# Immune-mediated liver injury caused by checkpoint inhibitors: A case series and review of the literature

MARIA KYRKASIADOU[1], ANASTASIOS KYRIAZOGLOU[1], IOANNIS KOTSANTIS[1], PANAGIOTA ECONOMOPOULOU[1], GEORGE KAVOURAKIS[1], ROUBINI ZAKOPOULOU[1], MARIA ANASTASIOU[1], ANASTASIOS PANTAZOPOULOS[1], ANNA BOULOUTA[1], MYRTO MOUTAFI[1], NIKI GAVRIELATOU[1], PERIKLIS FOUKAS[2], MENELAOS SAMARAS[2], KONSTANTINOS PALIALEXIS[3] and AMANDA PSYRRI[1]

[1]Second Department of Internal Medicine, Oncology Unit, Attikon University Hospital, 12462 Athens, Greece; [2]Second Department of Pathology, National and Kapodistrian University of Athens, Attikon University Hospital, 12462 Athens, Greece; [3]Second Department of Radiology, Interventional Radiology Unit, Attikon University Hospital, 12462 Athens, Greece

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**Abstract.** Immune checkpoint inhibitors (ICIs), including anti-PD-1 and anti-CTLA-4 agents, exhibit notable efficacy across various types of cancer. Nevertheless, they can trigger immune-related adverse events, among which immune-mediated liver injury (ILICI) occurs in 5-10% of patients. Corticosteroids are currently recommended for management of ILICI; however, the timing, presentation and response to treatment may vary widely. The present study retrospectively reviewed five male patients (median age, 69 years) with various malignancies receiving ICIs who developed ILICI. All patients were treated with anti-PD-1 therapy, and two additionally received anti-CTLA-4 therapy. No patients had a history of liver disease, autoimmune disorders or notable alcohol use, and no relevant drug allergies or toxic exposures were reported. Four patients developed grade 3-4 hepatotoxicity. The median time to onset was 15.5 months (range: 1-30 months), illustrating the delayed and unpredictable nature of ILICI. All patients underwent comprehensive evaluation to exclude other causes of liver injury. In selected cases, liver biopsy revealed features consistent with autoimmune-like hepatitis, aiding in diagnosis and assessment of severity. All patients received systemic glucocorticoids, with resolution of liver injury in most cases. One patient required additional immunosuppressive therapy due to steroid-refractory disease. Notably, liver function tests normalized in three patients following treatment, whereas two patients died from ILICI. The present case series highlights the variable onset and presentation of ILICI, which may occur shortly or long after initiation of ICIs. Timely recognition and prompt treatment are integral components of clinical care. In addition, liver biopsy, while not routinely recommended, can provide valuable diagnostic information in complex cases. The current study provides detailed clinical documentation and biopsy information; however, its interpretation is influenced by the small sample size and retrospective nature of the study. The findings support existing guidelines,and underscore the need for enhanced clinical awareness and standardized management protocols.

*Correspondence to:* Ms. Maria Kyrkasiadou, Second Department of Internal Medicine, Oncology Unit, Attikon University Hospital, 1 Rimini Street, Chaidari, 12462 Athens, Greece
E-mail: mariakirkasiadou@gmail.com

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## Introduction

Immune checkpoint inhibitors (ICIs) function by blocking the interaction between immune checkpoints and their corresponding partner proteins. This action hinders the transmission of the inhibitory signal enabling T cells to effectively eliminate cancer cells. Immune-related adverse events (irAEs) resulting from ICIs occur due to disrupted self-tolerance caused by the absence of T-cell suppression (1). Amongst the most common organs affected by ICIs are the endocrine glands, the gastrointestinal tract, the liver, the lungs and the skin. Hepatitis represents the predominant manifestation of hepatotoxicity linked to ICIs. This condition is characterized by hepatocellular damage, as indicated by increases in serum aminotransferases (ALT and AST), occasionally accompanied by rises in serum bilirubin levels (2).

'Immune-mediated liver injury caused by checkpoint inhibitors (ILICI)' is the preferred terminology characterizing ICI-induced liver injury which represents a different entity regarding the incidence, mechanism of action, and therapeutic approach (3,4). Typically, it manifests within the first months of treatment initiation, although it may appear as soon as after the first dose or even years later. It is also known that several irAEs, present following completion of treatment (1,2). Usually, patients are asymptomatic and ILICI is found incidentally in routine liver function tests (LFTs). Establishing the diagnosis is a challenging process, as it is made by excluding other possible

causes of hepatic disfunction, such as infectious, metabolic, vascular, autoimmune, tumor-related or other drug-induced liver injury. Liver biopsy is not routinely recommended and based on ESMO guidelines for management of toxicities from immunotherapy should be considered for grades 3 and 4 (5,6).

Management of ILICI is dependent on the extent of liver injury, which is determined by evaluating the AST and ALT levels. Immunotherapy may be continued, temporarily withheld with subsequent resumption, rechallenged under an individualized treatment plan or permanently discontinued. Corticosteroid administration is the gold standard treatment, followed by immunosuppressive agents, such as mycophenolate mofetil (MMF), azathioprine, cyclosporine etc. in refractory cases. This report aims to raise awareness of ILICI in patients receiving immunotherapy, underscoring its unpredictable onset and the importance of timely recognition and appropriate management in routine clinical practice.

## Case series

*Study population*. We retrospectively analyzed all consecutive patients treated at Attikon University Hospital, Chaidari, Greece, between 2020 and 2024 who developed ILICI, comprising a total of five cases. The median patient age was 69 years (range 50-85 years) and all patients were male. All cases had metastatic malignancies of different primary origins. Subjects enrolled in this study received at least one anti-PD1 agent, and two had additionally received an anti-CTLA4 agent, following the recommendations outlined in the National Comprehensive Cancer Network (NCCN) and ESMO guidelines. All presented with fatigue, jaundice, and abnormal liver function tests (LFTs). Liver function was evaluated by monitoring of i) LFTs including alanine transaminase (ALT) and aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), serum bilirubin, the international normalized ratio (INR), total protein and albumin and ii) imaging (computed tomography-CT). The adverse effects' severity was assessed using the grading system from version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE) (7). The diagnosis was confirmed by liver biopsy in three cases, while in two patients, immune-related hepatitis was diagnosis by exclusion. Patients received between one and forty doses of immunotherapy before developing immune-related adverse events (irAEs). In all cases, glucocorticoids were used as first line treatment; mycophenolate mofetil was used as a second line treatment in one case. Table I displays clinical information of these patients, along with their demographics, treatment, adverse event grading, management, and outcomes. The authors actively participated in the clinical care of the patients and collected data through chart reviews.

*Patient characteristics and outcomes*. A total of five male patients were included in this case series. Underlying malignancies were lung cancer (n=1), oropharyngeal cancer (n=1), cholangiocarcinoma (n=1), and renal cell carcinoma (n=2). Immunotherapy regimens consisted of pembrolizumab (n=2), nivolumab (n=1), or the combination nivolumab/ipilimumab (n=2). The median interval between immunotherapy initiation and ILICI was 15.5 months (range 1-30 months). According to CTCAE grading system three of the patients exhibited grade 3 hepatotoxicity, and the other two grade 2 and grade 4 respectively and the pattern was both hepatocellular and cholestatic. Patients exhibited symptoms after the first dose of immunotherapy (n=1), after two to three doses (n=2), and after thirty-four and forty doses of ICIs (n=2). Liver biopsy was performed in three cases. All biopsies revealed lobular inflammatory infiltrate, consisting mainly of $CD3^+$, $CD8^+$ T-lymphocytes and abundant $CD68^+$ histiocytes, and centrilobular cholestasis along with periportal fibrosis and interface hepatitis, which is characterized by the extension of the mononuclear inflammatory infiltrate to hepatocytes located at the limiting plate resulting in injury or necrosis ('piecemeal necrosis') (Table II; Fig. 1). These pathological findings could be attributed to ILICI based on current evidence (8,9). All patients were treated with corticosteroids, and only one required additionally the administration of mycophenolate mofetil. With regards to the patients' outcomes, four of our five patients died after the onset of ILICI: Two deaths were attributed to the immune-mediated liver injury, whereas the remaining two were related to complications arising during hospitalization and not directly caused by ILICI. Only one patient remained alive at follow-up. Disease resolution was achieved in three cases (60%), with an interval between the initiation of treatment and recovery that ranged from 1 to 5 months. Two patients (40%) showed no evidence of disease resolution.

## Literature review

Additionally, we conducted a review of published case reports regarding ILICI. A comprehensive search strategy was implemented for case reports published from 2016 until 2024 in PubMed database (https://pubmed.ncbi.nlm.nih.gov/) following the terms: [checkpoint inhibitors] AND [hepatitis]. After reviewing the titles and the abstracts of all 185 publications, we excluded 91 articles due to irrelevance. Apart from the PubMed search, four more cases were identified from the broader literature, including reference lists of relevant articles. We reviewed from patients' records demographic data and disease characteristics such as gender, age, primary tumor type, type and dosage of ICIs, toxicity grading, concomitant liver disease and immune related adverse events, performance of liver biopsy, treatment received and disease outcome. Case reports and case series were included if they described patients with an unambiguous diagnosis of ILICI and provided sufficient clinical detail regarding treatment exposure, liver toxicity, management, and outcomes. Articles providing inadequate clinical information or not clearly attributing hepatotoxicity to ICIs were excluded.

## Discussion

ICIs are monoclonal antibodies that target immune checkpoints, such as PD-1/PD-L1 and CTLA-4, that block. This leads to T-cell activation against cancer cells and an imbalance within the immune system, that often results in immune-related adverse events (irAEs). There are three categories of ICI approved for treatment of different types of cancer: PD-1 inhibitors, PD-L1 inhibitors, and CTLA-4 (10).

Table I. Baseline characteristics of our five patients.

| Patient no. | Sex | Age, years | Cancer type | Immunotherapy | Doses received | CTCAE grading | Liver biopsy | Treatment | Current status | Disease resolution |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 85 | Lung cancer | Pembrolizumab | 1 | 3 | Yes | mPSL, MMF | Deceased | No |
| 2 | M | 50 | Oropharyngeal cancer | Nivolumab | 2 | 3 | Yes | mPSL | Deceased | No |
| 3 | M | 81 | Cholangiocarcinoma | Pembrolizumab | 40 | 2 | Yes | mPSL | Deceased | Yes (5 months) |
| 4 | M | 80 | Renal cell carcinoma | Nivolumab/ipilimumab | 34/4 | 3 | No | mPSL | Deceased | Yes (1 month) |
| 5 | M | 51 | Renal cell carcinoma | Nivolumab/ipilimumab | 3/3 | 4 | No | mPSL, PSL | Alive | Yes (1 month) |

CTCAE, Common Terminology Criteria for Adverse Events; M, male; MMF, mycophenolate mofetil; mPSL, methylprednisolone; PSL, prednisolone.

Although several predictive biomarkers, such as PD-L1 expression, tumor mutation burden, microsatellite instability, microbial diversity, hypoxia, interferon-γ and extracellular matrix, are utilized to predict response to immunotherapy, the data regarding biomarkers for irAEs are scarce (10,11).

ILICI is a severe irAE that cannot be predicted nor confirmed, as there are not well-established specific biomarkers for the prediction or diagnosis of immune associated liver injury (12,13). Atallah *et al* (14) describe four risk factors associated with higher risk of liver damage: dual inhibition, female sex, low baseline ALP and high baseline ALT. Higher rates of liver damage are observed in individuals receiving anti-CTLA-4 agents combined with an anti-PD-1/PD-L1; indeed, up to 23% of patients receiving combined anti-PD-1/anti-CTLA-4 treatment have grade 3 LFT abnormalities (12,14-16). It is also observed that the coexistence of liver metastases is not related to the incidence or ILICI severity (14,16). At the time of ICI initiation, all patients had stage IV metastatic disease. Given the small sample size and heterogeneity of prior systemic treatments in our cohort, definitive conclusions cannot be drawn. However, published data suggest that prior treatment exposure, including history of ICI therapy and targeted therapies, may potentially influence the risk of ILICI, whereas its impact on prognosis remains unclear and appears to depend primarily on the severity and clinical course of hepatic involvement (17-19).

Data on the incidence of multiple irAEs is limited and originates from heterogeneous populations and retrospective studies. These studies support that the frequency of irAEs affecting multiple sites ranges from 13 to 53%, with higher prevalence amongst patients treated with combination therapy (16,20). It has also been noted that the occurrence of these irAEs is associated with response to treatment and a favorable prognosis (21-23). ILICI occurs in 5-10% of patients receiving monotherapy and in 25-30% of patients treated with combination therapy (6). In addition to our cohort, we identified 110 cancer patients from the literature who developed ILICI. The demographic and clinical characteristics of these patients, together with treatment details and outcomes, are summarized in the supplementary material (Table SI). Typically, it manifests within the first months of treatment initiation, although it may appear as soon as after the first dose or even years later. It is known that several irAEs, present following completion of treatment (1,2). The onset of ILICI in our patients was after 1 to 40 cycles of immunotherapy treatment, in accordance with the published literature, in which 25.4% of patients developed liver damage after the administration of a single dose of ICIs; nevertheless, there were also cases in which ILICI appeared after 28 to 51 doses. Furthermore, assessment of concomitant liver disease status, including hepatic metastases, revealed no correlation with the occurrence of hepatotoxicity, as 82 patients (74.5%) had no prior liver disease. Additionally, nearly half of the patients (48.2%) experienced at least one more immune-related adverse event.

Liver damage is characterized by the elevation of serum aminotransferases and/or total bilirubin, the severity of which is assessed by grading the elevation of the values according to CTCAEv5.0 guidelines (6,7). This adverse event usually occurs as an incidental finding, but in more severe cases, it manifests with jaundice, pain, fever and bruising, while encephalopathy

Table II. Ishak modified histological activity index and histological findings in our cases.

| Patient | Immunotherapy | Ishak score | Histological findings |
|---|---|---|---|
| Case 1 | Anti-PD1 | Grade: 4/18; stage: 1/6 | • Moderate periportal and mild lobular inflammatory infiltrate consisting mainly of CD3 (+), CD8 (+) T-lymphocytes and abundant CD68 (+) histiocytes.<br>• Interface hepatitis.<br>• Cholestasis.<br>• Few foci of necrotic debris in the hepatic lobules.<br>• Lymphocytic invasion of the portal tracts.<br>• Mild portal/periportal fibrosis.<br>• Rare PD(L)-1 expression. |
| Case 2 | Anti-PD1 | Grade: 6/18; stage: 1/6 | • Mild periportal and moderate lobular inflammatory infiltrate consisting mainly of CD3 (+), CD8 (+) T-lymphocytes and CD68 (+) histiocytes, especially in the hepatic lobules.<br>• Interface hepatitis.<br>• Cholestasis.<br>• Numerous foci of necrotic debris in the hepatic lobules.<br>• Mild periportal fibrosis.<br>• Rare PD(L)-1 expression. |
| Case 3 | Anti-PD1 | Grade: 4/18; stage: 1/6 | • Moderate periportal and mild lobular inflammatory infiltrate consisting mainly of CD3 (+), CD8 (+)<br>• T-lymphocytes and abundant CD68 (+) histiocytes.<br>• Interface hepatitis.<br>• Cholestasis.<br>• Mild periportal, focally 'bridging' fibrosis.<br>• Rare PD(L)-1 expression. |

and coagulation disorders indicating acute liver failure are rare at this point. The liver enzyme pattern is predominantly hepatocellular, with elevation of serum aminotransferases (AST, ALT). A cholestatic or mixed pattern of liver function test abnormalities occurs at rare occasions and elevated total bilirubin designates extended liver damage (5,9,24). The lack of diagnostic biomarkers makes ILICI a diagnosis by exclusion. This requires the exclusion of other possible causes of liver damage, such as viral or systemic infections, hepatic diseases (NAFLD, autoimmune hepatitis, alcoholic hepatitis, hepatic metastases), genetic liver diseases (Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency), biliary diseases (obstruction, cholecystitis, cholangitis), musculoskeletal and cardiovascular disorders, and drugs other than ICIs (5,24). Furthermore, there are substantial differences in laboratory findings between ILICI and autoimmune hepatitis (AIH). Patients with AIH demonstrate higher serum levels of bilirubin, gammaglobulin and immunoglobulin G (IgG) compared to those with ILICI. Circulating autoantibodies, such as ANA, ASMA, pANCA are positive in cases of AIH and normally absent or present in low titers in cases of ILICI (9,12,25).

Liver biopsy is not routinely recommended in the diagnostic work-up of ILICI, since the histopathological findings are non-specific and not pathognomonic, thereby limiting its utility in guiding clinical decision-making. That is reflected in current practice, as only 64 (58.2%) of the reviewed patients underwent liver biopsy. Nevertheless, histopathological findings between AIH and ILICI demonstrate several distinguishing differences. Active AIH is characterized by a predominately plasma cell rich portal infiltrate extending to the periportal parenchyma of the liver often causing necrosis (interface hepatitis). ILICI demonstrates a mainly lobular pattern of hepatic injury, which in the case of anti-PD(L)-1 agents, is heterogenous and may involve the periportal liver parenchyma, whereas in the case of anti-CTLA4 agents it is characterized by a multinucleated giant cell reaction with fibrin deposition and central vein endotheliitis (6,26,27). Additionally, ILICI is associated with $CD3^+$ and $CD8^+$ lymphocytic infiltration and lesser $CD20^+$ or $CD4^+$ lymphocytes, which are commonly observed in AIH (8,28,29). Variations in lymphocyte subtypes are anticipated due to the predominant expression of PD-1 and CTLA4 in $CD8^+$ cytotoxic T lymphocytes (8). The histopathological evaluation of our cases demonstrated a predominately $CD3^+$, $CD8^+$ T-lymphocytic infiltrate mainly distributed periportally with frequent extension to the hepatic lobules. $CD3^+$, $CD4^+$ T-lymphocytes were present to a lesser extent, mainly periportally. B-lymphocytes and plasma cells were infrequent. $CD68^+$ histiocytes were increased in the hepatic sinusoids in two of our cases (Fig. 1). In the cohort of the published

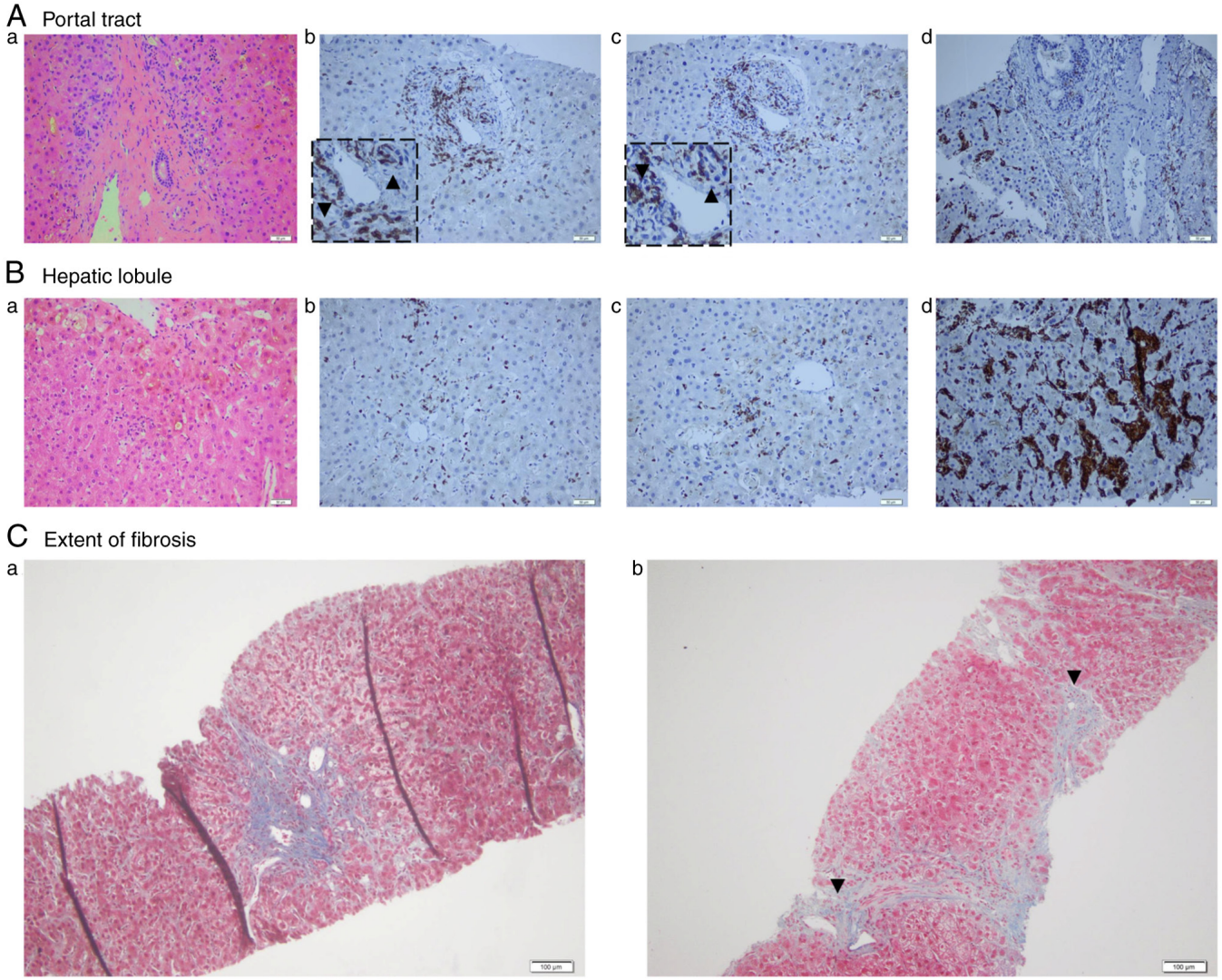


Figure 1. Representative images of the main morphological and immunohistochemical features of our cases, derived from different patients. (Aa) Portal tract and (Ba) hepatic lobule hematoxylin and eosin staining (magnification, x200) reveals mild to moderate hepatic injury. (Ab) Portal tract and (Bb) hepatic lobule CD3 immunostaining (magnification, x200), and (Ac) portal tract and (Bc) hepatic lobule CD8 immunostaining (magnification, x200). The inflammatory infiltrate consists mainly of $CD3^+$, $CD8^+$ T-lymphocytes and accumulates in the portal tracts with occasional extension to the hepatic lobules (interface hepatitis). In the portal tracts the T-lymphocytes invade the bile ductule epithelium (arrowheads in insets; magnification, x400). (Ad) Portal tract and (Bd) hepatic lobule CD68 immunostaining (magnification, x200). $CD68^+$ histiocytes are increased predominately around the portal tracts and within the hepatic sinusoids. (Ca) Masson trichrome staining (magnification, x100) showing mild portal-periportal fibrosis (Cb) Masson trichrome staining (magnification, x100) showing occasional bridging fibrosis between portal tracts and branches of the central vein (arrowheads).

clinical cases, liver biopsies revealed heterogeneous but recurring patterns, most notably lobular hepatitis with $CD8^+$ and $CD3^+$ T-cell-predominant infiltrates, which distinguish ILICI from classical AIH as described above.

Assessment of the toxicity grading is pivotal concerning the management of ILICI according to the ESMO and NCCN guidelines. For grades 1 and 2, a close monitoring of LFTs and differential diagnosis to exclude other causes of liver failure should be performed. Immunotherapy should be continued for grade 1 (AST/ALT elevated up to three times the upper limit of normal-ULN) with close monitoring of liver enzymes, while for grade 2 (AST/ALT three to five times the ULN) additional laboratory and imaging testing are required, and therapy should be temporarily withheld until grade 1 or full recovery of LFTs. If there is no improvement in laboratory findings in spite of ICIs discontinuation, administration of corticosteroids 0.5 to 1 mg/kg/day prednisone or equivalent is recommended, and the dose should be readjusted to 1-2 mg/kg/day if there is no response within 72 h after initiation. Immunotherapy shall be resumed after improvement of liver function. For grades 3 (AST/ALT up to five to twenty times ULN) and 4 (ASL/ALT more than twenty times the ULN), ICIs should be permanently discontinued and treatment with corticosteroids 1 to 2 mg/kg/day prednisone or equivalent should start promptly. In refractory cases, when corticosteroids do not yield a response within 2-3 days, it is advisable to contemplate alternative immunosuppressive agents, such as mycophenolate mofetil (MMF), azathioprine, cyclosporine etc.

Regarding our patients only one had grade 2 hepatotoxicity, while the rest exhibited grades 3 and 4. With respect to the published literature, 101 patients (91.9%) of

the presented with grade 3 and grade 4 hepatitis (45.5 and 46.4% respectively). The severity of the disease is evaluated using CTCAE grading system. We treated all five patients with corticosteroids, and one patient with persistent ILICI received mycophenolate mofetil five days after corticosteroid failure. Concerning the cohort of the published case reports, 108 patients were treated with glucocorticoids (98.2%), while of the two remaining patients, one was treated solely with budesonide and for the other one there is no information provided concerning the treatment. Out of 108 patients, 38 patients (34.5%) received only glucocorticoids, and 71 patients (64.5%) required more than one additional agent.

The administration of infliximab is contraindicated in immune mediated hepatitis as it predisposes in acute liver failure (6,8,30,31). Nonetheless, recent publications present evidence suggesting that the use of infliximab in cases of steroid-refractory ILICI could provide a positive and durable response, but more sufficient data are needed to establish its use as standard treatment (32). After patient's response, corticosteroid tapering should have a duration of 4-6 weeks, with the possibility of re-escalation if necessary. Of note, for grade 3 or 4 liver injury monotherapy with anti-PD(L)-1 agent may be resumed in patients previously treated with a combination regimen (6,33).

In our cases immunotherapy was permanently discontinued. Treatment continuation was not consistently reported across the published case reports, therefore a reliable conclusion cannot be reached. ICI resumption or rechallenge should follow an individualized strategy. Current clinical guidelines recommend permanent cessation of ICIs for most grade 4 toxicities, particularly in the context of severe or life threatening irAEs (e.g. myocarditis, nephritis) (6,34). Retreatment or rechallenge with ICIs is feasible and is typically reserved for patients whose toxicities have been completely resolved and were non-life-threatening (e.g. skin, endocrine, gastrointestinal) (35,36). Nevertheless, emerging evidence suggests that re-administration of ICIs is reasonable even after severe irAEs in carefully selected patients. This approach requires strict multidisciplinary supervision and close monitoring, along with the incorporation of risk-mitigation strategies, such as ICI class switching and organ-specific prophylaxis to reduce the risk of recurrent toxicity (37,38). Published data show that restarting ICIs after irAEs is associated with recurrent toxicity and increased safety concerns, while efficacy appears comparable to initial treatment (39,40).

The mean time between the first laboratory confirmation of hepatic disfunction in our cohort and corticosteroids initiation was seven days. Resolution of ILICI occurred in three patients (60%) and normalization of AST, ALT and bilirubin values was observed on average within three months of treatment, ranging from one to five months. In relation to literature-derived cohort, ILICI was resolved in 85.5% of the patients (94 patients), and median time to resolution was 2 months, ranging from 3 days to 24 months. Furthermore, of the five patients, four died subsequent to ILICI onset. Two fatalities were directly related to ILICI, whilst the other two were associated with complications during hospitalization unrelated to the immune-mediated adverse event. Regarding the cohort of the published case reports, death occurred in 14.5% (16 patients out of 110) highlighting that ILICI can be a fatal complication.

In conclusion, we present five cases of patients attended in our hospital after developing ILICI. All patients were treated with ICIs for different primary tumors and disease course. This small case series combined with an extensive literature review demonstrates that the time of occurrence of ILICI cannot be predicted, as it varies from a few days to several months after the first dose. Timely recognition and appropriate management are essential components of clinical care, although their prognostic impact was not formally assessed in the present study. Additionally, it needs to be noted that even if the majority of patients recover, there is a critical proportion that will succumb to the disease.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

MK, AK and APs substantially contributed to the conception and design of the study. GK, AB, IK and RZ contributed to data acquisition and curation. PE, APa, MA, MM and NG contributed to data analysis and interpretation. PF and MS performed pathological analysis and validation, while KP contributed to radiological analysis. IK and AB conducted the literature search and data visualization. MK, IK and PE drafted the original manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. AK and APs provided supervision, and AK acquired funding. MK and AK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Written informed consent was obtained from all patients (or their legal guardians/next of kin, where applicable) for the publication of anonymized clinical data and images. All identifying details have been removed to protect patient privacy. In cases where patients were deceased, informed consent for publication was obtained from the next of kin.

**Competing interests**

The authors declare that they have no competing interests.

## References


1. Spain L, Diem S and Larkin J: Management of toxicities of immune checkpoint inhibitors. Cancer Treat Rev 44: 51-60, 2016.
2. Reddy HG, Schneider BJ and Tai AW: Immune checkpoint inhibitor-associated colitis and hepatitis. Clin Transl Gastroenterol 9: 180, 2018.
3. Regev A, Avigan MI, Kiazand A, Vierling JM, Lewis JH, Omokaro SO, Di Bisceglie AM, Fontana RJ, Bonkovsky HL, Freston JW, *et al*: Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development. J Autoimmun 114: 102514, 2020.
4. Shojaie L, Ali M, Iorga A and Dara L: Mechanisms of immune checkpoint inhibitor-mediated liver injury. Acta Pharm Sin B 11: 3727-3739, 2021.
5. Remash D, Prince DS, McKenzie C, Strasser SI, Kao S and Liu K: Immune checkpoint inhibitor-related hepatotoxicity: A review. World J Gastroenterol 27: 5376-5391, 2021.
6. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, Lyon AR, Wick W, Kostine M, Peters S, *et al*: Management of toxicities from immunotherapy: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 33: 1217-1238, 2022.
7. National Cancer Institute: Common terminology criteria for adverse events (CTCAE), version 5.0. U.S. Department of Health and Human Services, Bethesda, MD, 2017. Available at: https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/ctcae-v5-5x7.pdf, Accessed March 10, 2025.
8. Zen Y and Yeh MM: Hepatotoxicity of immune checkpoint inhibitors: A histology study of seven cases in comparison with autoimmune hepatitis and idiosyncratic drug-induced liver injury. Mod Pathol 31: 965-973, 2018.
9. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, Roche B, Antonini TM, Coilly A, Laghouati S, *et al*: Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol 68: 1181-1190, 2018.
10. Shiravand Y, Khodadadi F, Kashani SM, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K and Kulasinghe A: Immune checkpoint inhibitors in cancer therapy. Curr Oncol 29: 3044-3060, 2022.
11. Xu Y, Fu Y, Zhu B, Wang J and Zhang B: Predictive biomarkers of immune checkpoint inhibitors-related toxicities. Front Immunol 11: 2023, 2020.
12. Riveiro-Barciela M, Barreira-Díaz A, Vidal-González J, Muñoz-Couselo E, Martínez-Valle F, Viladomiu L, Mínguez B, Ortiz-Velez C, Castells L, Esteban R and Buti M: Immune-related hepatitis related to checkpoint inhibitors: Clinical and prognostic factors. Liver Int 40: 1906-1916, 2020.
13. Chennamadhavuni A, Abushahin L, Jin N, Presley CJ and Manne A: Risk factors and biomarkers for immune-related adverse events: A practical guide to identifying high-risk patients and rechallenging immune checkpoint inhibitors. Front Immunol 13: 779691, 2022.
14. Atallah E, Welsh SJ, O'Carrigan B, Oshaughnessy A, Dolapo I, Kerr AS, Kucharczak J, Lee CYC, Crooks C, Hicks A, *et al*: Incidence, risk factors and outcomes of checkpoint inhibitor-induced liver injury: A 10-year real-world retrospective cohort study. JHEP Rep 5: 100851, 2023.
15. Da Cunha T, Wu GY and Vaziri H: Immunotherapy-induced hepatotoxicity: A review. J Clin Transl Hepatol 10: 1194-1204, 2022.
16. Biewenga M, van der Kooij MK, Wouters MWJM, Aarts MJB, van den Berkmortel FWPJ, de Groot JWB, Boers-Sonderen MJ, Hospers GAP, Piersma D, van Rijn RS, *et al*: Checkpoint inhibitor induced hepatitis and the relation with liver metastasis and outcome in advanced melanoma patients. Hepatol Int 15: 510-519, 2021.
17. Li Z, Zhou Z, Zhang N, Tian B, Chen X, Zhao H and Wang H: Hepatitis associated with immune checkpoint inhibitors-based combinations of other therapies: A real-world pharmacovigilance analysis based on the FDA adverse event reporting system (FAERS) database. Cancer Immunol Immunother 74: 25, 2024.
18. Miah A, Tinoco G, Zhao S, Wei L, Johns A, Patel S, Li M, Grogan M, Lopez G, Husain M, *et al*: Immune checkpoint inhibitor-induced hepatitis injury: risk factors, outcomes, and impact on survival. J Cancer Res Clin Oncol 149: 2235-2242, 2023.
19. Wang B, Zhuang S, Lin S, Lin J, Zeng W, Du B and Yang J: Analysis of risk factors for immune checkpoint inhibitor-associated liver injury: A retrospective analysis based on clinical study and real-world data. Hepatol Int 19: 1172-1186, 2025.
20. Remolina-Bonilla YA, Jimenez-Franco B, Lam ET and Bourlon MT: Immune-related adverse events involving multiple organ sites in a patient treated with nivolumab plus ipilimumab. Oncology (Williston Park) 34: 171-174, 2020.
21. Maher VE, Fernandes LL, Weinstock C, Tang S, Agarwal S, Brave M, Ning YM, Singh H, Suzman D, Xu J, *et al*: Analysis of the association between adverse events and outcome in patients receiving a programmed death protein 1 or programmed death ligand 1 antibody. J Clin Oncol 37: 2730-2737, 2019.
22. Petrelli F, Grizzi G, Ghidini M, Ghidini A, Ratti M, Panni S, Cabiddu M, Ghilardi M, Borgonovo K, Parati MC, *et al*: Immune-related adverse events and survival in solid tumors treated with immune checkpoint inhibitors: A systematic review and meta-analysis. J Immunother 43: 1-7, 2020.
23. Shimozaki K, Sukawa Y, Beppu N, Kurihara I, Suzuki S, Mizuno R, Funakoshi T, Ikemura S, Tsugaru K, Togasaki K, *et al*: Multiple immune-related adverse events and anti-tumor efficacy: Real-world data on various solid tumors. Cancer Manag Res 12: 4585-4593, 2020.
24. Liu Z, Zhu Y, Xie H and Zou Z: Immune-mediated hepatitis induced by immune checkpoint inhibitors: Current updates and future perspectives. Front Pharmacol 13: 1077468, 2023.
25. Johncilla M, Misdraji J, Pratt DS, Agoston AT, Lauwers GY, Srivastava A and Doyle LA: Ipilimumab-associated hepatitis: Clinicopathologic characterization in a series of 11 cases. Am J Surg Pathol 39: 1075-1084, 2015.
26. Cohen JV, Dougan M, Zubiri L, Reynolds KL, Sullivan RJ and Misdraji J: Liver biopsy findings in patients on immune checkpoint inhibitors. Mod Pathol 34: 426-437, 2021.
27. Lasagna A and Sacchi P: The ABC of immune-mediated hepatitis during immunotherapy in patients with cancer: From pathogenesis to multidisciplinary management. Cancers (Basel) 16: 795, 2024.
28. Sunago K, Abe M, Yoshida O, Watanabe T, Nakamura Y, Imai Y, Koizumi Y, Hirooka M, Tokumoto Y and Hiasa Y: Clinical and pathological features of immune checkpoint inhibitor-induced liver injury in comparison with drug-induced liver injury and autoimmune hepatitis. J Gastrointestin Liver Dis 32: 488-496, 2023.
29. Hagiwara S, Watanabe T, Kudo M, Minaga K, Komeda Y, Kamata K, Kimura M, Hayashi H, Nakagawa K, Ueshima K, *et al*: Clinicopathological analysis of hepatic immune-related adverse events in comparison with autoimmune hepatitis and graft-versus host disease. Sci Rep 11: 9242, 2021.
30. Björnsson HK, Gudbjornsson B and Björnsson ES: Infliximab-induced liver injury: Clinical phenotypes, autoimmunity and the role of corticosteroid treatment. J Hepatol 76: 86-92, 2022.
31. Zhang HC, Luo W and Wang Y: Acute liver injury in the context of immune checkpoint inhibitor-related colitis treated with infliximab. J Immunother Cancer 7: 47, 2019.
32. Burri E, Mangana J, Cheng PF, Schneider A, Weber A, Dummer R and Ramelyte E: Infliximab in steroid-refractory immune-related hepatitis does not demonstrate hepatotoxicity and may shorten time on steroids. J Immunother Cancer 12: e008074, 2024.
33. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, *et al*: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. J Clin Oncol 36: 1714-1768, 2018.
34. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, Atkins MB, Brassil KJ, Caterino JM, Chau I, *et al*: Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol 39: 4073-4126, 2021.
35. Wu CY, Zubiri L, Rouhani SJ, Merkin RD, Holt A, Falade AS, Grealish K, Hathaway N, and Reynolds KL: Immune checkpoint inhibitor (ICI) rechallenge after immune-related adverse events (irAE) requiring hospitalization: A single-center 10-year experience. J Clin Oncol 42 (16 Suppl): e14609, 2024.
36. Gang X, Yan J, Li X, Shi S, Xu L, Liu R, Cai L, Li H and Zhao M: Immune checkpoint inhibitors rechallenge in non-small cell lung cancer: Current evidence and future directions. Cancer Lett 604: 217241, 2024.

37. Haanen J, Ernstoff M, Wang Y, Menzies A, Puzanov I, Grivas P, Larkin J, Peters S, Thompson J and Obeid M: Rechallenge patients with immune checkpoint inhibitors following severe immune-related adverse events: Review of the literature and suggested prophylactic strategy. J Immunother Cancer 8: e000604, 2020.
38. Mizuno K, Maeda O and Ando Y: Efficacy and safety of immune checkpoint inhibitor rechallenge following immune-related adverse events: A review. Jpn J Clin Oncol: hyaf200, 2025 (Epub ahead of print).
39. Zhao Q, Zhang J, Xu L, Yang H, Liang N, Zhang L, Zhang F and Zhang X: Safety and efficacy of the rechallenge of immune checkpoint inhibitors after immune-related adverse events in patients with cancer: A systemic review and meta-analysis. Front Immunol 12: 730320, 2021.
40. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, Fedrizzi S, Chrétien B, Da-Silva A, Plane AF, *et al*: Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. JAMA Oncol 6: 865-871, 2020.