8 months (group 2) (fig. 1). Causes of death are

Table 1. Causes of death during follow-up in group 2 patients with liver cirrhosis (n = 16)

	Patients, n
HRS	5
Liver failure	3
Upper gastrointestinal bleeding	1
Rectum carcinoma	1
Cerebral bleeding	1
Sepsis	1
Unknown	4

Table 2. Baseline characteristics of both groups at t_0

	Group 1 (n = 28)	Group 2 (n = 16)
Etiology, n		
Alcohol abuse	17 (60%)	12 (75%)
Chronic hepatitis B or C	7 (25%)	3 (19%)
Wilson's disease	1 (4%)	0
Autoimmune hepatitis	1 (4%)	0
Primary biliary cirrhosis	0	1 (6%)
Cryptogenic	2 (7%)	0
Biochemical parameters		
Serum bilirubin, mg/dl	2.7 ± 3.0	5.8 ± 10.0
Serum albumin, g/dl	3.5 ± 0.8	3.1 ± 0.8
Prothrombin index, %	72 ± 17	59 ± 16
Serum creatinine, mg/dl	0.9 ± 0.3	1.0 ± 0.5
Clinical parameters		
Ascites	12 (43%)	12 (75%)
Encephalopathy	13 (46%)	6 (37%)
Grade I	1 (4%)	4 (25%)
Grade II	12 (43%)	12 (75%)
Blood pressure, systolic	115 ± 18	117 ± 13
Blood pressure, diastolic	72 ± 13	73 ± 7
Heart rate	82 ± 8	77 ± 10
BMI	26.7 ± 3.5	25.3 ± 5.1
Body weight, kg	80.8 ± 11.2	74.6 ± 13.7
Portal vein flow	16 ± 5	16 ± 6
Portal vein reversal, n	4 (14%)	4 (25%)

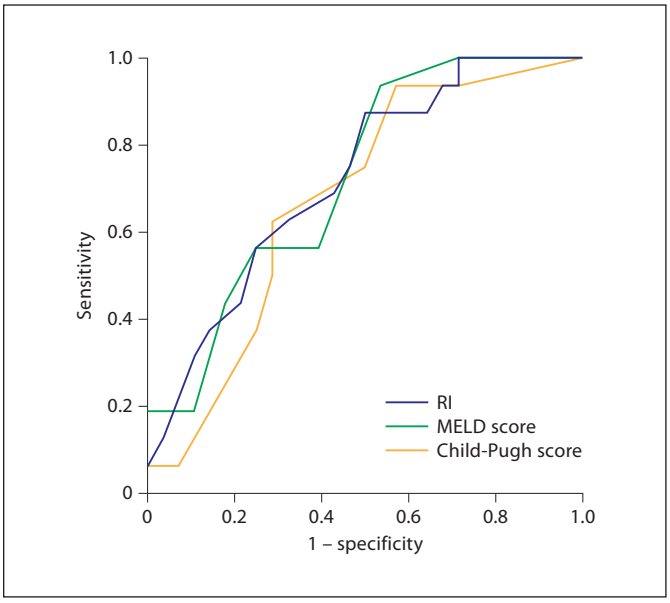

Fig. 2. ROC curve for the MELD score, Child-Pugh score and RI. The ROC curve for the MELD score and RI value showed similar performances.

shown in table 1 and patients' baseline characteristics of both groups, in table 2. Group 2 patients showed a baseline RI of 0.76 ± 0.05 at t_0, which is significantly higher than the baseline RI of group 1 (RI = 0.72 ± 0.06, $p < 0.05$). The RI was the only documented parameter that differed significantly between the two groups at t_0 (table 3). In ROC analysis, the RI and the MELD score showed similar sensitivity and specificity [area under the curve (AUC): 0.722; 95% confidence interval (95% CI): 0.575–0.873 vs. AUC: 0.724; 95% CI: 0.575–0.873, z = 0.029, n.s.] in predicting survival and were superior to the Child-Pugh score (AUC: 0.677; 95% CI: 0.518–0.837) (fig. 2). According to the best accuracy derived from ROC analysis, we chose a cut-off of 0.74 to compare survival among patients (sensitivity: 62.5%; specificity: 68%). Kaplan-Meier survival curves showed a significant difference in survival between patients with RI >0.74 and RI ≤0.74 in the short-term as well as the long-term course (p = 0.037, log-rank test) (fig. 3).

On the basis of previous studies, an RI >0.70 was considered elevated and thus indicative of renal vasoconstriction [17, 18]. In group 2, only 2 patients had RIs <0.70 at t_0. One of these patients died of sepsis due to pneumonia. The cause of death of the second patient with a normal RI at t_0 is unknown. All other patients (88%) of group 2 had RIs ≥0.72 at t_0 compared to only 50% of patients in group 1. Among the patients who died, the highest RIs (0.78 ± 0.04) were found in patients with the HRS.

In group 1, the results at t_0 and t_1 revealed a stable course of the liver disease. Some patients' clinical condition even improved. At t_0, 12 patients presented with ascites, but only 7 patients did so at t_1. Consistent with the clinical results, patients showed a slight improvement in their Child-Pugh score, RI and MELD score (table 4). A subgroup of 3 patients showed impairment in serum cre-

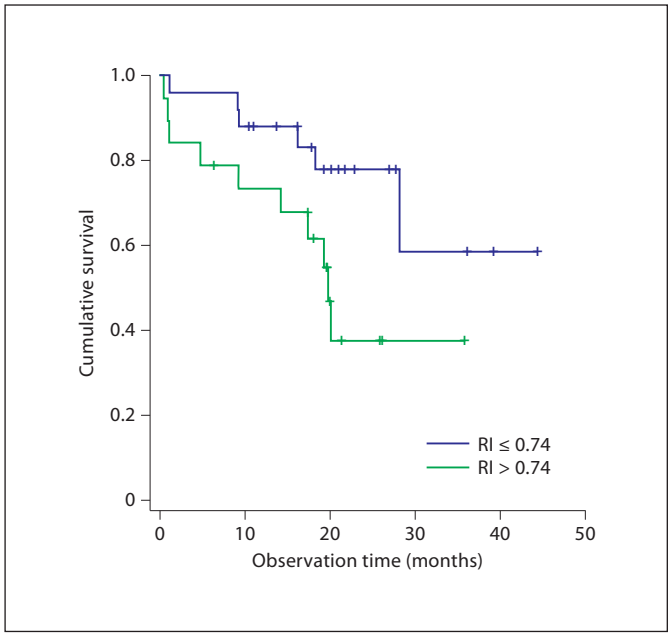

Fig. 3. Kaplan-Meier survival curves according to RI demonstrated a significantly better outcome in patients with RI ≤ 0.74 (p = 0.037, log-rank test).

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Table 3. Parameters at t_0 of group 1 (alive at the end of follow-up) and group 2 (dead at the end of follow-up)

	Group 1 (n = 28)	Group 2 (n = 16)	p
Age, years	57 ± 10	62 ± 9	n.s.
Male/female	21/7	9/7	
RI	0.72 ± 0.06	0.76 ± 0.05	<0.05
cGFR, ml/min	91.1 ± 25.0	81.2 ± 33.8	n.s.
Serum creatinine, mg/dl	0.9 ± 0.3	1.0 ± 0.5	n.s.
MELD score	12 ± 4	16 ± 6	n.s.
Child-Pugh score	7.7 ± 2.4	9.2 ± 2.0	n.s.

cGFR = Calculated glomerular filtration rate estimated according to the Modification of Diet in Renal Disease (MDRD) formula.

Table 4. Comparison of parameters in patients of group 1 at t_0 and t_1

Group 1 (n = 28)	t_0	t_1	p
Age, years	57 ± 10	59 ± 10	n.s.
RI	0.72 ± 0.06	0.69 ± 0.06	<0.03
GFR, ml/min	91.1 ± 25.0	83 ± 24	n.s.
Serum creatinine, mg/dl	0.9 ± 0.3	1.0 ± 0.4	n.s.
MELD score	12 ± 4	11 ± 4	n.s.
Child-Pugh score	7.7 ± 2.4	6.6 ± 2.0	<0.02

atinine during the follow-up. Two patients with serum creatinine >2 mg/dl at t_1 had elevated RIs already at t_0 (RI = 0.78 and 0.77, respectively). The patient with RI = 0.77 at t_0 fulfilled the criteria of HRS at t_1. The third patient demonstrated a drastically increased RI from 0.65 to 0.79 whereas serum creatinine was only slightly increased to 1.2 mg/dl at t_1.

Discussion

The current study is the first to show the similar sensitivity and specificity of the intrarenal RI and the MELD score in assessing survival in patients with liver cirrhosis. Both parameters were superior to the Child-Pugh score in ROC analysis. In addition, we could confirm the findings of previous studies showing that cirrhotic patients with elevated RIs have impaired short- and long-term survival and are at higher risk of developing the HRS. Kaplan-Meier survival curves demonstrated a significantly better outcome in patients with RI ≤0.74.

Liver cirrhosis is characterized by complex changes in systemic hemodynamics. Especially renal dysfunction frequently complicates the clinical course of this disease. Doppler ultrasound measurement of intrarenal resistance can estimate renal blood flow and correlates with portal pressure [19]. Some studies have shown that intrarenal RIs are significantly increased in cirrhotic patients compared with healthy controls and are even higher in patients with ascites than in patients without ascites [9, 10]. Patients with decompensated cirrhosis but normal serum creatinine can already present with elevated RIs [12]. So far, two teams performed follow-up investigations of cirrhotic patients after measuring renal resistance. Maroto et al. [20] investigated 32 cirrhotic with ascites. The subgroup of 17 cirrhotic patients with renal failure showed elevated RIs of 0.74 ± 0.01. Follow-up revealed the RI as an indicator of impaired survival in the univariate analysis. Platt et al. [18] measured intrarenal resistance in 180 cirrhotic patients without kidney dysfunction. During the follow-up, the HRS developed in 26% (n = 20) of patients with an initial RI >0.70, but only in 1% of those with normal RIs. The mean initial RI in patients who subsequently developed the HRS was 0.77 ± 0.05. Our findings are in agreement with previous results showing a mean RI of 0.78 ± 0.04 in the 5 patients

of group 2 who died due to the HRS. In the present study, a further RI was obtained at t_1. The patients who were still alive at t_1 exhibited a stable course of their liver disease, possibly due to close clinical management. These results confirm that RIs and renal hemodynamics can improve with time. However, in a subgroup of 3 patients, impaired serum creatinine was found during the follow-up. Two patients with considerable worsening already had elevated RIs at t_0, comparable to those of patients of group 1. This supports the assumption that an elevated RI is an earlier indicator of development of renal dysfunction followed by a rise in serum creatinine with time.

RIs >0.70 were defined as elevated in a number of studies [17, 18]. Our data reveal that most of the high-risk patients had RIs ≥0.72. The optimal cut-off level for elevated RIs should be validated on a larger number of subjects. Two patients in group 2 (12%) showed normal RIs at baseline, which would have led to false-negative results in these cases. One of these patients died due to pneumonia during follow-up. The cause of death of the other patient is unknown. Apart from these aspects, other possible limitations of our results are important to consider: our study was designed as a single-center study and did not have an external validation group to further confirm the results.

In conclusion, we demonstrated for the first time that the RI is not inferior in sensitivity and specificity to the MELD score. At the present time, the MELD score is mainly used in the transplantation setting [5]. It is based on easily measured variables (prothrombin time, bilirubin and creatinine). Serum creatinine is an indicator of impaired renal function; however, it has disadvantages as it depends on muscle mass and physical activity. Therefore, renal function based on serum creatinine can be overestimated in patients with advanced cirrhosis [22]. Thus, it is still necessary to develop improved prognostic markers feasible in daily practice. Our study confirms that the RI, based on sonographic measurements of intrarenal resistance, is an effective, noninvasive, economical functional test that provides useful information for the prognosis and management of cirrhotic patients. Elevated RIs may even disclose progress of the liver disease before changes in laboratory results. Therefore, the RI may help identify a subgroup of high-risk patients with a poor prognosis that require special therapeutic care. According to clinical practice guidelines, cirrhotic patients should be entered into surveillance programs and undergo ultrasound examination every 6–12 months [23]. Hence, our data suggest to include the measurement of renal resistance in these surveillance programs.

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