EJMI

DOI: 10.14744/ejmi.2025.12489
EJMI 2025;9(4):246–254

Research Article

Clinicopathological Features and Prognostic Factors in Immune Checkpoint Inhibitor-Related Hepatotoxicity: A Single-Center Experience

Alper Coşkun[1], Ece Tolgay[2], Çağla Karaoğlu[1], Ali Aktaş[1], Seda Salı[1], Ahmet Bilgehan Şahin[1], Adem Deligönül[1], Erdem Çubukçu[1], Türkkan Evrensel[1]

[1]Department of Medical Oncology, Uludağ University Faculty of Medicine, Bursa, Turkey
[2]Uludağ University Faculty of Medicine, Bursa, Turkey

Abstract

Objectives: Immune checkpoint inhibitor (ICI)-related hepatotoxicity (ICH) occurs in 1–17% of patients treated with ICIs. Although most cases are grade 1–2, ICH remains a clinically significant cause of morbidity. This study aimed to characterize the clinicopathological features of patients who developed ICH and to identify factors influencing survival.

Methods: Patients treated with ICIs for metastatic solid malignancies at our center between January 2018 and May 2023 were retrospectively analyzed. Thirty-six patients who developed ICH during this period were included.

Results: The median age at ICH onset was 62 years (range, 23–83), and the median number of ICI cycles before ICH was four (range, 1–44). The median progression-free survival (PFS) was 5.96 months (95% CI, 0.23–11.69), and the median overall survival (OS) was 11.26 months (95% CI, 2.85–19.67). In multivariate Cox regression analysis, baseline hemoglobin level and the number of ICI cycles before ICH were independent predictors of both PFS and OS.

Conclusion: Patients who developed ICH after four or more ICI cycles had significantly better PFS and OS. ICH occurred earlier in those with liver metastases. Larger, multicenter prospective studies are warranted to validate these findings and improve management strategies.

Keywords: Cancer, Hepatotoxicity, Immune Checkpoint Inhibitor, Immunotherapy, Survival

Cite This Article: *Coşkun A, Tolgay E, Karaoğlu Ç, Aktaş A, Salı S, Şahin AB, et al. Clinicopathological Features and Prognostic Factors in Immune Checkpoint Inhibitor-Related Hepatotoxicity: A Single-Center Experience. EJMI 2025;9(4):246–254.*

Immunotherapy has emerged as a major treatment modality for various types of cancer, either as monotherapy or in combination with chemotherapy (CT), radiotherapy, or targeted agents. It has significantly improved treatment responses and survival outcomes across multiple malignancies. Among immunotherapeutic approaches, immune checkpoint inhibitors (ICIs) have become an integral part of clinical oncology over the past two decades. ICIs exert their antitumor effects by inhibiting regulatory molecules involved in the negative costimulatory pathways of T-cell activation, including cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and lymphocyte-activation gene-3.[1]

Address for correspondence: Alper Coskun, MD. Department of Medical Oncology, University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Turkey
Phone: +90 535 631 10 94 **E-mail:** dralpercoskun90@gmail.com, alpercoskun@uludag.edu.tr

Submitted Date: November 08, 2025 **Accepted Date:** December 26, 2025

Despite their clinical efficacy, ICIs are associated with a unique spectrum of toxicities, termed immune-related adverse events (irAEs), which result from nonspecific immune activation against normal tissues. Approximately 65% of patients receiving ICIs experience systemic adverse effects, most commonly involving the thyroid gland, skin, gastrointestinal tract, and liver. Of these, 13–23% are classified as grade 3 or 4 in severity.[2,3] Consequently, the early diagnosis, monitoring, and appropriate management of irAEs are essential aspects of daily oncology practice.

ICI-related hepatotoxicity (ICH) is reported in 1–17% of patients treated with ICIs. Although the majority of cases are grade 1–2, severe ICH (grade 3–4) can occur less frequently.[4,5] Fatal cases (grade 5) are rare, with reported mortality rates for fulminant hepatitis ranging between 0.07% and 0.5%.[6,7] The pathophysiology of ICH is thought to involve cytotoxic T-lymphocyte (CTL)–mediated damage to hepatocytes outside the tumor microenvironment. In addition to CTLs, ICIs can directly or indirectly modulate other immune cell subsets, including B cells, T helper cells, T regulatory cells, macrophages, and dendritic cells, thereby exerting broad effects on the immune milieu.[8] Furthermore, ICIs alter the cytokine and chemokine landscape within the tumor microenvironment. Elevated serum levels of interleukin (IL)-6, IL-1β, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and chemokines such as C-X-C motif ligand (CXCL) 9, CXCL10, CXCL11, and CXCL13 before or after ICI therapy have been associated with an increased risk of ICH.[9]

Previous meta-analyses and real-world studies have identified several risk factors for ICH, including female sex, younger age, dual ICI therapy, prior ICI exposure, pre-existing autoimmune disease, elevated baseline alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, low alkaline phosphatase (ALP) levels, high baseline lymphocyte (LYM) counts, and treatment for malignant melanoma (MM).[10-14]

Although the mortality associated with ICH is relatively low, it remains a clinically significant cause of morbidity among patients receiving ICI therapy. Therefore, heightened awareness and timely recognition of ICH are critical in clinical practice. In this context, the present study aimed to characterize the clinicopathological features of metastatic solid tumor patients who developed ICH and to evaluate progression-free survival (PFS), overall survival (OS), progression-free survival with second-line therapy after ICI therapy (PFS2), and potential risk factors influencing survival outcomes.

Methods

In this retrospective study, the data of patients who were followed in our oncology clinic between January 1, 2018 and May 31, 2023 and received ICI therapy for metastatic solid malignancies were analyzed using the hospital electronic information system. During this period, hepatotoxicity was detected in 41 patients receiving ICI treatment. Hepatotoxicity was associated with ischemic hepatitis following cholangitis in two patients, ascitic infection in one patient, liver metastases progression in one patient, and hypoxemic respiratory failure in one patient. These five patients were excluded from the study, and the data of the remaining 36 patients were evaluated retrospectively.

Demographic and clinical characteristics including age, sex, pathological diagnosis, ICI type and regimen, treatment line, presence of liver metastases before treatment, and baseline laboratory parameters such as hemoglobin (HGB), platelet (PLT), neutrophil (NEU), and LYM counts, albumin, C-reactive protein (CRP), AST, ALT, ALP, gamma-glutamyl transferase (GGT), and bilirubin levels were recorded. Data on combination with CT or tyrosine kinase inhibitors (TKIs), prior systemic therapies, ICI interruption or permanent discontinuation due to ICH, treatment dose, and abdominal imaging findings, if available, were also collected. In addition, information regarding glucocorticoid therapy used for ICH, including steroid type, dose, and duration, biochemical response to steroid therapy, presence of steroid-refractory ICH, treatments administered for steroid-refractory cases, response to subsequent immunosuppressive therapy, resumption or re-discontinuation of ICI treatment, disease progression status under ICI therapy, and best response (BR) and objective responses (OR) were analyzed. The status of receiving systemic therapy after ICI discontinuation, the type of agents used, and patient survival outcomes were also recorded.

Based on hemogram and biochemistry parameters, systemic inflammatory and nutritional indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), hemoglobin-albumin-lymphocyte-platelet score (HALP), and prognostic nutritional index (PNI) were calculated as previously described in studies showing their prognostic value in different cancer types.[15-20]

Tumor response to ICI therapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Adverse events of any grade were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

PFS was defined as the time from the initiation of ICI therapy to disease progression or death from any cause. PFS2 was defined as the time from the initiation of ICI therapy to progression or death that occurred under subsequent systemic therapy following progression on ICI treatment. OS was defined as the time from the start of ICI therapy to death from any cause.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 25.0. Categorical variables were expressed as numbers and percentages, and continuous variables were presented as mean, standard deviation, median, minimum, and maximum values. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of distribution. The Kaplan-Meier method was used for survival analysis, and survival curves were compared using the Log Rank test. Cox regression analysis was performed to determine factors influencing survival outcomes. Cutoff values were calculated using receiver operating characteristic curve analysis for PFS and OS. A p value of less than 0.05 was considered statistically significant.

Ethical Approval Statement

This study was approved by the Health Research Ethics Committee of our center (Approval Number: 2025/4-21, Approval Date: February 19, 2025).

Results

The median age of the patients at diagnosis was 56 years (range, 23-81), and 25 patients (69.4%) were male. The most common histological subtype was non-small cell lung cancer (NSCLC), observed in 14 patients (38.9%). The most frequently administered ICI regimen was nivolumab monotherapy, given to 29 patients (80.6%). Five patients (13.9%) received ICI therapy as first-line metastatic treatment, 18 patients (50.0%) as second-line, nine patients (25.0%) as third-line, and four patients (11.1%) as fourth-line treatment. The median age of the patients at the time of ICH was 62 years (range, 23–83). The median number of ICI cycles administered before the development of ICH was four (range, 1-44). Treatment was interrupted in eight patients (22.2%) following ICH, and ICI therapy was permanently discontinued in four patients (11.1%). The general characteristics of the patients are summarized in Table 1.

In Kaplan-Meier survival analyses, the median PFS was 5.96 months (95% confidence interval [CI], 0.23-11.69), and the median OS was 11.26 months (95% CI, 2.85-19.67). When analyzed by tumor type, the median PFS among patients with NSCLC was 4.2 months (95% CI, 2.37-6.03), and the median OS was 4.7 months (95% CI, 1.84-7.56). Among

Table 1. The general characteristics of the patients

Characteristics	n=36
Age at diagnosis*	56.3±13.3
Gender**	
Female	11 (30.6%)
Male	25 (69.4%)
Pathological type**	
NSCLC	14 (38.9%)
MM	9 (25%)
ccRCC	5 (13.9%)
Other	8 (22.2%)
Type of ICI**	
Nivolumab	29 (80.6%)
Nivolumab + İpilimumab	2 (5.5%)
İpilimumab	1 (2.8%)
Pembrolizumab	3 (8.3%)
Atezolizumab	1 (2.8%)
Liver metastases before ICI treatment**	
Yes	9 (25%)
No	27 (75%)
ICI treatment line**	
First-line	5 (13.9%)
Second-line	18 (50%)
Third-line	9 (25%)
Fourth-line	4 (11.1%)
Age during ICH*	59.7±13.0
Number of ICI treatment cycle before ICH***	4 (1-44)
ICI ınterruption after ICH**	
Yes	8 (22.2%)
No	28 (77.8%)
ICI discontinuation after ICH***	
Yes	4 (11.1%)
No	32 (88.9%)
Laboratory parameters before ICI treatment	
HGB*	11.79±1.87
Laboratory parameters before ICI treatment	
PLR***	185.38 (75.12-1150.56)
SII***	712.8 (47.13-7409.58)
CAR***	3.25 (0.44-90.26)
HALP*	0.31±0.19
PNI*	39.79±5.76

*mean ± SD ** n (%) *** median (minimum - maximum); CAR: C-reactive protein to albumin ratio; ccRCC: Clear cell renal cell carcinoma; HALP: Hemoglobin albumin lymphocyte platelet score; HGB: Hemoglobin; ICH: Immune checkpoint inhibitor-related hepatotoxicity; ICI: Immune checkpoint inhibitor; NLR: Neutrophil-to-lymphocyte ratio; NSCLC: Non-small cell lung carcinoma; MM: Cutaneous malignant melanoma; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.

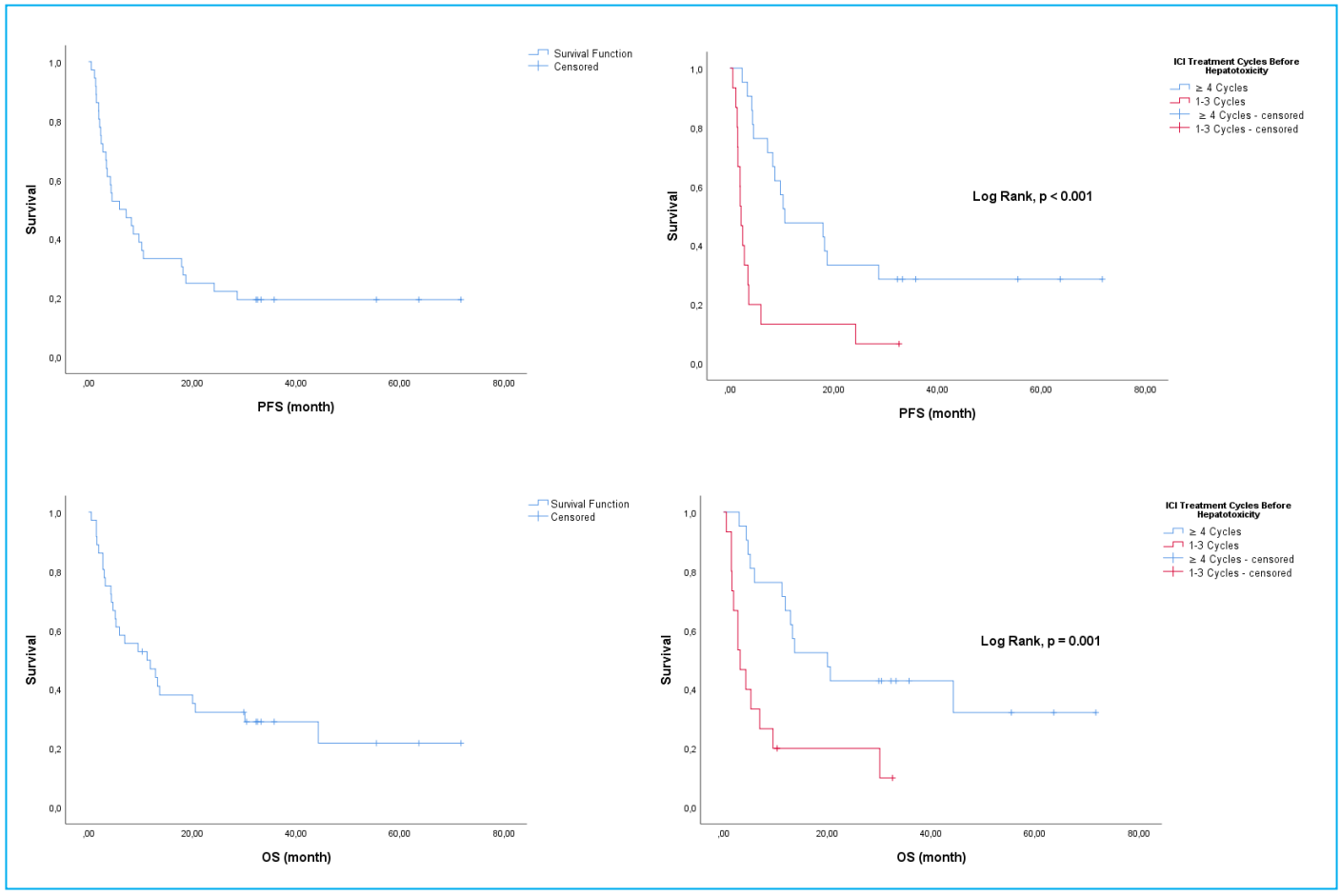

Figure 1. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) of the patients.

patients with cutaneous MM, the median PFS was 7.23 months (95% CI, 0.00-17.84), and the median OS was 30.1 months (95% CI, 6.06-54.14). Patients who developed ICH after four or more cycles of ICI therapy had significantly longer PFS and OS compared with those who developed ICH earlier (Log Rank p<0.001 for PFS, Log Rank p=0.001 for OS). Kaplan-Meier survival plots are shown in Figure 1.

The median time to the development of ICH was 2.33 months (95% CI, 1.74-2.92). ICH developed significantly earlier in patients who had liver metastases prior to ICI initiation compared with those without liver metastases (Log Rank p=0.003). Hepatocellular-type ICH was observed in 17 patients (47.2%), while mixed (hepatocellular plus cholestatic) ICH occurred in 19 patients (52.8%).

In univariate Cox regression analyses, the presence of liver metastases before ICI treatment, number of cycles administered before ICH, presence of hyperbilirubinemia at the time of ICH, and baseline HGB, PLT, NEU, NLR, and SII were significantly associated with PFS. The number of ICI cycles before ICH, baseline HGB, NEU, LYM, CRP, NLR, SII, and CAR were found to be prognostic factors for OS. In multivariate Cox regression analyses, baseline HGB level and number of ICI cycles before ICH remained independent predictors of both PFS and OS. The results of univariate and multivariate Cox regression analyses are presented in Table 2 and 3.

AST elevation was recorded as grade 1 in 20 patients (55.6%), grade 2 in five patients (13.9%), grade 3 in six patients (16.7%), and grade 4 in three patients (8.3%). ALT elevation was observed as grade 1 in 22 patients (61.1%), grade 2 in eight patients (22.2%), and grade 3-4 in three patients (8.3%). Hyperbilirubinemia occurred in eight patients (22.2%), including grade 1 in three patients (8.3%), grade 2 in one patient (2.8%), and grade 3-4 in two patients (5.6%). Increased GGT was noted in 17 patients (47.2%), and ALP elevation was detected in 14 patients (38.9%).

Four patients (11.1%) who developed grade 4 ICH were treated with glucocorticoids (methylprednisolone). Three patients (8.3%) showed a favorable response to steroid therapy, while one patient (2.8%) exhibited steroid-refractory disease. This patient subsequently received mycophenolate mofetil (MMF), azathioprine, and plasmapheresis

Table 2. Univariate Cox Regression Analysis of Clinical Variables for PFS and OS

Factors	Reference group	PFS		OS	
		HR (95% CI)	p	HR (95% CI)	p
Age during ICH	Age ≥ 60	1.329 (0.638- 2.769)	0.447	1.097 (0.505-2.384)	0.815
Histological subtype	NSCLC		0.587		0.262
MM		0.784 (0.307-1.998)	0.609	0.497 (0.173-1.428)	0.194
ccRCC		0.429 (0.120-1.536)	0.193	0.270 (0.058-1.246)	0.093
Other		1.013 (0.398-2.579)	0.979	0.905 (0.352-2.330)	0.837
Gender	Male sex	1.434 (0.663-3.103)	0.360	1.103 (0.474-2.566)	0.821
Liver metastases before ICI treatment	No liver metastases	**2.649 (1.160-6.051)**	**0.021**	2.295 (0.948-5.559)	0.066
ICI treatment line	First-line		0.379		0.365
Second-line		2.411 (0.695-8.364)	0.166	2.884 (0.656-12.673)	0.161
Third-line and above		1.983 (0.543-7.234)	0.300	2.335 (0.501-10.880)	0.280
ICI interruption after ICH	No ICI interruption	0.686 (0.279-1.689)	0.413	0.470 (0.162-1.368)	0.166
ICI Discontinuation after ICH	No ICI discontinuation	0.702 (0.212-2.326)	0.562	0.211 (0.029-1.561)	0.127
Number of ICI cycles before ICH	≥ 4 cycles	**3.555 (1.675-7.542)**	**0.001**	**3.530 (1.571-7.933)**	**0.002**
Bilirubin	Low	**2.502 (1.057-5.923)**	**0.037**	1.683 (0.662-4.278)	0.274
Grade of ICH	Grade 4	1.425 (0.430-4.726)	0.562	4.742 (0.641-35.087)	0.127
Laboratory parameters before ICI treatment					
HGB	High*	**2.767 (1.292-5.297)**	**0.009**	**3.928 (1.653-9.331)**	**0.002**
PLT		**0.467 (0.221-0.983)**	**0.045**	0.552 (0.238-1.284)	0.168
NEU		**0.325 (0.151-0.699)**	**0.004**	**0.284 (0.125-0.646)**	**0.003**
LYM		1.724 (0.821-3.620)	0.150	**2.448 (1.070-5.602)**	**0.034**
Albumin		1.752 (0.841-3.649)	0.134	1.773 (0.802-3.918)	0.157
CRP		0.574 (0.271-1.219)	0.149	**0.344 (0.153-0.766)**	**0.010**
NLR		**0.334 (0.156-0.714)**	**0.005**	**0.246 (0.103-0.583)**	**0.001**
PLR		0.446 (0.180-1.109)	0.082	0.453 (0.201-1.018)	0.055
SII		**0.381 (0.172-0.844)**	**0.017**	0.408 (0.183-0.911)	**0.029**
CAR		0.574 (0.271-1.219)	0.149	**0.344 (0.153-0.776)**	**0.010**
HALP		1.376 (0.659-2.874)	0.395	1.767 (0.790-3.951)	0.166
PNI		1.752 (0.841-3.649)	0.134	1.773 (0.802-3.918)	0.157

*Cut-off values were determined using ROC curve analysis and applied separately for PFS and OS, respectively, as follows: HGB: 11.45, PLT: 247.40, NEU: 4.42, LYM: 1.42, Albumin: 4.15, CRP: 28.45, NLR: 2.90, PLR: 128.99, SII: 642.62, CAR: 6.94, HALP: 0.30, and PNI: 41.51 for PFS; and HGB: 11.45, PLT: 362.20, NEU: 4.73, LYM: 1.42, Albumn: 4.15, CRP: 31.05, NLR: 2.90, PLR: 243.48, SII: 984.86, CAR: 8.67, HALP: 0.30, and PNI: 41.51 for OS.
CAR: C-reactive protein to albumin ratio; CRP: C-reactive protein; ccRCC: Clear cell renal cell carcinoma; HALP: Hemoglobin albumin lymphocyte platelet score; HGB: Hemoglobin; ICH: Immune checkpoint inhibitor-related hepatotoxicity; ICI: Immune checkpoint inhibitor; LYM: Lymphocyte; MM: Cutaneous malignant melanoma; NEU: Neutrophil; NLR: Neutrophil-to-lymphocyte ratio; NSCLC: Non-small cell lung carcinoma; OS: Overall survival; PFS: Progression-free survival; PLR: Platelet-to-lymphocyte ratio; PLT: Platelet; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.

sequentially, resulting in regression of ICH. Among patients with grade 4 ICH, PR, SD, and PD were observed in two patients (5.6%) and one patient (2.8%), respectively. In terms of OR, PR persisted in one patient (2.8%), while PD developed in three patients (8.3%).

When BR was evaluated across all patients, CR was observed in five patients (13.9%), PR in eight patients (22.2%), SD in eight patients (22.2%), and PD in 15 patients (41.7%). The OR included five patients (13.9%) with ongoing CR, two patients (5.6%) with PR, and 29 patients (80.6%) with PD.

Three patients (8.3%) received ICI therapy in combination with CT (one cisplatin plus etoposide, one carboplatin plus etoposide, and one carboplatin plus paclitaxel), and one patient (2.8%) received combination therapy with

Table 3. Multivariate cox regression analysis of clinical variables for PFS and OS

	Factors	HR	%95 CI		p
			Min	Max	
PFS[a]	Liver metastases*	1.767	0.651	4.795	0.264
	HGB*	**3.422**	**1.453**	**8.342**	**0.007**
	NLR*	0.774	0.338	1.771	0.544
	Number of ICI cycles**	**3.353**	**1.360**	**8.264**	**0.009**
OS[a]	HGB*	**3.142**	**1.069**	**9.235**	**0.037**
	NLR*	0.571	0.215	1.514	0.260
	CAR*	0.535	0.218	1.311	0.171
	Number of ICI cycles**	**3.641**	**1.420**	**9.334**	**0.007**

CAR: C-reactive protein to albumin ratio; HGB: Hemoglobin; ICI: Immune checkpoint inhibitor; NLR: Neutrophil-to-lymphocyte ratio; OS: Overall survival; PFS: Progression-free survival.
[a]Enter method; *Before ICI treatment. **Before ICI-related hepatotoxicity.

cabozantinib, a TKI. Abdominal imaging was performed in five patients (13.9%) at the time of ICH, revealing acute hepatitis findings such as periportal and pericholecystic edema in two patients.

PFS2 was evaluated in 12 patients (33.3%) who received subsequent systemic therapy after ICI treatment. The median PFS2 was 3.06 months (95% CI, 2.63–3.49). The median PFS2 was 3.03 months (95% CI, 1.94–4.12) in patients with grade 1–3 ICH. Among patients with grade 4 ICH, PFS2 durations were 3.5, 5.7, and 67.56 months, respectively.

Discussion

In this study, we evaluated the clinicopathological features, PFS, OS, and prognostic factors affecting survival in patients with solid malignancies who received ICI therapy in the metastatic setting and subsequently developed ICH. We found that both PFS and OS were significantly better in patients who received ≥ 4 cycles of ICI treatment prior to the onset of ICH. Cox regression analyses identified several variables influencing PFS and/or OS, including the presence of liver metastases before ICI initiation, the number of ICI cycles prior to ICH, the presence of hyperbilirubinemia at the onset of ICH, and baseline levels of HGB, PLT, NEU, LYM, CRP, NLR, SII, and CAR.

Van Buren et al.[21] evaluated 20,163 patients treated with ICIs and demonstrated that those who received corticosteroid therapy for irAEs within the first two months of ICI initiation had a worse prognosis compared with patients who received corticosteroids later. This finding parallels our results, even though only a small number of patients (n=4, 11.1%) in our study required corticosteroid therapy for ICH.

Drug-induced liver injury is typically classified into hepatocellular, cholestatic, and mixed types. Previous studies have shown that ICH can present in all three patterns, with the hepatocellular type being the most common, particularly for grade ≥3 toxicity.[22] In our cohort, hepatocellular and mixed-type ICH were observed, with the mixed type being predominant. The difference between our findings and previous studies may be attributed to the relatively small sample size and the single-center, retrospective design of our study.

Several studies have reported that ICH typically develops between 3 and 14 weeks after ICI initiation, with a shorter latency period observed for anti CTLA-4 agents than for anti PD-1 agents.[23] Another study found that ICH occurred most frequently within the first 12 weeks, with a median onset time of 2-3 months for the hepatocellular type and 6 months for the cholestatic type.[24] Consistent with these findings, the median time to ICH onset in our study was 2.33 months (10.13 weeks). Additionally, since there were no patients with cholestatic type in our study, subtype-specific comparisons could not be performed.

Corticosteroid therapy remains the cornerstone of ICH management. Current American and European guidelines recommend initiating methylprednisolone (1-2 mg/kg/day) or an equivalent corticosteroid for grade ≥3 ICH, and switching to second-line immunosuppressive agents in the absence of clinical improvement after 3-5 days.[25-27] In a recent retrospective analysis, no additional benefit was observed with higher steroid doses (1.5 mg/kg/day methylprednisolone or equivalent treatment), while increased risks of infection and hyperglycemia were noted.[28] In our cohort, all patients with grade 4 ICH (n=4, 11.1%) received methylprednisolone at a dose of 1-1.5 mg/kg/day (80–100 mg/day). Three of these patients exhibited a rapid and marked improvement within 3 days, whereas one patient required escalation to MMF due to steroid-refractory disease.

For steroid-refractory ICH, MMF is the preferred second-line agent and has demonstrated clinical improvement in approximately 83-93% of cases.[29,30] Combination therapy with azathioprine and corticosteroids has also been reported as an effective option in select cases.[31] Furthermore, plasma exchange (plasmapheresis) has been shown to be beneficial in steroid- and immunosuppressant-refractory ICH based on limited retrospective data and case reports.[32,33]

Numerous studies have explored the association between systemic inflammatory markers and prognosis in patients treated with ICIs. Consistent with the literature, our study found that pretreatment values of HGB, PLT, NEU, LYM, CRP, NLR, SII, and CAR significantly influenced survival outcomes (PFS and/or OS).[15-20] These findings support the role

of host immune and inflammatory status as important determinants of ICI response and prognosis.

Our study has several limitations. The most important limitation is its retrospective, single-center design and relatively small sample size, which may limit the generalizability of the findings. Second, due to national reimbursement restrictions during the study period, most patients received nivolumab monotherapy, and very few were treated with dual or alternative ICIs, precluding comparative analyses between different agents or regimens. Third, the small number of patients who received corticosteroid therapy (n=4, 11.1%) limited the statistical power to assess steroid dose-response relationships or refractory status. Finally, none of the patients underwent liver biopsy, and only five patients (13.9%) had abdominal imaging during ICH, which restricted the ability to perform histopathologic or radiologic correlations.

Conclusion

In conclusion, our study demonstrated that both PFS and OS were significantly better in patients with solid malignancies who developed ICH after receiving four or more cycles of ICI therapy in the metastatic setting. ICH was observed to develop earlier in patients with preexisting liver metastases. Furthermore, the presence of liver metastases before ICI initiation, the number of ICI cycles administered prior to ICH, the occurrence of hyperbilirubinemia at the time of ICH, and baseline hematological and inflammatory markers-including HGB, PLT, NEU, LYM, CRP, NLR, SII, and CAR-were identified as prognostic factors influencing survival outcomes (PFS and/or OS). Although several studies and case reports have investigated ICH in patients receiving ICIs, the current evidence remains limited. Multicenter, prospective studies with larger cohorts are warranted to better define the risk factors, optimize management strategies, and guide the development of combined or sequential treatment approaches for ICH.

Declarations

Ethical Approval Statement: This study was approved by the Health Research Ethics Committee of Bursa Uludağ University (Approval Number: 2025/4-21, Approval Date: February 19, 2025).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflicts of interest related to this work.

Funding: The authors disclosed that they did not receive any grants or contracts during the conduction or writing of this manuscript.

Author Contributions: Concept – A.C., E.T.; Design – A.C., A.B.S.; Supervision – A.B.S., A.D.; T.E.; Materials – A.D., E.C., T.E.; Fundings – A.D., E.C., T.E.; Data collection &/or processing – A.C., E.T., C.K., A.A., S.S.; Analysis and/or interpretation – A.C.; Literature search – A.B.S., A.D., E.C.; C.K., A.A., S.S., A.C., E.T.; Writing – A.C.; Critical review – A.C., T.E.

References

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359(6382):1350–55.
2. Postow MA, Callahan MK, Wolchok JD. Immune Checkpoint Blockade in Cancer Therapy. J Clin Oncol 2015;33(17):1974–82.
3. Puzanov I, Diab A, Abdallah K, Bingham CO 3rd, Brogdon C, Dadu R, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5(1):95.
4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373(1):23–34.
5. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al; KEYNOTE-006 investigators. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372(26):2521–32.
6. Bhave P, Buckle A, Sandhu S, Sood S. Mortality due to immunotherapy related hepatitis. J Hepatol 2018;69(4):976–8.
7. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. JAMA Oncol 2018;4(12):1721–8.
8. Yang Y, Li X, Ma Z, Wang C, Yang Q, Byrne-Steele M, et al. CTLA-4 expression by B-1a B cells is essential for immune tolerance. Nat Commun 2021;12(1):525.
9. Lim SY, Lee JH, Gide TN, Menzies AM, Guminski A, Carlino MS, et al. Circulating Cytokines Predict Immune-Related Toxicity in Melanoma Patients Receiving Anti-PD-1-Based Immunotherapy. Clin Cancer Res 2019;25(5):1557–63.
10. Miah A, Tinoco G, Zhao S, Wei L, Johns A, Patel S, Li M, Grogan M, Lopez G, Husain M, Hoyd R, Mumtaz K, Meara A, Bertino EM, Kendra K, Spakowicz D, Otterson GA, Presley CJ, Owen DH. Immune checkpoint inhibitor-induced hepatitis injury: risk factors, outcomes, and impact on survival. J Cancer Res Clin Oncol. 2023 May;149(5):2235-2242.
11. Atallah E, Welsh SJ, O'Carrigan B, Oshaughnessy A, Dolapo I, Kerr AS, et al. Incidence, risk factors and outcomes of checkpoint inhibitor-induced liver injury: A 10-year real-world retrospective cohort study. JHEP Rep 2023;5(10):100851.
12. Pan J, Liu Y, Guo X, Bai Z, Levi Sandri GB, Méndez-Sánchez N, et al. Risk factors for immune-mediated hepatotoxicity in patients with cancer treated with immune checkpoint in-

hibitors: a systematic review and meta-analysis. Expert Opin Drug Saf 2022;21(10):1275–87.
13. Kawano M, Yano Y, Yamamoto A, Yasutomi E, Inoue Y, Kitadai J, et al. Risk factors for immune checkpoint inhibitor-induced liver injury and the significance of liver biopsy. Diagnostics (Basel) 2024;14(8):815.
14. Tison A, Garaud S, Chiche L, Cornec D, Kostine M. Immune-checkpoint inhibitor use in patients with cancer and pre-existing autoimmune diseases. Nat Rev Rheumatol 2022;18(11):641–56.
15. Tan S, Zheng Q, Zhang W, Zhou M, Xia C, Feng W. Prognostic value of inflammatory markers NLR, PLR, and LMR in gastric cancer patients treated with immune checkpoint inhibitors: a meta-analysis and systematic review. Front Immunol 2024;15:1408700.
16. Kou J, Huang J, Li J, Wu Z, Ni L. Systemic immune-inflammation index predicts prognosis and responsiveness to immunotherapy in cancer patients: a systematic review and meta-analysis. Clin Exp Med 2023;23(7):3895–905.
17. Tian BW, Yang YF, Yang CC, Yan LJ, Ding ZN, Liu H, et al. Systemic immune-inflammation index predicts prognosis of cancer immunotherapy: systemic review and meta-analysis. Immunotherapy 2022;14(18):1481–96.
18. Dai M, Wu W. Prognostic role of C-reactive protein to albumin ratio in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Front Oncol 2023;13:1148786.
19. Şahin TK, Güven DC, Durukan M, Baş O, Kaygusuz Y, Arik Z, et al. The association between HALP score and survival in patients treated with immune checkpoint inhibitors. Expert Rev Anticancer Ther 2025;25(1):81–9.
20. Tanaka S, Uchino J, Yokoi T, Kijima T, Goto Y, Suga Y, et al. Prognostic nutritional index and lung immune prognostic index as prognostic predictors for combination therapies of immune checkpoint inhibitors and cytotoxic anticancer chemotherapy for patients with advanced non-small cell lung cancer. Diagnostics (Basel) 2022;12(2):423.
21. Van Buren I, Madison C, Kohn A, Berry E, Kulkarni RP, Thompson RF. Survival among veterans receiving steroids for immune-related adverse events after immune checkpoint inhibitor therapy. JAMA Netw Open 2023;6(10):e2340695.
22. Hountondji L, Ferreira De Matos C, Lebossé F, Quantin X, Lesage C, Palassin P, et al. Clinical pattern of checkpoint inhibitor-induced liver injury in a multicentre cohort. JHEP Rep 2023;5(6):100719.
23. Vozy A, De Martin E, Johnson DB, Lebrun-Vignes B, Moslehi JJ, Salem JE. Increased reporting of fatal hepatitis associated with immune checkpoint inhibitors. Eur J Cancer. 2019;123:112–5.
24. Fontana RJ, Li YJ, Chen V, Kleiner D, Stolz A, Odin J, et al. Genetic variants associated with immune-mediated liver injury from checkpoint inhibitors. Hepatol Commun 2024;8(9):E0518.
25. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, 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 2018;36(17):1714–68.
26. Dougan M, Wang Y, Rubio-Tapia A, Lim JK. AGA clinical practice update on diagnosis and management of immune checkpoint inhibitor colitis and hepatitis: Expert review. Gastroenterology 2021;160(4):1384–93.
27. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(Suppl 4):iv264–6.
28. Li M, Wong D, Vogel AS, Sack JS, Rahma OE, Hodi FS, et al. Effect of corticosteroid dosing on outcomes in high-grade immune checkpoint inhibitor hepatitis. Hepatology 2022;75(3):531–40.
29. Chen K, He J, Xu J, Chen J. Effectiveness of immunosuppressant use for the treatment of immune checkpoint inhibitor-induced liver injury: A systematic review and meta-analysis. Front Oncol 2023;13:1088741.
30. Luo J, Beattie JA, Fuentes P, Rizvi H, Egger JV, Kern JA, et al. Beyond steroids: immunosuppressants in steroid-refractory or resistant immune-related adverse events. J Thorac Oncol 2021;16(10):1759–64.
31. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63(4):971–1004.
32. Cao R, Zhang S, Zhang J, Zhao Y, Zhang X, Guo Z. Treatment experience in managing severe immune-mediated hepatotoxicity induced by immune checkpoint inhibitors. Front Oncol 2025;15:1657332.
33. Liu C, Li X, Deng Y. Case Report: Immune-mediated acute liver failure induced by tislelizumab in a patient with advanced cervical cancer. Front Oncol 2025;15:1604601.