

# Transjugular Liver Biopsy for Histological Diagnosis of Refractory Ascites and Evaluation of Portal Hypertension

TORU ISHIKAWA, RYO SATO, HIROKI NATSUI, TAKAHIRO IWASAWA, MASAHIRO OGAWA, YUJI KOBAYASHI, TOSHIFUMI SATO, JUNJI YOKOYAMA and TERASU HONMA

Department of Gastroenterology, Saiseikai Niigata Hospital, Niigata, Japan

## Abstract

**Background/Aim:** Determining the etiology of underlying liver disease is important when deciding on the optimal treatment course for refractory hepatic ascites. However, percutaneous liver biopsy is not recommended for such patients. To address this issue, we investigated the safety profile and diagnostic efficacy of wedged hepatic venous pressure (WHVP) measurement and transjugular liver biopsy (TJLB) to facilitate the histological diagnosis and evaluation of portal hypertension in cases of refractory ascites.

**Patients and Methods:** The clinical background, laboratory diagnostic success rate, complication rate, and survival-related factors were analyzed in 24 patients with refractory ascites, extracted from among 314 patients who underwent TJLB between May 2002 and December 2024.

**Results:** Overall, 15/9 cases were male/female, respectively, the mean age, Alb level, MELD score, and WHVP were 67.21 years, 2.61 g/dl, 24.917, and 38.24 cmH<sub>2</sub>O, respectively. The overall diagnostic success rate of the TJLB procedure was 100.0%, providing sufficient material for diagnosis. No severe complications were observed. Cases of ascites caused by chronic myelomonocytic leukemia (n=1) and amyloidosis (n=4) had a poor prognosis, whereas cases caused by autoimmune hepatitis (AIH) had a good prognosis following disease treatment. AIH and Child-Pugh class B were identified as factors contributing to survival.

**Conclusion:** TJLB has the advantage of allowing the assessment of portal venous pressure with WHVP, facilitating the histological diagnosis in cases of refractory ascites. TJLB could thus represent an alternative to percutaneous liver biopsy in patients with ascites, possibly contributing to better prognosis by allowing treatment strategy decisions according to the underlying disease cause.

**Keywords:** Transjugular liver biopsy, refractory ascites, portal hypertension, Child Pugh grade, wedged hepatic venous pressure.



Toru Ishikawa (ORCID: 0000-0002-5470-9694), MD, Ph.D., Director, Department of Gastroenterology, Saiseikai Niigata Hospital, Teraji 280-7, Niigata 950-1104, Japan. Tel: +81 252336161, Fax: +81 252338880, e-mail: toruishi@ngt.saiseikai.or.jp

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## Introduction

The European Association for the Study of the Liver (EASL) guidelines define refractory ascites as “a disease that responds inadequately to diuretics and salt restriction for at least one week or recurs within four weeks”, although some patients with refractory ascites may also present with pancytopenia and coagulopathy (1). Identifying the cause of ascites is difficult in cases of liver injury. Nevertheless, histological diagnosis of liver disease, which causes refractory ascites, is extremely important in determining the treatment strategy.

Transjugular liver biopsy (TJLB) is a minimally invasive procedure that allows the collection of liver tissue in cases where standard percutaneous liver biopsy is not indicated due to severe ascites (2-6). In addition, because refractory ascites may be associated with a background factor driving portal hypertension, TJLB has the advantage of simultaneously allowing the measurement of wedged hepatic venous pressure (WHVP) and hepatic venous-portal gradient (HVPG), along with hepatic venography (7, 8).

In the present study, we investigated the utility of TJLB for the histological diagnosis and evaluation of portal hypertension in patients with refractory ascites.

## Patients and Methods

*Patient enrollment.* This study enrolled 24 patients with refractory ascites and liver injury who received histological diagnosis after undergoing TJLB at our hospital. These patients were extracted from among the 314 patients who underwent TJLB at our institution between May 2002 and December 2024.

*Overview of the TJLB procedure.* During the TJLB procedure, the cannula was inserted into the right internal jugular vein via a 0.035-inch guidewire under the Seldinger technique by an experienced hepatologist under ultrasound and fluoroscopic guidance, followed by insertion of the 9-F 45 cm vascular sheath (Cook Medical, Bloomington, IN, USA) and a 7-F multipurpose catheter under fluoroscopic

control. Contrast-enhanced venography was performed to determine the actual position of the catheter prior to biopsy (9), and the LABS-100 system [Liver Access and Biopsy Kit, 18-gauge, 60 cm long, side-cut automated biopsy device (Quick-Core needle liver access kit; Cook Medical) 18 G; Cook Medical] was performed according to standard techniques (10). For TJLB, preoperative computed tomography (CT) was applied to confirm the degree of liver atrophy and the course of major blood vessels, to identify hepatic veins from which specimens could be safely collected, and to determine needle orientation and distance. A balloon catheter was applied during venography to confirm the position of the puncture and measure the WHVP (Terumo, Tokyo, Japan) (11).

Fluoroscopy and electrocardiography monitoring were performed throughout the procedure, and contrast medium was injected through the catheter to rule out capsular perforation after the biopsy.

*Measurement of laboratory factors.* The following parameters were measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T.Bil), direct bilirubin (D.Bil), mean platelet count, mean prothrombin (PT) activity, and mean prothrombin time-international normalized ratio (PT INR) following standard procedures in all patients preoperatively.

*Clinical scoring.* All patients underwent measurement of the Model for End-Stage Liver Disease (MELD) score (12), Child-Pugh score (13), and Albumin-Bilirubin (ALBI) score (14) following standard procedures.

*Evaluation of adverse events.* Postoperative vital signs, including oxygen saturation, were initially monitored every 30 min for 2 h, and then every 6 h for 24 h. Minor and major adverse events were classified according to the Society of Interventional Radiology criteria (15). Patients suspected of experiencing adverse events were closely monitored and underwent serial hemoglobin, hematocrit, and blood chemistry tests.

Table I. Characteristics of patients with refractory ascites.

Characteristics	Value
Age (years)	67.21±11.58
Sex (Male: Female)	15:9
WHVP (cmH <sub>2</sub> O)	38.24±8.04
Creatinine (mg/dl)	1.93±2.63
T.Bil (mg/dl)	5.72±7.30
D.Bil (mg/dl)	4.18±5.73
AST (IU/l)	131.87±206.96
ALT (IU/l)	63.92±87.24
Albumin (g/dl)	2.61±0.52
NH <sub>3</sub> (μg/dl)	76.24±42.12
Platelet (×10 <sup>4</sup> /μl)	11.19±5.22
PT (%)	59.77±31.33
PT INR	1.58±0.81
MELD score	24.92±8.07
Child Pugh score	11.35±1.85
ALBI score	-1.11±0.55
Child-Pugh (8/9/10/11/12/13/14/15)	(1/5/3/3/5/5/1/1)

Values are shown as mean±SD (standard deviation) or number. ALBI: Albumin Bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; D.Bil: direct bilirubin; MELD: Model for End-stage Liver Disease; PT INR: mean prothrombin time-international normalized ratio; PT: prothrombin; T.Bil: total bilirubin; WHVP: wedged hepatic venous pressure.

**Ethics approval and informed consent.** The study protocols were approved by the Institutional Review Board of Saiseikai Niigata Hospital (approval no.: E05-13), and the study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013). Prior to participation in this study, written informed consent was obtained from all patients.

**Statistical analysis.** Sex ratios were compared using Fisher's exact test, while background diseases were analyzed using the  $\chi^2$  test. Age, WHVP, Child-Pugh score and MELD were assessed using the Mann-Whitney *U*-test. Overall survival during the follow-up period was compared using the Kaplan-Meier method, and evaluated using the log-rank test. A *p*-value <0.05 was considered significant. All statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R version 3.2.2 (The R Foundation for Statistical Computing, Vienna, Austria) (16).

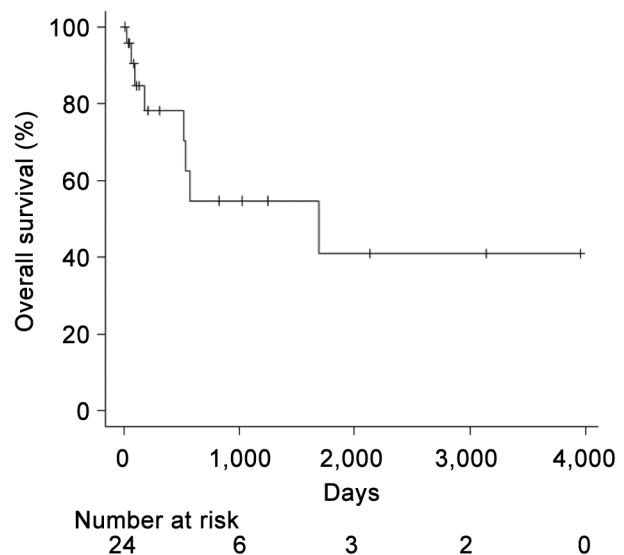


Figure 1. Kaplan-Meier curve demonstrating the overall survival of patients with refractory ascites following the transjugular liver biopsy-based diagnosis.

## Results

The mean age of the 24 enrolled patients was 67.21±11.58 years, and the cohort comprised 15 males and 9 females. The following laboratory indicators were measured: mean AST 131.87 IU/l, mean ALT 63.92 IU/l, mean T.Bil 5.72 mg/dl, mean D.Bil 4.18 mg/dl, mean platelet count 111,900/μl, mean PT activity 59.77%, mean PT INR 1.58. Finally, the mean WHVP was 38.24 cm H<sub>2</sub>O, mean MELD score was 24.92, mean Child-Pugh score was 11.35, and mean ALBI score was -1.11 (Table I).

Histological diagnosis was possible in all patients, including 4 cases of amyloidosis, 1 case of chronic myelomonocytic leukemia (CMMoL) liver infiltration, 9 cases of alcoholic cirrhosis, 2 cases of Burn-out non-alcoholic steatohepatitis, 4 cases of ACLF-like conditions with acute cellular damage at the base of cirrhosis, and 4 cases of autoimmune cirrhosis (Table II).

The median survival time of all patients was 1,688 days (Figure 1). The median survival of the Child-Pugh class B group (n=6) was not reached, and was better than that of the Child-Pugh class C group (n=18), although this

Table II. Histological diagnosis and characteristics of enrolled patients.

Categories	CMMoL (n=1)	Amyloidosis (n=4)	Alcoholic LC (n=9)	Burn-out NASH (n=2)	Acute damage (n=4)	Autoimmune (n=4)	p-Value
Age (years)	68	66.75±8.50	64.00±14.77	70.50±19.09	74.00±6.97	66.25±10.14	0.847
Sex (Male: Female)	1/0	2/2	6/3	2/0	2/2	2/2	0.889
WHVP (cmH2O)	28	30.75±6.18	36.50±9.24	47.00±1.41	43.15±5.79	36.00±3.46	0.089
MELD	8	31.50±4.04	26.11±6.62	26.50±2.12	22.50±10.34	21.50±8.66	0.116
Child-Pugh	9	10.25±2.21	11.88±2.14	11.50±0.70	11.00±1.82	11.50±1.29	0.619

Values are shown as mean±SD (standard deviation) or number. CMMoL: Chronic myelomonocytic leukemia; MELD: LC: liver cirrhosis; Model for End-stage Liver Disease; NASH: non-alcoholic steatohepatitis; WHVP: wedged hepatic venous pressure.

difference was not statistically significant ( $p=0.304$ ) (Figure 2).

The patient cohort included one Child Pugh 8 case of amyloidosis, with a median survival of 575 days; Child Pugh 9 was not reached in five cases; three cases of Child Pugh 10 with a median survival of 1,103 days; three cases of Child Pugh 11 with a median survival of 176 days; five cases of Child Pugh 12 with a median survival of 535 days; Child Pugh 13 was not reached in five patients; one patient with Child Pugh 14 with alcoholic cirrhosis; and one patient with Child Pugh 15 with alcoholic cirrhosis, who remained alive for 97 days ( $p=0.0064$ ).

There were no statistically significant differences in sex ( $p=0.981$ ), age ( $p=0.823$ ), WHVP ( $p=0.55$ ), or MELD ( $p=0.829$ ).

Adverse events included intraoperative grade 1 arrhythmia in one patient (4.16%) and grade 1 pain during biopsy in one patient (4.16%); however, no bleeding or other serious adverse events were observed.

## Discussion

Liver biopsy is the gold standard for evaluating acute and chronic liver injury (17). TJLB, a useful alternative, was first described by Dotter in 1964 (18), and first performed clinically by Hanafee in 1967 (19). TJLB usually involves obtaining liver tissue through a rigid cannula introduced into the hepatic vein, using jugular venous access, and is indicated for patients with coagulopathy, ascites, hepatitis,

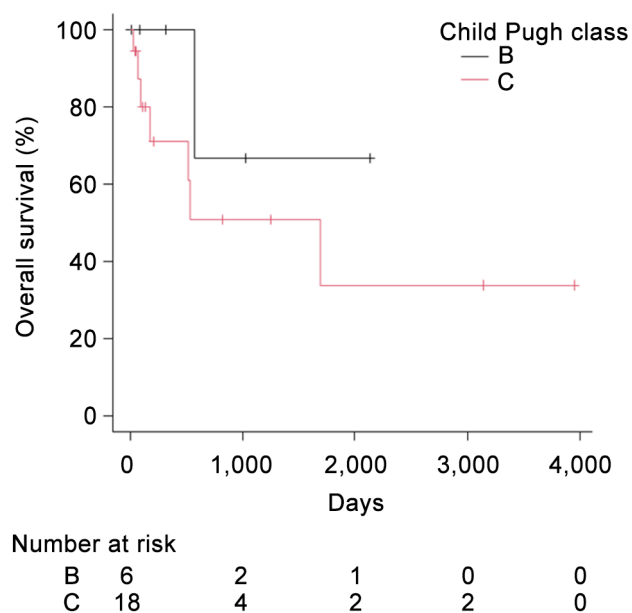


Figure 2. Kaplan-Meier curve demonstrating the overall survival of patients with refractory ascites patients following the transjugular liver biopsy-based diagnosis: stratified according to Child Pugh grade ( $p=0.304$ ).

morbid obesity, liver transplantation, or undergoing transjugular intrahepatic portal venous major circulation shunt surgery.

Although portal hypertension is presumed to occur in refractory ascites, direct measurement of portal venous pressure (PVP) is invasive. Nevertheless, evaluation of PVP is essential in understanding the pathophysiology and hemodynamics of portal hypertension (PH), and may

reflect the status of refractory ascites. In 1951, Myers and Taylor first reported WHVP as an indirect method for measuring PVP (20). The WHVP can be measured during TJLB, allowing the simultaneous diagnosis of portal hypertension and tissue diagnosis in cases of refractory ascites (4, 21).

Although we have previously reported on the technical innovations of TJLB and its utility in the treatment of various pathological conditions (22-25), its significance in patients with refractory ascites is not yet clear. Therefore, in the present study, we investigated WHVP and background liver factors during TJLB in patients with refractory ascites, as well as survival factors after TJLB intervention. Our results revealed that even in patients with a high WHVP, the prognosis improved with improved hepatic reserve in patients whose current disease could be controlled under treatment guidelines, such as those with autoimmune hepatitis. However, survival analysis showed no difference based on WHVP. Therefore, factors of the current disease were extracted. Subsequent analysis suggested that even in cases of refractory ascites, it is important to treat the current disease based on histological diagnosis by TJLB.

In fact, according to the liver transplant registry data analysis of patients with Child-Pugh class C cirrhosis in Japan, the median survival times (MST) of patients with Child-Pugh 10, 11, and 12 points were 719, 521, and 438 days, respectively, whereas the MST of Child-Pugh 13 points was 132 days, clearly indicating a poor prognosis (26).

In the present study, the MSTs of Child-Pugh 10-, 11-, and 12-point cases were 1,103, 176, and 535 days, respectively, although the prognosis was influenced by the case background. Indeed, Child-Pugh 13-point cases did not reach the MST, indicating the importance of establishing histological evidence by TJLB for aggressive therapeutic intervention. These results highlight the importance of establishing histological evidence using TJLB to facilitate aggressive therapeutic interventions.

The complication rates of patients in the present study were low, ranging from 1.3% to 6.5% (4). Most complications are minor and associated with bleeding at

the puncture site or abdominal pain related to the presence of a small hematoma that distends the liver sac. Major complications based on the published SIR criteria have been reported in 0.6% of patients (4). In the present study, all cases of elevated WHVP were identified, in which the patient had portal hypertension; however, no serious complications were observed.

*Study limitations.* Firstly, the sample size was relatively small. Second, due to the limited sample size, we did not conduct a comparison of patients with various disease stages. Third, the retrospective design may have introduced bias in patient selection. Finally, this study only considered data from a single center. Future prospective clinical trials with larger sample sizes and varied multicenter patient populations are required to verify our findings.

## Conclusion

Proactive histological diagnosis by TJLB in patients with refractory ascites liver lesions could be expected to improve the prognosis if the treatment of the current disease is successful. In the future, as more cases are accumulated, it will be important to investigate the usefulness of TJLB for patients with refractory ascites.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

Conceptualization: Toru Ishikawa; Data Curation: Toru Ishikawa; Formal Analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Ryo Sato, Hiroki Natsui, Takahiro Iwasawa, Masahiro Ogawa, Yuji Kobayashi, Toshifumi Sato, Junji Yokoyama and Terasu Honma; Methodology: Toru Ishikawa; Project Administration: Toru Ishikawa; Resources: Toru Ishikawa; Software: Toru Ishikawa;

Visualization: Toru Ishikawa; Writing – Original Draft: Toru Ishikawa; Writing – Review & Editing: Toru Ishikawa, Ryo Sato, Hiroki Natsui, Takahiro Iwasawa, Masahiro Ogawa, Yuji Kobayashi, Toshifumi Sato, Junji Yokoyama, and Terasu Honma.

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