Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Absence of Survival Impact from Hepatitis During Immunotherapy in 193 Patients with Advanced Hepatocellular Carcinoma – An Observational Study from Taiwan

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Background: Hepatitis often occurs after initiating immune checkpoint inhibitor (ICI) treatment. The time and grade of hepatitis after ICI starts and the prognostic role of immune-related hepatitis in patients with advanced hepatocellular carcinoma (aHCC) remain unclear.

Methods: In this real-world analysis, we enrolled aHCC patients receiving ICIs, documented the highest level of liver enzymes during/after ICIs, and analyzed the survival impact of different hepatitis patterns.

Results: One hundred and ninety-three aHCC patients receiving ICIs were recruited. During ICIs, 88.6% of patients experienced aspartate transaminase (AST) elevations (Grade III/IV: 7.8%). For alanine transaminase (ALT), 81.3% had elevated levels (Grade III/IV: 3.6%), and 41.5% of patients had elevated bilirubin levels (Grade 3/4: 6.7%). The median AST, ALT, and total bilirubin values significantly increased after ICI treatment initiated (all $p < 0.001$) and, similarly, after excluding progressive disease ($p = 0.014$, $p = 0.002$, $p < 0.001$). The median time of hepatitis occurrence is from the 4.0th to 15.9th weeks. Multivariable analysis showed that patterns of liver enzyme change of AST and total bilirubin in patients receiving ICIs significantly correlate to overall survival (OS, $p = 0.009$ and 0.001, respectively). After ICI termination, patients with elevated bilirubin ($p = 0.003$) and AST ($p = 0.005$) would indicate poor survival, with adjustment of viral hepatitis and ICI responses.

Conclusion: Hepatitis emerges between the 4th and 20th weeks post-ICI initiation. Changes in liver enzymes during ICI therapy do not directly affect OS, implying the safety of ICI use when corticosteroids are promptly administered if clinically indicated.

Keywords: hepatitis, immune checkpoint inhibitor, advanced hepatocellular carcinoma, liver enzymes, overall survival

Introduction

Hepatocellular carcinoma (HCC) is the sixth most prevalent cancer and the fourth leading cause of cancer deaths worldwide, with high overall mortality and an incidence rate of 0.95.[1,2] HCC accounts for 7.5% (fifth) of cancer cases in males, compared to 3.4% (ninth) in females.[3] Globally, the highest age-adjusted incidence rates (43/100,000) are reported in East Asia (Taiwan [43.48 in males; 16.17 in females], North and South Korea, China, and Vietnam) and sub-Saharan Africa.[4,5] In HCC, 80% of cases are closely related to hepatitis B virus (HBV) or hepatitis C virus (HCV) infection,

Received: 8 June 2024
Accepted: 27 September 2024
Published: 2 October 2024

primarily in patients with cirrhosis.[3] In the last 20 years, there has been an apparent increase in cancer-associated death rates, constituting a significant public health problem worldwide, especially in Asia.[3,6] The primary modalities of HCC treatment and standard treatments before 2018 were surgery, transplantation, transarterial chemoembolization, radio-frequent ablation, hepatic arterial infusion chemotherapy, and targeted therapies.[7,8] While the prognosis of unresectable, advanced hepatocellular carcinoma (aHCC) remains poor for traditional treatments, the development of immune checkpoint inhibitors (ICIs) has renewed the hope for aHCC treatment.[9–13]

In recent years, immune checkpoint inhibitors have tremendously improved the survival of patients with various types of advanced cancers,[14–18] including HCC.[19] Cytotoxic T-lymphocyte protein 4 (CTLA-4), programmed cell death receptor 1 (PD-1), its ligand (PD-L1), or in combination with TIM-3 or LAG-3 have been proven to be able to inhibit T-cell activation and promote T-cell exhaustion.[19,20] Despite their anti-tumor effects, multi-organ inflammatory side effects have been reported as immune-related adverse events (irAEs) in patients receiving ICI therapy.[21] Hepatotoxicity accounts for about 22% of all PD-1/PD-L1-related fatal toxicities. The combination of CTLA-4 and PD-1/PD-L1 blockade is related to more frequent and more severe irAEs.[22–24] Although acute hepatitis induced by ICIs for advanced cancer is rare (3.5%) and manageable in most cases, it has a higher incidence rate in HCC receiving ICIs therapy than other types of cancer.[25,26] The severity of immunotherapy-related or -induced liver injury may be associated with the specific ICIs, the ICI-dose levels, any preexisting autoimmune disorders, chronic viral infections, or cancer infiltration percentages in the liver parenchyma.[27] When patients develop liver injury during ICI treatment, a prompt assessment of the etiology of the injury should be undertaken in conjunction with optimal management.[27] Although most immune-related liver injuries could be well controlled with proper management, its fatal toxicity in patients with aHCC could be more severe and should not be ignored.[22,28–30] This highlights the importance of analyzing the underlying reasons for the higher rate of immune-related hepatotoxicity compared to other cancers.

However, the timing and severity of hepatitis in terms of aspartate transaminase (AST), alanine transaminase (ALT), and total bilirubin levels remain unclear. The difficulty of a differential diagnosis between disease-related hepatitis or immune-related hepatitis has been a common issue in aHCC, which causes the prognostic or predictive role of immune-related hepatitis in patients with aHCC to be still under debate. Therefore, in this real-world observational study, we aimed to analyze patients with aHCC who received ICIs and provide some information to predict outcomes after ICI initiation or termination.

Materials and Methods

Selection and Description of Patients

A retrospective study of patients with HCC at Chang Gung Memorial Hospital at Linkou, a medical center in Taiwan, was evaluated for enrollment. The Institutional Review Board approved the study protocol of Chang Gung Memorial Hospital with the ID 201901740B0C501. The inclusion criteria are as follows: (i) pathologically or cytologically confirmed HCC, to avoid confusion with other types of liver tumors that might be misdiagnosed when using imaging combined with AFP criteria.[31]; and (ii) patients received at least two doses of ICI therapy (nivolumab, or pembrolizumab) between 2016 and 2020 to ensure adequate drug exposure. ICI monotherapy or combination therapies are permitted, as the study did not influence the physicians' treatment decisions. The exclusion criteria consisted of (i) no pathology-proven liver cancer, (ii) only one dose of administered ICI, (iii) concurrent local therapies, including transarterial chemoembolization or radiofrequency ablation". Patients were identified through an electronic medical chart system, and further information relating to the patient demographics, inpatient admissions, and outpatient clinic records was gathered for analysis. The clinical data included the following: sex, age, serial alpha-fetoprotein (AFP) levels, serial liver enzymes, the highest grade of hepatotoxicity, Eastern Cooperative Oncology Group (ECOG) performance status, Barcelona Clinic Liver Cancer (BCLC) classification, Child-Pugh score, sites of metastasis, portal vein invasion, etiology of chronic liver cirrhosis, prior therapies if any, date of disease progression, and death from any causes. The serial monitoring of liver function enzymes was generally ordered before starting systemic therapies at each cycle and when suspected hepatitis occurs, following the National Comprehensive Cancer Network (NCCN Inc.) guidelines. All ICIs were administered following the recommendations from the local tumor board and the NCCN guidelines.[32] The

treatment was discontinued when any of the following conditions (ie, objective disease progression, deterioration of clinical status, intolerable drug-related toxicity, or patient refusal) are presented. This study's modified RECIST criteria for HCC assessed the tumor responses for ICIs.[33]

Toxicity Assessment and Management

Hepatotoxicity was defined as transaminitis or hyperbilirubinemia after the beginning of the ICI therapy and exclusion of all possible causes, such as viral hepatitis liver injury by tumor progression. The severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[34] Toxicity information was extracted by reviewing the medical records of oncology or hepatology clinic visit notes, laboratory results, and any hospitalizations or other relevant records. The most recent AST, ALT, and total bilirubin levels before starting ICIs were documented and defined as the baseline data. Between the first and the last dose of ICIs, the highest AST, ALT, and total bilirubin levels were recorded. After the end of ICI treatment, the highest levels of AST, ALT, and total bilirubin within six months from the end date of ICIs were documented, irrespective of the reasons (ie, disease progression, intolerance, or patients' preference). The response to ICIs was categorized as complete response, partial response, stable disease, and progressive disease according to computed tomography or magnetic resonance imaging reports after ICI treatment. In this analysis, we planned to calculate the percentages of hepatotoxicity (ie, AST, ALT, and total bilirubin), the timing of the highest grade, and the highest grade after physicians stopped using ICI according to the CTCAE 5.0 (Supplementary Table S1). Furthermore, the liver toxicity (ie, AST/ALT/Total bilirubin elevation) rates were expressed in this study in 2 ways: (i) percentages by grading despite baseline liver function; (ii) percentages only in patients with normal baseline liver function.

Etiology Surveys During Hepatitis Occurrence

When Grade II or greater hepatic adverse effects on ICI therapy occurred, physicians evaluated the titers and the activity of viral hepatitis (HBV deoxyribonucleic acid [DNA], HCV ribonucleic acid [RNA], Herpes simplex virus IgM, polymerase chain reaction (PCR), Epstein-Barr Virus PCR, Cytomegalovirus PCR, Varicella-Zoster Virus IgM, autoimmune serologies (antinuclear antibody, anti-smooth muscle antibody, immunoglobulin [IgA, IgE, IgG, IgM, etc]), abdominal echo, and liver biopsy if the patient consented and the safety was confirmed. The management of treatment-related hepatitis was documented, including the kinds and doses of corticosteroids corresponding to the severity.[35]

Classifications of Liver Enzyme Changes for Survival Impact Analysis

Theoretically, the changes (ie, increase and decrease) of liver enzymes at three time points (ie, before [baseline], the highest level during ICI treatment, the highest level in six months after ICI termination) could be classified into four groups (patterns) by any unit change (1 U/L or 0.1 mg/dL): "decrease-decrease", "increase-decrease", "decrease-increase", and "increase-increase". Based on whether the level of liver enzymes in the six months after ICI termination increased compared with the highest level of liver enzymes during ICIs, the four groups (patterns) were classified into two groups (patterns): "no increase vs increase of liver enzyme after ICI termination", and "no increase vs increase of liver enzyme during ICI use".

Statistical Analysis

All statistical analyses were performed by SPSS (V.25, IBM, New York, USA). Descriptive statistics (ie, mean or median, as indicated, and quadriceps interval) were used to summarize the patient demographic data, characteristics, incidence, severity, survey, and management of hepatitis after immunotherapy. Mann–Whitney *U*-test was used for statistical significance. The follow-up time was calculated from the date of the first dose of ICIs to the death or last clinic follow-up. Overall survival (OS) was calculated from the first ICI dose to death from any cause. Patients who were still alive were censored during the last recorded clinic follow-up. Median follow-up time was determined from the date of ICI administration to the latest follow-up date. We used univariate and multivariable Cox regression models to elucidate the independent role(s) of liver enzyme patterns after ICI initiation. All the factors in the univariate analysis were analyzed using the multivariable model in this study. We further applied the Kaplan-Meier method with Log rank tests to

illustrate the survival curves by different patterns of liver enzyme changes. Categorical outcomes were compared using Fisher's exact test or the χ^2 test for trend. Statistical significance was indicated by p values less than 0.05.

Results

Patient Enrollment

Between April 2016 and May 2020, 2577 patients with hepatocellular carcinoma who received a cancer diagnosis, treatment, and follow-up in Chang Gung Memorial Hospital at Linkou, a tertiary medical center in Taiwan, were screened. As demonstrated in Figure 1, 193 patients were enrolled in this study per the inclusion and exclusion criteria. Table 1 summarizes the basic characteristics of the patients in this cohort. The median age was 63 (Q1-Q3 57–69) years old. The majority of patients had an ECOG performance status of zero to one (93.8%), Child-Pugh score A (85.0%), and BCLC stage C (87.0%). More than half of the patients were male (78.8%), had extrahepatic metastases (52.3%), no major portal vein invasion (57.5%), and HBV (64.8%). The median baseline AFP was 215.4 (Q1-Q3 19.075–5387.0) ng/mL, and 37.8% were greater or equal to 400 ng/mL. About 71.5% of patients had been previously treated by targeted therapy, and 71.5% received ICIs at ≥ the second line. The median interval between the last and the first dose of ICIs was 2.4 (Q1-Q3 1.0–6.1) months. The majority (61.7%) of responses to ICIs were progressive diseases. The OS in the whole cohort was 10.8 (95% CI = 7.8–13.8) months (Supplementary Figure S1) after a median follow-up time of 9.0 (range, 0.5–54.6) months at a data cutoff date of April 2021.

Monitoring Hepatitis Before, During, and After ICI Treatment

Normal or abnormal liver enzymes were documented and displayed in Supplementary Table S2. In the real-world scenarios, 78.2% (n = 151) patients had baseline abnormal AST (reference, ≤34 U/L) levels, while 58.0% (n = 112) of patients had abnormal baseline ALT levels (reference, ≤36 U/L), and 18.1% (n = 35) had abnormal total bilirubin values (reference, ≤1.4 mg/dL). During ICI therapy, patients were found to have abnormal AST, ALT, and total bilirubin levels, accounting for 88.6%, 81.3%, and 41.5% of total patients, respectively. Among those whose baseline liver function was normal, 11.9% (5/42, including 4.8% with grade 3/4 toxicity), 6.2% (5/81, including 1.2% with grade 3/4 toxicity), and 8.2% (14/158, including 1.3% with grade 3/4 toxicity) had equal or greater than Grade II elevation of liver function (Supplementary Table S2). In addition, after the end of ICI treatment (within six months), the abnormality rates of the

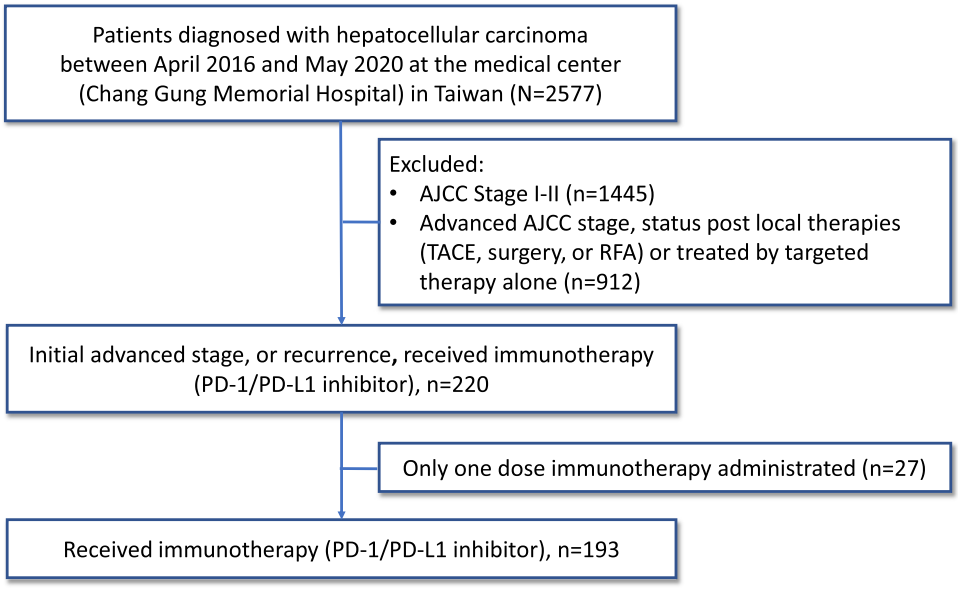

Figure 1 Algorithm of Patient Enrollment.
Abbreviations: AJCC, American Joint Committee on Cancer; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1.

Table 1 Basic Characteristics of Enrolled Patients (n = 193)

Parameters	n	(%)
Age, median (range), years	63 (25–91)	
Sex		
Male	152	78.8%
Female	41	21.2%
ECOG PS before immunotherapy		
0–1	181	93.8%
≥ 2	12	6.2%
Child-Pugh score before immunotherapy		
A	164	85.0%
B	25	13.0%
C	4	2.1%
BCLC before immunotherapy		
A*	9	4.7%
B*	12	6.2%
C	172	89.1%
Extrahepatic spread status		
Yes	101	52.3%
No	92	47.7%
Major portal vein invasion		
Yes	82	42.5%
no	111	57.5%
Etiology of chronic liver cirrhosis		
HBV	125	64.8%
HCV	46	23.8%
Alcohol	94	48.7%
Non-HBV, non-HCV, non-alcohol	10	5.2%
Baseline AFP, median (range)	215.4 (1.8–1,820,974.0)	
≥ 400	73	37.8%
< 400	120	62.2%
Previous systemic therapy		
Targeted therapy[a]	138	71.5%
Chemotherapy	15	7.8%
Systemic treatment-naïve	55	28.5%

(*Continued*)

Table 1 (Continued).

Parameters	n	(%)
Line of Immunotherapy		
First-line	55	28.5%
Second-line	114	59.1%
≥ Third line	24	12.4%
Response of ICIs		
Complete response	10	5.2%
Partial response	22	11.4%
Stable disease	42	21.8%
Progressive disease	119	61.7%
Duration of ICIs, median (range), months	2.4 (0.4–40.4)	

Notes: *21 patients received immunotherapy because of failure of repeated transarterial chemoembolization. [a]The targeted therapies included sorafenib, regorafenib and lenvatinib.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; ICIs, immune check point inhibitors.

highest levels of AST, ALT, and total bilirubin were 47.2%, 45.6%, and 53.4%, respectively. After the initiation of ICIs, there was a trend of increased liver enzymes for AST (78.2% to 88.6%), ALT (58.0% to 81.3%), and total bilirubin levels (18.1% to 41.5%). After terminating ICI therapy, most patients had decreased AST (88.6% to 47.2%) and ALT (81.3% to 45.6%) levels. However, the patients' bilirubin values (41.5% to 53.4%) appeared to be persistently elevated after ICI termination. Most of the highest hepatotoxicity after ICIs was grade I (Supplementary Table S2). The box plots (Figure 2A–C) show a simultaneous increase of the median levels of AST, ALT, and total bilirubin ($p < 0.001$), respectively. Similar results were found after excluding patients with progressive disease (Figure 2D–F; $p = 0.014$, $p = 0.002$, $p < 0.001$, respectively). Another way of presenting the highest grade of hepatotoxicity in box plots was illustrated in Supplementary Figures S2A–C. Grade IV hepatitis (AST, ALT, and total bilirubin) occurs at the 3.5th, 13.0th, and 2.7th weeks after ICI initiated, respectively. Grade III hepatitis (AST, ALT, and total bilirubin) occurs at the 10.7th, 15.9th, and 10.2nd weeks after ICI initiated, respectively. We also analyzed the minimum, maximum, and range of liver enzyme changes according to the different timing of ICIs (Supplementary Table S3). In brief, before ICI, the median (IQR) values of AST, ALT, and Bilirubin (total) were 59.5 (39.0–100.8) U/L, 44.0 (28.8–74.0) U/L, and 0.8 (0.6–1.3) mg/dL, respectively. During the ICI therapy, the median (IQR) values of AST, ALT, and Bilirubin (total) were 83.0 (48.0–162.0) U/L, 60.5 (37.8–100.3) U/L, and 1.2 (0.8–1.6) mg/dL, respectively. As for the values after ICIs, the median (IQR) values of AST, ALT, and Bilirubin (total) were 98.5 (54.0–255.5) U/L, 69.0 (43.3–145.3) U/L, and 1.9 (1.0–5.4) mg/dL, respectively.

Overall Survival Impacts of the Changes in Liver Enzymes

We further analyzed the changes in the liver enzymes AST, ALT, and total bilirubin and how they impact the clinical outcome. Because some patients died very soon of missed checking AST/ALT or total bilirubin, we have 162, 172, and 166 patients, respectively, to analyze the impact of liver enzyme changes after ICIs therapy. Four groups (patterns) were classified by the criteria mentioned above in the material and methods section. The multivariable Cox regression model showed AFP values before ICIs, Child-Pugh Scores before ICIs, BCLC stages before ICIs, the best response of ICIs, AST change patterns, and total bilirubin change patterns are independent prognostic factors to overall survival in patients receiving ICIs, with p values of 0.003, 0.002, 0.041, <0.001, 0.009, and 0.001 (Table 2). Utilizing Kaplan–Meier curves,

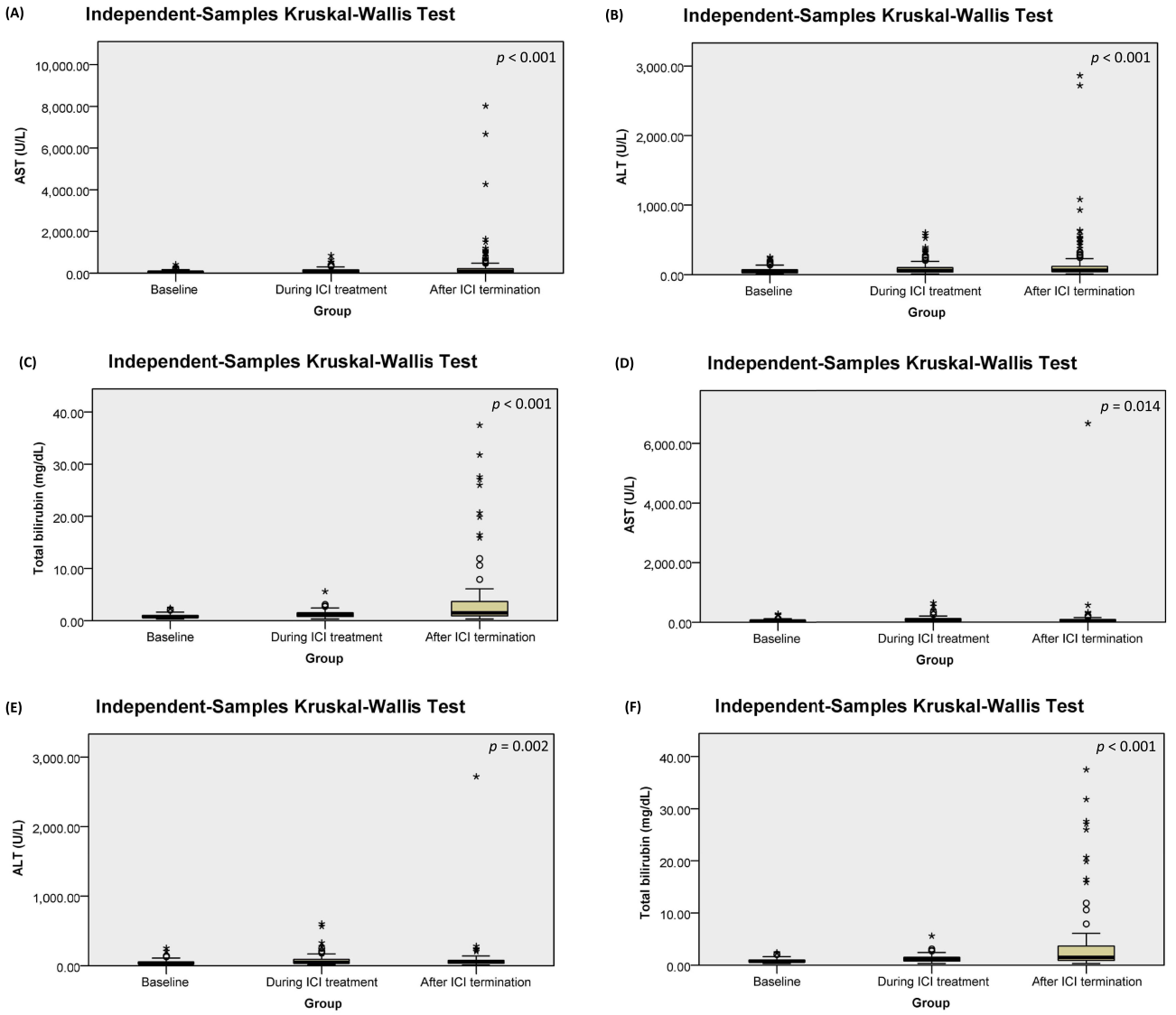

Figure 2 The trends of baseline and the highest levels of ASThT, ALT, and total bilirubin in the period of immune checkpoint inhibitors The box plots showed the median levels of AST, ALT, and total bilirubin simultaneous increase (**A**–**C**, respectively), and similar results were demonstrated after excluding patients with progressive disease (**D**–**F**, respectively). In (**A**–**F**), the numbers presented in the group of "during ICI treatment" were the highest values of the liver enzyme during ICI treatment; the numbers are shown in the group of "after ICI termination" were defined as the highest values of liver enzyme in six months after ICI termination. *Indicates a single elevated level of AST, ALT, or total bilirubin.

Abbreviations: ICI, immune checkpoint inhibitor; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Figure 3A and B show the OS of patients in the four groups (patterns) representing the different status changes of AST and total bilirubin, respectively. Patients in "decrease-decrease AST" and "increase-decrease AST" groups (patterns) seemed to have prolonged OS of 27.9 months and "not reached", respectively ($p = 0.001$, Figure 3A). Similarly, a better median OS of 27.9 months (95% CI: 12.8–43.0) and "not reached" was observed in both groups (patterns) of "decrease-decrease total bilirubin" and "increase-decrease total bilirubin" ($p = 0.006$, Figure 3B). The pattern of ALT changes does not seem to be statistically significant ($p = 0.064$, Supplementary Figure S3).

To elucidate the liver enzyme change patterns at different time points (ICIs initiation and termination), we found that AST changes after ICI termination and total bilirubin changes after ICI termination are independent prognostic factors for OS, with p values of 0.005 and 0.003, respectively (Table 2, Figure 3C and D). Notably, none of the liver enzymes, including AST, ALT, or total bilirubin elevation during ICI use, have been found to impact oncologic outcomes with p values of 0.607, 0.316, and 0.095, respectively (Table 2).

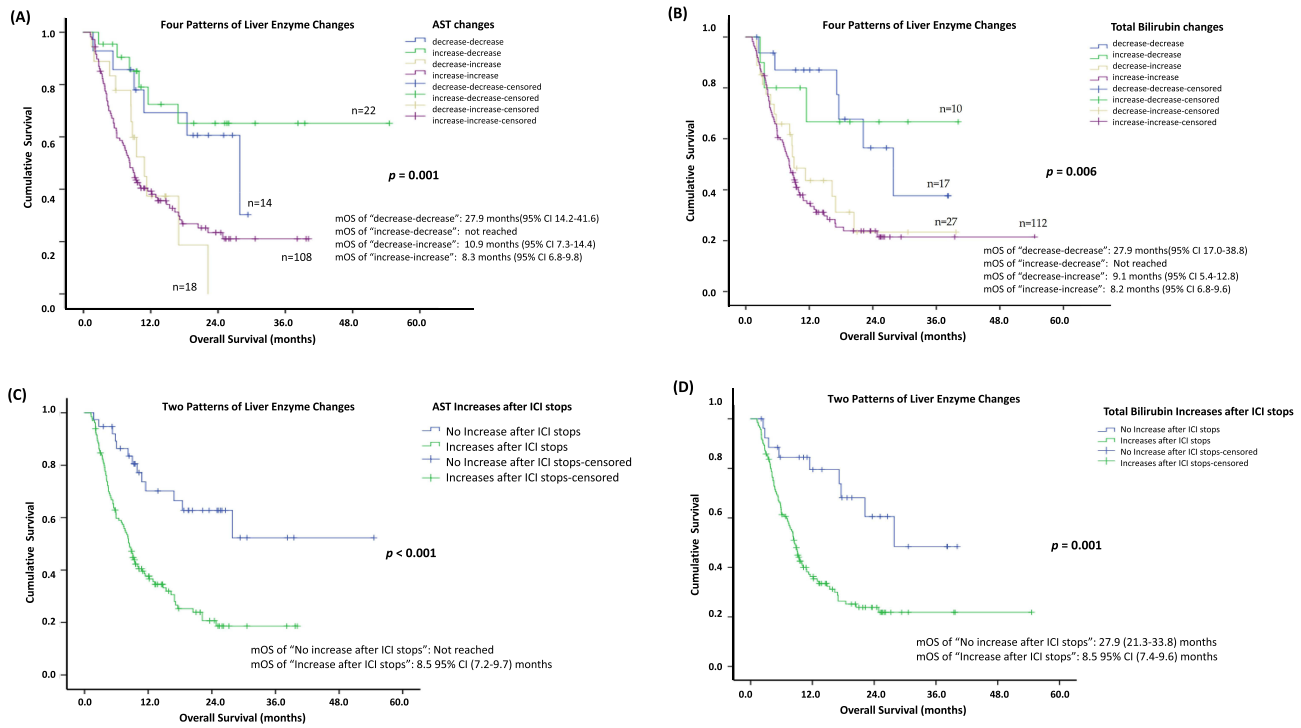

Figure 3 Overall Survival impacts of the AST, ALT, and total bilirubin level changes after initiation of ICIs. The overall survival was statistically different among patients by the changes of AST (**A**) and total bilirubin (**B**) after initiation of ICIs (decrease-decrease, decrease-increase, increase-increase, and increase-decrease) with *p* values of 0.001 and 0.006, respectively. The pattern of ALT change did not show any statistical significance (not shown). The levels of AST (**C**) and total bilirubin (**D**) significantly impact overall survival after stopping ICI, with p-values of <0.001 and 0.001, respectively.

Abbreviations: ICI, immune checkpoint inhibitor; mOS, median overall survival; 95% CI, 95% confidence interval.

The Percentage of the Etiology Survey for Grade II Hepatitis and Its Management

According to the CTCAE 5.0 criteria, the grading considers individual baseline liver function. Among 193 patients, 42 (21.8%) patients had greater than or equal to Grade II hepatitis, as illustrated in Supplementary Figure S4, who traditionally require medical intervention during ICIs. Among all patients with ≥ Grade II hepatitis (n = 42), sixteen (38.1%) patients had received corticosteroids, and thirteen (31.0%) underwent standard surveys to exclude other etiologies of hepatitis (Supplementary Table S4). Among patients receiving ICI treatment, 64.8% were HBV carriers receiving prophylactic antiviral medication, and 23.8% had a history of HCV with completed therapy with direct-acting antiviral agents, which the Taiwanese government reimburses. Among patients with ≥ Grade II hepatitis who received corticosteroids (n = 16), 56.3% had completed surveys for any other causes of hepatitis, while 43.8% did not have any

Table 2 The Highest Grading of Liver Toxicity Before, During, and After ICIs

	Baseline*		Highest During ICI		Highest After ICI	
	n	%	n	%	n	%
AST	**151**	**78.2%**	**171**	**88.6%**	**91**	**47.2%**
Grade I	113	58.5%	107	55.4%	46	23.8%
Grade II	26	13.5%	49	25.4%	18	9.3%
Grade III	12	6.2%	11	5.7%	21	10.9%
Grade IV	0	0.0%	4	2.1%	6	3.1%

(*Continued*)

Table 2 (Continued).

	Baseline*		Highest During ICI		Highest After ICI	
	n	%	n	%	n	%
ALT	**112**	**58.0%**	**157**	**81.3%**	**88**	**45.6%**
Grade I	93	48.2%	113	58.5%	54	28.0%
Grade II	15	7.8%	37	19.2%	17	8.8%
Grade III	4	2.1%	5	2.6%	14	7.3%
Grade IV	0	0.0%	2	1.0%	3	1.6%
Total Bilirubin	**35**	**18.1%**	**80**	**41.5%**	**103**	**53.4%**
Grade I	18	9.3%	46	23.8%	31	16.1%
Grade II	16	8.3%	21	10.9%	32	16.6%
Grade III	0	0.0%	12	6.2%	24	12.4%
Grade IV	1	0.5%	1	0.5%	16	8.3%

Notes: *The grade of baseline liver function was defined according to CTCAE 5.0, which was summarised in supplementary file.
Abbreviations: ICIs, immune checkpoint inhibitors; AST, aspartate transaminase; ALT, alanine transaminase.

surveys. Besides, among patients with ≥ Grade II hepatitis without corticosteroids (n = 26), 84.6% did not perform any tests for etiology. Besides, none received a liver biopsy in this cohort. Given that almost all clinical trials enrolled patients with nearly normal baseline liver function, we calculated the percentage of liver toxicity in those normal hepatic enzymes at baseline to avoid misleading the readers.

Discussion and Conclusion

This real-world data analysis found that hepatitis occurred after ICI use/termination with statistical significance ($p < 0.001$). The median OS was 10.8 (95% CI: 7.8–13.8) months in this cohort (Supplementary Figure S1), which was a little bit inferior compared to that of patients with HCC receiving ICI monotherapy in prospective trials.[36,37] In our analysis, the highest grade of hepatitis (Grade III AST, ALT, total bilirubin) occurred at the 7.3th, 20.9th, and 4.0th weeks after ICI initiation, respectively, which were similar to the literature.[24] Hepatitis patterns in AST and total bilirubin levels independently correlated to the prolonged OS in this cohort ($p = 0.009$ and 0.001, respectively, Table 3), which did better than ALT levels after adjustment of age, sex, baseline AFP, viral hepatitis, and disease response to ICIs. Compared with the literature, a similar finding was reported from a US FDA clinical trial database containing 406 hCC patients. Dr. David J. Pinato et al found that developing grade 2 or higher treatment-related adverse events correlates with improved outcomes in patients with HCC receiving ICI.[38] Additionally, Dr. Heechul Nam et al also reported on an Asian cohort treated with atezolizumab plus bevacizumab. They found that mild immune-related adverse events (irAEs) were independently associated with favorable survival, suggesting their potential role as surrogate indicators of HCC prognosis.[39] In this study, we found that patients with increased total bilirubin after termination of ICIs had shorter OS statistically after adjustment of ICI responses and all other factors ($p = 0.003$, hazard ratio [HR] = 2.206 (95% Confidence interval [CI] = 1.319–3.691), Table 2). Intriguingly, patients with elevated AST levels (but not ALT) after ICI termination had a shorter OS ($p = 0.005$, HR = 2.465 [95% CI = 1.313–4.629], Table 2), which might reflect a natural course after disease progression or liver decompensation (including progressive or newly onset ascites, hepatic encephalopathy, esophagogastric variceal bleeding, and hepatorenal syndrome) after multiple cancer therapies.[40]

In a further exploratory analysis, we found that AST and total bilirubin levels after ICI termination (but not ALT) potentially serve as independent poor prognostic factors after adjustment of all related factors. Notably, no prognostic

Table 3 Univariate and Multivariate Analysis for Overall Survival

	Four Categories of Liver Enzyme Change Patterns				Liver Enzymes Changes			
	Univariate		Multivariate		Univariate		Multivariate	
Variables	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**
Age	0.317	0.992 (0.976–1.008)			0.317	0.992 (0.976–1.008)		
Sex	0.339	0.816 (0.538–1.238)			0.339	0.816 (0.538–1.238)		
Baseline AFP values before ICIs	0.001	1.000 (1.000–1.000)	0.003	1.000 (1.000–1.000)	0.001	1.000 (1.000–1.000)	0.022	1.000 (1.000–1.000)
ECOG Performance before ICIs	<0.001	1.779 (1.412–2.242)	0.076	1.400 (0.966–2.030)	<0.001	1.779 (1.412–2.242)	0.051	1.453 (0.998–2.115)
HBV carrier yes vs no	0.039	1.525 (1.022–2.276)			0.039	1.525 (1.022–2.276)		
HCV carrier yes vs no	0.797	0.946 (0.618–1.448)			0.797	0.946 (0.618–1.448)		
Alcohol yes vs no	0.687	0.949 (0.735–1.224)			0.687	0.949 (0.735–1.224)		
Child-Pugh Score before ICIs (A vs B vs C)	<0.001	2.556 (1.734–3.768)	0.002	2.126 (1.332–3.393)	<0.001	2.556 (1.734–3.768)	0.004	1.964 (1.236–3.118)
BCLC stages before ICIs	0.002	3.153 (1.498–6.635)	0.041	2.249 (1.034–4.888)	0.002	3.153 (1.498–6.635)	0.024	2.433 (1.122–5.275)
Best response (CR vs PR vs SD vs PD)	<0.001	2.510 (1.862–3.385)	<0.001	2.329 (1.618–3.352)	<0.001	2.510 (1.862–3.385)	<0.001	2.443 (1.690–3.532)
Four Patterns of Liver Enzyme Changes								
AST change patterns	<0.001	1.532 (1.212–1.935)	0.009	1.388 (1.086–1.775)	NA	NA		
ALT change patterns	0.034	1.201 (1.014–1.423)			NA	NA		
Bilirubin (Total) change patterns	0.001	1.491 (1.176–1.890)	0.001	1.556 (1.185–2.045)	NA	NA		
Two Patterns of Liver Enzyme Changes								
AST change after ICI termination	NA	NA			<0.001	3.222 (1.795–5.783)	0.005	2.465 (1.313–4.629)
ALT change after ICI termination	NA	NA			0.139	1.408 (0.894–2.216)		
Bil-T change after ICI termination	NA	NA			0.001	3.150 (1.584–6.265)	0.003	2.206 (1.319–3.691)
AST change during ICI therapy	NA	NA			0.363	1.253 (0.771–2.037)		
ALT change during ICI therapy	NA	NA			0.009	1.699 (1.145–2.523)		
Bil-T change during ICI therapy	NA	NA			0.056	1.542 (0.989–2.406)		

Abbreviations: AFP, α-fetoprotein; ECOG, Eastern Cooperative Oncology Group; HBV, hepatitis B virus; HCV, hepatitis C virus; Bil-T, total bilirubin; ICI, immune checkpoint inhibitors; BCLC, Barcelona Clinic Liver Cancer; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CR, complete remission; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

outcomes were noted when hepatitis occurs during ICI use in our report. When examining related literature beyond HCC, improved outcomes have been reported in cancer patients receiving ICIs experiencing irAEs,[41–43] in which there are limited data about immune-related hepatitis. On the contrary, liver dysfunction has been reported to be associated with poor prognosis in lung cancer, urothelial cancer, gastric cancer, and renal cell carcinoma patients after ICIs therapy,[44] but not in HCC patients. In 2023, Ciro Celsa et al[40] observed a similar trend to our study. Conducting a real prospective observational study involving 375 patients with HCC receiving atezolizumab plus bevacizumab, they noted a higher incidence and earlier onset of immune-related liver injury in these patients. Similar to us, liver injury during ICI therapy appears not to significantly affect oncological outcomes.

Table 4 summarizes the incidence of immune-related hepatotoxicity during ICI use, but none of the studies reported the outcome of different liver enzyme changes after ICI termination except our study. Among all prospective trials,[11,36,37,45–54] the all-grade hepatic toxicity ranged from 1.8% (Grades III/IV 1.0%)[36,53] to 16.9% (Grades III/IV: 9.5%),[50] compared with 4.0% (Grades III/IV: 4.0%)[55] to 12.2% (Grades III/IV: 1.8%) in the real-world analysis. Regarding the details of hepatotoxicity in prospective trials,[11,36,37,40,45–54,56] patients presented hepatotoxicity with all-grade ALT elevation ranging from 5.0% (Grades III/IV: 4.0%)[37] to 20.0% (Grades III/IV: 5.0%),[47,54] compared with 6.2% (Grades III/IV: 1.2%) in retrospective reports.[52,55] The incidence of hepatotoxicity in our report seems within the average, indicating that the population is relatively comparable. The details in our study are complete compared with prospective trials and other real-world analyses. In addition, we did not report the subsequent therapy after ICIs because there is no clear evidence that subsequent systemic therapies after ICIs could statistically prolong OS in this population.

There are some limitations to this study. First, this is a real-world retrospective analysis, which might contain inherent bias compared with randomized trials. However, designing and conducting a prospective trial for liver toxicity or injury after or during ICI therapy is difficult. Second, the elevation of liver enzymes was documented initially only on the dates with the highest values. The results can clearly show the highest toxicity time points but potentially bring some disadvantages. The overall results are not as detailed as the data for every time point. Based on the design, the actual curve of functional liver progression or revolution during or after ICI therapy would not be clearly represented. Third, the elevated liver enzymes in our study (Supplementary Table S2) did not represent the rate of immune-related hepatitis because we could not distinguish their respective influence on disease progression, assuming a higher incidence of hepatitis in our study. This limitation has been widely discussed in the literature.[24] Fourth, liver biopsy was not done for the whole cohort, although surveys for other etiologies were undertaken, making the pathological confirmation of the immune-related hepatitis diagnosis difficult. In 2018, De Martin et al reported liver biopsies from 16 patients with equal to or greater than Grade III hepatitis.[52] The study concluded that histology findings (granulomatous hepatitis, including fibrin ring granulomas and central vein endothelitis for anti-CTLA4 vs lobular hepatitis for anti-PD-1/PD-L1 monoclonal antibodies) could suggest and tailor corticosteroid treatments. However, 10 (62.5%, n = 10/16) patients took oral or intravenous corticosteroids for ≥ Grade III hepatitis in De Martin et al's report,[52] and 38.1% (n = 16/42) used corticosteroids for patients with ≥ Grade II hepatitis in our study. Among all patients with immune-related hepatitis, only 5% required corticosteroid treatment,[57] compared with 8.3% (16/193) in our study. The evidence suggests there was no noticeable delay in corticosteroid use in our study compared with the literature. In addition, it is challenging to differentiate cholestasis-type liver injury or other patterns in this real-world cohort because some patients lacked alkaline phosphatase and gamma-glutamyl transpeptidase data.

In conclusion, elevated liver enzymes typically occur between the 4th and 20th weeks after ICI initiation. While patients showing specific liver enzyme patterns such as increased AST or total bilirubin after ICI termination may have shorter OS after adjusting for viral hepatitis and ICI responses, none of the liver enzyme changes during ICI therapy appear to directly impact OS. These findings suggest the safety of using ICIs, even in patients with elevated liver enzymes, particularly when prompt administration of corticosteroids is clinically indicated and implemented.

Table 4 Incidences of Immune-Related Hepatic Toxicity in HCC in Previous Studies

Year	Author	Study Design	Immune Checkpoint Inhibitors	N	Immune-Related Hepatic Toxicity		Aspartate Transaminase		Alanine Transaminase		Total Bilirubin	
					All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
PROSPECTIVE TRIALS												
2017	El-Khoueiry, AB et al[45]	P, Phase I/II CheckMate-040	Nivolumab monotherapy	48	N/A	N/A	21.0%	10.0%	15.0%	6.0%	N/A	N/A
2017	Wainberg, ZA et al[46]	P, phase I/II	Durvalumab monotherapy	40	N/A	N/A	22.5%	7.5%	10.0%	5.0%	N/A	N/A
2017	Kelley RK et al[47]	P, phase I/II	Durvalumab 300mg + Tremelimumab 1500mg	74	0%	0%	16.2%	12.2%	14.9%	4.1%	5.4%	1.4%
2018	Zhu, AX et al[37]	P, Phase II KEYNOTE-224	Pembrolizumab monotherapy	104	I: 3.0%	I: 3.0%	7.0%	5.0%	5.0%	4.0%	5.0%	2.0%
2019	Finn, RS et al[36]	P, Phase III, 2L KEYNOTE-240	Pembrolizumab monotherapy	279	I: 1.8%	I: 1.4	22.6%	13.3%	17.6%	6.1%	N/A	N/A
2019	Yau, T et al[53]	P, phase I/II ChekMate-040	Asian cohort	85	6.0%	1.0%	4.0%	1.0%	5.0%	0.0%	1.0%	0.0%
2020	Kudo, M et al[48]	P, phase Ib Study 117	Nivolumab + Lenvatinib	30	N/A	N/A	16.7%	10.0%	N/A	N/A	N/A	N/A
2020	Finn, RS et al[54]	P, phase Ib KEYNOTE-524	Pembrolizumab (+ Lenvatinib)	104	N/A	N/A	20.0%	11.0%	N/A	N/A	N/A	N/A
2020	Finn, RS et al[11]	P, phase III, 1L IMbrave 150	Atezolizumab + Bevacizumab	336	N/A	N/A	19.5%	7.0%	14.0%	3.0%	13.1%	2.4%
2020	Lee, MS et al[49]	P, phase Ib GO30140	(Group A[¶]) Atezolizumab 1200 mg + bevacizumab 15 mg/kg	104	N/A	N/A	16.0%	5.0%	N/A	N/A	N/A	N/A
		P, phase Ib, randomized GO30140	(Group F[§]) Atezolizumab 1200 mg + bevacizumab 15 mg/kg	60	N/A	N/A	5.0%	3.0%	N/A	N/A	N/A	N/A
			(Group F) Atezolizumab 1200 mg monotherapy	58	N/A	NA	13.0%	3.0%	N/A	N/A	N/A	N/A
2021	Yau, T et al[50]	P, phase III, 1L CheckMate-459	Nivolumab monotherapy	367	16.9%	9.5%	21.0%	12.5%	N/A	N/A	N/A	N/A

2021	El-Khoueiry, AB et al[51]	P, phase I/II CheckMate-040	Arm A (NIVO1+IPI3 Q3W)	49	I: 20%	I: 20%	20.0%	16.0%	16.0%	8.0%	N/A	N/A
			Arm B (NIVO3+IPI1 Q3W)	49	I: 12%	I: 10%	20.0%	8.0%	14.0%	6.0%	N/A	N/A
			Arm C (NIVO3 Q2W+IPI1 Q6W)	48	I: 8%	I: 6%	13.0%	4.0%	8.0%	0.0%	N/A	N/A
RETROSPECTIVE OR REAL-WORLD DATA												
2018	De Martin, E et al[52]	R	Anti-PD-1/PD-L1 or anti-CTLA-4	16	N/A	3.5%	N/A	N/A	N/A	N/A	N/A	N/A
2021	Wong, JSL et al[55]	R	Ipilimumab + Nivolumab or Pembrolizumab	25	4.00%	4.00%	N/A	N/A	N/A	N/A	N/A	N/A
2024	Present study	R	Nivolumab or Pembrolizumab monotherapy	193	12.2%*	1.8%*	11.9%*	4.8%*	6.2%*	1.2%*	8.2%*	1.3%*

Notes: Group A, all patients received atezolizumab and bevacizumab every 3 weeks. § Group F, patients were randomly assigned (1:1) to receive atezolizumab plus bevacizumab or atezolizumab alone every 3 weeks. *The rates of immune-related liver toxicity in this study were calculated based on patients with normal baseline liver function, which might cause underestimated bias.

Abbreviations: P, Prospective; R, Retrospective; HCC, hepatocellular carcinoma; N/A, not available; I, immune-related; NIVO, nivolumab; IPI, ipilimumab; I, Immune-mediated hepatic toxicity.

https://doi.org/10.2147/JHC.S464105 DovePress

Abbreviations

ICI, Immune checkpoint inhibitor; aHCC, advanced Hepatocellular carcinoma; AST, Aspartate transaminase; ALT, Alanine transaminase; OS, Overall Survival; HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus; CTLA-4, Cytotoxic T-lymphocyte protein 4; PD-1, Programmed cell death Receptor 1; PD-L1, Programmed cell death ligand 1; irAEs, Immune-related adverse events; AFP, Alpha-fetoprotein; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; NCCN, National Comprehensive Cancer Network; CTCAE, Common Terminology Criteria for Adverse Events; DNA, Deoxyribonucleic acid; RNA, Ribonucleic acid; PCR, Polymerase chain reaction; CI, Confidence Interval.

Data Sharing Statement

The data underlying this article will be shared with the corresponding author upon reasonable request, except for patients' personally identifiable information.

Ethics Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (IRB ID 201901740B0C501) and with the 1964 helsinki Declaration and its later amendments or comparable ethical standards. The informed consent was waved by Chang Gung Medical Foundation Institution Review Board because the study carried no higher than minimal risk to the enrolled subjects. All the individual information has been de-linked and protected well.

Acknowledgments

The authors thank all members of the Cancer Center, Chang Gung Memorial Hospital at TuCheng, and Linkou for their invaluable help.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was partially funded by a Chang Gung Memorial Hospital grant (CMRPVVK0091, CMRPVVL0021, CORPVVP0151 and CMRPVVL0262) and a grant from the National Science and Technology Council, Taiwan (MOST-112-2314-B-182A-028 and 113-2314-B-182A-045-). The funders have no role in the preparation of the manuscript.

Disclosure

All the authors declare no competing interests.

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