

# Immune Checkpoint Inhibitor-induced Hepatitis, an Emerging Issue in Precision Cancer Therapy Era: A Narrative Literature Review

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**Abbreviations:** AASLD, American Association for the Study of Liver Disease; ALT, alanine transaminase; AST, aspartate aminotransferase; CHILI, checkpoint inhibitor-induced liver injury; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T lymphocyte-associated protein-4; DILI, drug-induced liver injury; HBV, hepatitis B virus; HCV, hepatitis C virus; ICH, immune checkpoint inhibitor-related hepatotoxicity; ICI(s), immune checkpoint inhibitor(s); ILICI, immune-mediated liver injury caused by ICIs; IMH, immune-mediated hepatitis; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

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## ABSTRACT

Immunotherapy using immune checkpoint inhibitor (ICI) has been increasingly used in the oncology treatment field. Although ICIs could help suppress cancer and improve survival rates, it could also lead to certain adverse events, including immune-mediated liver injury caused by ICIs (ILICI). The manifestation of ILICI ranged greatly from asymptomatic disease to liver failure and even death. In this review article, we will discuss the pathogenesis, manifestation, and clinical approach of ILICI.

**KEY WORDS:** Hepatitis, immune checkpoint inhibitor, immunotherapy, review

## INTRODUCTION

Immunotherapy has revolutionized the landscape of cancer management, especially in terms of precision medicine. In this context, “precision” also includes individualized risk assessment and management of immune-related toxicities—an important determinant of whether patients can safely continue effective immune checkpoint inhibitor (ICI) therapy. Increasing numbers of new ICIs have been discovered, along with their approved indications for various types of cancer.<sup>1</sup>

Immune checkpoint inhibitors modulate immune checkpoint pathways, which can lead to tumor regression and durable disease control in selected patients. There are three ICI classes: cytotoxic T lymphocyte-associated protein-4 (CTLA-4) inhibitors, programmed cell death protein 1 (PD-1) inhibitors, and programmed death-ligand 1 (PD-L1) inhibitors. Immune checkpoint inhibitors can be administered either alone or in combination with other cancer therapies such as surgery, conventional chemotherapy, radiotherapy, and other modalities.<sup>2</sup>

The widespread use of ICIs has been associated with improved prognosis and quality of life of specific groups of cancer patients, including melanoma, non-small cell lung cancer (NSCLC), breast cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck cancer, and urothelial carcinoma.<sup>3</sup> However, as use expands, the incidence of ICI-related toxicity is expected to increase. Although ICI toxicities can be acute or long-term, they are typically associated with immune reactions and present acutely. These toxicities may lead to significant morbidity, impaired quality of life, and abrupt discontinuation of ICI therapy. The toxicity of ICIs varies depending on the ICI class and may affect various organs. In a previous paper, we discussed ICI-induced colitis.<sup>4</sup> This narrative review discusses ICI hepatitis, a common ICI immune-related adverse event (irAE) affecting the liver.

## METHODS

This narrative review synthesizes current evidence on immune-mediated liver injury caused by ICIs (ILICI), with emphasis on recent clinical guidelines and management strategies. A comprehensive literature search was conducted using PubMed, Embase, and Web of Science databases from inception through October 2024. Search terms included combinations of “immune checkpoint inhibitor,” “immunotherapy,” “hepatotoxicity,” “hepatitis,” “liver injury,” “PD-1,” “PD-L1,” “CTLA-4,” and related terms. Randomized controlled trials, observational studies, case series, clinical practice guidelines, and expert consensus statements were included. Priority was given to current guidelines from major societies. This review provides an updated synthesis of ILICI epidemiology, pathogenesis, clinical presentation, diagnosis, and management, based on the included literature. An emphasis is placed on the conceptual framework of ILICI as a distinct form of indirect drug-induced liver injury. Hence, a detailed comparative analysis of management recommendations across guidelines is provided, with particular attention given to special populations, including patients with hepatocellular carcinoma, chronic viral hepatitis, autoimmune liver disease, and liver transplant recipients—groups that are often underrepresented in clinical trials but frequently encountered in practice. This emphasis supports a practical precision-oncology approach to risk stratification, monitoring, and management, discussed herein.

## DEFINITIONS

Several different terms have been used to describe ICI hepatitis, including ILICI, immune-mediated hepatitis (IMH) induced by ICI, checkpoint inhibitor-induced liver injury (CHILI), and immune checkpoint inhibitor-related hepatotoxicity (ICH).<sup>5–7</sup>

While ILICI can be seen as part of drug-induced liver injury (DILI), many experts consider ILICI a

distinct type of DILI. Classically, DILI is divided into two types: intrinsic (direct) and idiosyncratic. Intrinsic DILI is usually predictable, dose-dependent, and has rapid onset after drug initiation. Idiosyncratic DILI, on the other hand, is dose-independent, unpredictable, and may have delayed onset.<sup>8</sup> The DILI Initiative of the International Consortium for Innovation and Quality in Pharmaceutical Development proposed that ILICI represents a third DILI category, distinct from the traditional intrinsic (direct) and idiosyncratic types. This proposal was based on its distinct mechanism, clinical presentation, and response to immunosuppression as well as the indirect, immune-mediated effects of ICIs on the liver.<sup>6</sup> In 2023, the American Association for the Study of Liver Diseases (AASLD) also proposed a third type of DILI called "indirect hepatotoxicity." Accordingly, ILICI has been classified within this third DILI type. In contrast to intrinsic and idiosyncratic DILI, indirect hepatotoxicity is partially predictable, dose-independent, and may have a latency for months. Additionally, it arises when the biological action of the drug affects the host immune system, leading to a secondary form of immune-mediated liver injury.<sup>9</sup>

## EPIDEMIOLOGY

During ICI therapy, excessive T cell activation and reduced regulatory T cell function can trigger immune-related adverse events across multiple organs, including ILICI. The incidence of ILICI has increased in recent years, making it the third most common ICI-related adverse effect (up to 30%) after dermatologic and gastrointestinal toxicity.<sup>7,10-12</sup> In a retrospective study, Hountondji et al. observed three distinct clinical patterns of ILICI, namely hepatocellular (38.5%), cholestatic (36.8%), and mixed (24.8%); no severe acute cases were seen.<sup>5</sup> Other studies have also shown that the hepatocellular pattern was the most commonly observed pattern in patients with ILICI.<sup>7</sup>

Cases of ILICI are characterized by a significant increase in transaminases, followed by a gradual or rapid decrease.<sup>13</sup> The onset of transaminase elevation usually occurs 4 to 12 weeks following the initiation of ICI treatment, or after receiving one to three doses of ICI.<sup>14-18</sup> Importantly, ILICI can present with a delayed onset, occurring several months after treatment initiation or even after treatment cessation.<sup>9-22</sup>

Cases have been reported as early as 2–3 weeks and as late as 21 months after initiation.<sup>16,19,20</sup> Delayed-onset cases have been documented, occurring 7–9 weeks or even up to 24 months after the last dose of ICI, emphasizing the need for prolonged clinical vigilance and monitoring.<sup>19-22</sup> Clinicians should maintain a high index of suspicion for ILICI in patients with prior ICI exposure, even months after treatment discontinuation, and monitoring for immune-related adverse events, including liver function, should be individualized and may extend up to 12 months post-treatment cessation.<sup>21,22</sup>

Liver injury with a mixed pattern is usually seen at the beginning, while the hepatocellular injury pattern is seen at its peak. Fever may also be a clinical manifestation. In rare cases, acute liver failure is the first presentation.<sup>16</sup>

Distinct patterns of liver injury have been observed with CTLA-4 versus PD-1/PD-L1 inhibitors: ILICI associated with anti-CTLA-4 is often more severe than with anti-PD-1 and anti-PD-L1. Most ILICI cases are mild, but if they are not treated properly, there is a risk of acute liver failure and even death. In addition, inappropriate ILICI management can lead to the failure of cancer therapy. Therefore, ILICI has become an increasing concern.<sup>10</sup>

It is important to note that published studies use heterogeneous definitions of ILICI, ranging from any degree of liver enzyme elevation to clinically significant immune-mediated hepatitis requiring immunosuppression (e.g. Common Terminology Criteria for Adverse Events [CTCAE] grade  $\geq 3$ ). This variability contributes substantially to the wide range of incidence figures reported in the literature. The incidence of ILICI varies according to the type of ICI.<sup>11,23</sup> Hepatotoxicity with PD-1 inhibitors was found to be between 1% and 3%, while the incidence of various grades of autoimmune hepatotoxicity with CTLA-4 inhibitors has been reported between 3% and 9%.<sup>14</sup> Furthermore, combination therapy is associated with a much higher incidence of hepatotoxicity, with incidence rates ranging from 13% to 30% for all grades and 6% to 19% for grade 3 or higher.<sup>6,13,14,24,25</sup> The incidence of the different agents of ICI have been listed in Table 1. These wide incidence ranges largely reflect the heterogeneity of case definitions, differences in monitoring frequency, and variable attribution methods used across clinical trials and observational studies.

Table 1. List of ICI agents and incidence of ILICI.

Drug <sup>ref</sup>	Incidence of ILICI*
PD-1 inhibitor	
Nivolumab <sup>22,26-31</sup>	2%-11%
Pembrolizumab <sup>32-42</sup>	0.7%-26.8%
PD-L1 inhibitor	
Atezolizumab <sup>43-54</sup>	4%-35.9%
Durvalumab <sup>55</sup>	2.1%
Avelumab <sup>56-58</sup>	3.3%-17.7%
CTLA-4 inhibitor	
Ipilimumab <sup>59-62</sup>	3.8%-59.2%
Tremelimumab <sup>63</sup>	6%

\*Ranges reflect reported incidence across studies; definitions and regimens vary.

CTLA-4, cytotoxic T lymphocyte-associated protein-4; ICI, immune checkpoint inhibitor; ILICI, immune-mediated liver injury caused by immune checkpoint inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1.

## RISK FACTORS

Numerous risk factors—including the type and dosage of ICI, whether it is used alone or in conjunction with other ICIs or small molecule inhibitors, genetic predisposition, and concomitant medications (e.g. acetaminophen and statins)—could influence the occurrence of ILICI.<sup>13,21</sup> The different risk factors for ILICI are summarized in Box 1.

Several studies have reported a higher incidence of ILICI in patients treated with two or more ICIs

**Box 1: Risk Factors for ILICI**

- Female
- Younger age
- Anti-CTLA-4 > anti-PD-1 > anti-PD-L1
- Use of  $\geq 2$  ICI agents
- Higher dose\*
- Pre-existing liver disease (hepatitis B and C)
- Liver malignancy
- Autoimmune disease

\* Only applies to anti-CTLA-4 agents; anti-PD-1 and anti-PD-L1 are not dose-dependent.

compared to a single agent. The incidence of increased aminotransferase (AST)/alanine transaminase (ALT) in those receiving combination therapy ranged from 4.0% to 22.3% compared to 1.7%-12.0% in the monotherapy group. The incidence of grade 3 or 4 hepatic irAEs was also greater in the combination group (6.1%-14.9% versus 0%-1%).<sup>64-67</sup> A meta-analysis of 17 clinical trials found that those receiving anti-CTLA-4 agents had higher odds for hepatotoxicity (anti-CTLA-4 versus control: odds ratio [OR] 4.67, 95% CI 3.42-6.39; anti-PD-1 versus control: OR 1.58, 95% CI 0.66-3.78; *P* value for anti-CTLA-4 versus anti-PD-1:  $<0.00001$ ), and elevation in AST/ALT when compared to anti-PD-1 agents (AST elevation in anti-CTLA-4 versus control compared to anti-PD-1 versus control: OR 3.36 versus 2.10, *P* value for anti-CTLA-4 versus anti-PD-1:  $<0.00001$ ; ALT elevation in anti-CTLA-4 versus control compared to anti-PD-1 versus control: OR 4.45 versus 2.13, *P* value for anti-CTLA-4 versus anti-PD-1:  $<0.00001$ ).<sup>68</sup> Compared to anti-PD-1 agents, anti-PD-L1 also had a lower incidence for elevations in AST and ALT (AST: 6.84% versus 3.72%, *P*<0.001; ALT: 6.01% versus 3.60%, *P*<0.001).<sup>69</sup> A higher dosage of anti-CTLA-4 has been linked to a higher incidence of hepatitis (ipilimumab 3 mg/kg: 3%-5%; ipilimumab 10 mg/kg: 15%-16%).<sup>70</sup> On the other hand, hepatic irAEs due to anti-PD-1/PD-L1 did not seem to be dose-dependent.<sup>71</sup>

The risk of ILICI also appeared to vary by cancer type, with reported incidences expressed as the percentage of patients experiencing aminotransferase elevation. Patients with hepatocellular carcinoma have been reported to have a higher incidence of ALT elevation (8%) compared with other cancers, such as lung cancer (0%) and melanoma (0%-4%).<sup>65,72-77</sup> A meta-analysis of 117 studies also confirmed that patients with liver cancer had a higher incidence of hepatotoxicity compared to other solid tumors (ALT increase: 13.2% [95% CI 8.54%-20.4%] versus 4.92% [95% CI 4.21%-5.76%]; AST increase: 14.2% [95% CI 9.93%-20.4%] versus 5.38% [95% CI 4.52%-6.39%]). In addition, the incidence of elevated aminotransferase levels that were of grade 3 or above was also higher in the liver cancer group compared to other solid tumors (ALT increase: 4.57% [95% CI 3.38%-6.17%] versus 1.26% [95% CI 1.02%-1.56%], *P*<0.001; AST increase: 6.74% [95% CI 4.09%-11.11%] versus 1.19% [95% CI 0.95%-1.48%], *P*<0.001).<sup>69</sup> Overall, hepatocellular carcinoma patients may have a 2-3-fold higher risk of ILICI compared to other cancer types, and

underlying chronic liver disease and cirrhosis may contribute to increased susceptibility. Therefore, baseline liver function assessment (Child–Pugh score) should be performed before ICI initiation, and more frequent monitoring of liver function may be warranted in hepatocellular carcinoma patients on ICIs. It is also important to distinguish ILICI from tumor progression, portal vein thrombosis, or decompensation of underlying liver disease.

One cohort study observed that females were more likely to experience ILICI than were males (OR 2.54, 95% CI 1.09–6.06,  $P=0.03$ ).<sup>78</sup> This was also reported by another study involving 1096 participants ( $P=0.038$ ).<sup>79</sup> A meta-analysis of 13 studies indicated that younger age was significantly associated with higher incidence of ILICI (weighted mean difference [WMD]: -5.200, 95% CI -7.481 to -2.919) and grade 3 or above ILICI (WMD: -5.193, 95% CI -9.669 to -0.718).<sup>80</sup>

The presence of pre-existing liver diseases, such as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, is thought to be a risk factor for hepatotoxicity when receiving ICIs. Animal studies have shown that ICI exposure in HBV- or HCV-infected animals was associated with elevated aminotransferase levels.<sup>81,82</sup> The available data on humans are limited, since most studies excluded patients with pre-existing liver conditions. A case series of nine individuals with HBV or HCV infection who received ICIs experienced elevations in aminotransferase levels.<sup>83</sup> Cirrhotic patients with HCV infection treated with tremelimumab also had a higher incidence of ALT elevation than did those without HCV (25% versus 3%).<sup>84</sup> Although these few human studies suggest an association between hepatitis infection and a higher risk for hepatotoxicity, elevations in transaminase levels may also be due to the underlying hepatitis infection rather than ICI exposure. Thus, patients with chronic HBV should be considered for antiviral prophylaxis before ICI initiation to prevent reactivation. Reactivation of HBV can occur during or after ICI therapy; therefore HBV DNA should be monitored regularly.<sup>85</sup> Chronic HCV infection does not appear to increase ILICI risk significantly; successful HCV treatment prior to ICI is preferred when feasible. Appropriate serological and virological testing should be carried out to distinguish ILICI from viral hepatitis reactivation.<sup>86</sup>

Very few studies have assessed the safety of ICIs in individuals with liver transplants. One of the concerns regarding ICI usage in this population is

the risk of allograft rejection. In one study, as many as 7 out of 19 patients (39%) experienced allograft rejection, with the highest rates of rejection seen in those receiving combination therapy (50%), followed by nivolumab (33%), pembrolizumab (25%), and ipilimumab (12.5%) monotherapy.<sup>87</sup> On the other hand, several other cases have reported tolerability of ICIs in solid-organ transplant recipients.<sup>88–90</sup> Such mixed results make it difficult to conclude the safety of ICIs in liver transplant recipients. However, given the high rate of allograft rejection, ICIs should be used cautiously, with careful risk-benefit assessment.

Patients with autoimmune diseases are another unique population that requires special attention with ICI usage. Studies have found that autoimmune patients have a notably higher occurrence of irAEs (29%–45%) and disease exacerbation (29%–47%) when on ICIs.<sup>91–96</sup> Despite the higher irAE rates, these events did not have a significant impact on overall survival.<sup>92</sup> Furthermore, most of the cases were easily resolved without discontinuing ICIs.<sup>94</sup> Therefore, pre-existing autoimmune disease is not an absolute contraindication to ICI therapy. More frequent monitoring for both disease flares and immune-related adverse events are recommended. Multidisciplinary management is also recommended.<sup>95</sup>

## PATHOGENESIS

### Indirect Hepatotoxicity Mechanism of DILI

As previously stated, a third subtype mechanism of DILI—the indirect hepatotoxicity subtype—has been proposed.<sup>8–9</sup> This third mechanism was mainly attributed to the effects of a drug towards the host's immune response.<sup>9</sup> This type of DILI is mainly described in ILICI patients and in those who experience HBV reactivation after administration of immunosuppressants.<sup>97</sup> This third type can be distinguished from direct hepatotoxicity and idiosyncratic hepatotoxicity based on its distinct mechanisms.<sup>8,9</sup>

### Immune-mediated Liver Injury Caused by ICIs

In ILICI, T cell activation and loss of tolerance against the patient's own cells lead to liver injury.<sup>10</sup> The mechanism by which ICIs elicit ILICI varies by class. For example, anti-CTLA-4 agents affect T cells primarily at the priming stage, whereas anti-PD-1/PD-L1 act mainly at the effector stage.<sup>10,98</sup> During the priming stage, CTLA-4 on T cells competitively

binds B7-1 and B7-2 on antigen-presenting cells, thereby inhibiting CD28-mediated T cell activation.<sup>10</sup> Anti-CTLA-4 agents bind to CTLA-4 on T cells and block this inhibitory signal, promoting T cell activation.<sup>10,99</sup>

The binding of PD-1 on T cells to PD-L1 on tumor cells promotes evasion by inhibiting T cell activation.<sup>10</sup> Overactivation of T cells leads to clonal expansion of Th1 and Th17 CD4+ T cells, which produce proinflammatory cytokines, such as IL-2, IFN- $\gamma$ , and TNF- $\alpha$ .<sup>10,98</sup> These cytokines will then activate the innate immune system, as well as CD8+ cytotoxic T lymphocytes, leading to increased production of intracellular granzyme B and perforin.<sup>99</sup> Overactivation of CD8+ T cells also contributes to overcoming immune tolerance and hepatocyte injury.<sup>98</sup> In addition, regulatory T cells (Tregs) are also suppressed, resulting in reduced production of anti-inflammatory cytokines (IL-10, IL-35, and TGF- $\beta$ ) and a proinflammatory environment.<sup>10,98</sup>

### Comparison of ILICI versus Other Type of DILI

In general, direct DILI occurs due to an imbalance between toxin production and the detoxification capacity of hepatocytes, leading to increased oxidative stress and mitochondrial dysfunction.<sup>98</sup> On the other hand, the pathogenic mechanisms of idiosyncratic drug-induced liver injury (iDILI) and ILICI are more similar to one another, in that both involve overactivation of the innate and adaptive immune systems.<sup>99,100</sup> However, iDILI occurs due to the production of neoantigens following drug metabolism; inflammation is only triggered once hepatocyte damage occurs.<sup>99,100</sup> Meanwhile, ILICI occurs due to ICI exposure, which inhibits the ability of CTLA-4, PD-1, and PD-L1 to suppress T cell activation.<sup>10,101</sup>

### CLINICAL MANIFESTATION

The manifestation of ILICI ranges from asymptomatic to acute liver failure. Most ILICI cases are asymptomatic and diagnosed incidentally when monitoring for liver function tests after ICI therapy. Those with more severe disease may present with right upper quadrant abdominal pain, fever, fatigue, rash, jaundice, dark urine, and easy bruising.<sup>102-106</sup> Although this is rare, patients with ILICI may also manifest with acute liver failure during the initial stages.<sup>103</sup> Some common grading systems used to classify ILICI severity are the CTCAE and the Drug-induced

Liver Injury Network (DILIN) grading systems (Table 2).<sup>107,108</sup>

### DIAGNOSTIC APPROACH

Clinically, ILICI is often asymptomatic, but it may occasionally present with abdominal pain in the right upper quadrant, accompanied by fever, rash, fatigue, dark urine, and jaundice. Clinicians should review the patient's medication history, including the ICI agent used and duration of therapy. Typically, ILICI occurs within 4–12 weeks of starting ICIs or after approximately three ICI infusions. Importantly ILICI is a diagnosis of exclusion; therefore, alternative causes should be ruled out, including hepatotoxicity from other medications (e.g. acetaminophen), viral hepatitis, other infections, tumor-related liver involvement, biliary disease, autoimmune hepatitis, myositis, and rhabdomyolysis. The recommended workup is provided in Box 2.<sup>5,7,109</sup>

#### Box 2: Diagnostic Workup for ILICI<sup>7,109</sup>

- Complete blood count
- ALT, AST, total serum bilirubin, ALP
- INR
- Viral hepatitis panel (anti-HAV IgM, HBsAg, anti-HBc IgM and IgG  $\pm$  HBV DNA, anti-HCV  $\pm$  HCV RNA, anti-HEV IgM, EBV IgM and IgG, CMV IgM and IgG  $\pm$  CMV DNA)
- Autoimmune panel (ANA, ASMA, anti-LKM1, serum IgG)
- Serum CK
- Iron studies (ferritin, transferrin saturation)
- Abdominal imaging (CT scan, MRI, or USG with Doppler)

**Abbreviations:** ALP, alkaline phosphatase; ALT, alanine transaminase; ANA, anti-nuclear antibodies; Anti-HBc, anti-Hepatitis B core antibody; Anti-LKM1, anti-liver-kidney microsomal 1 antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CK, creatine kinase; CMV, cytomegalovirus; CT, computed tomography; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalized ratio; MRI, magnetic resonance imaging; RNA, ribonucleic acid; USG, ultrasonography

Table 2. Grading of ILICI Severity According to Two Common Grading Systems.<sup>107,108</sup>

Grade*	CTCAE	DILIN
Grade 1	<ul style="list-style-type: none"> <li>ALT &gt;ULN to <math>\leq 3 \times</math> ULN</li> <li>AST &gt;ULN to <math>\leq 3 \times</math> ULN</li> <li>Total serum bilirubin ULN to <math>\leq 1.5 \times</math> ULN</li> <li>ALP ULN to <math>\leq 2.5 \times</math> ULN</li> </ul>	<ul style="list-style-type: none"> <li>Elevation in ALT and/or ALP levels</li> <li>Total serum bilirubin <math>&lt; 2.5</math> mg/dL</li> <li>INR <math>&lt; 1.5</math></li> <li>Present with or without symptoms (nausea, vomiting, asthenia, fatigue, RUQ pain, jaundice, rash, pruritus, weight loss)</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>ALT <math>&gt; 3-5 \times</math> ULN</li> <li>AST <math>&gt; 3-5 \times</math> ULN</li> <li>Total serum bilirubin <math>&gt; 1.5-3 \times</math> ULN</li> <li>ALP <math>&gt; 2.5-5 \times</math> ULN</li> </ul>	<ul style="list-style-type: none"> <li>Elevation in ALT and/or ALP levels</li> <li>Total serum bilirubin <math>\geq 2.5</math> mg/dL or INR <math>\geq 1.5</math></li> <li>Symptoms may become aggravated</li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>ALT <math>&gt; 5-20 \times</math> ULN</li> <li>AST <math>&gt; 5-20 \times</math> ULN</li> <li>Total serum bilirubin <math>&gt; 3-10 \times</math> ULN</li> <li>ALP <math>&gt; 5-20 \times</math> ULN</li> </ul>	<ul style="list-style-type: none"> <li>Elevation in ALT, ALP, and total serum bilirubin <math>\geq 2.5</math> mg/dL and/or INR <math>\geq 1.5</math></li> <li>Symptoms are further aggravated</li> <li>Indication for hospitalization</li> <li>No evidence of hepatic encephalopathy</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>ALT <math>&gt; 20 \times</math> ULN</li> <li>AST <math>&gt; 20 \times</math> ULN</li> <li>Total serum bilirubin <math>&gt; 10 \times</math> ULN</li> <li>ALP <math>&gt; 20 \times</math> ULN</li> </ul>	<ul style="list-style-type: none"> <li>Elevation in ALT, ALP, and total serum bilirubin <math>\geq 2.5</math> mg/dL</li> <li>Signs of hepatic failure (INR <math>\geq 1.5</math>, ascites, hepatic encephalopathy) and/or DILI-related dysfunction of another organ</li> </ul>
Grade 5	Death/mortality due to ILICI	<p>Death/mortality due to ILICI OR Requires liver transplantation for survival</p>

Note: CTCAE and DILIN grades are not directly interchangeable.

\* Severity grade is determined by the highest grade for which at least one criterion is met.

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; CTCAE, Common Terminology Criteria for Adverse Events; DILI, drug-induced liver injury; DILIN, Drug-induced Liver Injury Network; dL, deciliter; INR, international normalized ratio; mg, milligram; RUQ, right upper quadrant; ULN, upper limit of normal.

One of the most common presentations of ILICI is abnormal liver function tests. The *R*value, defined as the ratio of ALT to ALP after normalization to their upper limit of normal (ULN), [ $R = (ALT/ULN)/(ALP/ULN)$ ], can be used to determine the pattern of liver injury. There are three patterns: cholestatic ( $R \leq 2$ ), hepatocellular ( $R \geq 5$ ), and mixed ( $2 < R < 5$ ).<sup>5</sup> The hepatocellular pattern (60%) is the most common presentation in ILICI. However, cholestatic (30%) or mixed (10%) patterns are more common in patients receiving anti-PD-1/PD-L1 compared with anti-CTLA-4. Elevated total serum bilirubin may also be observed in ILICI and may indicate greater severity.<sup>7,12</sup> Due to limited reports of cholestatic-type ILICI, its pattern of occurrence and risk factors are not well defined. This pattern is typically characterized by predominant elevation of ALP and gamma-glutamyl transferase, a more severe disease course,

less responsiveness to corticosteroid therapy, and may be associated with a poorer prognosis compared to hepatocellular patterns.<sup>110-114</sup>

Abdominal imaging may be useful in excluding other potential diagnoses such as metabolic dysfunction-associated steatohepatitis, portal vein/hepatic vein thrombosis, ischemic hepatitis, and hepatic tumors.<sup>7</sup> Magnetic resonance cholangiopancreatography may be recommended when evaluating cholestatic-pattern liver injury, as it can help identify biliary abnormalities, including possible biliary strictures.<sup>6,114</sup>

Similarly, liver biopsy might also be considered to exclude differential diagnoses and evaluate the disease severity.<sup>9</sup> However, this examination is invasive and expensive; hence, clinicians should consider the risks and benefits.<sup>9,115</sup> Liver biopsy is not routinely

required for ILICI diagnosis but should be considered in specific clinical circumstances. Liver biopsy may be recommended when: (1) patients fail to improve after empirical therapy; (2) bilirubin levels are elevated without radiographic evidence of biliary obstruction; (3) clinical features are atypical, or the clinical course is unusual; (4) CTCAE grade 2 or 3 is present; (5) exclusion of other etiologies is needed, including malignant biliary obstruction, diffuse hepatic metastases, drug-induced liver injury from concurrent medications, or opportunistic viral infections; or (6) patients with cholestatic patterns require differentiation from primary biliary cholangitis or malignant biliary obstruction.<sup>115-120</sup> The most common histological patterns include panlobular hepatitis (hepatocellular pattern) with lobular inflammation and hepatocyte injury, or portal-based inflam-

mation with bile duct injury (cholangiopathy pattern),<sup>115,117,118</sup> though no pathognomonic findings exist exclusively for ILICI.<sup>9,115</sup>

Histologic findings in ILICI are characterized by periportal and lobular inflammation, hepatocyte dropout, and centrilobular necrosis. Although the infiltrates can be mixed, they are usually dominated by T lymphocytes and histiocytes with few or no plasma cells.<sup>7,121</sup> Other sources have described the pathological features of ILICI as panlobular hepatitis (lobular inflammation: lymphocytes and macrophages), cholestatic pattern (portal-based inflammation with bile duct injury: lymphocytes, plasma cells, neutrophils, and eosinophils), and mixed pattern.<sup>121</sup> Figure 1 summarizes the diagnostic approach for ILICI.<sup>9,122</sup>

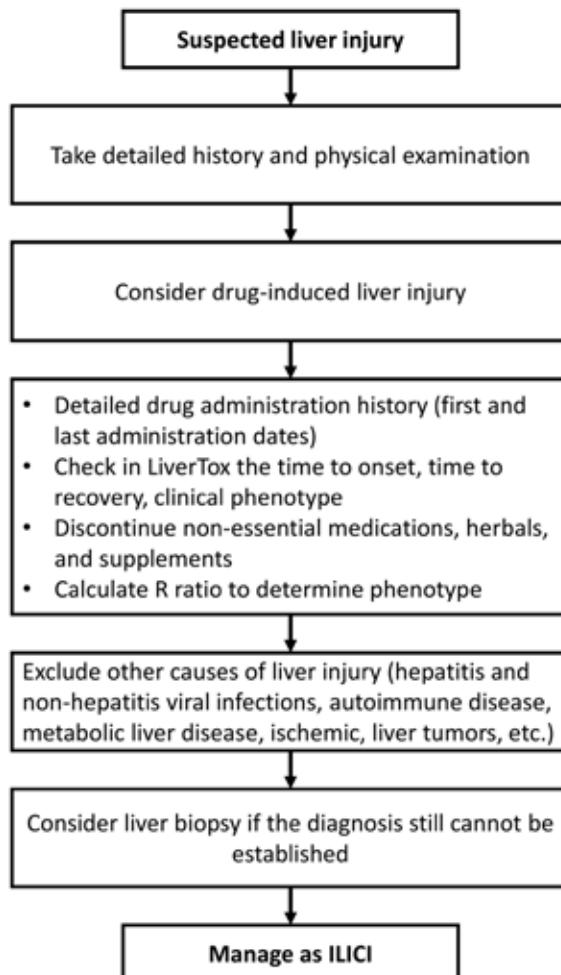


Figure 1. Diagnostic Flowchart for Immune-mediated Liver Injury Caused by Immune Checkpoint Inhibitors (ILICI).<sup>9,122</sup>

## MANAGEMENT APPROACH

Several societies have published guidance regarding the diagnosis and management of ILICI. This includes the AASLD,<sup>9</sup> American Gastroenterology Association (AGA),<sup>116</sup> American Society of Clinical Oncology (ASCO),<sup>119</sup> European Association for the Study of the Liver (EASL),<sup>8</sup> European Society for Medical Oncology (ESMO),<sup>123</sup> Multinational Association of Supportive Care in Cancer (MASCC),<sup>124</sup> National Comprehensive Cancer Network (NCCN),<sup>125</sup> and Society for Immunotherapy of Cancer (SITC).<sup>126</sup> A comparison of these guidelines is summarized in [Supplementary Table 1](#).

### Grade 1 Hepatotoxicity

For grade 1 hepatotoxicity, the ILICI guidelines recommend continuing ICIs, especially if the condition is asymptomatic.<sup>8,9,13,116,119,123</sup> When symptomatic, clinicians may give symptomatic treatment while monitoring the patient's condition closely, including periodic liver testing.<sup>8,9,13,116,119,125,126</sup> Clinicians are advised to also perform other tests to eliminate other possible causes of hepatitis. These include testing for viral hepatitis infection, human immunodeficiency virus, autoimmune etiologies (e.g. antinuclear antibody, anti-smooth muscle antibody, antineutrophil cytoplasmic antibody, anti-mitochondrial antibody), iron studies (e.g. iron, ferritin, total-iron binding capacity), and radiologic evaluation for biliary obstruction.<sup>8,116,119,123–126</sup> It is also important to reassess the patient's history of alcohol consumption and withhold other potentially hepatotoxic medications.<sup>8,116,119,123–126</sup>

### Grade 2 Hepatotoxicity

All eight guidelines agree to temporarily withhold ICIs in grade 2 hepatotoxicity.<sup>8,9,116,119,123–126</sup> All except for EASL agree to start 0.5–1.0 mg/kg/day oral prednisone.<sup>9,116,119,123–126</sup> Both ASCO<sup>119</sup> and MASCC<sup>124</sup> suggest adding immunosuppressive therapy, such as mycophenolate mofetil, if the patient does not respond to steroid therapy. Resumption of ICI therapy may be considered once the corticosteroids have been tapered to  $\leq 10$  mg/day prednisone (or equivalent) over 2–4 weeks and hepatotoxicity has improved to grade  $\leq 1$ .<sup>8,116,119,123–126</sup> Several of the guidelines also recommend monitoring liver parameters, international normalized ratio (INR), and albumin every 3–7 days.<sup>8,116,123,124,126</sup> The AGA,<sup>116</sup> ASCO,<sup>119</sup> MASCC,<sup>124</sup> and SITC<sup>126</sup> guidelines also suggest considering liver biopsy in grade 2 hepatotoxicity to confirm the underlying pathology. The ESMO<sup>123</sup> and MASCC<sup>124</sup>

guidelines only recommend screening for other possible causes of hepatitis starting from grade 2 hepatotoxicity or higher. Meanwhile, other guidelines from AASLD,<sup>9</sup> AGA,<sup>116</sup> ASCO,<sup>119</sup> EASL,<sup>8</sup> NCCN,<sup>125</sup> and SITC<sup>126</sup> recommend this examination starting from grade 1 hepatotoxicity.

### Grade 3 or 4 Hepatotoxicity

The AASLD, AGA, ASCO, EASL, and SITC all recommend permanently stopping ICIs in grade 3 or higher hepatotoxicity.<sup>9,116,119,126</sup> However, MASCC did not specify whether ICIs should be temporarily or permanently discontinued in grade  $\geq 3$  hepatotoxicity.<sup>124</sup> Meanwhile, ESMO and NCCN both suggest withholding ICIs temporarily in grade 3 hepatotoxicity and permanently discontinuing ICIs in grade 4 hepatotoxicity. If the patient's condition has improved to grade 1 hepatotoxicity, ICIs can be resumed.<sup>123,125</sup> All guidelines agree to administer intravenous steroids, such as methylprednisolone, in grade 3–4 hepatotoxicity, but with varying doses. The most commonly recommended dose was 1–2 mg/kg/day of intravenous methylprednisolone or its equivalent.<sup>8,116,119,125</sup> Other guidelines such as NCCN suggest 1.0 mg/kg/day, AASLD suggests 1–1.5 mg/kg/day, and MASCC recommends 0.5–2 mg/kg/day.<sup>9,124,125</sup> Meanwhile, ESMO recommended giving 1 mg/kg/day if the AST/ALT levels were  $<400$  U/L and the patient had normal bilirubin, INR, and albumin. Otherwise, 2 mg/kg/day should be administered.<sup>123</sup> If the patient is refractory to steroids, immunosuppressive regimens, such as mycophenolate mofetil, tacrolimus, or azathioprine, can be given.<sup>8,9,116,119,123–126</sup> Antithymocyte globulin may also be considered in patients with fulminant hepatitis.<sup>116,124,126</sup> Patients with grade  $\geq 3$  hepatotoxicity should also be hospitalized, possibly referred to a hepatologist, and undergo routine liver tests every 1–3 days.<sup>8,9,116,119,123–126</sup> Whenever possible, a liver biopsy should also be considered at this stage.<sup>8,116,119,123–126</sup>

Based on the synthesis of current guidelines and clinical evidence, we propose the practical approach to ILICI management shown in Table 3.

## CONCLUSION

As ICI use continues to expand, ILICI may become an increasing clinical issue. Therefore, clinicians should consider ILICI in patients who develop abnormal liver function tests after initiating ICIs. Further studies are needed to refine diagnostic and therapeutic approaches for ILICI.

**Table 3. Proposed Practical Approach for Management of Immune-mediated Liver Injury Caused by Immune Checkpoint Inhibitors (ILICI).**

ILICI Grade	Management
Grade 1	<ul style="list-style-type: none"> <li>Continue immune checkpoint inhibitors (ICI)</li> <li>Close monitoring</li> <li>Investigate other possible causes of hepatitis and withhold hepatotoxicity drugs</li> <li><i>If asymptomatic</i>, no specific treatment is required</li> <li><i>If symptomatic</i>, continue ICI unless symptoms are concerning or worsening. Give symptomatic treatment and frequent monitoring. Manage as grade 2 if clinical condition worsens</li> </ul>
Grade 2	<ul style="list-style-type: none"> <li>Temporarily withhold ICI</li> <li>Investigate other possible causes of hepatitis and withhold hepatotoxicity drugs</li> <li>Initiate prednisone 0.5-1.0 mg/kg/day</li> <li>Monitor liver function every 3 days</li> <li><i>If no improvement</i>, consider liver biopsy and start adding immunosuppressant</li> <li><i>If there is improvement</i>, begin gradual steroid taper over 4-6 weeks</li> <li>Consider ICI rechallenge after resolution, with close monitoring</li> </ul>
Grade 3	<ul style="list-style-type: none"> <li>Permanently discontinue ICI</li> <li>Investigate other possible causes of hepatitis and withhold hepatotoxicity drugs</li> <li>Hospitalization and close monitoring</li> <li>Start IV methylprednisolone 1-2 mg/kg/day</li> <li>Monitor liver function every 1-2 days</li> <li>Consider liver biopsy if not previously performed</li> <li><i>If no improvement</i>, add immunosuppressant: Preferred first line, mycophenolate mofetil; preferred second line, azathioprine, tacrolimus; preferred as rescue therapy, anti-thymocyte globulin</li> <li>Once improved to grade <math>\leq 1</math>, begin gradual steroid taper over 4-6 weeks</li> </ul>
Grade 4	<ul style="list-style-type: none"> <li>Same management as grade 3</li> <li>IV methylprednisolone can be considered, starting at 2 mg/kg/day</li> <li>Monitor liver function daily</li> </ul>

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