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Clinical Significance of Transjugular Liver Biopsy in Liver Dysfunction During Immune Checkpoint Inhibitor Therapy

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Abstract

Background/Aim: Transjugular liver biopsy (TJLB) is indicated for patients unsuitable for percutaneous liver biopsy owing to coagulation abnormalities or ascites. While immune checkpoint inhibitors (ICIs) are cornerstone therapies for cancers, immune-related adverse events (irAEs) remain a concern. Specifically, concurrent pancytopenia or coagulation abnormalities often preclude percutaneous biopsy in these patients. The aim of this study was to evaluate the outcomes and utility of TJLB in patients with suspected ICI-induced liver injury.

Patients and Methods: This study involved seven patients who developed liver injury while receiving ICI therapy at our institution and required histological diagnosis *via* TJLB. All TJLB procedures were performed using the right internal jugular vein approach.

Results: The mean age of patients (six male and one female) was 68.14±9.61 years. Among patients with liver cancer receiving ICIs, two received atezolizumab plus bevacizumab and two received durvalumab plus tremelimumab. Among patients with lung cancer, three received pembrolizumab. Laboratory findings at TJLB were as follows: alanine aminotransferase, 553.28±903.76 U/l; aspartate aminotransferase, 440.57±571.05 U/l; total bilirubin, 4.82±4.77 mg/dl; and gamma-glutamyltransferase, 267.42±320.21 U/l. In one patient with liver cancer, liver dysfunction worsened due to underlying liver disease. Both patients with liver cancer treated with durvalumab plus tremelimumab had confirmed irAEs. One patient with lung cancer had confirmed irAEs, whereas another was diagnosed with drug-induced liver injury. One patient with lung cancer treated with later-line ICIs showed no tumor lesions in the liver on imaging but had elevated wedged hepatic venous pressure, indicating liver dysfunction due to tumor infiltration.

Conclusion: TJLB is a valuable tool for the early diagnosis of ICI-related liver injury and establishing treatment guidelines based on the underlying etiology.

Keywords: Transjugular liver biopsy, liver dysfunction, immune checkpoint inhibitor, wedged hepatic venous pressure.

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Introduction

Immune checkpoint inhibitors (ICIs) block immune checkpoint pathways, reactivating T cell responses against cancer cells and improving survival rates in patients with a variety of malignancies (1, 2). Nivolumab and pembrolizumab target programmed cell death 1 (PD-1) on the surface of T lymphocytes, inhibiting its interaction with programmed death ligands (PD-L) 1 and 2 expressed on cancer cells (3, 4). Atezolizumab and durvalumab inhibit PD-L1 expression (5, 6), whereas ipilimumab targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) on T cell surfaces (7). Blocking this ligand–receptor interaction prevents T-lymphocyte inactivation and restores antitumor efficacy (8). However, the clinical benefits of ICIs can be compromised by immune-related adverse events (irAEs) stemming from immune system imbalance. The mechanism of hepatic irAEs is thought to be similar to that of autoimmune hepatitis, but it is not yet fully understood (9).

Corticosteroids are the first-line treatment for liver irAEs, with mycophenolate mofetil considered in steroid-resistant cases (10). Characterizing hepatic irAEs is crucial for optimizing patient management, as long-term immunosuppression can lead to serious treatment-related complications.

Liver biopsy aids in the definitive diagnosis of ICI-induced liver injury by excluding alternative diagnoses and allowing for the assessment of disease severity and underlying pathology. Ideally, biopsy should be performed before administering corticosteroids, especially when other etiologies must be excluded or when severe liver damage is observed. However, percutaneous liver biopsy is often contraindicated in cases of coagulation abnormalities, severe liver damage, ascites, or a high risk of bleeding associated with irAEs. In such instances, transjugular liver biopsy (TJLB) may be utilized after a thorough evaluation of indications; however, its utility specifically for managing irAE-related liver injury has not yet been extensively investigated. In this study, we aimed to examine the clinical significance of TJLB in diagnosing and managing liver injury during ICI therapy.

Patients and Methods

Participants. This retrospective study involved seven patients who developed severe hepatic impairment while receiving ICI therapy for solid malignant tumors at our institution between January 2020 and December 2025. In all patients, imaging confirmed the absence of tumor lesions near the hepatic veins. TJLB was performed in all patients to determine disease etiology and severity; additionally, wedged hepatic venous pressure (WHVP) was simultaneously measured.

Hepatitis severity was assessed using the Common Terminology Criteria for Adverse Events classification. Patterns with liver injury were evaluated using the R value, calculated as follows: R=(alanine aminotransferase level/upper limit of normal level)/(alkaline phosphatase level/upper limit of normal level). Cases were classified as cholestatic ($R \leq 2$), hepatocellular ($R \geq 5$), or mixed ($2 < R < 5$) (11).

TJLB procedure. During the TJLB procedure, a cannula was inserted into the right internal jugular vein using a 0.035-inch guidewire following the Seldinger technique, by an experienced hepatologist under ultrasound and fluoroscopic guidance. This was followed by the insertion of a 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 verify the position of the catheter prior to biopsy (12). Tissue collection was then performed using 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] or transjugular liver biopsy system [TLAB flexcore biopsy system, 18-gauge, 60-cm long, side-cut automated biopsy device; Argon Medical Devices, Inc. (Plano, TX, USA)] following standard techniques (13).

Prior to the procedure, preoperative computed tomography was used to assess the degree of liver atrophy and the anatomical course of major blood vessels. This

allowed for the identification of hepatic veins from which specimens could be safely collected and helped determine optimal needle orientation and distance. A balloon catheter (Terumo, Tokyo, Japan) was employed during venography to confirm the puncture site and measure the WHVP (Terumo) (14). Fluoroscopy and electrocardiography findings were monitored throughout the procedure, and the contrast medium was injected through the catheter to rule out capsular perforation following the biopsy.

Evaluation of AEs. Postoperative vital signs, including oxygen saturation, were monitored every 30 min for the first 2 h, and subsequently every 6 h for the following 24 h. Minor and major AEs were classified according to the Society of Interventional Radiology criteria (15). Patients suspected of experiencing AEs were closely monitored *via* serial hemoglobin, hematocrit, and blood chemistry analyses.

Ethics approval and informed consent. The study protocol was 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 (revised 2013). Written informed consent was obtained from all patients prior to their participation in this study.

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

Results

The mean age of patients (six male and one female) was 68.14±9.61 years. The primary tumors were as follows: hepatocellular carcinoma (HCC, four patients) and lung cancer (three patients). Among the patients with HCC, two were administered ICI therapy comprising atezolizumab (anti-PD-1 antibody) in combination with bevacizumab and two were administered durvalumab (anti-PD-L1 antibody) and tremelimumab (anti-CTLA-4 antibody). For lung cancer, pembrolizumab (an anti-PD-1 antibody) was used in all three patients; it was used as a post-ICI line in two patients (Table I).

The results of liver function assessment with TJLB were as follows: alanine aminotransferase level, 553.28±903.76 U/l; aspartate aminotransferase level, 440.57±571.05 U/l; total bilirubin level, 4.82±4.77 mg/dl; direct bilirubin level, 3.25±3.48 mg/dl; alkaline phosphatase level, 284.14±193.94 U/l; gamma-glutamyltransferase level, 267.42±320.21 U/l; lactate dehydrogenase level, 461.42±383.81 U/l; prothrombin time, 76.70%±51.09%; and prothrombin time–international normalized ratio, 1.38±0.49 (Table I). The mean R value was 3.8. Symptoms developed during hepatic impairment were diverse. The mean ICI course was 5.28±4.96 and duration was 167.86±191.82 days (Table I).

In one patient with HCC presenting with a metabolic dysfunction-associated steatohepatitis background and mild ascites during atezolizumab plus bevacizumab therapy, histological assessment revealed CD4 > CD8, with a high WHVP of 46 cmH_2O. This was diagnosed along with ascites and jaundice due to portal hypertension from bevacizumab or worsening of underlying cirrhosis and was not considered an irAE. Anti-HB core antibody–positive patients with HCC receiving atezolizumab and bevacizumab showed signs of irAEs, in addition to exhibiting hepatitis B virus reactivation (Table II). Nucleoside analogs were administered concurrently with steroids, as blind introduction of steroids alone was considered risky. Two patients with hepatitis C virus-related HCC treated with durvalumab plus tremelimumab

received steroids based on a confirmed diagnosis of irAEs. A woman with lung cancer who was receiving pembrolizumab therapy as first-line treatment and had normal WHVP also received steroids. Additionally, one patient with lung cancer receiving pembrolizumab as a later-line ICI was diagnosed with drug-induced liver injury but not irAEs (Table II). Another patient with lung cancer who received various ICIs developed liver injury after pembrolizumab treatment. Although no tumor lesions were detected in the liver, prominent lacunar lesions were identified on imaging. The patient had elevated WHVP, and tumor infiltration was histologically confirmed (Table II); consequently, a change in the treatment strategy was required to replace steroids. No complications related to TJLB were observed in this study.

Table I. *Demographic details and characteristics of patients with liver dysfunction due to immune-checkpoint inhibitor (ICI) use.*

Characteristic	Value
Age (years)	68.14±9.61
Sex (Male:Female)	6:1
Etiology (HBcAb/HCV/MASH/Others)	1/2/1/3
Primary Cancer (HCC/Lung Cancer)	4/3
T.Bil (mg/dl)	4.82±4.77
D.Bil (mg/dl)	3.25±3.48
ALT (U/l)	553.28±903.76
AST (U/l)	440.57±571.05
ALP (U/l)	284.14±193.94
GGTP (U/l)	267.42±320.21
LDH (U/l)	461.42±383.81
PT (%)	76.70±51.09
INR	1.38±0.49
Course	5.28±4.96
Duration (days)	167.86±191.82

ALT: Alanine aminotransferase; AST: aspartate aminotransferase; T.Bil: total bilirubin; D.Bil: direct bilirubin; ALP: alkaline phosphatase; GGTP: gamma-glutamyltransferase; LDH: lactate dehydrogenase; PT: prothrombin time; INR: international normalized ratio; HCC: hepatocellular carcinoma; MASH: metabolic dysfunction-associated steatohepatitis; HBcAb: Anti-HB core antibody; HCV: hepatitis C virus.

Discussion

In this study, we evaluated the clinical utility of TJLB in seven patients who developed liver dysfunction during ICI therapy. Histological assessment using TJLB revealed that the liver injury was attributable to not only irAEs, but also other etiologies such as drug administration, tumor infiltration, and exacerbation of underlying liver disease. These findings led to changes in clinical management, including appropriate use or avoidance of corticosteroid therapy. In addition, measurement of WHVP provided complementary information regarding portal hypertension and underlying pathophysiology. Patients with suspected irAE-associated liver injury eligible for TJLB could be managed by switching to tissue-specific treatment strategies based on histological diagnosis rather than relying primarily on steroid administration. Notably, TJLB was performed safely in all cases without procedure-related complications.

Since the approval of ipilimumab, an anti-CTLA-4 antibody, for the treatment of unresectable malignant melanoma in 2010 (1), ICI immunotherapy has advanced beyond CTLA-4 antibodies to include anti-PD-1 and anti-PD-L1 antibodies. These antibodies have gained approval for use in the treatment of various cancer types alongside surgical treatment, radiation therapy, and chemotherapy. AEs associated with ICIs are considered immune-related owing to their mechanism of action. The frequency of liver injury varies according to the primary disease, drug type, and method of administration (17); however, severity assessments, including histopathological findings of immune-related liver injury, have been proposed (18). It is important to actively diagnose and determine disease severity based on histopathological findings.

Liver biopsy is performed for diagnosis, severity assessment, and treatment decision-making in cases of liver injury due to irAEs. The purpose of liver biopsy in irAE-related liver injury is to validate the diagnosis by differentiating it from other liver disorders (such as viral hepatitis, drug-induced liver injury, and autoimmune hepatitis). In contrast, even when the risk of bleeding from percutaneous liver biopsy is deemed clinically acceptable, some patients avoid biopsy owing to this concern and instead opt to be treated with steroids or other agents. However, indiscriminate steroid use may affect subsequent treatments; in such cases, TJLB is considered an appropriate option.

Table II. *Clinical features of patients with suspected hepatic immune-related adverse events (irAEs).*

Age, years	Sex	Primary cancer	ICIs	Course	Duration (days)	Clinical symptoms	WHVP (cmH_2O)	Histological analysis
59	Male	HCC	DurTre	1	10	Fever, Fatigue	39.0	CD8 > CD4 irAE
59	Male	HCC	Atez/Beva	11	242	Edema	46.0	CD4 > CD8 irAE negative
75	Male	HCC	Atez/Beva	12	561	Fatigue	26.2	CD8.CD4 irAE, Victoria Blue(HBsAg)(+)
84	Male	HCC	DurTre	1	36	Anorexia	20.5	CD8 > CD4 irAE
74	Female	Lung Cancer	Pem	7	181	Abd pain	15.3	CD8 > CD4 irAE
64	Male	Lung Cancer	Pem	2	68	Fatigue	26.0	Drug liver injury
62	Male	Lung Cancer	Pem	3	77	Epigastralgia	51.0	Cancer invasion

DurTre: Durvalumab/tremelimumab; AB: atezolizumab/bevacizumab; Pem: pembrolizumab; Abd: abdominal; WHVP: wedged hepatic venous pressure.

TJLB is indicated for irAE-related liver injury when percutaneous liver biopsy is contraindicated, such as in patients with severe coagulation abnormalities, bleeding risk, ascites, steroid-refractory disease, and suspected concomitant autoimmune hepatitis and those receiving immunosuppressive therapy. Furthermore, it enables the assessment of portal hypertension through hepatic venous pressure gradient measurement. TJLB has reportedly been utilized in severe cases of irAE-related liver injury (19); additionally, some studies have demonstrated its diagnostic value in cases with high bleeding risk (12, 20).

A previous study has classified pathological subtypes (hepatitis or cholangitis type) and examined the relationship with treatment response in some TJLB cases (21). However, studies focusing solely on TJLB are scant. Moreover, owing to the lack of comparative studies on biopsy timing and steroid treatment initiation, the correlation between pathological patterns and treatment response, such as steroid sensitivity and the need for additional immunosuppressants, remains to be fully established. Prompt biopsy during the early disease phase and prior to steroid initiation is crucial, underscoring the importance of TJLB. The reported incidence of severe cases (Grade III-IV hepatitis) of irAE-related liver injury is approximately 3%-8% (22); such cases are considered optimal indications for TJLB.

Although reports explicitly describing TJLB use in irAE-related liver injury cases are limited, we have previously demonstrated the usefulness of TJLB in acute liver failure (23), liver injury secondary to hematologic disease treatment (24), and refractory ascites-related cases (25).

In one case report of ICI-induced irAEs, a middle-aged woman undergoing gastric cancer treatment with the combination of chemotherapy and nivolumab developed jaundice and liver dysfunction approximately five months after treatment initiation. TJLB revealed extensive confluent parenchymal and bridging necrosis. Despite initiating high-dose steroid therapy (prednisone), liver failure progressed and the patient died. This case demonstrates the potential for ICI-induced liver injury to become fulminant, emphasizing the importance of rapid detection, diagnosis, and intervention (26).

TJLB is instrumental in assessing histological severity, particularly necrosis extent and inflammation degree after excluding etiologies such as choledochal obstruction. It remains a useful tool in clinically feasible scenarios, such as when the bleeding risk precludes biopsy or when biliary tract evaluation is necessary. Although ICI-induced liver failure is extremely rare, its early detection and prompt intervention are crucial. In such cases, liver biopsy provides definitive diagnostic information, allowing for precise assessment of tissue necrosis and injury severity.

Although irAE-related liver injury onset typically occurs early after ICI administration, it may also develop up to one year after treatment cessation. As anti-PD-1 antibodies can remain bound to T cells for over 20 weeks after the final dose, their immunological effects are thought to persist

well beyond the treatment period. Consequently, if a history of ICI use is known, the possibility of delayed-onset irAE-related liver injury should be considered (27).

Compared with autoimmune hepatitis, irAE-related liver injury is characterized by less zone-selective hepatocyte damage and minimal infiltration of plasma or CD4+ T cells. Anti-PD-1 and anti-PD-L1 antibodies typically induce lobular hepatitis, whereas anti-CTLA-4 antibodies are associated with fibrin ring granulomas. Cases of sclerosing cholangitis-like liver injury with nonobstructive cholangiectasis (immune-related cholangitis) have also been reported (18). Additionally, in some cases of irAE-related liver injury, elevated bilirubin levels persist despite improvements in transaminase levels following immunosuppressant use, consistent with vanishing bile duct syndrome. This finding underscores the necessity of considering both liver injury and cholangitis in these patients (28-30).

Immunotherapy based on immune checkpoint inhibitors (ICIs) represents a novel anticancer treatment strategy. On the other hand, various types of irAE have been observed across different cancer types, and it has been established that irAE are associated with treatment response and survival rates in cancer patients receiving ICI therapy (31, 32). Regarding liver biopsy in cases of liver dysfunction where diagnosis is challenging, although there is debate concerning when it should be performed (33), its correlation with biomarkers (34) and its indications (35), it is considered feasible to perform the procedure in many cases of TLLB.

Study limitations. First, the cohort size was small, which limits the generalizability of the findings and precludes robust statistical analysis. Second, this was a single-center, retrospective study, introducing potential selection bias, as only patients with severe liver dysfunction who required TJLB were included. Third, there was no control group undergoing percutaneous liver biopsy or empirical treatment alone; therefore, direct comparisons regarding diagnostic yield, safety, and clinical outcomes could not be performed. Fourth, the timing of TJLB and corticosteroid therapy initiation was not standardized, which may have influenced histopathological findings and subsequent treatment responses. Fifth, heterogeneity in underlying diseases (hepatocellular carcinoma and lung cancer), ICI regimens, and prior liver conditions (*e.g.,* viral hepatitis and metabolic dysfunction-associated steatohepatitis) may have confounded the interpretation of liver injury patterns. Finally, long-term outcomes and prognostic implications of TJLB-guided management were not fully evaluated, and prospective studies are required to validate our findings.

Conclusion

TJLB was primarily performed to assess irAE severity; notably, cases of drug-induced liver injury and tumor infiltration, rather than irAEs, were identified. While TJLB remains essential for a definitive diagnosis, initiating steroid therapy without histological evidence may be inappropriate. Given that most current data are derived from retrospective observations or small case series, further prospective studies are needed to identify prognostic factors and predict treatment responses. It is also necessary to investigate the characteristics of irAEs in patients with concurrent liver diseases, such as fatty liver, viral hepatitis, and pre-existing fibrosis, and to explore correlations between biopsy findings, blood markers (such as cytokines, immune cell subsets, and autoantibodies), and clinical outcomes. Ultimately, early diagnosis *via* TJLB has the potential to improve prognosis in patients with irAE-related hepatic injuries.

Conflicts of Interest

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

Authors' Contributions

Conceptualization: Toru Ishikawa; Data Curation: Toru Ishikawa; Formal Analysis: Toru Ishikawa; Investigation: Toru Ishikawa, Masaya Goto, Ryo Jimbo, Shun Yamazaki, Takahiro Iwasawa, 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, Masaya Goto, Ryo Jimbo, Shun Yamazaki, Takahiro Iwasawa, and Terasu Honma.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used for manuscript preparation or data analysis or presentation.

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