Reversed portal flow: Clinical influence on the long-term outcomes in cirrhosis

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Abstract

AIM: To elucidate the natural history and the longitudinal outcomes in cirrhotic patients with non-forward portal flow (NFPF).

METHODS: The present retrospective study consisted of 222 cirrhotic patients (120 males and 102 females; age, 61.7 ± 11.1 years). The portal hemodynamics were evaluated at baseline and during the observation period using both pulsed and color Doppler ultrasoundography. The diameter (mm), flow direction, mean flow velocity (cm/s), and mean flow volume (mL/min) were assessed at the portal trunk, the splenic vein, the superior mesenteric vein, and the collateral vessels. The average values from 2 to 4 measurements were used for the data analysis. The portal flow direction was defined as follows: forward portal flow (FPF) for continuous hepatopetal flow; bidirectional flow for to-and-fro flow; and reversed flow for continuous hepatofugal flow. The bidirectional flow and the reversed flow were classified as NFPF in this study. The clinical findings and prognosis were compared between the patients with FPF and those with NFPF. The median follow-up period was 40.9 mo (range, 0.3-156.5 mo).

RESULTS: Twenty-four patients (10.8%) demonstrated NFPF, accompanied by lower albumin level, worse Child-Pugh scores, and model for end-stage liver disease scores. The portal hemodynamic features in the patients with NFPF were smaller diameter of the portal trunk;
The prevalence of chronic liver disease is increasing worldwide with an extensive range of etiologies\(^1\,\text{a}\) to \(^3\). Cirrhosis, which is the end stage of liver disease, continues one of the leading causes of death because of the increased risk for developing variceal bleeding, hepatic failure, and hepatocellular carcinoma (HCC)\(^3\,\text{b}\) to \(^7\). Managing cirrhosis should be based on the proper assessment of disease severity and the prediction of outcomes\(^8\,\text{a}\) to \(^10\).

Portal hypertension, which represents the underlying pathophysiology of cirrhosis, is the basic mechanism responsible for several major complications. The impaired hemodynamics typified by the development of collateral vessels might explain the clinical presentations\(^3\,\text{a}\) to \(^13\). Doppler ultrasound (US), which is a frequently used diagnostic tool, offers real-time observation of hemodynamics with simple and reliable methodology\(^14\,\text{a}\) to \(^18\). It may also be the only method that can demonstrate the direction of blood flow in vessels under physiological conditions.

Non-forward portal flow (NFPF), i.e., reversed or bidirectional flow in the portal venous system, is an abnormal but not rare condition in cirrhosis. The unique and impaired hemodynamics associated with NFPF are based on the anatomical features of the portal venous system and may represent a sign of advanced portal hypertension\(^19\,\text{a}\) to \(^22\). However, the influence of NFPF on the long-term clinical outcomes in patients with portal hypertension remains undetermined.

We designed the current study to compare the clinical manifestations and the long-term outcomes between patients with forward flow in the portal venous system and those with NFPF. The aim of the study was to elucidate the effect of portal flow direction on the long-term clinical outcomes of patients with cirrhosis.

INTRODUCTION

The prevalence of chronic liver disease is increasing worldwide with an extensive range of etiologies\(^1\) to \(^3\). Cirrhosis, which is the end stage of liver disease, continues one of the leading causes of death because of the increased risk for developing variceal bleeding, hepatic failure, and hepatocellular carcinoma (HCC)\(^3\) to \(^7\). Managing cirrhosis should be based on the proper assessment of disease severity and the prediction of outcomes\(^8\) to \(^10\).
the West-Haven grading system\textsuperscript{[24]}, and grade II or above was classified as overt HE. The degree of ascites was defined according to the following established guidelines\textsuperscript{[25]}: mild for ascites that were only detectable by US examination, moderate for ascites that caused moderate symmetrical distention of the abdomen, and severe for ascites that caused marked abdominal distension. Moderate or severe ascites was classified as overt ascites. Portal vein thrombosis was defined as an echogenic structure that partially or completely occupied the lumen of the portal vein.

Decompensated cirrhosis was defined by the detection of at least one of the following presentations: variceal bleeding, overt ascites, overt HE, or jaundice (bilirubin level, $>$ 3.0 mg/dL)\textsuperscript{[26,27]}. The observation period was defined as the time between the initial US examination and the date of the last hospital visit, death, or liver transplantation.

Informed written consent for research use of medical records was obtained from all of the patients. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Chiba University Graduate School of Medicine.

Definition and treatment of varices

Gastroesophageal varices were assessed according to the general guidelines of the Japan Research Society for Portal Hypertension\textsuperscript{[28]}. Variceal bleeding was defined by both of the following criteria: (1) presence of bleeding history, such as hematemesis or melena; and (2) endoscopic evidence of active bleeding or a fibrin clot on the varices.

The study applied endoscopic band ligation for the patients with active bleeding from esophageal varices followed by sclerotherapy. Regarding the primary prophylaxis in patients with medium/large grade varices, endoscopic sclerotherapy was the treatment of choice. However, repeated band ligation was performed in patients with poor liver function (Child-Pugh C classification) or advanced liver cancer. Meanwhile, in patients with active bleeding from gastric varices, cyanoacrylate injection therapy (Histocacyl, B. Braun, Melsungen AG, Germany) was performed to achieve hemostasis.

Characteristics of the study subjects

There were 606 consecutive patients with cirrhosis who underwent Doppler US examinations to evaluate portal hemodynamics during the study period. Because 384 patients were considered to be ineligible for this study according to the exclusion criteria (Figure 1), the study included a total of 222 patients: age range, 20-89 years; mean age ± SD, 61.7 ± 11.1 years; and 120 males, 102 females. The routine blood tests for chronic liver disease, including serum albumin, bilirubin, prothrombin time, and platelet count, were performed within 5.5 mo (median, 0.1 mo; range, 0-5.5 mo) before and after the Doppler US examinations. The follow-up US and physical examinations were performed at least once per year in all of the patients. The median observation period was 40.9 mo (range, 0.3-156.5 mo).

US examination

The US equipment used was an SSA-390A or an SSA-770A (Toshiba, Tokyo, Japan) and a 3.75-MHz convex probe. The examination was performed with the patients placed in the supine position after fasting for more than 4 h.

The portal hemodynamics were evaluated using both pulsed and color Doppler US\textsuperscript{[15,16]}. The diameter (mm), flow direction, mean flow velocity (cm/s), and mean flow volume (mL/min) were assessed at the portal trunk, splenic vein (SV), superior mesenteric vein (SMV), and collateral vessels. The blood flow was
Table 1 Flow direction in the portal venous system (n (%))

|                  | Forward portal flow | Non-forward portal flow | Bidirectional flow | Reversed flow |
|------------------|---------------------|-------------------------|--------------------|--------------|
| Total            | 198 (89.2)          | 5 (2.3)                 | 19 (8.6)           |              |
| In portal trunk  | 137 (74.0)          | 10 (5.5)                | 19 (10.0)          |              |
| In splenic vein  | 20 (10.5)           | 2 (1.0)                 | 0 (0.0)            |              |
| In superior mesenteric vein | 15 (7.5) | 1 (0.5)                | 0 (0.0)            |              |

Table 2 Portal hemodynamics using Doppler sonograms (n (%))

| Characteristics of the largest collateral vessel | Forward portal flow | Non-forward portal flow | Bidirectional flow | Reversed flow |
|--------------------------------------------------|---------------------|-------------------------|--------------------|--------------|
| Number of subjects                               | 198                 | 17 (16.9)               | 3 (3.8)            |              |
| Portal vein thrombosis (-/+)                     | 15/17               | 6 (5.5)                 | 1 (1.0)            |              |
| Diameter of portal trunk (mm)                    | 11.9 ± 2.4          | 10.1 ± 2.0              | 10.2 ± 1.8         | 10.2 ± 2.0   |
| mean ± SD (range)                                | (4.9-22.7)          | (7.7-14.0)              | (7.7-14.0)         | (7.7-14.0)   |
| Collateral vessels (-/+)                          | 25/138              | 10/24                   | 4 (3.8)            |              |
| Left gastric vein (hepatofugal)                  | 19/173              | 10/24                   | 3 (3.8)            |              |
| Short gastric vein (hepatofugal)                 | 12 (6.2)            | 6 (5.5)                 | 1 (1.0)            |              |
| Splenorenal shunt (hepatofugal)                  | 13 (6.7)            | 6 (5.5)                 | 1 (1.0)            |              |
| Paraumbilical vein (hepatofugal)                 | 6 (3.1)             | 3 (3.0)                 | 1 (1.0)            |              |
| Inferior mesenteric vein (hepatofugal)           | 9 (4.6)             | 4 (3.8)                 | 1 (1.0)            |              |

1: absence, +: presence; 2: cut-off value was determined using the receiver operating characteristics analysis.

RESULTS

Flow direction in the portal venous system

The patterns of the portal flow direction were forward in 198 patients (89.2%), bidirectional in 5 patients (2.3%), and reversed in 19 patients (8.6%). Therefore, NFPF was found in 24 patients (10.8%), portal trunk in 5 patients (2.7%), SV in 22 patients (9.9%), and SMV in 2 patients (0.9%) (Table 1).

The portal trunk diameter was smaller in the patients with NFPF than in those with FPF (P = 0.0013). The development of collateral vessels was closely associated with the portal flow direction (Table 2); the presence of the left gastric vein (LGV) (P = 0.0020) and the paraumbilical vein (P = 0.0482) was more frequent in the patients with FPF, whereas the presence of the short gastric vein (SGV) (P < 0.0001), the splenorenal shunt (SRS) (P = 0.0088), and the inferior mesenteric vein (P = 0.0169) was more frequent in those with NFPF.

The best cut-off values of diameter, flow velocity, and flow volume in the largest collateral vessel selected from each individual were calculated using the ROC analysis between the patients with FPF and those with NFPF. 8.7 cm for diameter (P < 0.0001), 10.2 cm/s for flow velocity (P = 0.0126), and 310 mL/min for flow volume (P < 0.0001) (Table 2).

Relationship between portal flow direction and clinical presentations at baseline

The presence of gastric varices was significantly more frequent in patients with NFPF than in those with FPF (P = 0.0093). The albumin level was lower in the patients with NFPF than in those with FPF (P = 0.0039). The Child-Pugh classification (P = 0.0015) and the model for end-stage liver disease (MELD) score (P = 0.0335) were worse in the patients with NFPF than in those with FPF (Table 3). The prevalence of decompensated cirrhosis did not differ between the patients with FPF and those with NFPF (P = 0.1074) (Table 3).

Development of decompensation

Among the patients with compensated cirrhosis at baseline, the development of decompensated cirrhosis during the study period was found in 40.2% (37/92) (16 overt ascites, 9 variceal bleeding, 8 jaundice, and 4 HE) of the patients with FPF, and 42.9% (3/7) (2 HE, and 1 jaundice) of the patients with NFPF, and the results did not differ significantly between the groups (P = 0.8909). However, regarding the causes of decompensation, the development of HE was observed to be significantly more frequent in the patients with NFPF (2/7) than in those with FPF (4/92) (P = 0.0096). measured with a sampling width corresponding to the diameter of the vessel and an angle less than 60° between the US beam and the vessel. The average values from 2 to 4 measurements were used for the data analysis. The portal flow direction was defined as follows: forward portal flow (FPF) for continuous hepatopetal flow; bidirectional flow for to-and-fro flow; and reversed flow for continuous hepatofugal flow. The bidirectional flow and reversed flow were classified as NFPF in this study.

The US examinations were performed by Maruyama H or Takahashi M, who have more than 8 years of experience.

Statistical analysis

All of the data are expressed as the mean ± SD, median, or percentages. The comparisons were made between the patients with FPF and those with NFPF. The continuous variables were analyzed using Student’s t-test or Mann-Whitney U-test, as appropriate. The categorical variables were analyzed using the χ² test. The best cut-off value was calculated based on the receiver operating characteristics (ROC) analysis. The cumulative survival rate was calculated using the Kaplan-Meier method, and multivariate analysis was performed using Cox regression analysis. A P value of less than 0.05 was considered to be statistically significant. Statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, United States).
Table 3  Clinical findings in the subjects

|                       | Forward portal flow | Non-forward portal flow | P value |
|-----------------------|---------------------|-------------------------|---------|
| Number of subjects    | 198                 | 24                      |         |
| Age (yr), mean ± SD (range) | 61.9 ± 10.9 (35-89)  | 60.0 ± 12.6 (20-78)    | 0.4070  |
| Sex (male/female)     | 110/88              | 10/14                   | 0.1973  |
| Etiology (Virus/Alcohol/NASH/PBC/AIH/others) | 93/33/9/20/11/32 | 8/4/1/4/0/7 | 0.4003 |
| Ascites (+/-/++)²     | 137/32/29           | 14/6/4                  | 0.4949  |
| Esophageal varices (+/-)² | 73/125            | 10/14                   | 0.6464  |
| Gastric varices (+/-)² | 155/43              | 13/11                   | 0.0093  |
| History of variceal bleeding (+/-)² | 140/58            | 18/6                    | 0.6610  |
| History of variceal treatment (+/-)² | 152/46            | 18/6                    | 0.8469  |
| Spleen (cm³), mean ± SD (range) | 28.9 ± 12.9 (10.3-99.6) | 29.0 ± 16.4 (10.5-90.5) | 0.9900 |
| Hepatic encephalopathy (+/-)² | 190/8             | 23/1                    | 0.9764  |
| Child-Pugh (A/B/C)    | 92/84/22           | 6/9/9                   | 0.0015  |
| Decompensated cirrhosis (+/-)² | 92/106            | 7/17                    | 0.1074  |
| Model for end-stage liver disease score³, mean ± SD (range) | 11.0 ± 3.9 (6-24) | 13.1 ± 4.8 (6-24) | 0.0335 |

¹Ascites: < none; +: mild; ++: moderate to severe; ²: absence; +: presence; ³: Hepatic encephalopathy: grades 0-I; ⁴: grades II-IV (West-Haven grading system); ⁵: Forty-seven patients were excluded because prothrombin time-international normalized ratio was not measured in our hospital until 2004. AIH: Autoimmune hepatitis; NASH: Nonalcoholic steatohepatitis; PBC: Primary biliary cirrhosis.

Table 4  Cox regression analyses of the predictive factors for the development of non-forward portal flow

|                         | Univariate hazard ratio (95%CI) | P value | Multivariate hazard ratio (95%CI) | P value |
|-------------------------|---------------------------------|---------|-----------------------------------|---------|
| Diameter of portal trunk (< 11.2 mm) | 2.677 (1.269-5.648) | 0.0097 | 3.070 (1.276-7.389) | 0.0123 |
| Collateral vessels (flow velocity > 9.5 cm/s) | 2.818 (1.238-6.416) | 0.0136 | 3.987 (1.736-9.158) | 0.0011 |
| Short gastric vein (hepatofugal) | 3.059 (1.374-7.270) | 0.0061 | 3.428 (1.143-10.278) | 0.0279 |
| Splenorenal shunt (hepatofugal) | 3.485 (1.323-9.180) | 0.0115 |                         |         |

¹Cut-off value was determined using the receiver operating characteristics analysis.

Development of NFPF

Thirty-one patients developed NFPF from FPF during the study period, and the cumulative occurrence rates of NFPF were 6.5% at 1 year, 14.5% at 3 years, and 23.1% at 5 years. A univariate analysis showed that the diameters of the portal trunk < 11.2 mm (P = 0.0097) and the collateral vessels with flow velocity > 9.5 cm/s (P = 0.0136) were the best cut-off values using the ROC analysis and that the presence of SGV (P = 0.0061) and the presence of SRS (P = 0.0115) were significantly associated with the development of NFPF (Table 4). In the multivariate analysis, the collateral vessels with flow velocity > 9.5 cm/s (P = 0.0123), the presence of SGV (P = 0.0011), and the presence of SRS (P = 0.0279) were significant predictive factors for the development of NFPF (Table 4).

Among the patients with NFPF at baseline, the bidirectional flow changed to reversed flow in 1 patient, and the reversed flow changed to bidirectional flow in 3 patients during the study period.

Flow direction and survival

The cumulative overall survival rate was significantly worse in the patients with NFPF (79.2% at 1 year, 48.0% at 3 years, and 48.0% at 5 years) than those with FPF (90.9% at 1 year, 82.0% at 3 years, and 69.0% at 5 years; P = 0.0009) (Figure 2).

When stratified using Child-Pugh classification, there was no significant difference in the cumulative survival rate between the patients with FPF (98.9% at 1 year, 98.9% at 3 years, and 85.3% at 5 years) and those with NFPF (100% at 1 year, 75.0% at 3 years, and 75.0% at 5 years; P = 0.2314) using Child-Pugh A classification. However, the cumulative survival rate was significantly lower in the patients with NFPF (72.2% at 1 year, 38.5% at 3 years, and 38.5% at 5 years) than in those with FPF (84.0% at 1 year, 67.8% at 3 years, and 54.3% at 5 years; P = 0.0123) using Child-Pugh B and C classifications (Figure 3).

Twelve patients received liver transplantations, and 56 died during the study period: 39 died from hepatic failure, 8 died from HCC, 3 died from unknown cause, 2 died from variceal bleeding, 1 died from sepsis, 1 died from peritonitis of unknown origin, 1 died from a ruptured thoracic aortic aneurysm, and 1 died from heart failure.

DISCUSSION

The alternation in the blood flow direction is a unique...
phenomenon, that is observed in the portal venous system because of anatomical features and disease progression\[^{19-21}\]. The present study focused initially on determining the frequency of this hemodynamic abnormality. NFPF was observed in 8.6% of the patients with reversed flow and 2.3% of the patients with bidirectional flow in the portal venous system in cirrhosis. This result may be comparable to the data in the literature, indicating that the overall incidence of reversed flow in the portal venous system in cirrhosis was 8.3% (3.1% in the portal vein, 3.1% in the SV, and 2.1% in the SMV\[^{20}\]). Other studies have reported frequency rates of 2.3% (3/132) in the portal trunk\[^{29}\] and 9% in the intrahepatic portal vein\[^{21}\]. However, presumably, the prevalence in chronic hepatitis is 1% in the SV, which is lower than the rate in cirrhosis\[^{21}\].

Our study reported the cumulative incidence of NFPF, 6.5% at 1 year, 14.5% at 3 years, and 23.1% at 5 years, which have not been reported elsewhere. The presence of collateral vessels characterized by higher velocity (> 9.5 cm/s) or location at the splenic hilum was identified as significant hemodynamic factors associated with the future development of NFPF. In fact, there was no patient with NFPF who did not develop shunt vessels in our study. These data may suggest the influence of potentially advanced portal hypertension on the alternation of portal flow direction, and clearly encourage us to give these patients proper management.

Previous studies have shown a close relationship between flow direction in the portal venous system and liver function; hepatofugal flow was found to be more frequent in patients with Child-Pugh C (15.4%) and B (12.5%) classification than in those with Child-Pugh A (2.7%, \(P < 0.02\)) classification and was associated with a higher prevalence of HE (21% vs 7.2%; \(P < 0.05\))\[^{20}\]. Another study reported that reversed flow in the intrahepatic portal vein was significantly common in patients with Child-Pugh C (8/31, 25.8%) classification than in those with Child-Pugh A (0%)/B (5/104, 4.8%) classification\[^{21}\]. One likely mechanism that could explain these results is the impaired nutritional metabolism with a poor hepatic clearance of toxic substance under the condition of NFPF\[^{30}\]. Our study found that NFPF was closely associated with poor liver function, represented by serum albumin level, Child-Pugh classification, and MELD score. However, the portal flow direction was not a significant factor for the presence of liver decompensation at baseline in our study, which may be due to the definition of decompensation employed, i.e., one of the major presentations is bleeding from the esophageal varices that is related to the development of LGV. In the present study, however, the prevalence of LGV was higher in the patients with FPF and there was no difference in the bleeding history between the patients with FPF and those with NFPF. Collectively, our data indicate that there is little, if any, relationship between NFPF and clinical decompensation.

A major clinical interest regarding NFPF in cirrhosis is its influence on the patient’s prognosis. A previous study reported no significant difference in the survival rates between the patients with and without NFPF\[^{20}\]. However, because the mean observation period in the study was only 13 mo (range, 12-18 mo), it may be difficult to draw a definite conclusion regarding the influence of NFPF on the long-term clinical course of patients with cirrhosis. The present study compared the long-term outcomes with a median observation time of 41 mo between the patients with FPF and those with NFPF. Although flow direction was not a significant survival factor in Child-Pugh A subjects, prognosis was significantly poorer in Child-Pugh B and C subjects with NFPF than in those with FPF. Thus, the influence

![Figure 2 Cumulative survival rates between the patients with forward portal flow and those with non-forward portal flow.](image-url)
of portal flow on the patient’s prognosis depends on the patient’s liver function, which is an important point to consider in clinical practice.

Our study had several limitations. First, the data were obtained from the analysis under a retrospective setting. Therefore, the data must be validated in a prospective study. Second, our study lacks portal pressure data. The hemodynamics in patients with reversed flow direction should be assessed from the perspective of portal pressure in the future.

In conclusion, this longitudinal study has demonstrated the underlying hemodynamic mechanism, natural course and clinical influence of bidirectional or reversed portal flow in patients with cirrhosis. The presence of collateral vessels with high velocity and those at the splenic hilum are predictive features of the alternation of portal flow direction. Moreover, NFPF has a significant negative effect on the prognosis of patients with impaired liver function reserve. These observations highlight the usefulness of hemodynamic assessment using Doppler US, and suggest a likely direction for improving the clinical management of patients with cirrhosis.

**COMMENTS**

**Background**

Non-forward portal flow, i.e., reversed or bidirectional flow in the portal venous system, is an abnormal but not rare condition in cirrhosis. However, the influence on the long-term clinical outcomes in patients with portal hypertension remains undetermined.

**Research frontiers**

Portal hemodynamic abnormality, which is the key pathophysiology of cirrhosis patients, may account for the various manifestations. It may determine the long-term outcomes, which are informative for the clinical management of these patients.
Innovations and breakthroughs

Non-forward portal flow is associated with the development of collateral vessels and poor liver function. Furthermore, non-forward portal flow has a significant negative effect on the prognosis of patients with worse liver function reserve.

Applications

Careful management may be needed in the clinical practice of cirrhotic patients with non-forward portal flow.

Terminology

Non-forward portal flow was defined for the bidirectional portal flow or reversed portal flow in this study.

Peer-review

This is a very solid study based on an interesting finding. The results of this study include important data.

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This is a very solid study based on an interesting finding. The results of this study include important data.
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