Original Article

Lung metastasis and lymph node metastasis are risk factors for hyperprogressive disease in primary liver cancer patients treated with immune checkpoint inhibitors

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Background: At present, some cancer patients experience hyperprogressive disease (HPD) after receiving immunotherapy. This study used the Response Evaluation Criteria in Solid Tumors 1.1 to evaluate the incidence of HPD in patients receiving immune checkpoint inhibitors (ICIs) for treating primary liver cancer (PLC) and to explore the risk factors for HPD.

Methods: This retrospective, single-center study included patients with PLC who were treated with ICIs. The RECIST 1.1 was used to determine patients with HPD. Univariate and multivariate regression analyses were performed to explore the risk factors for HPD, and clinical variables with prognostic significance for HPD were included to establish a risk model.

Results: Among 129 patients with PLC treated with ICIs, HPD occurred in 13 patients (10.1%). In the multivariate regression analysis, lymph node metastasis and lung metastasis were risk factors for HPD. The area under the curve of the risk model, established by including lymph node metastasis, lung metastasis, neutrophil-lymphocyte ratio, albumin, and performance status, was 0.801 ($P<0.001$). The progression-free survival of HPD patients was significantly worse than that of non-HPD patients ($P<0.001$).

Conclusions: In this study, 10.1% of patients with PLC had HPD. Compared with the non-HPD patients, lung metastasis and lymph node metastasis were independent risk factors of HPD.

Keywords: Immune checkpoint inhibitors (ICIs); lymphatic metastasis; lung neoplasms; liver neoplasms; regression analysis

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Introduction

Primary liver cancer (PLC) is a common malignant tumor of the digestive system. It mainly includes three different pathological categories: hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and HCC-ICC. HCC is the most common type, accounting for 85% to 90% of all PLCs, followed by ICC, which accounts for 15% of all PLCs (1). Globally, liver cancer ranks seventh among malignant tumors regarding the annual number of new cases, and third regarding the number of deaths (2).

Approximately 70% to 80% of liver cancer patients present with advanced-stage disease at diagnosis. By this time, such patients are unable to undergo radical surgery and can only receive palliative treatment, such as systemic treatment, and their prognosis is notably poor (3). Since 2017, lenvatinib has been approved as the first-line treatment for liver cancer, and regorafenib, cabozantinib, and ramucirumab have been approved as second-line treatment for liver cancer in clinical application, marking a new era of targeted therapy for liver cancer. Although the objective remission rate of patients with advanced liver cancer has significantly improved, their overall survival time has not been effectively extended (4).

In recent years, immune checkpoint inhibitors (ICIs), such as programmed cell death protein-1 (PD-1) antibody, programmed death ligand-1 (PD-L1) antibody, and cytotoxic T lymphocyte antigen (CTLA4) antibody, have been used for the treatment of liver cancer, with promising curative effects seen in clinical practice (5). With the widespread use of ICIs in clinical practice, increasing evidence has shown that some patients demonstrate a rapid increase in the tumor burden within a short period of time after receiving ICIs, resulting in a significant reduction in survival time. This phenomenon is known as hyperprogressive disease (HPD) (6). According to reports, the incidence of HPD in patients with non-small-cell lung cancer (NSCLC) and head and neck squamous cell carcinoma is approximately 13.8% and 29%, respectively (7,8). It has also been reported that tumors grow rapidly in patients with advanced liver cancer receiving PD-1/PD-L1 inhibitor therapy, occurring in approximately 9% and 8% of the treatment cohort, respectively (9,10). In most previous studies, some patients receiving immunotherapy experienced higher disease progression and mortality rates during the early stages of treatment, which seriously affected disease prognosis and survival outcomes (11-13). Therefore, it is important to identify the risk factors for HPD to guide treatment decisions. Many previous reports have attempted to identify the risk factors of HPD, which include advanced age, female sex, worse performance status score, and higher metastases prior to treatment (14-17). However, the association of HPD with these risk factors in patients with PLC remains to be explored. Therefore, in this study, we aimed to analyze the relationship between clinical variables and HPD in patients with PLC treated with PD-1/PD-L1 inhibitor, and to explore the risk factors for HPD. We constructed a risk model to assess the risk of HPD in patients with PLC prior to the commencement of PD-1/PD-L1 inhibitor treatment and described the treatment of patients with HPD in detail. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2023).

Methods

Patients and data collection

This was a retrospective study that included patients who received PD-1/PD-L1 inhibitor treatment after a histological or clinical diagnosis of PLC in Nanfang Hospital, between August 2018 and October 2020. The inclusion criteria were as follows: (I) patient information on PD-1/PD-L1 inhibitor infusion in the electronic medical records and in the doctor's orders; (II) Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2 points; and (III) Child-Pugh score A/B stage. The exclusion criteria were as follows: (I) missing baseline data; (II) without target lesions based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria; (III) lack of the required imaging examination before and after treatment; and (IV) presence of other tumors apart from PLC. The flowchart of the patient selection process is shown in *Figure 1*. We retrospectively collected the following data: age, sex, alcohol consumption, smoking history, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, ECOG PS, Child-Pugh score, circulating markers (neutrophil and lymphocyte counts), blood biochemistry (alanine aminotransferase, aspartate aminotransferase, total bilirubin, and albumin), organs with metastasis before PD-1/PD-L1 inhibitor treatment, number of organs with metastasis, portal vein tumor thrombus (PVTT), type of PVTT, and type of treatment undergone before PD-1/PD-L1 inhibitor treatment. As mentioned in previous studies, PVTT was divided into four types (18). All patients underwent enhanced computed tomography (CT) or magnetic resonance imaging before and after immunotherapy, and all target lesions underwent baseline and post-immunotherapy imaging examinations for evaluation. The pre-baseline scan was performed between 3 months before treatment and at baseline. The first scan for evaluation was performed approximately 2 months after the initial administration of immunotherapy. CT scans were used to assess the treatment response based on the RECIST 1.1 (19). The primary endpoint was the onset of HPD, which was defined as HPD from the date of

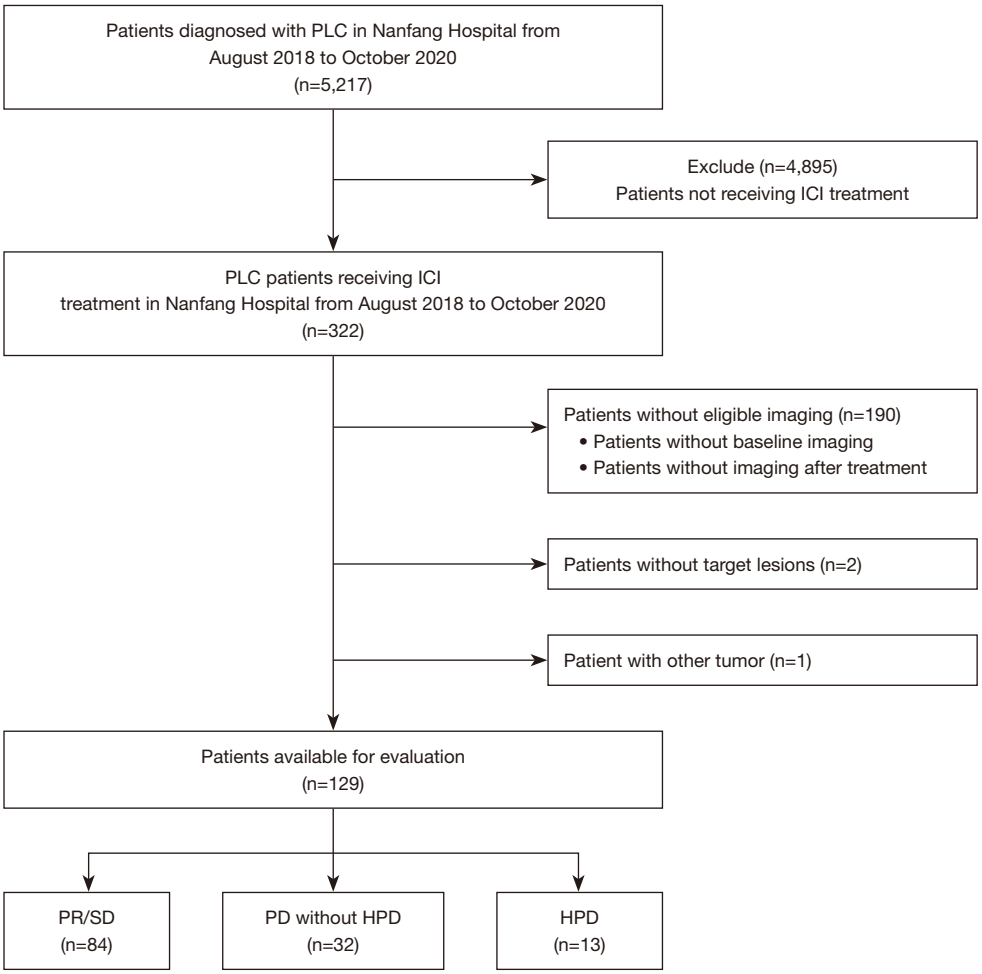

Figure 1 Flowchart of the patients included in the study. PLC, primary liver cancer; ICI, immune checkpoint inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; HPD, hyperprogressive disease.

the first administration of PD-1/PD-L1 inhibitor treatment to the first imaging evaluation based on the RECIST 1.1. The secondary endpoint was progression-free survival (PFS), which was defined as the time between the first immunosuppressive treatment and progression. RECIST 1.1 was used to evaluate the efficacy of the patient at the first imaging evaluation and to calculate the rates of partial response/stable disease (PR/SD), progressive disease (PD) without HPD, and HPD at the first imaging evaluation. This study was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (NFEC-2021-048). The requirement for informed consent from the patients was waived because of the retrospective nature of the study. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013).

Definition of HPD

According to a previous study, we defined HPD as PD within approximately 2 months after the initiation of treatment according to the RECIST 1.1, with a measurable lesion increase of ≥10 mm. The criteria for HPD were as follows: (I) the total diameter of the target lesion increased by ≥40% compared with baseline and/or (II) the total diameter of the target lesion increased by ≥20% compared with baseline and new lesions appeared in at least two different organs (20).

Statistical analysis

We divided patients into the non-HPD (PR, SD, and PD

without HPD) and HPD (PD with HPD) groups based on the patients' response to treatment. The independent sample *t*-test, chi-squared test, or Mann-Whitney U test were used to assess the correlation between HPD and categorical variables or continuous variables, as appropriate. RECIST 1.1 was used to evaluate the efficacy of the treatment. We used univariate and multivariate logistic regression analyses to determine the clinical variables related to HPD. Logistic regression was used to establish a risk model based on the clinical variables that had predictive significance for HPD. We calculated the area under the curve (AUC) to evaluate the predictive ability of the model. Kaplan-Meier survival curves were used to compare PFS of the HPD, non-HPD, and PR/SD groups. All tests were two-sided, and a P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 129 patients treated with PD-1/PD-L1 inhibitor were included in the analysis. The baseline clinical characteristics of the HPD and non-HPD groups are shown in *Table 1*. There were significant differences between the two groups in the number of organ metastases, lung metastases, lymph node metastases, and liver resection prior to immunotherapy (P<0.05). Most patients were below 65 years of age (n=108, 83.7%), were men (n=107, 82.9%), had Child-Pugh A (n=105, 81.4%), had Barcelona-Clinic Liver Cancer (BCLC) stage C (n=96, 74.4%), had a good ECOG PS (0 or 1: n=119, 92.2%), and had HBV infection (n=114, 88.4%). Forty-nine patients had extrahepatic metastasis; 35 patients had lung metastasis and 54 had lymph node metastasis. Fifty-eight patients had PVTT. We used the RECIST 1.1 to evaluate the 129 included patients. According to the RECIST 1.1, 84 (65.1%) patients had PR/SD, 32 (24.8%) had PD without HPD, and 13 (10.1%) had HPD. Basic information and the treatment details of HPD patients are shown in Table S1.

Assessment of HPD

We evaluated HPD according to the RECIST 1.1. We first assessed the percentage of tumor growth in patients treated with PD-1/PD-L1 inhibitor. The baseline tumor diameter of each patient was evaluated based on the imaging results obtained within 3 months prior to the first use of PD-1/PD-L1 inhibitor, and those results were compared to the imaging results obtained approximately 2 months after the patient's first immunotherapy session to evaluate the tumor growth percentage. The average tumor growth ratio of all patients was 4.98%. Seventeen patients (13.1%) had a tumor growth percentage of ≥20%, and 6 patients (4.7%) had a tumor growth percentage of ≥40%. Second, we evaluated the status of new metastases occurring within approximately 2 months after the initiation of immunotherapy. Regarding metastases, thirty-one patients (24.0%) developed new metastases in two or more different organs, whereas 50 patients had no new metastases. 48 patients had one new metastasis. Finally, according to the RECIST 1.1, we identified 13 (13/129, 10.1%) patients with HPD. Among these, 5 patients (38.5%) had a tumor growth percentage of ≥40%, and 8 (61.5%) had that of ≥20% with new metastases in more than two different organs. Based on the RECIST 1.1, 84 patients with PR/SD accounted for 65.1% of the study population, and 32 patients who had PD without HPD accounted for 24.8% of the study population.

PFS survival analysis and clinical variables related to HPD

We conducted a survival analysis of PFS in all patients, and the results are shown in *Figure 2*. Our results showed that patients with HPD had worse PFS as compared with non-HPD patients (P<0.001). Univariate and multivariate analyses were used to study the clinical variables associated with HPD. Univariate regression analysis revealed that lung metastasis, lymph node metastasis, and liver resection were significantly associated with HPD (*Table 2*). Variables with a P value of <0.2 in the univariate regression analysis [lung metastasis, lymph node metastasis, liver resection, neutrophil-lymphocyte ratio (NLR), total bilirubin, PVTT, and number of organs with extrahepatic metastasis] ECOG PS, albumin, and BCLC were included in the multivariate regression analysis (21). Among these, lymph node metastasis and lung metastasis were found to be significantly associated with HPD (*Table 3*). We included lymph node metastasis, lung metastasis, NLR, albumin, and PS in the logistic regression analysis and established a risk model to assess the risk of HPD. The receiver operating characteristic curve is shown in *Figure 3*, with an AUC of 0.801 (P<0.001).

Table 1 Clinicopathologic variables in patients with HPD or non-HPD

Variable	Groups	Total (n=129) (%)	Non-HPD (n=116) (%)	HPD (n=13) (%)	*P value
Age	<65 y	108 (83.7)	98 (84.5)	10 (76.9)	0.444
	≥65 y	21 (16.3)	18 (15.5)	3 (23.1)	
Sex	Male	107 (82.9)	95 (81.9)	12 (92.3)	0.696
	Female	22 (17.1)	21 (18.1)	1 (7.7)	
ECOG PS	<2	119 (92.2)	107 (92.2)	12 (92.3)	>0.999
	≥2	10 (7.8)	9 (7.8)	1 (7.7)	
Child-Pugh	A	105 (81.4)	94 (81.0)	11 (84.6)	>0.999
	B	24 (18.3)	22 (19.0)	2 (15.4)	
NLR	<3	84 (65.1)	78 (67.2)	6 (46.2)	0.130
	≥3	45 (34.9)	38 (32.8)	7 (53.8)	
ALB	<35 g/L	42 (32.6)	36 (31.0)	6 (46.2)	0.270
	≥35 g/L	87 (67.4)	80 (69.0)	7 (53.8)	
TBL	<34.2 μmol/L	96 (74.4)	84 (72.4)	12 (92.3)	0.182
	≥34.2 μmol/L	33 (25.6)	32 (27.6)	1 (7.7)	
AST	<40 IU/L	53 (41.1)	49 (42.2)	4 (30.8)	0.557
	≥40 IU/L	76 (58.9)	67 (57.8)	9 (69.2)	
ALT	<40 IU/L	78 (60.5)	71 (61.2)	7 (53.8)	0.607
	≥40 IU/L	51 (39.5)	45 (38.8)	6 (46.2)	
BCLC stage	A	6 (4.7)	4 (3.4)	2 (15.4)	0.975
	B	27 (20.9)	26 (22.4)	1 (7.7)	
	C	96 (74.4)	86 (74.1)	10 (76.9)	
Extrahepatic metastasis	Yes	49 (38.0)	42 (36.2)	7 (53.8)	0.214
	No	80 (62.0)	74 (63.8)	6 (46.2)	
No. of metastatic organs	<2	98 (76.0)	91 (78.4)	7 (53.8)	0.049
	≥2	31 (24.0)	25 (21.6)	6 (46.2)	
Lung metastasis	Yes	35 (27.1)	28 (24.1)	7 (53.8)	0.022
	No	94 (72.9)	88 (75.9)	6 (46.2)	
LN metastasis	Yes	54 (41.9)	44 (37.9)	10 (76.9)	0.015
	No	75 (58.1)	72 (62.1)	3 (23.1)	
PVTT	Yes	58 (45.0)	55 (47.4)	3 (23.1)	0.141
	No	71 (55.0)	61 (52.6)	10 (76.9)	
PVTT type	I	5 (8.6)	5 (9.1)	0 (0.0)	0.236
	II	27 (46.6)	24 (43.6)	3 (100.0)	
	III	16 (27.6)	16 (29.1)	0 (0.0)	
	IV	10 (17.2)	10 (18.2)	0 (0.0)	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Groups	Total (n=129) (%)	Non-HPD (n=116) (%)	HPD (n=13) (%)	*P value
Combination of targeted agents	Yes	98 (76.0)	89 (76.7)	9 (69.2)	0.511
	No	31 (24.0)	27 (23.3)	4 (30.8)	
Previous hepatic resection	Yes	21 (16.3)	16 (13.8)	5 (38.5)	0.022
	No	108 (83.7)	100 (86.2)	8 (61.5)	
Previous RFA	Yes	34 (26.4)	30 (25.9)	4 (30.8)	0.743
	No	95 (73.6)	86 (74.1)	9 (69.2)	
Previous HAIC	Yes	32 (24.8)	29 (25.0)	3 (23.1)	>0.999
	No	97 (75.2)	87 (75.0)	10 (76.9)	
Previous TACE	Yes	75 (58.1)	69 (59.5)	6 (46.2)	0.356
	No	54 (41.9)	47 (40.5)	7 (53.8)	
HBV infection	Yes	114 (88.4)	102 (87.9)	12 (92.3)	>0.999
	No	15 (11.6)	14 (12.1)	1 (7.7)	
HCV infection	Yes	4 (3.1)	3 (2.6)	1 (7.7)	0.350
	No	125 (96.9)	113 (97.4)	12 (92.3)	
Smoke	Yes	45 (34.9)	40 (34.5)	5 (38.5)	0.775
	No	84 (65.1)	76 (65.5)	8 (61.5)	
Drink	Yes	22 (17.1)	21 (18.1)	1 (7.7)	0.696
	No	107 (82.9)	95 (81.9)	12 (92.3)	

*, comparison between patients with HPD and non-HPD. HPD, hyperprogressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil to lymphocyte ratio; ALB, albumin-bilirubin; TLB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; LN, lymph node; PVTT, portal vein tumor thrombus; RFA, radiofrequency ablation; HAIC, hepatic artery infusion chemotherapy; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus.

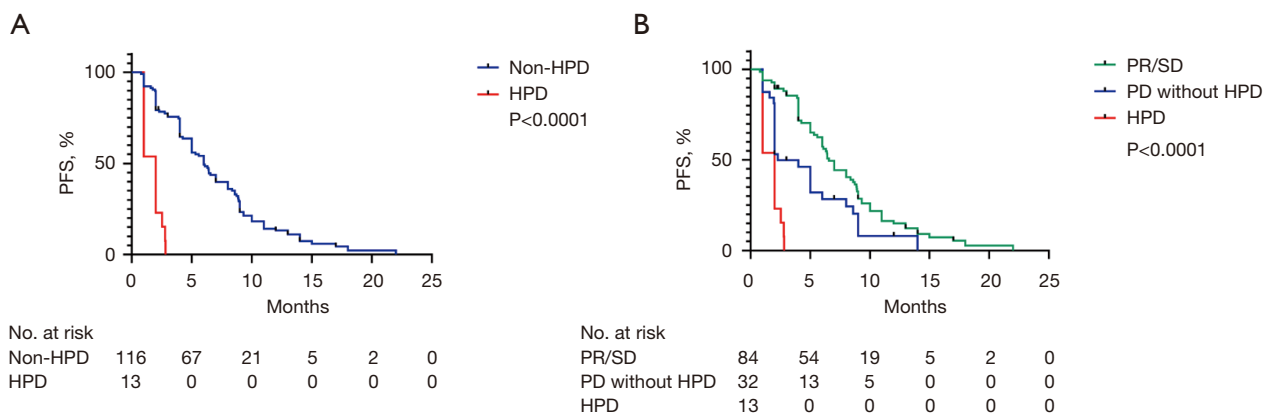

Figure 2 Kaplan-Meier curves for HPD in patients with primary liver cancer treated with PD-1/PD-L1 inhibitor. (A) Survival analysis comparing PFS between the HPD and non-HPD groups; (B) Kaplan-Meier curves comparing PFS between patients with PR/SD, PD without HPD, and HPD. HPD, hyperprogressive disease; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 2 Univariate analysis of risk factors for HPD

Variable	OR	95% CI	P value
Age (≥65 *vs.* <65 y)	1.633	0.409–6.523	0.487
Sex (male *vs.* female)	2.653	0.327–21.533	0.361
ECOG PS (≥2 *vs.* <2)	0.991	0.115–8.509	0.993
Child-Pugh A	Reference	–	–
Child-Pugh B	0.777	0.161–3.759	0.754
NLR (≥3 *vs.* <3)	2.395	0.753–7.619	0.139
ALB (≥35 *vs.* <35 g/L)	0.525	0.165–1.673	0.276
TBL (≥34.2 *vs.* <34.2 μmol/L)	0.219	0.027–1.751	0.152
AST (≥40 *vs.* <40 IU/L)	1.646	0.479–5.653	0.429
ALT (≥40 *vs.* <40 IU/L)	1.352	0.427–4.282	0.608
BCLC stage C (yes *vs.* no)	1.111	0.286–4.316	0.879
Extrahepatic metastasis (yes *vs.* no)	2.056	0.648–6.520	0.221
No. of metastatic organs (≥2 *vs.* <2)	3.120	0.962–10.121	0.058
Lung metastasis (yes *vs.* no)	3.667	1.138–11.819	0.030
LN metastasis (yes *vs.* no)	5.455	1.423–20.907	0.013
PVTT at baseline (yes *vs.* no)	0.333	0.087–1.272	0.108
Combination of targeted agents (yes *vs.* no)	0.683	0.195–2.392	0.551
Previous hepatic resection (yes *vs.* no)	3.906	1.135–13.441	0.031
Previous RFA (yes *vs.* no)	1.274	0.365–4.442	0.704
Previous HAIC (yes *vs.* no)	0.900	0.232–3.496	0.879
Previous TACE (yes *vs.* no)	0.584	0.185–1.847	0.360
HBV infection (yes *vs.* no)	1.647	0.199–13.655	0.644
HCV infection (yes *vs.* no)	3.139	0.302–32.589	0.338
Smoke (yes *vs.* no)	1.187	0.364–3.869	0.776
Drink (yes *vs.* no)	0.377	0.046–3.060	0.361

HPD, hyperprogressive disease; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil to lymphocyte ratio; ALB, albumin-bilirubin; TLB, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona clinic liver cancer; LN, lymph node; PVTT, portal vein tumor thrombus; RFA, radiofrequency ablation; HAIC, hepatic artery infusion chemotherapy; TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus.

Discussion

It is well known that immunotherapy changes the treatment patterns in liver cancer. However, a small number of patients receiving immunotherapy experience rapid tumor progression, and the median survival time for these patients is shorter than that of patients without HPD. In this study, 10.1% of patients with PLC who were administered immunosuppressive therapy experienced HPD. Kim *et al.* used the ratio of tumor growth kinetics to tumor growth rate to assess HPD and found that 12.7% of patients treated with nivolumab developed HPD (22). The incidence of HPD in our study was similar to that reported in theirs. In addition, the study by Champiat *et al.* included 20 solid tumors involving NSCLC, and HPD reportedly occurred in 12 (9.1%) of 131 patients receiving PD-1/PD-L1 inhibitor treatment (14). A report of head and neck squamous cell

Table 3 Multivariate analysis of risk factors for HPD

Variable	OR	95% CI	P value
LN metastasis (yes *vs.* no)	10.125	1.364–75.192	0.024
NLR (≥3 *vs.* <3)	3.796	0.745–19.338	0.108
TBL (≥34.2 *vs.* <34.2 μmol/L)	0.092	0.008–1.083	0.058
ALB (≥35 *vs.* <35 g/L)	0.476	0.104–2.189	0.340
Lung metastasis (yes *vs.* no)	11.750	1.252–110.300	0.031
ECOG PS (≥2 *vs.* <2)	1.311	0.093–18.406	0.841
BCLC C (yes *vs.* no)	0.288	0.039–2.104	0.220
Previous hepatic resection (yes *vs.* no)	4.804	0.798–28.942	0.087
PVTT (yes *vs.* no)	0.243	0.042–1.403	0.114
No. of metastatic organs (≥2 *vs.* <2)	0.154	0.012–1.992	0.152

HPD, hyperprogressive disease; LN, lymph node; NLR, neutrophil to lymphocyte ratio; TLB, total bilirubin; ALB, albumin-bilirubin; ECOG PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona clinic liver cancer; PVTT, portal vein tumor thrombus.

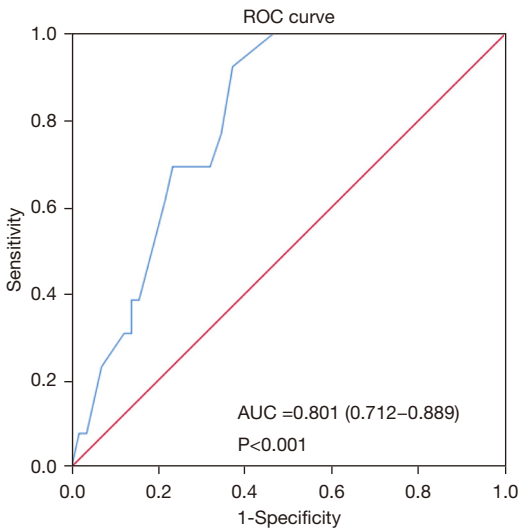

Figure 3 The receiver operating characteristic curves of a risk model for HPD in patients with primary liver cancer treated with PD-1/PD-L1 inhibitor. AUC, area under the curve; HPD, hyperprogressive disease; ROC, receiver operating characteristic.

carcinoma indicated that the use of PD-1/PD-L1 inhibitors resulted in a 29% incidence of HPD. Ferrara *et al.* included patients with advanced NSCLC and found that the HPD rate of the PD-1/PD-L1 inhibitor group was 13.8% (7). This may be because the probability of hyperprogression after ICI treatment varies based on different types of tumors and the research conducted.

In our study, multivariate analysis indicated that lymph node and lung metastases are risk factors for HPD in patients with PLC treated with ICIs and were positively associated with HPD. Lymph node metastasis is an important factor for poor survival in liver cancer patients, and according to reports, patients with lymph node metastases have worse survival outcomes compared to those without. It has been reported that lung metastasis is also an important factor for poor survival in liver cancer patients. Moreover, prognostic analysis shows that overall survival and cause-specific survival are both worse in liver cancer patients with lung metastasis than in those without distant metastasis (23).

Other clinical factors related to HPD have been reported in the literature, such as age, sex, local recurrence, poor ECOG PS, number of metastatic lesions, NLR, and C-reactive protein levels. Our research showed that NLR was not associated with HPD in the univariate or multivariate analysis, which may be due to differences in the sample size. The current study did not find a significant association between advanced age and HPD. However, a study published in 2017 by Champiat *et al.* (14) showed that elderly patients were more likely to develop HPD. It was found that patients over 65 years of age were more likely to develop HPD (22). However, this conclusion is not consistent across all retrospective studies and requires confirmation. Kanjanapan *et al.* found that HPD is more likely to occur in female patients after ICI monotherapy (15).

However, the present study shows that sex is not associated with HPD. Our univariate and multivariate logistics regression analyses also revealed that the number of metastatic organs was not significantly associated with HPD. In addition, liver function classification and PVTT have been found to be related to HPD in previous reports; however, in this study, liver function classification and PVTT were not associated with HPD (24). Previous studies have reported that NLR may be a risk factor for HPD (22,25). A poor PS has been reported to be significantly related to the occurrence of HPD (17). Albumin is an important indicator of the efficacy of immunotherapy (26). We incorporated lymph node metastasis, lung metastasis, NLR, albumin, and PS scores into the logistic regression analysis and established a risk model. The receiver operating characteristic curve indicated that this model had moderate predictive power.

In our univariate analysis, there was a significant difference in HPD rates between patients who had undergone liver resection and those who had not undergone partial hepatectomy. One patient underwent palliative liver resection, and one patient underwent partial hepatectomy for gallstones removal. The remaining patients had tumor remnant, recurrence of intrahepatic tumor, or distant metastasis after partial hepatectomy. Other treatments such as transarterial chemoembolization, hepatic arterial infusion chemotherapy, liver tumor ablation, and targeted drugs were not significantly related to HPD.

This study has some limitations. First, this was a retrospective study, and potential biases were inevitable; the data was obtained from a single center and only included a population of PLC in China. Owing to the differences in race, region, etiology, and the environment of liver cancer, these results may not be generalizable. Therefore, further research including large samples of data from various countries is required to verify our findings. In addition, because some patients do not have any measurable tumor lesions before or after treatment or do not have proper CT scans, some HPDs may be missed. In addition, chemotherapy or targeted therapy do not preclude the occurrence of hyperprogressive phenomena in a variety of preclinical and clinical research models; thus, the same analysis should be performed in a control group receiving non-immunotherapy drugs. Finally, because some patients were lost to follow-up, we were unable to conduct further analysis of overall survival to explore the survival outcome of patients. Previous reports have confirmed that patients with HPD have a significantly lower median overall survival than those with natural progression of the disease.

Conclusions

In our cohort, the HPD rate was 10.1% in patients with PLC receiving ICI therapy. Compared with non-HPD patients, HPD patients had worse PFS. Lung metastasis and lymph node metastasis were independent risk factors of HPD, and our HPD risk model had moderate predictive power. Considering our findings, a larger sample of prospective data is required to explore HPD-related risk factors and establish related risk assessment tools to guide clinical diagnosis and treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE Statement reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2023

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2023). The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University (NFEC-2021-048). The requirement for informed consent from the patients was waived because of the retrospective nature of the study. This study was performed in accordance with the ethical standards of the Declaration of Helsinki (as revised in 2013).

References

1. Llovet JM, Kelley RK, Villanueva A, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7:6.
2. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115-32.
4. Hilmi M, Neuzillet C, Calderaro J, et al. Angiogenesis and immune checkpoint inhibitors as therapies for hepatocellular carcinoma: current knowledge and future research directions. J Immunother Cancer 2019;7:333.
5. Salama AK, Moschos SJ. Next steps in immuno-oncology: enhancing antitumor effects through appropriate patient selection and rationally designed combination strategies. Ann Oncol 2017;28:57-74.
6. Sharon E. Can an Immune Checkpoint Inhibitor (Sometimes) Make Things Worse? Clin Cancer Res 2017;23:1879-81.
7. Ferrara R, Mezquita L, Texier M, et al. Hyperprogressive Disease in Patients With Advanced Non-Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy. JAMA Oncol 2018;4:1543-52.
8. Saâda-Bouzid E, Defaucheux C, Karabajakian A, et al. Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann Oncol 2017;28:1605-11.
9. Scheiner B, Kirstein MM, Hucke F, et al. Programmed cell death protein-1 (PD-1)-targeted immunotherapy in advanced hepatocellular carcinoma: efficacy and safety data from an international multicentre real-world cohort. Aliment Pharmacol Ther 2019;49:1323-33.
10. Wong DJ, Lee J, Choo SP, et al. Hyperprogressive disease in hepatocellular carcinoma with immune checkpoint inhibitor use: a case series. Immunotherapy 2019;11:167-75.
11. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med 2017;376:1015-26.
12. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med 2016;375:1856-67.
13. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:1627-39.
14. Champiat S, Dercle L, Ammari S, et al. Hyperprogressive Disease Is a New Pattern of Progression in Cancer Patients Treated by Anti-PD-1/PD-L1. Clin Cancer Res 2017;23:1920-8.
15. Kanjanapan Y, Day D, Wang L, et al. Hyperprogressive disease in early-phase immunotherapy trials: Clinical predictors and association with immune-related toxicities. Cancer 2019;125:1341-9.
16. Yu G, Xie X, Sun D, et al. EGFR mutation L747P led to gefitinib resistance and accelerated liver metastases in a Chinese patient with lung adenocarcinoma. Int J Clin Exp Pathol 2015;8:8603-6.
17. Sasaki A, Nakamura Y, Mishima S, et al. Predictive factors for hyperprogressive disease during nivolumab as anti-PD1 treatment in patients with advanced gastric cancer. Gastric Cancer 2019;22:793-802.
18. Shi J, Lai EC, Li N, et al. A new classification for hepatocellular carcinoma with portal vein tumor thrombus. J Hepatobiliary Pancreat Sci 2011;18:74-80.
19. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
20. Matos I, Martin-Liberal J, García-Ruiz A, et al. Capturing Hyperprogressive Disease with Immune-Checkpoint Inhibitors Using RECIST 1.1 Criteria. Clin Cancer Res 2020;26:1846-55.
21. Kim SY, Yoon MJ, Park YI, et al. Nomograms predicting survival of patients with unresectable or

metastatic gastric cancer who receive combination cytotoxic chemotherapy as first-line treatment. Gastric Cancer 2018;21:453-63.
22. Kim CG, Kim C, Yoon SE, et al. Hyperprogressive disease during PD-1 blockade in patients with advanced hepatocellular carcinoma. J Hepatol 2021;74:350-9.
23. Wu W, He X, Andayani D, et al. Pattern of distant extrahepatic metastases in primary liver cancer: a SEER based study. J Cancer 2017;8:2312-8.
24. Zhang L, Wu L, Chen Q, et al. Predicting hyperprogressive disease in patients with advanced hepatocellular carcinoma treated with anti-programmed cell death 1 therapy. EClinicalMedicine 2021;31:100673.
25. Petrioli R, Mazzei MA, Giorgi S, et al. Hyperprogressive disease in advanced cancer patients treated with nivolumab: a case series study. Anticancer Drugs 2020;31:190-5.
26. Mezquita L, Auclin E, Ferrara R, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. JAMA Oncol 2018;4:351-7.

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Supplementary

Table S1 Characteristics of patients with HPD

Patient	Age	Sex		ICI type	ECOG PS	BCLC	Child-Pugh	NLR	Tumor size (cm)	Tumor size increase (%)	Metastatic organs	PVTT	Combination of targeted agents	Previous hepatic resection
1	40–49	Male	HCC	Toripalimab	0	A	A	2.81	8.20	68.29	Lung, LN	Yes	Lenvatinib	No
2	40–49	Male	HCC	BGB-A317	1	C	A	1.4	9.70	21.65	LN	Yes	Sorafenib	No
3	30–39	Male	HCC	Sintilimab	1	C	A	3.49	15.90	40.25	Lung, LN	No	Non	No
4	40–49	Male	HCC	Sintilimab	1	C	A	3.13	15.50	24.52	Lung, Spleen, LN	No	Lenvatinib	Yes
5	30–39	Male	HCC	Sintilimab	1	C	A	7.63	8.30	54.22	Lung, LN	No	IBI305	No
6	40–49	Male	HCC	Sintilimab	1	B	A	3.17	5.60	33.93	Non	No	Non	No
7	40–49	Male	HCC	Sintilimab	0	C	A	7.65	11.40	21.93	LN	No	IBI305	No
8	60–69	Female	HCC	Camrelizumab	0	C	A	2.52	16.10	29.19	Lung, LN	No	apatinib	Yes
9	20–29	Male	HCC	Tislelizumab	0	C	A	1.26	7.80	39.74	Lung, brain, LN	No	Lenvatinib	Yes
10	30–39	Male	ICC	Toripalimab	0	C	A	6.01	9.60	51.04	LN	Yes	Lenvatinib	No
11	60–69	Male	HCC	Sintilimab	2	C	B	2.72	11.40	21.93	LN	No	Non	No
12	70–79	Male	HCC	Camrelizumab	1	C	A	2.1	7.30	21.92	LN	No	Lenvatinib	Yes
13	60–69	Male	HCC	Nivolumab	0	A	B	3.69	14.40	47.92	Non	No	Non	Yes

HPD, hyperprogressive disease; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil to lymphocyte ratio; BCLC, Barcelona clinic liver cancer; LN, lymph node; PVTT, portal vein tumor thrombus; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; LN, lymph node. For privacy protection purposes, the patient's specific age is not shown in the table.

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