

OPEN

Differential Clinical Impact of Ascites in Cirrhosis and Idiopathic Portal Hypertension

Hitoshi Maruyama, MD, PhD, Takayuki Kondo, MD, PhD, Tadashi Sekimoto, MD, PhD,
and Osamu Yokosuka, MD, PhD

Abstract: Cirrhosis and idiopathic portal hypertension (IPH) are 2 major diseases showing portal hypertension. However, characteristics and outcomes of IPH with ascites have not yet been determined. The aim of the study was to examine the influence of ascites on the long-term clinical course of IPH.

This observational study compared the long-term clinical findings including portal hemodynamics demonstrated by Doppler ultrasonography between 166 cirrhosis (87 males and 79 females; mean age \pm standard deviation, 62.5 ± 11.8 years; age range, 20–89 years) and 14 IPH patients (3 males and 11 females; mean age \pm standard deviation, 64.2 ± 6.6 years; age range, 51–78 years). Both groups comprised of consecutive patients from November 2007 through February 2013 and were studied retrospectively. The median observation period was 33.4 months for ascites and 34.5 months for survival.

Ascites was detected in 60/166 (36.1%) and 116/166 (69.9%) cirrhosis patients and in 7/14 (50%) and 9/14 (64.3%) IPH patients, at baseline and at the end of the observation period, respectively. The cumulative incidence of ascites was 12.3% at 1 year, 35.9% at 3 years, and 59.9% at 5 years in cirrhosis, and 25% at 3 years, and 50% at 5 years in IPH ($P=0.36$). Deterioration of ascites in patients showing mild ascites at baseline was found in 32.4% of cirrhosis patients and 42.9% of IPH patients ($P=0.41$). Serum creatinine (mg/dl) at baseline was significantly higher in IPH patients who developed ascites ($n=2$, 0.74 ± 0.14) than in those who did not ($n=5$, 0.526 ± 0.06 , $P=0.029$). The overall survival rate appeared to favor IPH (100% at 1 year, 92.9% at 3 and 5 years; $P=0.2$) more than cirrhosis (87.7% at 1 year, 75.2% at 3 years, and 63.6% at 5 years), but did not reach statistical significance. However, in patients with ascites at baseline, the survival rate was significantly better in IPH (100% at 1, 3, and 5 years, $P=0.04$) than in cirrhosis (69.1% at 1 year, 43% at 3 years, 34.4% at 5 years).

The presence of ascites at baseline correlated with worse survival rates in patients with cirrhosis as compared to those with IPH as the underlying etiology.

(*Medicine* 94(26):e1056)

INTRODUCTION

Chronic liver disease has a varied etiology and its incidence is increasing worldwide.^{1,2} The most advanced stage is

cirrhosis, the presence of which limits the prognosis of patients due to the risk of developing hepatocellular carcinoma (HCC), portal hypertension, and hepatic failure.^{3,4} Idiopathic portal hypertension (IPH) represents noncirrhotic portal hypertension with a wide spectrum of manifestations, though the precise mechanism for the pathogenesis and pathophysiology remains unclear.^{5,6} Cirrhosis and IPH differ in several aspects, such as the risk of HCC occurrence and prognosis,⁷ while they share common manifestations based on the pathophysiology of portal hypertension.

Ascites is one of the major presentations in portal hypertension. The incidence of ascites in cirrhosis has been reported to be 50% over a 10-year clinical course,⁸ and the 2-year survival rate is almost 50% in patients with advanced ascites.^{9–11} Thus, the presence of ascites is a poor prognostic sign in cirrhosis.¹²

The major mechanism for developing ascites is an increased pressure in the hepatic sinusoid; that is, sinusoidal portal hypertension.¹³ However, despite the underlying pathophysiology of presinusoidal blockage, which differs from that of cirrhosis, IPH patients also develop ascites. The incidence of ascites has been reported to be 2% in noncirrhotic portal hypertension and 10% in IPH patients.¹⁴ It has been demonstrated that the development of ascites is uncommon in IPH and may be seen only after an episode of gastrointestinal hemorrhage, as per the consensus statement for noncirrhotic portal fibrosis/IPH in Asia.¹⁵ It is also reported that up to 10% to 34% of cases with noncirrhotic portal hypertension develop ascites usually after a bleeding episode.¹⁶ However, the influence of ascites on the long-term outcome of IPH has not yet been determined. In addition, because of different clinical presentations reported between IPH from Japan and noncirrhotic portal fibrosis from India,^{6,14} more data are needed for a better understanding of the disease.

Against this background, we compared the incidence, characteristics, and prognosis between IPH and cirrhosis patients with respect to the presence/absence or degree of ascites. The aim of the study was to examine the influence of ascites on the long-term clinical course of IPH.

METHODS

Study Design

This is an observational study based on the retrospective review of medical records (both inpatient and outpatient) that were prospectively collected for studies conducted with written informed consent at Chiba University Hospital on the relationship between ultrasound findings and the grade of function/fibrosis of the liver. The study design was approved by the ethics committee of our department (Board member: Iyo M, Iwase H, Okabayashi S, Goto H, Kobayashi Y, Shimazu J, Shimoyama E, Nomura F, Hada A, Hanaoka A, Hori Y, Yamaura A, and Watanabe E). The research was carried out in accordance with the Helsinki Declaration.

Editor: Jun Yong Park.

Received: December 5, 2014; revised: May 28, 2015; accepted: June 2, 2015.

From Department of Gastroenterology and Nephrology, Chiba University Graduate School of Medicine, Chiba, Japan (HM, TK, TS, OY).

Reprints: Hitoshi Maruyama, MD, PhD, Department of Gastroenterology and Nephrology, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chiba 260-8670, Japan (e-mail: maru-cib@umin.ac.jp).

The authors have no funding and conflicts of interest to disclose.

Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0, where it is permissible to download, share and reproduce the work in any medium, provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 0025-7974

DOI: 10.1097/MD.0000000000001056

The study included consecutive patients with 2 types of liver diseases from November 2007 through February 2013. Cirrhosis with clinical signs of portal hypertension; splenomegaly or ascites diagnosed by imaging modality (ultrasound/computed tomography), gastroesophageal varices diagnosed by endoscopy, hyperammonemia, or overt hepatic encephalopathy. The diagnosis of cirrhosis was based on a combination of biochemical findings and 2 imaging tools, ultrasound and computed tomography/magnetic resonance imaging. IPH diagnosed based on blood tests, hepatic venography, and histology on biopsies in all patients according to the general protocol for the study of portal hypertension in Japan.¹⁷ This protocol includes the following: patency of hepatic veins on Doppler ultrasound at the time of diagnosis, evidence of portal hypertension with the presence of esophageal varices, hypersplenism, or ascites, no evidence of cirrhosis at the liver biopsy sample, exclusion of other liver diseases; alcoholic liver disease, chronic viral hepatitis, autoimmune hepatitis, nonalcoholic steatohepatitis, Budd-Chiari syndrome, congenital hepatic fibrosis, Wilson's disease, parasitic disease, hematological disorder, and granulomatous liver disease.

All subjects received a Doppler ultrasound to evaluate portal hemodynamics at the time of enrollment and thereafter.

The study excluded patients with malignant hepatic lesions, with vascular abnormalities, such as an intrahepatic arterioportal shunt or cavernomas diagnosed by the Doppler ultrasound examination, using vasoactive drugs, such as β -blockers which are not approved for treatment of portal hypertension in Japan, or receiving antiviral therapy during the study period; who already had received a peritoneovenous shunt or transjugular intrahepatic portosystemic shunt.

Clinical Presentations and Definitions

Gastroesophageal varices were evaluated by endoscopy, according to the general guidelines of the Japanese Research Society for Portal Hypertension.¹⁷ The median time interval between ultrasound examination and endoscopy was 6 days. Hepatic encephalopathy was assessed by the West-Haven grading system, and grade II or above was classified as overt hepatic encephalopathy.¹⁸

The degree of ascites was defined according to the clinical and ultrasound findings: mild for ascites only detectable by ultrasound (Grade 1), moderate for ascites causing moderate symmetrical distention of the abdomen (Grade 2), and severe for ascites causing marked abdominal distention (Grade 3). Patients with ascites were treated according to the guidelines,^{19,20} using diuretics and a salt-restricted diet with occasional paracentesis (the upper dose of diuretics approved in Japan is 80 mg/day for furosemide and 100 mg/day for spironolactone). Change of ascites grade was assessed by the difference between the initial grade and the final grade, and refractory ascites was diagnosed based on the definition in a previous report.²¹ The diagnosis of spontaneous bacterial peritonitis (SBP) was confirmed by ascetic fluid neutrophil count >250 cells/mm³ in the absence of an intraabdominal and surgically treatable source of sepsis.²⁰

The observation period was defined as the time between the initial ultrasound examination and the date of the last hospital visit, confirmation of death, or liver transplantation (LT).

Ultrasonography

Ultrasound examinations were performed with patients in the supine position, after fasting for 4 hours or more, using SSA-770A or 790A ultrasound system (Toshiba, Tokyo, Japan) with a 3.75-MHz convex probe. Blood flow was measured with the

sampling width corresponding to the diameter of the vessel and at an angle $<60^\circ$ between the ultrasound beam and the vessel. The data used for analysis were the average values, calculated using 2 or more measurements. Spleen size (mm²) was measured by multiplying the distance from the splenic hilum to the caudal polar angle measured by 2 intersecting lines, the upper limit in a normal subject used in the study was 2000 mm².²² Ultrasound examination was performed at least once per year, and findings such as changes in portal hemodynamics and the degree of ascites were monitored. All ultrasound examinations were performed by HM or MT, who each have more than 8 years of ultrasound experience.

Statistical Analysis

All data are expressed as mean \pm standard deviation (SD), median, or as percentages. The study used Student *t* test or Mann-Whitney *U* test for the analysis of continuous variables, and Fisher exact test or Chi-square test for the analysis of categorical variables, as appropriate. Kaplan-Meier method was used to calculate the cumulative incidence of ascites and survival rate, and the data were compared using log-rank test according to the liver diagnosis (cirrhosis or IPH) or presence/absence or degree of ascites. *P*-values < 0.05 were considered to be significant. The study used SAS (version 9.2 software, SAS Institute, Cary, NC) for the analysis.

RESULTS

Patient Characteristics

The study consisted of 180 patients; 166 with cirrhosis (87 males and 79 females; mean age \pm SD, 62.5 ± 11.8 years; age range, 20–89 years) and 14 with IPH (3 males and 11 females; mean age \pm SD, 64.2 ± 6.6 years; age range, 51–78 years) (Table 1). Statistical differences between the groups were found in the following baseline data; sex, grade of ascites, history of variceal bleeding, bilirubin, albumin, platelet count, and incidence of portal vein thrombosis. Hepatic venous pressure gradient (HVPG) in IPH patients showed 81.6 ± 19.9 (mmH₂O, mean \pm SD; range 50–135, *n* = 9).

Ascites

Ascites were detected in 60/166 (36.1%) cirrhosis patients and 7/14 (50%) IPH patients at baseline, and in 116/166 (69.9%) cirrhosis patients and 9/14 (64.3%) IPH patients at the end of the observation period. Cumulative incidence of ascites was 12.3% at 1 y, 35.9% at 3 years, and 59.9% at 5 years in patients with cirrhosis, and 25% at 3 years, and 50% at 5 years in patients with IPH (*P* = 0.36) during the median observation period of 33.4 months (Figure 1).

Changes in ascites grade over time were assessed in patients showing grade 1 ascites at baseline (Table 2); deterioration (changing to grade 2/3) was detected in 32.4% of cirrhosis patients and 42.9% of IPH patients (*P* = 0.41). There was no significant difference in the incidence of refractory ascites, which was 31/166 (18.7%) in cirrhosis patients and 2/14 (14.3%) in IPH patients (*P* = 0.68). SBP was detected in 9/166 (5.4%) in cirrhosis patients and 1/14 (7.1%) in IPH patients over the study course (*P* = 0.79).

Comparison of Cirrhosis and IPH Patients With Ascites at Baseline

The baseline characteristics of patients with cirrhosis and IPH who had ascites at the time of inclusion were compared

TABLE 1. Patient Characteristics

	Cirrhosis	Idiopathic Portal Hypertension	P Values
Number of subjects	166	14	
Age (years) (mean ± SD [range])	62.5 ± 11.8 (20–89)	64.2 ± 6.6 (51–78)	0.39
Sex (male/female)	87/79	3/11	0.029
Etiology (virus/alcohol/NASH/PBC/AIH/others)	58/37/10/18/9/34	–	–
Ascites (–/+ /++)	106/37/23	7/7/0	0.04
Gastroesophageal varices (–/+)	46/120	2/12	0.28
History of variceal treatment (–/+)	128/38	9/5	0.28
History of variceal bleeding (–/+)	115/51	6/8	0.04
Hepatic encephalopathy (–/+)	160/6	14/0	0.47
Child-Pugh (A/B/C)	73/68/25	–	–
Model for end-stage liver disease score (mean ± SD [range])	11.3 ± 4.1 (6–26)	9.8 ± 3.4 (6–20)	0.17
Blood test			
Bilirubin (mg/dl) (mean ± SD [range])	2.0 ± 2.5 (0.3–20.2)	1.2 ± 0.4 (0.6–1.9)	0.0002
Albumin (g/dl) (mean ± SD [range])	3.3 ± 0.5 (1.8–4.7)	3.7 ± 0.5 (2.9–4.4)	0.01
Prothrombin time (%) (mean ± SD [range])	67.7 ± 16.8 (32–107)	76.4 ± 15.1 (40–104)	0.06
Platelet count (10 ⁴ /μl) (mean ± SD [range])	9.7 ± 5.5 (1.7–43.9)	7.3 ± 3.2 (1.9–15.1)	0.018
Portal hemodynamics			
Diameter of portal trunk (mm) (mean ± SD [range])	11.3 ± 2.4 (4.9–18.3)	12.1 ± 1.8 (7.9–14.4)	0.21
Mean flow velocity in the portal trunk (cm/second) (mean ± SD [range])	13.0 ± 3.0 (6.3–21.8)	11.8 ± 4.0 (6.9–20.8)	0.18
Mean flow volume in the portal trunk (ml/minute) (mean ± SD [range])	836.6 ± 368.6 (130–2165)	873.1 ± 393.1 (310–1760)	0.73
Collateral vessels (–/+)	25/141	2/12	0.94
Collateral vessels (diameter > 10 mm) (–/+)	146/20	14/0	0.17
Left gastric vein (hepatofugal)	97 (58.4%)	6 (42.9%)	0.26
Short gastric vein (hepatofugal)	36 (21.7%)	1 (7.1%)	0.2
Splenorenal shunts (hepatofugal)	19 (11.4%)	0 (0%)	0.18
Paraumbilical vein (hepatofugal)	36 (21.7%)	3 (21.4%)	0.98
Inferior mesenteric vein (hepatofugal)	10 (6.0%)	1 (7.1%)	0.87
Spleen (cm ²) (mean ± SD [range])	29.2 ± 13.2 (10.3–90.5)	33.2 ± 10.2 (18.4–50.5)	0.29
Portal vein thrombosis (–/+)	155/11	10/4	0.004

–, Absence; +, presence. Ascites: –, none; +, mild; ++, moderate to severe. Hepatic encephalopathy: –, grade 0–I; +, grade II–IV (West-Haven grading system).

AIH = autoimmune hepatitis, NASH = nonalcoholic steatohepatitis, PBC = primary biliary cirrhosis, SD = standard deviation.

(Table 3). History of variceal bleeding and portal vein thrombosis were significantly more frequent in IPH patients (5/7, 3/7) than in cirrhosis patients (16/60, $P = 0.016$; 4/60, $P = 0.003$).

Based on the data in Tables 1 and 3, baseline data were compared between cirrhosis/IPH patients with and without ascites (Table 4). The degree of Child-Pugh classification, model for end-stage liver disease (MELD) score, bilirubin level, and incidence of inferior mesenteric vein with hepatofugal flow direction were higher, and albumin and prothrombin activity were lower in cirrhosis patients with ascites than those without ascites. In contrast, lower albumin level and larger spleen size was noted in IPH patients with ascites. There was no significant difference in the HVPG between IPH patients with ascites (91.3 ± 36.8 , $n = 4$) and those without (71.8 ± 22.9 , $n = 5$; $P = 0.36$) at baseline.

Two of the 7 IPH patients who had no ascites at baseline developed ascites over the study period. A comparison of the baseline data between the 2 groups revealed the serum creatinine level (mg/dl) to be higher in those who developed ascites (0.74 ± 0.14) than those who did not (0.526 ± 0.06 , $P = 0.029$). Meanwhile, in 106 cirrhosis patients without ascites at baseline,

56 patients developed ascites and 50 patients did not. A history of variceal treatment was the only baseline factor that showed a significant difference between the 2 groups (cirrhosis without ascites 6/50, cirrhosis with ascites 20/56; $P = 0.005$).

Comparison of Prognosis Between Cirrhosis and IPH

The overall survival rate did not differ between cirrhosis (87.7% at 1 year, 75.2% at 3 years, and 63.6% at 5 years) and IPH (100% at 1 year, 92.9% at 3 and 5 years; $P = 0.21$) groups (Figure 2A). However, when ascites were present at baseline, the survival rates in cirrhosis patients (69.1% at 1 year, 43% at 3 years, 34.4% at 5 years) were significantly worse than those in IPH patients (100% at 1, 3, and 5 years, $P = 0.04$) (Figure 2B).

There were significant differences in the cumulative survival rates in cirrhosis groups according to the baseline ascites grade: 98.1% at 1 year, 93.4% at 3 years, and 80.4% at 5 years in the no ascites group; 77.8% at 1 year, 54.3% at 3 years, and 48.3% at 5 years in the grade 1 ascites group; 55.1% at 1 year, 25.2% at 3 years, and 12.6% at 5 years in the grade 2/3 ascites

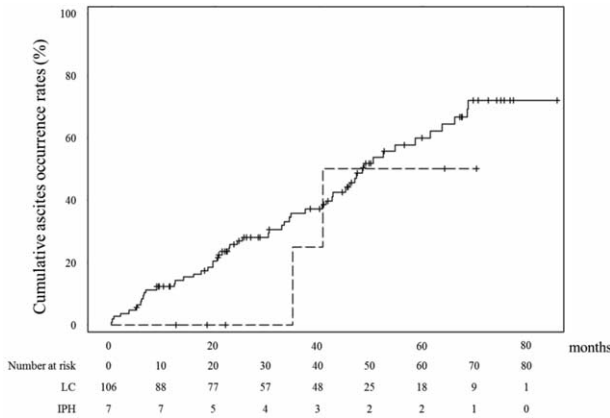


FIGURE 1. Cumulative incidence of ascites. There was no significant difference in cumulative incidence of ascites between cirrhosis (12.3% at 1 year, 35.9% at 3 years, 59.9% at 5 years) and idiopathic portal hypertension (25.0% at 3 years, 50.0% at 5 years; $P = 0.36$). Solid line, cirrhosis; dash line, idiopathic portal hypertension. Median observation period, 33.4 months (0.1–85.9).

group; overall, $P < 0.001$; none versus grade 1, $P < 0.001$; grade 1 versus grade 2/3, $P = 0.004$ (Figure 3A). In IPH patients, however, the survival rate showed no significant difference between patients with ascites (all showing grade 1 ascites at baseline; 100% at 1 year, 3 and 5 years) and those without (100% at 1 year, 85.7% at 3 and 5 years, $P = 0.92$) (Figure 3B).

HCC developed in 27/166 (16.3%) cirrhosis patients, and the cumulative incidence rate was 4.0% at 1 year, 14.7% at 3 years, and 27.4% at 5 years. None of the IPH patients developed HCC. In the cirrhosis group, 39 patients died (hepatic failure 31, unknown 2, variceal bleeding 1, gastrointestinal perforation 1, sepsis 1, rupture of abdominal aortic aneurysm 1, lung cancer 1, gingival cancer 1), and 9 patients received living-donor LT. In the IPH group, 2 patients died (hepatic failure in 1 and breast cancer in 1), and none received LT. The median observation period was 34.5 months (range, 0.3–86 m).

DISCUSSION

The development of ascites strongly suggests the presence of morphological and/or functional impairment of the liver.¹³ Previous studies have reported the incidence of ascites in noncirrhotic portal hypertension; that is, 12% in patients with IPH, according to the consensus guideline in Asia,¹⁵ and 9.9% (15/151) in patients with noncirrhotic portal hypertension, as reported in a study conducted in India.²³ The present study showed a relatively higher incidence of ascites; ascites was detected in more than 30% patients at baseline and more than 60% in total in patients with either cirrhosis or IPH. There may be some reasons for the higher incidence. The first is the early

detection of ascites by ultrasound, and the second is the advanced disease severity of IPH because the mean age of IPH patients was 64 years which may be higher than the age in the literatures.^{24,25} The last is that the heterogeneity of pathophysiology in IPH may account for the difference in the frequency of ascites, as previous reports suggest the different clinical aspects, age, gender, pathology, clinical manifestations, and portal hemodynamics between Japan and India.^{6,14,23}

The presence or absence of ascites may reflect the differences in baseline clinical characteristics among patients with chronic liver disease. We found that albumin levels in both cirrhosis and IPH were significantly lower in patients with ascites than in those without. There may be common underlying mechanisms of low osmotic pressure and a repeated drainage of the third-spaced fluid containing albumin. Additionally, a synthetic dysfunction due to worse liver disease may explain the lower albumin level. The incidence of refractory ascites and SBP was also similar between cirrhosis and IPH patients. The data are supported by a more recent study which showed that 35.3% (18/51) of IPH patients developed ascites during a mean study period of 6.7 years; 89% (16/18) of ascites cases were controlled after resolution of the trigger events or with small doses of diuretics, and only 11% (2/18) of cases had treatment-resistant ascites.²⁴ Our study also examined changes in the ascites grade over time in patients with grade 1 ascites at baseline, and deterioration was found in 32.4% of cirrhosis patients and 42.9% of IPH patients, being not significantly different.

Meanwhile, some findings were identified specific to IPH. First is that splenomegaly was a significant finding associated with the presence of ascites in IPH. Hyperdynamic flow into the portal system might have a greater stimulatory influence on the development of ascites in patients with IPH. The second is that the higher serum creatinine level was predictive for the future occurrence of ascites in IPH patients who have never had ascites. In contrast, portal vein thrombosis did not show any significant relationship with ascites despite its high incidence in IPH patients, which was comparable to the result of a previous study (13/28, 46.4%).²⁵ However, as the sample size of the IPH patient group in our study was small, further study would be needed to elucidate the interaction between ascites and portal vein thrombosis.

The prognosis of cirrhosis patients depends on the severity of liver disease; that is, 6-year survival was 54% in compensated and 21% in decompensated patients.¹⁰ Particularly, ascites is associated with a poor survival rate, 40% to 50% at 1 year, 50% at 2 years, and 20% at 5 years in cirrhosis patient with ascites.^{8,19} However, the present study found the relatively better prognosis in cirrhosis patients with ascites, which might be explained by following factors: the early diagnosis of low-level ascites by ultrasound, preserved liver function represented by the MELD score at baseline (mean, 11.3), and the fact that no cirrhosis patients died of HCC during the study period. Nonetheless, the first reason qualifies as “lead time bias,” and this

TABLE 2. Changes of Ascites Grade in Patients With Grade 1 Ascites at Baseline

	Grade 0	Grade 1	Grade 2/3	P-Value
Cirrhosis (N = 37)	10 (27.0%)	15 (40.5%)	12 (32.4%)	0.41
Idiopathic portal hypertension (N = 7)	3 (42.9%)	1 (14.3%)	3 (42.9%)	

Ascites: grade 0, none; grade 1, mild; grade 2/3, moderate to severe.

TABLE 3. Comparison of Baseline Clinical Data Between Cirrhosis and Idiopathic Portal Hypertension With Ascites

	Cirrhosis	Idiopathic Portal Hypertension	P-Value
Number of subjects	60	7	
Gastroesophageal varices (-/+)	19/41	0/7	0.08
History of variceal bleeding (-/+)	44/16	2/5	0.015
Hepatic encephalopathy (-/+)	58/2	7/0	0.62
Child-Pugh (A/B/C)	9/30/21	–	–
Model for end-stage liver disease score (mean ± SD [range])	12.5 ± 4.9 (7–26)	10.4 ± 5.9 (6–20)	0.29
Platelet count (10 ⁴ /μl) (mean ± SD [range])	9.9 ± 5.4 (1.8–24.4)	6.9 ± 4.1 (1.9–15.1)	0.18
Portal hemodynamics			
Diameter of portal trunk (mm) (mean ± SD [range])	11.4 ± 2.3 (5.3–17.4)	12.1 ± 1.9 (7.9–13.6)	0.42
Mean flow velocity in the portal trunk (cm/s) (mean ± SD [range])	12.6 ± 3.3 (6.3–21.1)	11.8 ± 4.9 (6.9–20.8)	0.55
Mean flow volume in the portal trunk (ml/min) (mean ± SD [range])	834.6 ± 404.2 (290–2150)	858.6 ± 520.0 (310–1760)	0.89
Collateral vessels (-/+)	9/51	2/5	0.36
Collateral vessels (diameter > 10 mm) (-/+)	54/6	7/0	0.38
Left gastric vein (hepatofugal)	36 (60.0%)	3 (42.9%)	0.38
Short gastric vein (hepatofugal)	12 (20.0%)	1 (14.3%)	0.72
Splenorenal shunts (hepatofugal)	9 (15.0%)	0 (0%)	0.27
Paraumbilical vein (hepatofugal)	13 (21.7%)	2 (28.6%)	0.68
Inferior mesenteric vein (hepatofugal)	8 (13.3%)	1 (14.3%)	0.94
Spleen (cm ²) (mean ± SD [range])	29.9 ± 15.5 (10.9–90.5)	39.8 ± 8.7 (30.5–50.5)	0.13
Portal vein thrombosis (-/+)	56/4	4/3	0.003

–, absence; +, presence. Hepatic encephalopathy: –, grade 0~I; +, grade II~IV (West-Haven grading system). SD = standard deviation.

might also explain the second reason by picking up the patients earlier in their disease course. These issues remain to be solved.

Investigators have reported a better prognosis in IPH than cirrhosis patients.^{6,14} In contrast, a relatively poor prognosis of

IPH was also reported in a study of 62 patients, which showed a 40% LT-free survival at 10 years.²⁶ However, the liver-related mortality was only 17.4%, and the difference in the prognosis may be dependent on the severity of the associated

TABLE 4. Significant Clinical Data Between Patients With and Without Ascites

	Ascites		P-Value
	–	+	
Cirrhosis			
Number of subjects	106	60	
Child-Pugh (A/B/C)	64/38/4	9/30/21	<0.001
Model for end-stage liver disease score (mean ± SD [range])	10.6 ± 3.4 (6–24)	12.5 ± 4.9 (7–26)	0.009
Blood test			
Bilirubin (mg/dl) (mean ± SD [range])	1.5 ± 1.1 (0.3–7.7)	2.9 ± 3.7 (0.5–20.2)	0.006
Albumin (g/dl) (mean ± SD [range])	3.5 ± 0.5 (2.3–4.7)	3.1 ± 0.6 (1.8–4.5)	<0.001
Prothrombin time (%) (mean ± SD [range])	70.5 ± 16.1 (34–107)	62.8 ± 17.0 (32–93)	0.004
Portal hemodynamics			
Inferior mesenteric vein (hepatofugal)	2 (1.9%)	8 (13.3%)	0.003
Idiopathic portal hypertension			
Number of subjects	7	7	
Blood test			
Albumin (g/dl) (mean ± SD [range])	4.1 ± 0.2 (3.8–4.3)	3.4 ± 0.5 (2.9–4.4)	0.015
Portal hemodynamics			
Spleen (cm ²) (mean ± SD [range])	27.5 ± 8.1 (18.4–41.9)	39.8 ± 8.7 (30.5–50.5)	0.022

SD = standard deviation.

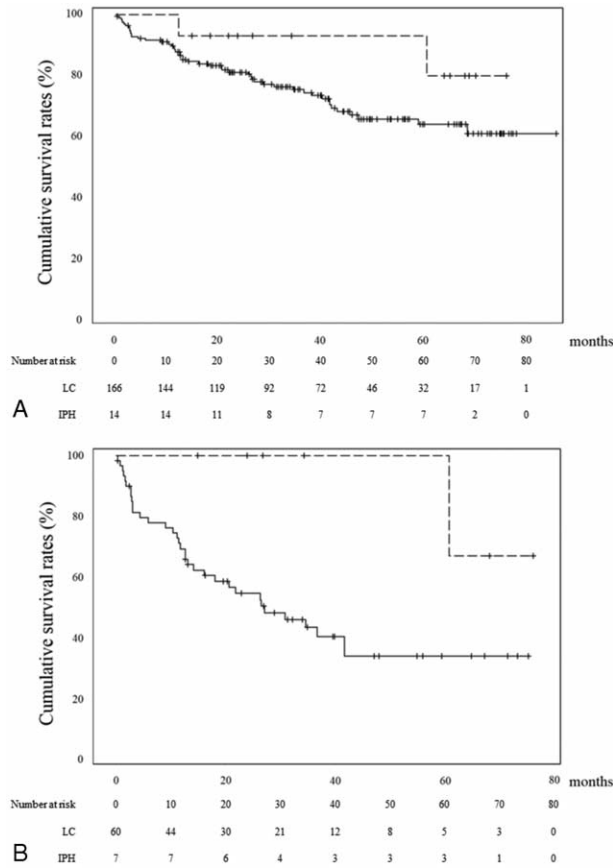


FIGURE 2. Cumulative survival rates between cirrhosis and idiopathic portal hypertension. (A) Overall survival rate. There was no significant difference in cumulative survival rates between cirrhosis (87.7% at 1 year, 75.2% at 3 years, 63.6% at 5 years) and idiopathic portal hypertension (100% at 1 year, 92.9% at 3 years, 92.9% at 5 years; $P=0.21$). Solid line, cirrhosis; dash line, idiopathic portal hypertension. Median observation period, 34.5 months (0.3–86.0). (B) Patients with ascites at baseline ($N=67$). Cumulative survival rate was significantly lower in cirrhosis (69.1% at 1 year, 43.0% at 3 years, 34.4% at 5 years) than idiopathic portal hypertension (100% at 1 year, 100% at 3 years, 100% at 5 years; $P=0.04$). Solid line, cirrhosis; dash line, idiopathic portal hypertension. Median observation period, 21.9 months (0.3–76.3).

comorbidities. The present study showed a favorable prognosis in IPH patients (100% at 1 year, 92.9% at 3 and 5 years) and only 2 patients died of hepatic failure or breast cancer. Although precise mechanism remains to be clarified, previous reports show no evidence of HCC occurrence in IPH patients^{14,16,24,27} and in fact, no HCC had developed in IPH patients in our study. In addition, the survival rate of IPH patients showed no significant difference between those with and without ascites at baseline, contrary to the results for cirrhosis patients. The lesser impact of ascites on survival in IPH patients may be due to potential differences in liver function between cirrhosis and IPH patients. Also, pathophysiological differences between sinusoidal and presinusoidal portal hypertension might account for the differential influence of ascites on survival.

The major limitation of this study is the retrospective setting in nature. Next, the number of IPH patients was so small that the statistical bias should be taken into account when

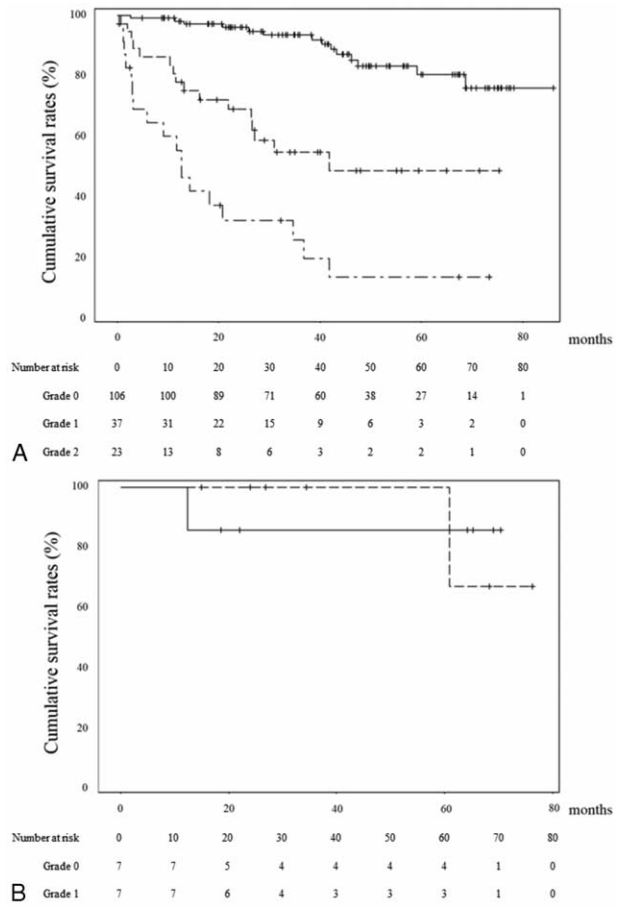


FIGURE 3. Comparison of survival rates between patients with and without ascites at baseline. (A) Cirrhosis ($N=166$). There were significant differences in cumulative survival rates according to the ascites grade at baseline; 98.1% at 1 year, 93.4% at 3 years, and 80.4% at 5 years in no ascites group; 77.8% at 1 year, 54.3% at 3 years, and 48.3% at 5 years in grade 1 ascites group; 55.1% at 1 year, 25.2% at 3 years, and 12.6% at 5 years in grade 2/3 ascites group; overall, $P<0.001$; none versus grade 1, $P<0.001$; grade 1 versus grade 2/3, $P=0.004$. Solid line, grade 0; dash line, grade 1; dash-dot line, grade 2/3. Ascites grade 0, none; grade 1, mild; grade 2/3, moderate to severe. (B) Idiopathic portal hypertension ($N=14$). Cumulative survival rate showed no significant difference between in patients with ascites (all showing grade 1 ascites; 100% at 1, 3, and 5 years) and those without (100% at 1 year, 85.7% at 3 and 5 years, $P=0.92$). Solid line, idiopathic portal hypertension without ascites; dash line, idiopathic portal hypertension with ascites.

the data are interpreted. Thirdly, there are some differences in the practical management of ascites and definition of refractory ascites between Western countries and Japan; for example, different dose limits for diuretics probably due to differences in race and physical size of patients. These issues need to be considered when the present study is evaluated.

In conclusion, this retrospective study demonstrated that the incidence and changes in ascites over time were similar between cirrhosis and IPH. However, it suggests an association between ascites at baseline in cirrhosis patients and increased mortality, but not in IPH. Presence of ascites in cirrhosis, therefore, might help prognosticate better.

REFERENCES

- Torres DM, Harrison SA. Diagnosis and therapy of nonalcoholic steatohepatitis. *Gastroenterology*. 2008;134:1682–1698.
- Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med*. 2012;156:271–278.
- Durand F, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis*. 2008;28:110–122.
- Cárdenas A, Ginès P. Management of patients with cirrhosis awaiting liver transplantation. *Gut*. 2011;60:412–421.
- Hillaire S, Valla DC, Lebre C. Non cirrhotic portal hypertension. *Clin Liver Dis*. 1997;1:1223–1240.
- Okuda K. Non-cirrhotic portal hypertension versus idiopathic portal hypertension. *J Gastroenterol Hepatol*. 2002;17:S204–S213.
- Orozco H, Takahashi T, Garcia-Tsao G, et al. A comparative clinical study of idiopathic portal hypertension, extrahepatic portal vein thrombosis, and cirrhosis. *J Clin Gastroenterol*. 1994;19:217–221.
- Gines P, Quintero E, Arroyo V, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology*. 1987;7:12–18.
- Powell WJ, Klatskin G. Duration of survival in patients with Laennec's cirrhosis of the liver. *Am J Med*. 1968;44:406–420.
- D'Amico G, Morabito A, Pagliaro L, et al. Survival and prognostic indicators in compensated and decompensated cirrhosis. *Dig Dis Sci*. 1986;31:468–475.
- Llach J, Gines P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoconstrictive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology*. 1988;94:482–487.
- Ginès P, Cárdenas A, Arroyo V, et al. Management of cirrhosis and ascites. *N Engl J Med*. 2004;350:1646–1654.
- Sanyal AJ, Bosch J, Blei A, et al. Portal hypertension and its complications. *Gastroenterology*. 2008;134:1715–1728.
- Sarin SK, Kapoor D. Non-cirrhotic portal fibrosis: current concepts and management. *J Gastroenterol Hepatol*. 2002;17:526–534.
- Sarin SK, Kumar A, Chawla YK, et al. Noncirrhotic portal fibrosis/idiopathic portal hypertension: APASL recommendations for diagnosis and treatment. *Hepatol Int*. 2007;1:398–413.
- Khanna R, Sarin SK. Non-cirrhotic portal hypertension—diagnosis and management. *J Hepatol*. 2014;60:421–441.
- The Japan Society for Portal Hypertension. The General Rules for Study of Portal Hypertension. 3rd ed. Tokyo, Japan: The Japan Society for Portal Hypertension; 2013.
- Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, and quantification: final report of the working party at the 11th World Congress of Gastroenterology, Vienna, 1998. *Hepatology*. 2002;35:716–721.
- European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53:397–417.
- Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. *Gut*. 2006;55:1–12.
- Moore KP, Wong F, Ginès P, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. *Hepatology*. 2003;38:258–266.
- Maruyama H, Kamezaki H, Kondo T, et al. Sonographic and clinical features of collateral vessels at the splenic hilum in cirrhosis. *Clin Radiol*. 2014;69:e140–e145.
- Dhiman RK, Chawla Y, Vasishta RK, et al. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. *J Gastroenterol Hepatol*. 2002;17:6–16.
- Siramolpiwat S, Seijo S, Miquel R, et al. Idiopathic portal hypertension: natural history and long-term outcome. *Hepatology*. 2014;59:2276–2285.
- Hillaire S, Bonte E, Denninger MH, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a re-evaluation in 28 patients. *Gut*. 2002;51:275–280.
- Schouten JN, Nevens F, Hansen B, et al. Idiopathic noncirrhotic portal hypertension is associated with poor survival: results of a long-term cohort study. *Aliment Pharmacol Ther*. 2012;35:1424–1433.
- Sawada S, Sato Y, Aoyama H, et al. Pathological study of idiopathic portal hypertension with an emphasis on cause of death based on records of Annuals of Pathological Autopsy Cases in Japan. *J Gastroenterol Hepatol*. 2007;22:204–209.