Comparative Safety, Efficacy and Survival Outcome of Anti-PD-1 Immunotherapy in Colorectal Cancer Patients With vs Without Hepatitis B Virus Infection: A Multicenter Cohort Study

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INTRODUCTION: **Antiprogrammed cell death protein-1 (PD-1) immunotherapy has substantially broadened in scope for the treatment of colorectal cancer (CRC). However, comparative safety, efficacy and survival outcome of anti-PD-1 therapy in CRC patients with and without hepatitis B virus (HBV) infection remain unclear.**

METHODS: **This multicenter, retrospective cohort study included 180 advanced-stage CRC patients with available serological markers for HBV infection treated with anti-PD-1 therapy at the Sixth Affiliated Hospital, Sun Yat-sen University and Sun Yat-sen University Cancer Center between December 2016 and December 2019. A propensity score-matched analysis was performed to compare the safety, efficacy, and survival outcome between HBV and non-HBV groups.**

RESULTS: **The incidences of deficient mismatch repair and metastatic disease were significantly different between HBV and non-HBV groups (both $P < 0.05$). After propensity score-matched analysis, any grade immune-related adverse events and grade ≥ 3 immune-related adverse events were 47% vs 38% ($P = 0.25$) and 5% vs 6% ($P = 1.0$) between HBV and non-HBV groups, respectively. The overall response rate was 39% with 17 complete responses and 13 partial responses for the HBV infection cohort and 39% with 11 complete responses and 19 partial responses for the non-HBV infection cohort ($P = 1.0$). Two-year progression-free survival rates were 38% vs 40% ($P = 0.596$) and 2-year overall survival rates were 55% vs 63% ($P = 0.401$) for HBV vs non-HBV infection cohorts.**

DISCUSSION: **The incidences of toxicity, efficacy and survival outcome were similar between patients with HBV infection and non-HBV patients receiving anti-PD-1 therapy, which supports to include CRC patients with HBV in clinical trials of anti-PD-1 therapy.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A782

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INTRODUCTION

Antiprogrammed cell death protein-1(PD-1) blockade is transforming the treatment of colorectal cancer (CRC) (1,2). The promising outcomes with anti-PD-1 immunotherapy in clinical trials led to approval by the US Food and Drug Administration in mismatch repair-deficient (dMMR) CRC (3). Most clinical trials of immunotherapy for CRC excluded specific patient populations with preexisting viral infection, such as hepatitis B virus (HBV), hepatitis C virus (HCV), or HIV infections. Therefore, the safety and efficacy of a PD-1 inhibitor in these populations remain unclear.

The challenge is that the incidence of chronic HBV infection in southern China is as high as 8%–15% (4,5), and recent case series research showed that HBV reactivation might occur in cancer

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patients with HBV infection undergoing anti-PD(L)-1 immunotherapy (6–8). Thus, the toxicity of immunotherapy in CRC patients with chronic HBV infection from an endemic area needs to be clarified. Although other retrospective series reported similar rates of toxicity and efficacy in cancer patients with HIV, HCV, and HBV infections to those reported in patients without viral infections (9,10), these data included no CRC patient with HBV infection and there was no direct comparison of safety and efficacy between patients with and without viral infection.

There are limited data from the literature on the comparison of toxicity, efficacy, and survival outcome of immunotherapy between CRC patients with or without HBV infection. Because dMMR CRC is a well-established predictive biomarker for anti-PD-1 immunotherapy in patients with CRC (11) and patients with metastasis disease received more intensive therapy and might have poorer performance status, it is rational to account for the MMR status and metastasis disease when assessing the toxicity and efficacy. To clarify whether CRC patients with concomitant HBV infection could be safely and effectively treated with anti-PD-1 immunotherapy, we performed this propensity score-matched (PSM) analysis for patients with or without HBV infection who underwent anti-PD-1 immunotherapy.

METHODS

Participants and study design

Data of CRC patients treated with anti-PD-1 immunotherapy at the Sixth Affiliated Hospital, Sun Yat-sen University and Sun Yat-sen University Cancer Center were collected. According to the guidelines from the American Association for the Study of Liver Diseases in 2018, chronic HBV infection was defined as HBsAg-positive and clinical resolved HBV infection was defined as HBsAg-negative and anti-HBc-positive (12). Moreover, since patients with either of these HBV infections might experience HBV reactivation (9,12), patients with chronic or clinical resolved HBV infection were defined as patients with HBV infection. This study was approved by the Institutional Review Board of our institution.

The major end points were immune-related adverse events (irAEs) assessed by the Common Terminology Criteria for Adverse Events, version 4.0, and overall response rate (ORR) and disease control rate (DCR) using the Response Evaluation Criteria in Solid Tumors, version 1.1 (13). The patients with no follow-up scans due to clinical deterioration or loss to follow-up were presumed as progressive disease (PD). Overall survival was defined as the duration from the initiation of anti-PD-1 immunotherapy to death or last follow-up while alive. Progression-free survival was defined as the duration from the initiation of anti-PD-1 immunotherapy to progression or last follow-up while in remission. The Response Evaluation Criteria in Solid Tumors confirmed that response and irAEs were manually collected and verified for each patient by 2 physicians and any disagreement would be resolved by discussion to reach consensus. HBsAg, HBsAb, HBcAb, HBeAb, HBV viral load, prophylactic antiviral therapy, pretreatment values and highest values of liver function test, use of corticosteroids during immunotherapy, patients' demographics, comorbidities, MMR testing, or microsatellite instability (MSI) testing results were extracted from the intelligence platform. Pretreatment values were defined as the values obtained before the initiation of anti-PD-1 immunotherapy and highest values as the highest values of the liver function test during the period of immunotherapy.

Statistical analysis

The frequency (percentage) and median value (range) were provided to report categorical and continuous variables, respectively. Clinicopathological parameters were compared among HBV infection and non-HBV infection groups using the Mann-Whitney *U* test for continuous variables and the $\chi 2$ test (or the Fisher exact test, if appropriate) for categorical variables. The comparative incidences of irAEs and ORRs between patients with and without HBV infection were evaluated by the odds ratio (OR) and corresponding 95% confidence interval (CI) using the Fisher exact test. The primary analysis was conducted in the whole cohort with the comparison of characteristics, toxicity, and efficacy between with and without HBV infection groups.

A sensitivity analysis was used to account for the main clinical parameters distributed unequally between patients with HBV infection and non–HBV-infected patients. Association of HBV status with toxicity and efficacy was analyzed with PSM analysis to account for potential heterogeneity in clinicopathological features between 2 groups. The propensity score construction is on the basis of the probability estimation with a multivariate logistic regression model including main unbalanced parameters among patients with HBV infection and non-HBV-infected patients. The PSM technique was performed with a ratio of 1:1 (1 non-HBV patient matched to 1 patient with HBV) to select 2 well-balanced samples. Univariate survival was compared using the log-rank test, and Kaplan-Meier curves were used to generate time-to-event data. All statistical analyses were performed using SPSS, version 26 (IBM, Armonk, NY). *P* values of less than 0.05 for both sides were considered statistically significant.

RESULTS

Overall cohort

A total of 187 patients received anti-PD-1 immunotherapy (nivolumab, pembrolizumab, teriprizumab, toripalimab, and camrelizumab) either as a single agent or in combination with chemotherapy/targeted therapy during December 2016 to December 2019. A total of 180 patients received serological markers for HBV infection (including hepatitis B surface antigen [HBsAg], anti-HBs antibody, anti-hepatitis B core [anti-HBc], HBeAg, and anti-HBe antibody), HCV, HEV, and HIV infections. No patient had HCV, HEV, and HIV infections. Seventy-seven patients had HBV infection. The selection process is outlined in Figure S1 (see Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782). A total of 180 patients with CRC were included, and 77 patients (43%) had HBV comorbidity and 103 (57%) had no HBV infection. For the whole population, the median age was 48 years (interquartile range: 15–80) and 111 patients (62%) were male. Twenty-nine patients (16%) had locally advanced disease, and 151 patients (84%) had metastatic diseases. For the overall cohort, 160 patients were tested with MMR or MSI, and 85 patients had dMMR tumors.

When compared with patients without HBV infection, patients with HBV infection had more dMMR tumors (57% vs 40%, $P = 0.045$) and more local disease (25% vs 10%, $P = 0.007$). Baseline median alanine aminotransferase (ALT) levels (19.8 vs 17.9 IU/L, $P = 0.80$), aspartate aminotransferase (AST) levels (23.1 vs 21.0 IU/L, $P = 0.75$), total bilirubin (9.6 vs 10.3 μmol/L, $P = 0.28$), and albumin (39.7 vs 40.9 g/L, $P = 0.12$) among 2 groups were comparable. Clinical characteristics are summarized in Table 1.

Table 1. Clinicopathological characteristics in patients with and without HBV infection

Characteristics	All patients (N = 180, %)	HBV (N = 77, %)	Non-HBV (N = 103, %)	*P* value
Age, median (range)				0.88
≤50	97 (54)	41 (53)	56 (54)	
>50	83 (46)	36 (47)	47 (46)	
Sex				0.22
Male	111 (62)	43 (56)	68 (66)	
Female	69 (38)	34 (44)	35 (34)	
MMR status				0.045[a]
dMMR	85 (47)	44 (57)	41 (40)	
pMMR	75 (42)	27 (35)	48 (47)	
NS	20 (11)	6 (8)	14 (14)	
Tumor location				0.54
Colon	112 (62)	49 (64)	63 (61)	
Rectum	68 (38)	28 (36)	40 (39)	
Histopathology				0.65
Well differentiation	13 (7)	7 (9)	6 (6)	
Moderate differentiation	80 (44)	38 (49)	42 (41)	
Poor differentiation	60 (33)	22 (29)	38 (37)	
Adenocarcinoma (NS)	27 (15)	10 (13)	17 (17)	
Stage				0.02[a]
II	5 (3)	4 (5)	1 (1)	
III	24 (13)	15 (20)	9 (9)	
IV	151 (84)	58 (75)	93 (90)	
Anti-PD-1 therapy type				0.56
Monotherapy	103 (57)	46 (60)	57 (55)	
Combined therapy[b]	77 (43)	31 (40)	46 (45)	
Baseline ALT, median (U/L)	18.5	19.8	17.9	0.80
Baseline AST, median (U/L)	22.3	23.1	21.0	0.75
Baseline TBL, median (μmol/L)	9.6	9.6	10.3	0.28
Baseline ALB, median (g/L)	40.5	39.7	40.9	0.12

ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dMMR, deficient mismatch repair; HBV, hepatitis B virus; MMR, mismatch repair; NS, not sure; PD-1, programmed cell death protein-1; pMMR, proficient mismatch repair; TBL, total bilirubin.
[a]Significantly different.
[b]Combined therapy included targeted therapy combined with anti-PD-1 therapy, chemotherapy combined with anti-PD-1 therapy, COX2 inhibitor combined with anti-PD-1 therapy, and CTLA-4 antibody combined with anti-PD-1 therapy.

Safety, efficacy, and survival outcomes of anti-PD-1 immunotherapy for patients with and without HBV

The viral status for 77 patients with HBV infection was as follows: 20 patients with positive HBsAg and 75 patients with HBsAg (−) and HBcAb (+). Among 77 patients with HBV infection, 11 received prophylactic antiviral therapy. Five cases underwent antiviral prophylaxis because of detectable pretreatment HBV DNA levels and other 6 cases because of physicians' discretion. Pretreatment HBV DNA levels were available in 28 patients, 22 of them had undetectable levels and the remaining 6 had detectable viral loads (33 IU/mL, 4370 IU/mL, 56 IU/mL, 1.6 IU/mL, 710 IU/mL, and 21 IU/mL). Routing testing of HBV DNA levels was available in 12 patients, and no HBV reactivation was observed. The detailed serologies of the HBV cohort are summarized in Table S1 (see Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782).

The incidences of any grade irAEs were 47% (n = 36) and 35% (n = 36) in the HBV and non-HBV groups, respectively (P = 0.11). The rates of any grade ≥ 3 were 5% (n = 4) and 6% (n = 6), respectively (P = 1.0), as presented in Table S1 (see Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782). Highest median ALT levels (37.8 vs 28.6 IU/L, P = 0.34) and AST levels (36.7 vs 31.0 IU/L, P = 0.16) during anti-PD-1 immunotherapy in these 2 groups were comparable. Proportions of patients with baseline elevated ALT levels among 2 groups were similar (16% [12/77] vs 15% [15/103], P = 0.65). Proportions of patients with baseline elevated AST levels among 2 groups were similar (19% [15/77] vs 19% [20/103], P = 0.99). The specific irAEs for patients with HBV infection and without HBV infection are listed in Table 2. One patient had baseline grade 1 hepatic enzyme elevation, which progressed to grade 3.

Among patients who responded to anti-PD-1 immunotherapy, the ORRs were 39% (17 complete responses [CRs], 13 partial responses [PRs], 13 SD, and 34 PD) and 32% (12 CRs, 21 PRs, 11 SD, and 59 PD) for the cohorts with and without HBV infection, respectively (P = 0.34). The DCRs were 56% and 43% for these 2 groups, respectively (P = 0.08) (see Table S2, Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782). Two-year progression-free survival rates were 38% vs 32% (P = 0.205) and 2-year overall survival rates were 55% vs 62% (P = 0.351) for HBV vs non-HBV infection cohorts (Figure 1).

Propensity score matching

In univariate analysis, MSI status and stage were significantly different between the 2 groups. Owing to the limited sample of patients with CRC who received anti-PD-1 immunotherapy, only MSI status and stage were used for PSM analysis. The baseline characteristics were comparable after PSM analysis (see Table S3, Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782).

Safety, efficacy, and survival outcomes of anti-PD-1 immunotherapy for patients with and without HBV infection among matched cohort

After PSM analysis, 77 of the 103 patients without HBV infection (75%) could be matched successfully with 77 patients with HBV infection (see Table S2, Supplementary Data, Supplementary Digital Content 1, http://links.lww.com/CTG/A782).

Table 2. Subgroup analysis of safety according to anti-PD-1 therapy types in HBV and non-HBV groups

	Anti-PD-1 monotherapy				Anti-PD-1 combined therapy[a]			
	HBV (46)		Non-HBV (57)		HBV (31)		Non-HBV (46)	
	Any grade irAEs	Grade≥ 3 irAEs	Any grade irAEs	Grade ≥ 3 irAEs	Any grade irAEs	Grade ≥ 3 irAEs	Any grade irAEs	Grade ≥ 3 irAEs
Total, n (%)	18 (39)	3 (7)	14 (25)	1 (2)	18 (55)	1 (3)	22 (48)	5 (11)
Colitis	3	0	1	0	0	0	3	0
Hepatitis	4	2	6	1	10	0	16	1
Rash	3	0	1	0	3	0	3	1
Hypothyroidism	6	0	3	0	3	0	2	0
Hyperthyroidism	3	0	1	0	1	0	1	0
Fatigue	4	0	1	0	1	0	3	0
Hypertension	0	0	0	0	1	0	0	0
Thrombocytopenia	1	1	0	0	0	0	3	3
Leukopenia	0	0	0	0	2	1	4	1
Anemia	0	0	0	0	2	0	0	0
Pneumonia	2	0	3	0	2	0	2	0
Renal dysfunction	0	0	0	0	4	0	2	0
Adrenal insufficiency	0	0	0	0	1	0	0	0

HBV, hepatitis B virus; irAEs, immune-related adverse events; PD-1, programmed cell death protein-1.
[a]Combined therapy included targeted therapy combined with anti-PD-1 therapy, chemotherapy combined with anti-PD-1 therapy, COX2 inhibitor combined with anti-PD-1 therapy, and CTLA4 antibody combined with anti-PD-1 therapy.

The incidences of any grade irAEs were 47% (n = 36) and 38% (n = 29) in the HBV and matched non-HBV groups, respectively ($P = 0.25$). The rates of any grade ≥ 3 were 5% (n = 4) and 6% (n = 5), respectively ($P = 1.0$) (Table 3). Highest median ALT levels (37.8 vs 26.3 IU/L, $P = 0.18$) and AST levels (36.7 vs 30.4 IU/L, $P = 0.07$) during anti-PD-1 immunotherapy in these 2 groups were comparable.

Among patients who responded to anti-PD-1 immunotherapy, the ORRs were 39% (17 CRs, 13 PRs, 13 SD, and 34 PD) and 39% (11 CRs, 19 PRs, 4 SD, and 43 PD) for the matched cohorts with and without HBV infection, respectively ($P = 1.0$) (Table 3). DCRs were 56% and 44% for these 2 groups, respectively ($P = 0.42$). Two-year progression-free survival rates were 38% vs 40% ($P = 0.596$), and 2-year overall survival rates were 55% vs 63% ($P = 0.401$) for HBV vs non-HBV infection cohorts (Figure 1).

Safety and efficacy according to the type of anti-PD-1 therapy for patients with HBV infection and non-HBV patients

A total of 77 patients received anti-PD-1 combined therapy (targeted therapy, chemotherapy or cyclooxygenase-2 (COX2) inhibitor, and CTLA4 antibody); only 20 patients (30%) had dMMR tumors, and 47 patients (70%) had pMMR tumors. Meanwhile, of the 103 patients treated with anti-PD-1 monotherapy, 70% had dMMR tumors and 30% had pMMR tumors.

The irAEs for patients receiving different anti-PD-1 therapy types are depicted in Table 2. For the anti-PD-1 monotherapy group, the incidences of any grade irAEs were 39% (hypothyroidism [n = 6], hepatitis, fatigue [n = 4 each], pneumonia [n = 2], and thrombocytopenia [n = 1]) vs 25% (hepatitis [n = 6], hypothyroidism, pneumonia [n = 3 each], fatigue, colitis, rash, hyperthyroidism [n = 1 each]) for patients with vs without HBV infection, respectively ($P = 0.11$). The incidences of grade ≥ 3 irAEs for patients with HBV infection and non-HBV-infected patients were 7% (baseline hepatitis, n = 2, and thrombocytopenia, n = 1) vs 2% (hepatitis, n = 1) ($P = 0.32$), respectively. The incidence of any grade irAEs for patients treated with anti-PD-1 combined therapy was 55% (hepatitis [n = 10], renal dysfunction [n = 4], rash, hypothyroidism [n = 3 each], leukopenia, pneumonia, anemia [n = 2 each], hyperthyroidism, hypertension, fatigue, and adrenal insufficiency [n = 1 each]) vs 48% (hepatitis [n = 16], leukopenia [n = 4], colitis, rash, fatigue, thrombocytopenia [n = 3 each], hypothyroidism, pneumonia, renal dysfunction [n = 2 each], and hyperthyroidism [n = 1]) ($P = 0.38$) in HBV vs non-HBV group, and the rate of grade ≥ 3 irAEs was 3% (leukopenia, n = 1) vs 11% (thrombocytopenia [n = 3], leukopenia, hepatitis, and rash [n = 1 each]) ($P = 0.39$).

The ORR for anti-PD-1 monotherapy was 50% (12 CRs, 11 PRs, 8 SD, and 15 PD) vs 47% (10 CRs, 17 PRs, 3 SD, and 27 PD) ($P = 0.79$), respectively, for patients with vs without HBV infection, while the DCR was 67% vs 53% ($P = 0.13$). As for anti-PD-1 combined therapy, the ORR in HBV and non-HBV cohorts was 23% (5 CRs, 2 PRs, 5 SD, and 19 PD) and 13% (2 CRs, 4 PRs, 8 SD, and 32 PD) ($P = 0.27$), respectively. The DCR was 39% vs 30% ($P = 0.45$) for these 2 groups (Table 4).

DISCUSSION

Anti-PD-1 immunotherapy has revolutionized the treatment of CRC, especially for dMMR patients (2). Patients with HBV infection were historically excluded from clinical trials of immunotherapy for CRC. Therefore, the safety, efficacy, and survival

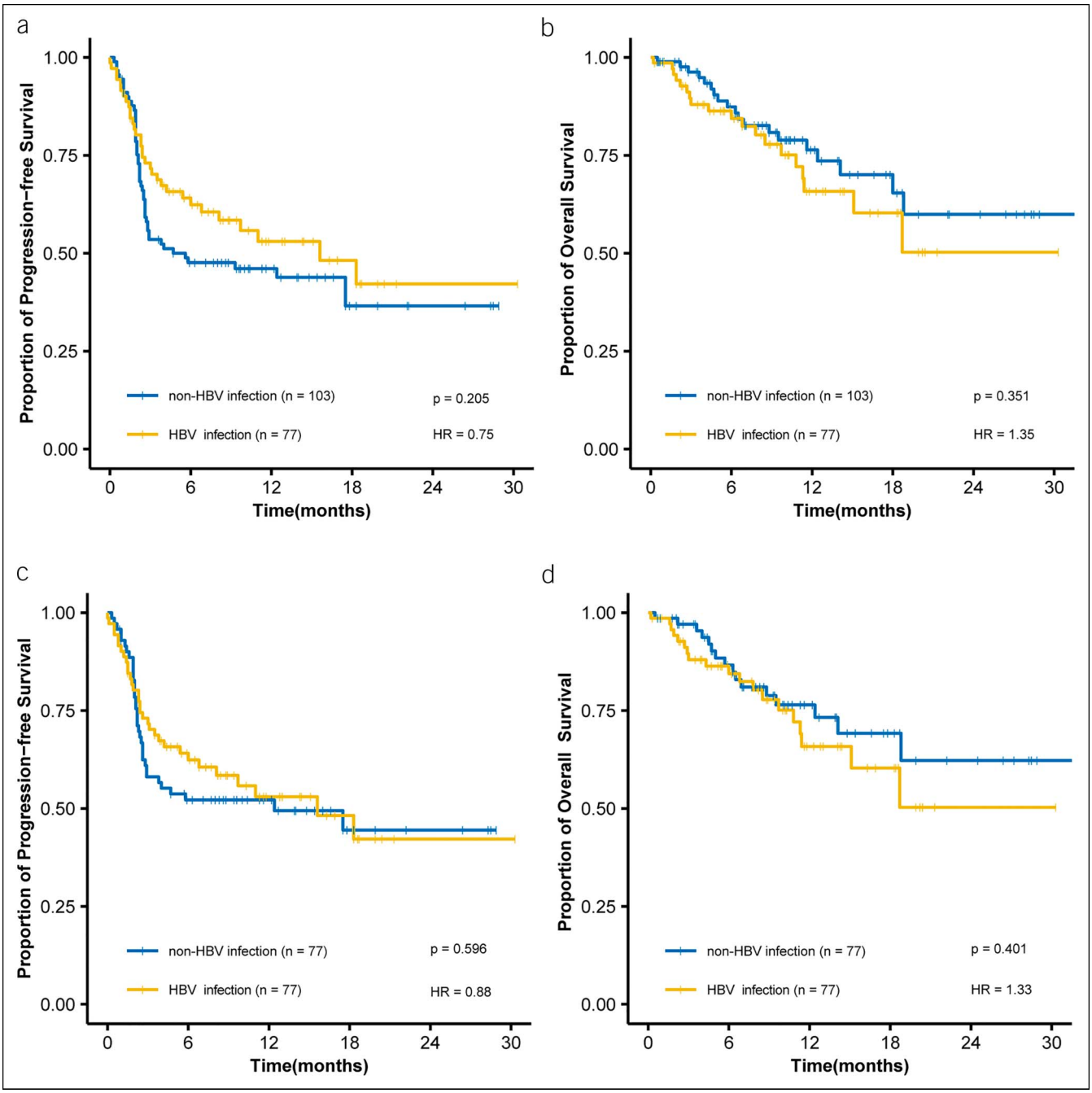

Figure 1. Kaplan-Meier survival curves according to the hepatitis B virus (HBV) infection status for (**a**) progression-free survival and (**b**) overall survival analyses. After propensity score-matched analysis, Kaplan-Meier survival curves according to the HBV infection status for (**c**) progression-free survival and (**d**) overall survival analyses. Log-rank test *P* values are shown for each plot.

outcome of anti-PD-1 immunotherapy for these patients remain largely unexplored, which provides limited evidence for patients to make informed treatment decisions and rare opportunities to participate in clinical trials with immunotherapy, especially in HBV-endemic areas. To the best of our knowledge, this is the first multicenter, comparative analysis of the safety, efficacy, and survival outcome of anti-PD-1 immunotherapy in a large cohort of patients with HBV infection and non-HBV-infected patients.

In a case series with 16 patients with HBV infection receiving immune checkpoint immunotherapy (anti-PD-[L]1 therapy and anti-CTLA4 therapy), no HBV reactivation or changes in HBV medications were observed in any patient (9). In another case series with 14 patients with HBV infection treated with anti-PD-(L)1 therapy, none of them developed hepatitis (10). Although these data indicated that the incidences of toxicity seemed relatively similar to those observed in non-HBV patients from clinical trials, patients with different tumor types may have different safety profile, and no CRC patient with HBV infection was recruited in these studies. Moreover, there was also very limited evidence regarding safety and efficacy in CRC patients

Table 3. Comparison of efficacy and toxicity between patients with and without HBV infection after propensity score-matched analysis

Events	No. (%) of patients			OR (95%CI)	*P* value
	Total (n = 154)	HBV (n = 77)	Non-HBV (n = 77)		
Any grade irAEs	65 (42)	36 (47)	29 (38)	1.45 (0.76–2.76)	0.25
Grade≥ 3 irAEs	9 (6)	4 (5)	5 (6)	0.80 (0.20–3.06)	1.0
ORR (CR + PR)	60 (39)	30 (39)	30 (39)	1.0 (0.52–1.91)	1.0
DCR (CR + PR + SD)	77 (50)	43 (56)	34 (44)	1.30 (0.70–2.45)	0.42

CI, confidence interval; CR, complete response; DCR, disease control rate; HBV, hepatitis B virus; irAEs, immune-related adverse events; OR, odds ratio; ORR, overall response rate; PR, partial response; SD, stable disease.

with HBV infection from prospective studies. Therefore, this multicenter study filled the knowledge gap for immunotherapy in CRC patients with HBV infection.

Among patients with HBV infection, the proportion of dMMR tumors was 57%, much higher than that in patients without HBV infection, which seems reasonable because of physicians' discretion to recommend anti-PD-1 immunotherapy for HBV patients with dMMR tumors. Furthermore, this study showed that patients with HBV infection had less metastatic disease. dMMR has been the only indication for anti-PD-1 immunotherapy for CRC and metastases affect performance status, both of which were unbalanced between patients with HBV infection and non-HBV patients. Thus, we took these variables into account and performed PSM analysis to compare the safety and efficacy among patients with HBV infection and non-HBV patients. Although the incidences of irAEs and ORRs were comparable between patients with HBV infection and non-HBV patients, the DCRs were significantly different. After matching MMR status and stage in our study, the toxicity and efficacy rates were similar. The ORRs from landmark trials were 28%–57% for dMMR CRC (2,3,14–16). ORRs were 39% and 43% after PSM analysis for these 2 groups, which were largely consistent with these trials and indicated that the efficacy rates were similar between patients with HBV infection and non-HBV patients. Similar to our study, a recent multicenter, large case series also found that immune checkpoint immunotherapy might be a safe and effective treatment option for patients with chronic viral infection (9). Moreover, this study was the first to report similar survival outcomes for patients with HBV infection and non-HBV patients, which further indicated the application of immunotherapy in patients with CRC.

Table 4. Subgroup analysis of efficacy according to anti-PD-1 therapy types in HBV and non-HBV groups

	Anti-PD-1 monotherapy		Anti-PD-1 combined therapy[a]	
	HBV (46)	Non-HBV (57)	HBV (31)	Non-HBV (46)
CR, n (%)	12 (26)	10 (18)	5 (16)	2 (4)
PR, n (%)	11 (24)	17 (30)	2 (6)	4 (9)
SD, n (%)	8 (17)	3 (5)	5 (16)	8 (17)
PD, n (%)	15 (33)	27 (47)	19 (61)	32 (70)
ORR, n (%)	23 (50)	27 (47)	7 (23)	6 (13)
DCR, n (%)	31 (67)	30 (53)	12 (39)	14 (30)

CR, complete response; DCR, disease control rate; HBV, hepatitis B virus; ORR, overall response rate; PR, partial response; PD-1, programmed cell death protein-1; PD, progressed disease; SD, stable disease.
[a]Anti-PD-1 combined therapy included targeted therapy, chemotherapy or cyclooxygenase-2 (COX2) inhibitor, and CTLA4 antibody.

Although a recent study showed that HBV reactivation might occur in a small subset of patients with HBsAg-positive cancer undergoing anti-PD-1 immunotherapy (8), there was no reactivation among 12 patients with available HBV DNA levels. This finding was in line with the results from clinical trials with anti-PD-1 therapy for patients with hepatocellular carcinoma (17,18). In the CheckMate 040 clinical trial, 15 HCC patients with HBV infection received nivolumab and none of them experienced HBV reactivation. Owing to the limited sample size, further studies with longitudinal data of HBV DNA levels are warranted to assess the incidence of and risk factors for HBV reactivation.

Anti-PD-1 combined therapy, especially with targeted therapy, is being increasingly explored in patients with pMMR CRC to improve efficacy (19–22). The treatment regimen in our study did not seem to increase the risk of irAEs in patients with HBV infection but still needs to be verified in future studies. The efficacy of this regimen was not promising with ORRs of 23% and 13% among patients with and without HBV infection, respectively, which is consistent with preliminary results of several clinical trials.

This study has several limitations to be mentioned. First, the HBV viral load was not collected continuously during and after anti-PD-1 immunotherapy in most of the patients with HBV infection, limiting our ability to comprehensively elaborate the risk of HBV reactivation. Second, patients included in this study were from an HBV-endemic area whose genotype may be distinct from other population. Thus, whether the findings can be applied elsewhere needs to be further validated. Finally, although response to tumor was evaluated in most patients, several patients have not received imaging after anti-PD-1 immunotherapy, mainly because of deterioration of disease or loss to follow-up. Despite these limitations, this study is of particular clinical relevance to help gastroenterologists and patients to make better decisions about anti-PD-1 immunotherapy for CRC patients with HBV infection.

In conclusion, in this multicenter cohort study, CRC patients with HBV infection undergoing anti-PD-1 therapy can respond to immunotherapy with no apparent increase in toxicity compared with uninfected patients, which supported the use of anti-PD-1 therapy in these patients and the inclusion of them in future clinical trials. HBV reactivation was not observed. Further prospective research is needed to validate these findings.

CONFLICTS OF INTEREST

Guarantor of the article: Ping Lan, PhD, and Shu-Biao Ye, PhD.

Specific author contributions: Conception and design and financial support: P.L., Y-K.C., and S-B Y. Provision of study materials or patients: P.L. and P.C. Collection and assembly of data: Y.-K. C., P.C., D.-W. C., and Z.-S. L. Data analysis and interpretation: P.L., Y-K.C., and S.-B Y. Manuscript writing: All authors. Final approval of manuscript: All authors.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

- ✓ Anti-programmed cell death protein-1 (PD-1) therapy has substantially broadened in scope for the treatment of colorectal cancer.
- ✓ Comparative safety and survival outcome of anti-PD-1 therapy between patients with hepatitis B virus (HBV) infection and non-HBV patients remains unclear.

WHAT IS NEW HERE

- ✓ The toxicity, efficacy and survival outcome were similar between patients with HBV infection and non-HBV patients receiving anti-PD-1 therapy.

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