Impact of the timing of hepatitis B virus (HBV) identification and anti-HBV therapy initiation on the risk of adverse liver outcomes in patients receiving cancer therapy

Running title: Liver outcomes in HBV cancer patients

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Precis: Early identification of chronic HBV infection reduced the risk of liver failure after chemotherapy among solid tumor patients. Early anti-HBV therapy was associated with a reduction in all-cause mortality among hematologic patients with chronic HBV infection.

Abstract

Background. Data on incidence of adverse liver outcomes is limited for cancer patients with chronic (HBsAg+/anti-HBc+) or past (HBsAg-/anti-HBc+) hepatitis B virus (HBV) after chemotherapy. We aimed to determine the impact of test timing and anti-HBV therapy on adverse liver outcomes in these patients.

Methods. We retrospectively studied patients with solid or hematologic malignancies who received chemotherapy during 2004-2011. We defined HBV testing and anti-HBV therapy to be e*arly* at initiation of cancer therapy and *late* after initiation. Outcomes included hepatitis flares, hepatic impairment, liver failure, and death. Time-to-event analysis was used to determine incidence, and multivariable hazard models to determine predictors of outcomes.

Results: There were 18,688 study patients (80.4% solid tumors). Prevalence of chronic HBV was 1.1% (52/4905) and past HBV was 7.1% (350/4905). Among solid tumor patients, late identification of chronic HBV was associated with higher risk of hepatitis flare, hepatic impairment, liver failure, and death compared with early identification [HR (95% CI), 4.02 (1.26-12.86), 8.48 (1.86-38.66), 9.38 (1.50-58.86), and 3.90 (1.19-12.83), respectively]. Among patients with hematologic malignancies and chronic HBV, risk of death was 7.8 (1.73-35.27) times higher in persons with late compared to early anti-HBV therapy initiation. Patients with late identification of chronic HBV had late/no anti-HBV therapy. Chronic HBV predicted liver failure in patients with solid or hematologic malignancies while male sex and late identification were predictors for solid tumor patients.

Conclusion: Early identification correlates with early anti-HBV therapy and reduces the risk of liver failure and death in chronic HBV patients receiving chemotherapy.

Keywords: hematologic malignancies, cancer, hepatitis B, antiviral therapy, liver failure, hepatitis B screening, hepatitis flare, hepatitis B reactivation

INTRODUCTION

Hepatitis B virus (HBV) affects nearly 2 billion people worldwide and can lead to serious liver diseases.[1] The balance between liver injury and viral control is regulated by the host immune system,[2] and immunosuppressive therapies which disrupt immune balance can lead to reactivation of HBV replication, resulting in hepatitis flare, liver failure, and death.[3]

For patients receiving anti-cancer therapy, HBV testing[4-7] and anti-HBV medications[8,9] are recommended to prevent HBV reactivation. However, uptake has been low[10] particularly for patients with solid tumors[11] and may be in part due to the lack of clinical outcomes data to support an optimal management strategy. We conducted this retrospective study to determine the impact of early vs. late HBV identification and early vs. late/no initiation of anti-HBV therapy on the development of adverse liver outcomes among patients with chronic or past HBV infection receiving cancer therapy.

METHODS

We assembled a retrospective cohort of patients aged 18 or older with solid or hematologic malignancies who presented to The University of Texas MD Anderson Cancer Center and received the first outpatient administration of parenteral cancer therapy between 2004 and 2011. We excluded patients with hepatocellular carcinoma because they would be more likely to be screened for HBV and to be treated with anti-HBV therapy if they tested positive. Furthermore, hepatitis flares and liver failure in these patients may be due to underlying liver disease and not cancer treatment. Demographic and clinical characteristics were obtained from institutional databases. This study was conducted after approval from our Institutional Review Board.

Chronic HBV infection was defined as hepatitis B surface antigen (HBsAg)-positive/hepatitis B core antibody (anti-HBc)-positive or HBsAg-positive/anti-HBc-unknown. Past HBV infection was defined as HBsAg-negative/anti-HBc-positive or HBsAg-unknown/anti-HBc-positive, regardless of hepatitis B surface antibody (anti-HBs) status.

Chemotherapy initiation period was defined as 2 months prior to first administration of chemotherapy until beginning of second chemotherapy cycle (Figure 1). The post-chemotherapy initiation period was defined as the beginning of second chemotherapy cycle to the end of study period. We defined early HBV identification as ≥1 of the following: HBsAg or anti-HBc tests at MD Anderson during chemotherapy initiation period, known positive HBsAg or anti-HBc tests, or anti-HBV therapy prior to first chemotherapy. Late HBV identification was defined as HBsAg and/or anti-HBc tests at MD Anderson after the chemotherapy initiation period. Early initiation refers to anti-HBV medications started before or during chemotherapy initiation period and before any adverse liver outcome; late initiation refers to medications started after chemotherapy initiation period, before or after adverse liver outcome.

We identified outcomes between administration of second cycle of chemotherapy up to two years after last chemotherapy administration at MD Anderson, last follow up, or death (Figure 1). We defined a hepatitis flare as an alanine aminotransferase (ALT) ≥100 U/L that was also ≥3 times the baseline ALT in the chemotherapy initiation period.[12] Hepatitis impairment was defined as having hepatitis flare and either total bilirubin ≥2.5 mg/dl or international normalized ratio (INR) ≥1.5. Liver failure was defined as having hepatitis flare and either ascites or encephalopathy, as determined from claims using International Classification of Diseases, 9th revision (ICD-9) codes. All-cause mortality was determined through our tumor registry. HBV DNA testing was not performed for all HBV patients, thus we could not determine HBV reactivation as an outcome.

We employed descriptive statistics and Chi-square tests to analyze characteristics of the study cohort. Time-to-event analysis was used to compare liver-related outcomes among patients by HBV status and timing of HBV testing or anti-HBV therapy. Patients without outcomes were censored at last follow-up date, date of death, or at two years after last chemotherapy administration, whichever came first. Those who experienced outcomes >2 years after last chemotherapy administration were censored at 2 years. Competing risk analysis for hazard of outcomes was performed to account for

competing risks of death for those who died without liver outcomes. To compare likelihood of liver outcomes between groups, we estimated cumulative incidence function and hazard ratios (HR) for the liver failure subdistribution using the Fine-Gray model.[13] Multivariable subdistribution hazard models were developed to separately determine predictors of liver failure among HBV patients with solid tumors or hematologic malignancies. Covariates included demographics, HBV status, and timing of HBV identification and of anti-HBV therapy. Rituximab administration and stem cell transplantation (SCT), treated as a time-varying covariate, were also included for patients with hematologic malignancies. Model selection implemented stepwise methods where p-value for entry was $\leq$0.10 and to remain was $\leq$0.05. Due to the strong correlation between timing of HBV identification and timing of initiation of anti-HBV therapy, we explored multivariable models wherein either one of the two was excluded.

RESULTS

A total of 18,688 patients received chemotherapy during the study period, and 80.4% (n=15031) had solid tumors while 19.6% (n=3657) had hematologic malignancies (Table 1). Overall, 19.9% had early HBV testing, 6.3% had late testing, and 73.8% were not tested. Among the 4905 tested patients, the overall prevalence of chronic HBV infection was 1.1% (n=52) and that of past HBV infection was 7.1% (n=350). Patients with hematologic malignancies had higher rates of HBV testing (89.6%, n=3277), of which most was early (90.4%, n=2965), as compared to solid tumor patients (10.8% overall testing, n=1628; 46.4% early testing, n=756). There were high rates of HBV testing among patients who received rituximab (88.9%, 1602/1803), allogeneic SCT (100%, 479/479), or autologous SCT (99.4%, 709/713).

Chronic HBV prevalence among patients with hematologic malignancies was 0.8% (25/3277) and of past HBV 6.0% (196/3277). Chronic HBV prevalence among patients with solid tumors was 1.7% (27/1628) and of past HBV 9.5% (154/1628). Among Asian and black patients with solid tumors,

the prevalence was 11.8% and 2.1% for chronic and 34.2% and 12.2% for past infection, respectively. Of 52 chronic HBV patients, 26 had serum HBV DNA testing (median 16 days after HBV identification, range 2 days-7 months); 12 had undetectable HBV DNA, and 14 had detectable HBV DNA (median 49,350 IU/mL, range 1,930-50,000,000).

Median follow-up duration for the study cohort was 26 months (range 2 days-88.6 months). The incidence of each liver outcomes was higher in chronic or past HBV patients compared to HBV-negative patients and in patients with late compared to those with early HBV identification, and lowest among the untested patients (Table 2). The incidence of liver failure among patients with solid or hematologic tumors was 11.7% among those whose HBV infection was diagnosed late, 7.4% among those diagnosed early, and 7.8% in those without HBV infection (Table 2). Of the patients with chronic or past HBV infection with liver failure, 53% (n=18) developed liver failure while receiving chemotherapy, and 47% (n=16) developed liver failure after the last chemotherapy cycle.

Among patients with solid tumors, late identification of chronic HBV was significantly associated with higher risk of hepatitis flare, hepatic impairment, liver failure, and death compared with early identification [HR (95% confidence interval), 4.02 (1.26-12.86), 8.48 (1.86-38.66), 9.38 (1.50-58.86), and 3.90 (1.19-12.83), respectively; Table 3]. Among the 181 patients with solid tumors and chronic or past HBV infection, 15 patients had liver failure. Of these, 6 had colorectal cancer, 3 had other gastrointestinal cancers (1 each of the following: esophageal, stomach, and pancreas), 2 had breast cancer, 2 had lung cancer, 1 had melanoma, and 1 had thymoma. Figure 2 shows a significantly higher cumulative incidence of liver failure in solid tumor patients with late vs. early HBV identification of chronic HBV. For patients with hematologic malignancies, we could not fully evaluate the effect of timing of chronic HBV identification on liver impairment or liver failure due to the small numbers of patients with late identification.

There was no significant association between timing of anti-HBV therapy and liver failure (Table 4). However, we found that the timing of HBV identification and anti-HBV therapy was highly

correlated - among the 39 chronic HBV patients who had early testing, 23 started anti-HBV therapy before or at the initiation of cancer therapy, while all 13 chronic HBV patients who had late identification had late/no anti-HBV therapy. Among patients with hematologic malignancies, the risk of hepatitis flare or hepatic impairment for past HBV patients [HR 3.13 (1.24-7.92), 5.09 (1.19-21.74), respectively] or death for chronic HBV patients [HR 7.82 (1.73-35.27)] was significantly higher in persons with late compared to those with early anti-HBV therapy initiation (Table 4). Among patients who received rituximab, all 12 with chronic and 31 of 103 with past HBV had early initiation of anti-HBV therapy. For solid tumors patients, we could not fully evaluate the effect of timing of anti-HBV therapy on liver failure due to the small numbers of patients.

Among patients with solid tumors, those with chronic HBV had a higher risk of liver failure than past HBV [HR 4.94 (1.82-13.45)], and those with late identification of HBV infection had a higher risk of liver failure than those with early identification [HR 2.86 (0.99, 8.24)] (Table 5). Male sex was also a predictor of liver failure among solid tumor patients. For patients with hematologic malignancies, chronic HBV was a predictor of liver failure [HR 3.34 (1.10-10.17)] (Table 5).

DISCUSSION

In this analysis of a large cohort of patients receiving anti-cancer therapy, we found that late identification of chronic HBV after chemotherapy initiation for solid tumors led to higher risks of adverse liver outcomes compared with early HBV detection. We also found that late or no anti-HBV therapy was associated with higher rates of mortality than early anti-HBV therapy for chronic HBV patients with hematologic malignancies. Timing of identification of HBV infection was correlated with timing of anti-HBV therapy, suggesting that benefits of early HBV identification could be related to early use of anti-HBV therapy or to close monitoring and early anti-HBV treatment at the first sign of hepatitis flare.

Among the more than 15,000 patients in our study who had solid tumors, chronic HBV infection and late identification of chronic or past HBV infection were independent risk factors for liver failure. Late identification of chronic HBV infection was also associated with higher rates of hepatitis flare, hepatic impairment, and all-cause mortality. Previous studies have not examined the impact of early vs. late testing on adverse liver outcomes in patients with solid tumors. In one study where breast, colon, or lung cancer patients were screened before chemotherapy,[14] there were no cases of liver failure among 30 patients with chronic HBV infection with early HBV testing, of whom 28 had early anti-HBV therapy. In contrast, the rate of liver failure in our study was 6.7% for solid tumor patients with chronic HBV, likely higher because none had early anti-HBV therapy.

Among patients with hematologic malignancies who had HBV testing, over 90% were tested early. Due to low numbers of late testing, we did not observe any difference in outcomes between patients with early and late identification of HBV infection. However, we found a 7.82 (1.73-35.27) times higher risk of death in chronic HBV patients with late/no anti-HBV therapy than those with early therapy. Data from randomized clinical trials have supported the benefit of early anti-HBV therapy among patients with hematologic malignancies. In one study of 30 lymphoma patients with chronic HBV, 0 of15 patients in the prophylaxis group and 1 of 15 in the group that was closely monitored with anti-HBV medication initiated upon HBV DNA elevation died.[15] In our study, the mortality rate was higher, 3 of 17 in the early anti-HBV therapy group and 6 of 8 in the late/no anti-HBV therapy group, likely due to less rigorous monitoring and delays in starting anti-HBV treatment.

The strengths of our study include a large cohort of patients with different tumor types providing much needed information on HBV reactivation in patients with solid tumors in a country with a low HBV prevalence. The major limitation was the retrospective design, which limited our ability to ascertain whether patients meeting our criteria for liver failure truly had liver failure, identify the exact etiology of adverse liver outcomes, and assess adherence to anti-HBV therapy. We were unable to determine the effect of specific chemotherapy on adverse liver outcomes because many patients

received more than one chemotherapy drug simultaneously or changed treatment regimens over time. Also, HBV DNA testing was not routinely performed, and thus liver outcomes cannot be attributed to HBV reactivation. In addition, baseline hepatitis B e antigen and HBV DNA testing were not performed in all patients with chronic HBV infection, thus limiting the impact of chronic HBV phase on the risk of adverse liver outcomes. Finally, our study represents practice patterns of a single institution, and findings may not be representative.

In summary, our study demonstrated that among chronic HBV patients, early identification reduced the risk of liver failure among solid tumor patients and early anti-HBV therapy reduced all-cause mortality among patients with hematologic malignancies Alerts in electronic health systems could facilitate HBV screening and early anti-HBV therapy.[16,17] Future efforts should focus on the risk of HBV reactivation and optimal strategies for HBV screening and prophylactic antiviral in solid tumor patients.

Legends

Figure 1. Timeline of study periods

Abbreviation: Chemo: chemotherapy.

Chemotherapy initiation: 2 months before first chemotherapy administration until administration of second cycle of chemotherapy. Post-chemotherapy initiation: after administration of second cycle of chemotherapy until end of study period, 2011.

HBV identification. Early: Positive findings on HBsAg or anti-HBc tests performed before or during chemotherapy initiation period or anti-HBV therapy prior to first chemotherapy. Late: Positive findings on HBsAg or anti-HBc tests performed after chemotherapy initiation period.

Anti-HBV therapy initiation. Early: HBV medication started during chemotherapy initiation period and before any adverse liver outcome. Late: HBV medication started after chemotherapy initiation, before or after any adverse liver outcome.

Outcomes: from administration of second cycle of chemotherapy up to two years after last chemotherapy administration at MD Anderson, last follow up, or death.

Figure 2. Cumulative incidence of liver failure in chronic HBV patients with solid tumors, by timing of HBV identification

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Table 1. Patient characteristics by cancer type and HBV infection

Characteristic	All patients [1] (N=18,688) n (col %)	Solid tumors (n=15,031) HBV status identified [2a] (n=1628) n (% of [1])	Solid tumors (n=15,031) Total HBV+ (n=181) n (% of [2a])	Solid tumors (n=15,031) Chronic HBV (n=27) n (% of [2a])	Hematologic malignancies (n=3657) HBV status identified [2b] (n=3277) n (% of [1])	Hematologic malignancies (n=3657) Total HBV+ (n=221) n (% of [2b])	Hematologic malignancies (n=3657) Chronic HBV (n=25) n (% of [2b])
Age, years							
18-46	4612 (24.7)	531 (11.5)	40 (7.5)	11 (2.1)	1003 (21.7)	58 (5.8)	11 (1.1)
47-55	4460 (23.9)	433 (9.7)	57 (13.2)	6 (1.4)	727 (16.3)	59 (8.1)	8 (1.1)
56-64	4863 (26.0)	381 (7.8)	43 (11.3)	7 (1.8)	825 (17.0)	61 (7.4)	4 (0.5)
≥65	4753 (25.4)	283 (6.0)	41 (14.5)	3 (1.1)	722 (15.2)	43 (6.0)	2 (0.3)
Sex							
Female	10608 (56.8)	886 (8.4)	85 (9.6)	10 (1.1)	1362 (12.8)	66 (4.8)	6 (0.4)
Male	8080 (43.2)	742 (9.2)	96 (12.9)	17 (2.3)	1915 (23.7)	155 (8.1)	19 (1.0)
Race/ethnicity							
White	13108 (70.1)	1092 (8.3)	87 (8.0)	7 (0.6)	2355 (18.0)	114 (4.8)	12 (0.5)
Hispanic	2312 (12.4)	212 (9.2)	14 (6.6)	3 (1.4)	439 (19.0)	16 (3.6)	2 (0.5)
Black	2089 (11.2)	189 (9.0)	27 (14.3)	4 (2.1)	289 (13.8)	44 (15.2)	3 (1.0)
Asian	556 (3.0)	76 (13.7)	35 (46.1)	9 (11.8)	60 (10.8)	22 (36.7)	5 (8.3)
Other	623 (3.3)	59 (9.5)	18 (30.5)	4 (6.8)	134 (21.5)	25 (18.7)	3 (2.2)
Residence							
US	18090 (96.8)	1590 (8.8)	170 (10.7)	23 (1.4)	3142 (17.4)	212 (6.7)	25 (0.8)
Outside of US	598 (3.2)	38 (6.4)	11 (28.9)	4 (10.5)	135 (22.6)	9 (6.7)	0 (0.0)
HBV prevalence in birthplace[1]							
≥2%	1285 (6.9)	128 (10.0)	46 (35.9)	15 (11.7)	204 (15.9)	34 (16.7)	6 (2.9)
<2%	17403 (93.1)	1500 (8.6)	135 (9.0)	12 (0.8)	3073 (17.7)	187 (6.1)	19 (0.6)
Timing of HBV identification[2]							
Early	3721 (19.9)	756 (20.3)	99 (13.1)	15 (2.0)	2965 (79.7)	200 (6.7)	24 (0.8)
Late	1184 (6.3)	872 (73.6)	82 (9.4)	12 (1.4)	312 (26.4)	21 (6.7)	1 (0.3)
No HBV identified	13,783 (73.8)	n/a	n/a	n/a	n/a	n/a	n/a
Timing of anti-HBV therapy initiation[3]							
Early	n/a	n/a	15 (100.0)	6 (40.0)	n/a	56 (100.0)	17 (30.4)
Late/none	n/a	n/a	166 (10.3)	21 (1.3)	n/a	165 (5.1)	8 (0.2)

Abbreviations: HBV, hepatitis B virus; n/a, not applicable.

[1]From reference 7.

[2]**Early identification**: Positive findings on HBsAg or anti-HBc tests performed before or during chemotherapy initiation period or anti-HBV therapy prior to first chemotherapy. **Late identification**: HBsAg or anti-HBc tests performed after chemotherapy initiation period.

[3]**Early initiation**: During chemotherapy initiation period before any adverse liver outcome. **Late initiation**: after chemotherapy initiation period, before or after adverse liver outcome.

Table 2. Impact of HBV status on adverse liver outcomes by cancer type

HBV status/timing of HBV identification[1]	Total n	Hepatitis flare n (% of Total)	Hepatitis flare Hazard ratio (95% CI)	Hepatitis flare P-Value[2]	Hepatic impairment n (% of Total)	Hepatic impairment Hazard ratio (95% CI)	Hepatic impairment P-Value[2]	Liver failure n (% of Total)	Liver failure Hazard ratio (95% CI)	Liver failure P-Value[2]	Death, all cause n (% of Total)	Death, all cause Hazard ratio (95% CI)	Death, all cause P-Value[2]
All cancers													
HBV+/early	299	80 (26.8)	2.84 (2.26-3.56)	<0.01	48 (16.1)	3.62 (2.70-4.85)	<0.01	22 (7.4)	2.53 (1.65-3.89)	<0.01	115 (38.5)	1.03 (0.86-1.25)	0.72
HBV+/late	103	38 (36.9)	3.71 (2.70-5.10)	<0.01	31 (30.1)	6.49 (4.52-9.31)	<0.01	12 (11.7)	3.45 (1.92-6.21)	<0.01	47 (45.6)	0.98 (0.75-1.26)	0.85
HBV-/early or late	4503	1354 (30.1)	3.23 (3.00-3.47)	<0.01	728 (16.2)	3.66 (3.29-4.07)	<0.01	351 (7.8)	2.69 (2.33-3.11)	<0.01	1434 (31.8)	0.82 (0.77-0.87)	<0.01
HBV status unknown	13,779[3]	1433 (10.4)	Ref		636 (4.6)	Ref		394 (2.9)	Ref		4858 (35.3)	Ref	
Solid tumors													
HBV+/early	99	15 (15.2)	1.49 (0.90-2.49)	0.12	7 (7.1)	1.49 (0.71-3.13)	0.29	5 (5.1)	1.70 (0.71-4.06)	0.23	35 (35.4)	0.93 (0.67-1.28)	0.63
HBV+/late	82	29 (35.4)	3.49 (2.41-5.03)	<0.01	23 (28.0)	5.81 (3.84-8.77)	<0.01	10 (12.2)	3.47 (1.83-6.56)	<0.01	37 (45.1)	0.91 (0.68-1.22)	0.55
HBV-/early or late	1447	422 (29.2)	2.98 (2.67-3.32)	<0.01	235 (16.2)	3.50 (3.02-4.07)	<0.01	133 (9.2)	2.98 (2.44-3.62)	<0.01	530 (36.6)	0.90 (0.82-0.98)	0.02
HBV status unknown	13,399[3]	1394 (10.4)	Ref		622 (4.6)	Ref		391 (2.9)	Ref		4762 (35.5)	Ref	
Hematologic malignancies													
HBV+/early	200	65 (32.5)	3.48 (2.34-5.18)	<0.01	41 (20.5)	5.77 (3.14-10.59)	<0.01	17 (8.5)	10.17 (2.97-34.76)	<0.01	80 (40.0)	1.54 (1.14-2.07)	<0.01
HBV+/late	21	9 (42.9)	4.63 (2.31-9.27)	<0.01	8 (38.1)	11.99 (4.91-29.27)	<0.01	2 (9.5)	10.73 (1.70-67.79)	0.01	10 (47.6)	1.77 (1.00-3.12)	0.05
HBV-/early or late	3056	932 (30.5)	3.26 (2.36-4.51)	<0.01	493 (16.1)	4.51 (2.65-7.69)	<0.01	218 (7.1)	8.75 (2.80-27.39)	<0.01	904 (29.6)	1.10 (0.89-1.36)	0.39
HBV status unknown	380	39 (10.3)	Ref		14 (3.7)	Ref		3 (0.8)	Ref		96 (25.3)	Ref	

Abbreviations: HBV, hepatitis B virus; Ref, reference.

[1]Timing defined as in Table 1.

[2]From univariate Fine and Gray model of subdistribution hazard with death as competing risk.

[3]Four patients had invalid time to event and were excluded from the analysis.

Table 3. Impact of timing of HBV identification on adverse liver outcomes by cancer type

Timing of HBV identification[1]	Total (n=402)	Hepatitis flare n (% of Total)	Hepatitis flare Hazard ratio (95% CI)	Hepatitis flare P-Value[2]	Hepatic impairment n (% of Total)	Hepatic impairment Hazard ratio (95% CI)	Hepatic impairment P-Value[2]	Liver failure n (% of Total)	Liver failure Hazard ratio (95% CI)	Liver failure P-Value[2]	Death, all cause n (% of Total)	Death, all cause Hazard ratio (95% CI)	Death, all cause P-Value[2]
All cancers													
Chronic HBV													
Early	39	14 (35.9)	Ref		8 (20.5)	Ref		5 (12.8)	Ref		14 (35.9)	Ref	
Late	13	10 (76.9)	3.76 (1.62-8.72)	<0.01	10 (76.9)	7.28 (2.85-18.60)	<0.01	6 (46.2)	5.40 (1.71-17.00)	<0.01	10 (76.9)	4.55 (1.99-10.40)	<0.01
Past HBV													
Early	260	66 (25.4)	Ref		40 (15.4)	Ref		17 (6.5)	Ref		101 (38.8)	Ref	
Late	90	28 (31.1)	1.09 (0.71-1.67)	0.70	21 (23.3)	1.31 (0.78-2.21)	0.31	6 (6.7)	0.85 (0.34-2.12)	0.73	37 (41.1)	0.75 (0.53-1.07)	0.11
Solid tumors													
Chronic HBV													
Early	15	4 (26.7)	Ref		2 (13.3)	Ref		1 (6.7)	Ref		6 (40.0)	Ref	
Late	12	9 (75.0)	4.02 (1.26-12.86)	0.02	9 (75.0)	8.48 (1.86-38.66)	<0.01	5 (41.7)	9.38 (1.50-58.86)	0.02	9 (75.0)	3.90 (1.19-12.83)	0.02
Past HBV													
Early	84	11 (13.1)	Ref		5 (6.0)	Ref		4 (4.8)	Ref		29 (34.5)	Ref	
Late	70	20 (28.6)	1.97 (0.95-4.05)	0.07	14 (20.0)	2.77 (1.00-7.67)	0.05	5 (7.1)	1.15 (0.32-4.14)	0.83	28 (40.0)	0.73 (0.43-1.23)	0.24
Hematologic malignancies													
Chronic HBV													
Early	24	10 (41.7)	Ref		6 (25.0)	Ref		4 (16.7)	Ref		8 (33.3)	Ref	
Late	1	1 (100.0)	7.49 (2.45-22.86)	<0.01	1 (100.0)	n/a	n/a	1 (100.0)	n/a	n/a	1 (100.0)	23.49 (3.38-163.5)	<0.01
Past HBV													
Early	176	55 (31.3)	Ref		35 (19.9)	Ref		13 (7.4)	Ref		72 (40.9)	Ref	
Late	20	8 (40.0)	1.29 (0.64-2.60)	0.48	7 (35.0)	1.92 (0.86-4.26)	0.11	1 (5.0)	0.63 (0.08-4.97)	0.66	9 (45.0)	1.02 (0.56-1.84)	0.96

Abbreviations: HBV, hepatitis B virus; n/a, not applicable (statistically meaningful comparisons not possible because of insufficient sample size).

[1]Timing defined as in Table 1.

[2]From univariate Fine and Gray model of subdistribution hazard with death as competing risk.

Table 4. Impact of timing of anti-HBV therapy initiation on adverse liver outcomes by cancer type

Timing of anti-HBV therapy initiation[1]	Total (n=402)	Hepatitis flare n (% of Total)	Hepatitis flare Hazard ratio (95% CI)	Hepatitis flare P-Value[2]	Hepatic impairment n (% of Total)	Hepatic impairment Hazard ratio (95% CI)	Hepatic impairment P-Value[2]	Liver failure n (% of Total)	Liver failure Hazard ratio (95% CI)	Liver failure P-Value[2]	Death, all cause n (% of Total)	Death, all cause Hazard ratio (95% CI)	Death, all cause P-Value[2]
All cancers													
Chronic HBV													
Early	23	7 (30.4)	Ref		5 (21.7)	Ref		3 (13.0)	Ref		5 (21.7)	Ref	
Late/None	29	17 (58.6)	2.70 (1.21-5.99)	0.01	13 (44.8)	2.32 (0.87-6.20)	0.09	8 (27.6)	1.99 (0.54-7.38)	0.30	19 (65.5)	3.28 (1.25-8.59)	0.02
Past HBV													
Early	48	7 (14.6)	Ref		3 (6.3)	Ref		1 (2.1)	Ref		15 (31.3)	Ref	
Late/None	302	87 (28.8)	1.95 (0.90-4.23)	0.09	58 (19.2)	2.89 (0.90-9.30)	0.08	22 (7.3)	3.12 (0.42-23.37)	0.27	123 (40.7)	1.04 (0.63-1.74)	0.87
Solid tumors													
Chronic HBV													
Early	6	1 (16.7)	Ref		1 (16.7)	Ref		0 (0.0)	Ref		2 (33.3)	Ref	
Late/None	21	12 (57.1)	4.96 (0.78-31.77)	0.09	10 (47.6)	3.42 (0.47-25.03)	0.23	6 (28.6)	n/a	n/a	13 (61.9)	1.46 (0.30-7.26)	0.64
Past HBV													
Early	9	2 (22.2)	Ref		1 (11.1)	Ref		0 (0.0)	Ref		2 (22.2)	Ref	
Late/None	145	29 (20.0)	0.75 (0.19-2.91)	0.67	18 (12.4)	0.88 (0.14-5.42)	0.89	9 (6.2)	n/a	n/a	55 (37.9)	1.20 (0.26-5.55)	0.81
Hematologic malignancies													
Chronic HBV													
Early	17	6 (35.3)	Ref		4 (23.5)	Ref		3 (17.6)	Ref		3 (17.6)	Ref	
Late/None	8	5 (62.5)	2.67 (0.79-8.96)	0.11	3 (37.5)	1.73 (0.38-7.94)	0.48	2 (25.0)	1.40 (0.23-8.56)	0.71	6 (75.0)	7.82 (1.73-35.27)	<0.01
Past HBV													
Early	39	5 (12.8)	Ref		2 (5.1)	Ref		1 (2.6)	Ref		13 (33.3)	Ref	
Late/None	157	58 (36.9)	3.13 (1.24-7.92)	0.02	40 (25.5)	5.09 (1.19-21.74)	0.03	13 (8.3)	2.95 (0.38-22.68)	0.30	68 (43.3)	1.16 (0.67-2.00)	0.61

Abbreviations: HBV, hepatitis B virus; n/a, not applicable (statistically meaningful comparisons not possible because of insufficient sample size).

[1]Timing defined as in Table 1.

[2]From univariate Fine and Gray model of subdistribution hazard with death as competing risk.

Table 5. Model of risk of liver failure for 402 patients with chronic or past HBV infection

Parameter	Solid tumors N = 181 Hazard ratio (95% CI)	P-Value[1]	P-Value for overall effects[1]	Hematologic malignancies N = 221 Hazard ratio (95% CI)	P-Value[1]	P-Value for overall effects[1]
Age						
18-46	4.51 (0.51, 40.15)	0.18	0.13	1.60 (0.30, 8.52)	0.58	0.50
47-55	6.27 (0.79, 50.06)	0.08		2.20 (0.44, 11.01)	0.34	
56-64	0.91 (0.06, 14.24)	0.95		0.85 (0.13, 5.38)	0.86	
≥65	Ref			Ref		
Sex						
Female	Ref					
Male	10.25 (2.21, 47.59)	<0.01	<0.01			
Type of HBV infection						
Chronic	4.94 (1.82, 13.45)	<0.01	<0.01	3.34 (1.10, 10.17)	0.03	0.03
Past	Ref			Ref		
Timing of HBV identification[2]						
Early	Ref			Ref		
Late	2.86 (0.99, 8.24)	0.05	0.05	1.23 (0.26, 5.89)	0.79	0.79
Initiation of anti-HBV therapy[2]						
Early				Ref		0.26
Late/none				1.93 (0.61, 6.07)	0.26	

Abbreviations: HBV, hepatitis B virus.

[1]From multivariate Fine and Gray regression model of subdistribution hazard with death as competing risk.

[2]Timing defined as in Table 1.

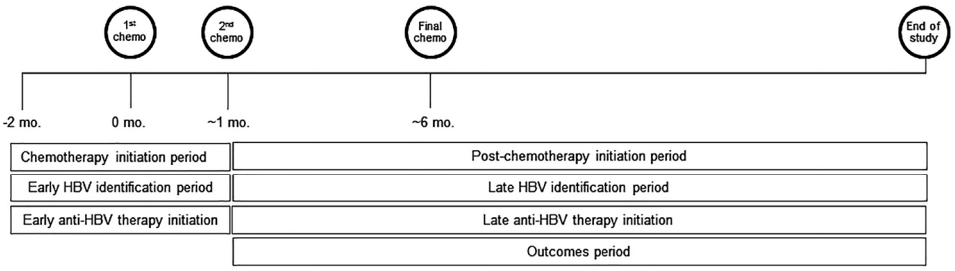

Figure 1. Timeline of study periods

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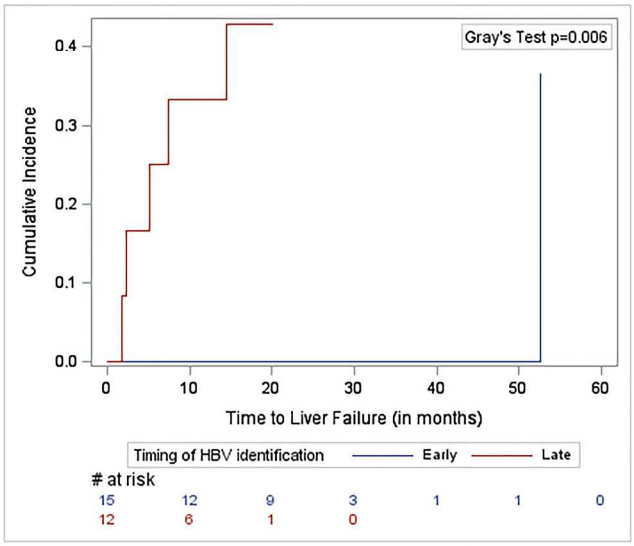
Figure 2. Cumulative incidence of liver failure in chronic HBV patients with solid tumors, by timing of HBV identification



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