Original Article

Impact of the Timing of Hepatitis B Virus Identification and Anti–Hepatitis B Virus Therapy Initiation on the Risk of Adverse Liver Outcomes for Patients Receiving Cancer Therapy

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BACKGROUND: Data on the incidence of adverse liver outcomes are limited for cancer patients with chronic (hepatitis B surface antigen [HBsAg]–positive/hepatitis B core antibody [anti-HBc]–positive) or past (HBsAg-negative/anti-HBc–positive) hepatitis B virus (HBV) after chemotherapy. This study was aimed at determining the impact of test timing and anti-HBV therapy on adverse liver outcomes in these patients. **METHODS:** Patients with solid or hematologic malignancies who received chemotherapy between 2004 and 2011 were retrospectively studied. HBV testing and anti-HBV therapy were defined as early at the initiation of cancer therapy and as late after initiation. Outcomes included hepatitis flares, hepatic impairment, liver failure, and death. Time-to-event analysis was used to determine incidence, and multivariate hazard models were used to determine predictors of outcomes. **RESULTS:** There were 18,688 study patients (80.4% with solid tumors). The prevalence of chronic HBV was 1.1% (52 of 4905), and the prevalence of past HBV was 7.1% (350 of 4905). Among patients with solid tumors, late identification of chronic HBV was associated with a higher risk of hepatitis flare (hazard ratio [HR], 4.02; 95% confidence interval [CI], 1.26-12.86), hepatic impairment (HR, 8.48; 95% CI, 1.86-38.66), liver failure (HR, 9.38; 95% CI, 1.50-58.86), and death (HR, 3.90; 95% CI, 1.19-12.83) in comparison with early identification. Among patients with hematologic malignancies and chronic HBV, the risk of death was 7.8 (95% CI, 1.73-35.27) times higher for persons with late initiation of anti-HBV therapy versus early initiation. Patients with late identification of chronic HBV had late or no anti-HBV therapy. Chronic HBV predicted liver failure in patients with solid or hematologic malignancies, whereas male sex and late identification were predictors for patients with solid tumors. **CONCLUSIONS:** Early identification correlates with early anti-HBV therapy and reduces the risk of liver failure and death in chronic HBV patients receiving chemotherapy. ***Cancer* 2017;123:3367-76**. © *2017 American Cancer Society.*

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

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 that disrupt the immune balance can lead to reactivation of HBV replication and result in hepatitis flares, liver failure, and death.[3]

For patients receiving anticancer 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 this may be in part due to the lack of clinical outcome data to support an optimal management strategy. We conducted this retrospective study to determine the impact of early HBV identification versus late identification and the impact of early initiation of

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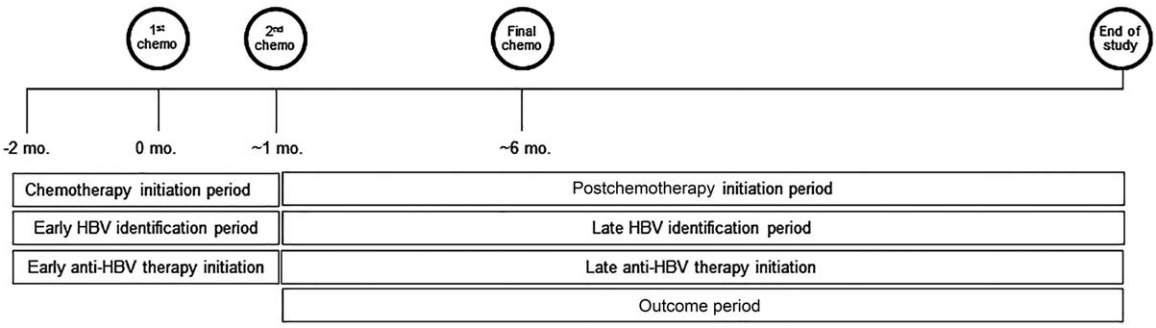

Figure 1. Timeline of the study periods. Chemotherapy initiation occurred from 2 months before the first chemotherapy administration until the administration of the second cycle of chemotherapy. Postchemotherapy initiation occurred after the administration of the second cycle of chemotherapy until the end of the study period (2011). Early HBV identification was defined as positive findings on HBsAg or anti-HBc tests performed before or during the chemotherapy initiation period or anti-HBV therapy before first chemotherapy. Late HBV identification was defined as positive findings on HBsAg or anti-HBc tests performed after the chemotherapy initiation period. Early anti-HBV therapy initiation was defined as HBV medication started before or during the chemotherapy initiation period and before any adverse liver outcome. Late anti-HBV therapy initiation was defined as HBV medication started after chemotherapy initiation and before or after any adverse liver outcome. Outcomes occurred from the administration of the second cycle of chemotherapy up to 2 years after the last chemotherapy administration at The University of Texas MD Anderson Cancer Center, the last follow-up, or death. Anti-HBc indicates hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

anti-HBV therapy versus late/no initiation on the development of adverse liver outcomes among patients with chronic or past HBV infections receiving cancer therapy.

MATERIALS AND METHODS

We assembled a retrospective cohort of patients aged 18 years 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 to cancer treatment. Demographic and clinical characteristics were obtained from institutional databases. This study was conducted after approval by our institutional review board.

A 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. A past HBV infection was defined as HBsAg-negative/anti-HBc–positive or HBsAg-unknown/anti-HBc–positive, regardless of the hepatitis B surface antibody status.

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

We identified outcomes between the administration of the second cycle of chemotherapy and 2 years after the last chemotherapy administration at MD Anderson, last follow-up, or death (Fig. 1). We defined a hepatitis flare as an alanine aminotransferase level $\geq$ 100 U/L that was also $\geq$3 times the baseline alanine aminotransferase level in the chemotherapy initiation period.[12] Hepatitis impairment was defined as a hepatitis flare and either a total bilirubin level $\geq$ 2.5 mg/dL or an international normalized ratio $\geq$ 1.5. Liver failure was defined as a hepatitis flare and either ascites or encephalopathy as determined from claims using *International Classification of Diseases, Ninth Revision* 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 used 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 by the timing of HBV testing or anti-HBV therapy. Patients without outcomes were censored at the last follow-up date, the date of death, or 2 years after the last chemotherapy administration, whichever came first. Those who experienced outcomes more than 2 years after the last chemotherapy administration were censored at 2 years. Competing risk analysis for the hazard of outcomes was performed to account for competing risks of death for those who died without liver outcomes. To compare the likelihood of liver outcomes between groups, we estimated the cumulative incidence function and hazard ratios (HRs) for the liver failure subdistribution with the Fine-Gray model.[13] Multivariate subdistribution hazard models were developed to separately determine predictors of liver failure among HBV patients with solid tumors or hematologic malignancies. Covariates included demographics, the HBV status, and the timing of HBV identification and anti-HBV therapy. Rituximab administration and stem cell transplantation, treated as time-varying covariates, were also included for patients with hematologic malignancies. The model selection implemented stepwise methods by which the *P* value for entry was $\leq$.10 and the *P* value to remain was $\leq$.05. Because of the strong correlation between the timing of HBV identification and the timing of the initiation of anti-HBV therapy, we explored multivariate models in which either one of the two was excluded.

RESULTS

A total of 18,688 patients received chemotherapy during the study period, and 80.4% (n = 15,031) had solid tumors, whereas 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 the overall prevalence of past HBV infection was 7.1% (n = 350). Patients with hematologic malignancies had higher rates of HBV testing (89.6% [n = 3277]), most of which occurred early (90.5%, n = 2965), in comparison with patients with solid tumors (overall testing, 10.8% [n = 1628]; early testing, 46.4% [n = 756]). There were high rates of HBV testing among patients who received rituximab (88.9% [1602 of 1803]), allogeneic stem cell transplantation (100% [479 of 479]), or autologous stem cell transplantation (99.4% [709 of 713]).

The prevalence among patients with hematologic malignancies was 0.8% for chronic HBV (25 of 3277) and 6.0% (196 of 3277) for past HBV. The prevalence among patients with solid tumors was 1.7% (27 of 1628) for chronic HBV and 9.5% (154 of 1628) for past HBV. Among Asian and black patients with solid tumors, the prevalence was 11.8% and 2.1% for chronic infection and 34.2% and 12.2% for past infection, respectively. Twenty-six of 52 chronic HBV patients had serum HBV DNA testing (median, 16 days after HBV identification; range, 2 days to 7 months); 12 had undetectable HBV DNA, and 14 had detectable HBV DNA (median, 49,350 IU/mL; range, 1930-50,000,000 IU/mL).

The median follow-up duration for the study cohort was 26 months (range, 2 days to 88.6 months). The incidence of each liver outcome was higher for chronic or past HBV patients versus HBV-negative patients and for patients with late HBV identification versus those with early HBV identification and was lowest for the untested patients (Table 2). The incidence of liver failure for patients with solid or hematologic tumors was 11.7% when the HBV infection was diagnosed late, 7.4% when the HBV infection was diagnosed early, and 7.8% without an HBV infection (Table 2). Of the patients with a chronic or past HBV infection and 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 a higher risk of hepatitis flare (hazard ratio [HR], 4.02; 95% confidence interval [CI], 1.26-12.86), hepatic impairment (HR, 8.48; 95% CI, 1.86-38.66), liver failure (HR, 9.38; 95% CI, 1.50-58.86), and death (HR, 3.90; 95% CI, 1.19-12.83) in comparison with early identification (Table 3). Among the 181 patients with solid tumors and chronic or past HBV infections, 15 patients had liver failure. Of these, 6 had colorectal cancer, 3 had other gastrointestinal cancers (esophageal cancer [n = 1], stomach cancer [n = 1], and pancreatic cancer [n = 1]), 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 for solid tumor patients with late identification of chronic HBV versus early identification. For patients with hematologic malignancies, we could not fully evaluate the effect of the timing of chronic HBV identification on liver impairment or liver failure because of the small numbers of patients with late identification.

TABLE 1. Patient Characteristics by Cancer Type and HBV Infection

Characteristic	All Patients (n = 18,688), No. (%)	Solid Tumors (n = 15,031)			Hematologic Malignancies (n = 3657)		
		HBV Status Identified (n = 1628), No. (% of All Patients)	Total HBV+ (n = 181), No. (% of Patients With HBV Status Identified)	Chronic HBV (n = 27), No. (% of Patients With HBV Status Identified)	HBV Status Identified (n = 3277), No. (% of All Patients)	Total HBV+ (n = 221), No. (% of Patients With HBV Status Identified)	Chronic HBV (n = 25), No. (% of Patients With HBV Status Identified)
Age							
18-46 y	4612 (24.7)	531 (11.5)	40 (7.5)	11 (2.1)	1003 (21.7)	58 (5.8)	11 (1.1)
47-55 y	4460 (23.9)	433 (9.7)	57 (13.2)	6 (1.4)	727 (16.3)	59 (8.1)	8 (1.1)
56-64 y	4863 (26.0)	381 (7.8)	43 (11.3)	7 (1.8)	825 (17.0)	61 (7.4)	4 (0.5)
≥65 y	4753 (25.4)	283 (6.0)	41 (14.5)	3 (1.1)	722 (15.2)	43 (6.0)	2 (0.3)
Sex							
Female	10,608 (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	13,108 (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							
United States	18,090 (96.8)	1590 (8.8)	170 (10.7)	23 (1.4)	3142 (17.4)	212 (6.7)	25 (0.8)
Outside United States	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[a]							
≥2%	1285 (6.9)	128 (10.0)	46 (35.9)	15 (11.7)	204 (15.9)	34 (16.7)	6 (2.9)
<2%	17,403 (93.1)	1500 (8.6)	135 (9.0)	12 (0.8)	3073 (17.7)	187 (6.1)	19 (0.6)
Timing of HBV identification[b]							
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[c]							
Early	N/A	15	15 (100.0)	6 (40.0)	56	56 (100.0)	17 (30.4)
Late/none	N/A	1613	166 (10.3)	21 (1.3)	3221	165 (5.1)	8 (0.2)

Abbreviations: anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; N/A, not applicable.

[a] From Weinbaum et al.[7]

[b] Early identification was defined as positive findings on HBsAg or anti-HBc tests performed before or during the chemotherapy initiation period or anti-HBV therapy before first chemotherapy. Late identification was defined as HBsAg or anti-HBc tests performed after the chemotherapy initiation period.

[c] Early initiation occurred during the chemotherapy initiation period before any adverse liver outcome. Late initiation occurred after the chemotherapy initiation period before or after an adverse liver outcome.

TABLE 2. Impact of the HBV Status on Adverse Liver Outcomes by Cancer Type

HBV Status/Timing of HBV Identification[a]	Total No.	Hepatitis Flare			Hepatic Impairment			Liver Failure			Death (All Causes)		
		No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b
All cancers													
HBV+/early	299	80 (26.8)	2.84 (2.26-3.56)	<.01	48 (16.1)	3.62 (2.70-4.85)	<.01	22 (7.4)	2.53 (1.65-3.89)	<.01	115 (38.5)	1.03 (0.86-1.25)	.72
HBV+/late	103	38 (36.9)	3.71 (2.70-5.10)	<.01	31 (30.1)	6.49 (4.52-9.31)	<.01	12 (11.7)	3.45 (1.92-6.21)	<.01	47 (45.6)	0.98 (0.75-1.26)	.85
HBV–/early or late	4503	1354 (30.1)	3.23 (3.00-3.47)	<.01	728 (16.2)	3.66 (3.29-4.07)	<.01	351 (7.8)	2.69 (2.33-3.11)	<.01	1434 (31.8)	0.82 (0.77-0.87)	<.01
HBV status unknown	13,779[c]	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)	.12	7 (7.1)	1.49 (0.71-3.13)	.29	5 (5.1)	1.70 (0.71-4.06)	.23	35 (35.4)	0.93 (0.67-1.28)	.63
HBV+/late	82	29 (35.4)	3.49 (2.41-5.03)	<.01	23 (28.0)	5.81 (3.84-8.77)	<.01	10 (12.2)	3.47 (1.83-6.56)	<.01	37 (45.1)	0.91 (0.68-1.22)	.55
HBV–/early or late	1447	422 (29.2)	2.98 (2.67-3.32)	<.01	235 (16.2)	3.50 (3.02-4.07)	<.01	133 (9.2)	2.98 (2.44-3.62)	<.01	530 (36.6)	0.90 (0.82-0.98)	.02
HBV status unknown	13,399[c]	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)	<.01	41 (20.5)	5.77 (3.14-10.59)	<.01	17 (8.5)	10.17 (2.97-34.76)	<.01	80 (40.0)	1.54 (1.14-2.07)	<.01
HBV+/late	21	9 (42.9)	4.63 (2.31-9.27)	<.01	8 (38.1)	11.99 (4.91-29.27)	<.01	2 (9.5)	10.73 (1.70-67.79)	.01	10 (47.6)	1.77 (1.00-3.12)	.05
HBV–/early or late	3056	932 (30.5)	3.26 (2.36-4.51)	<.01	493 (16.1)	4.51 (2.65-7.69)	<.01	218 (7.1)	8.75 (2.80-27.39)	<.01	904 (29.6)	1.10 (0.89-1.36)	.39
HBV status unknown	380	39 (10.3)	Ref		14 (3.7)	Ref		3 (0.8)	Ref		96 (25.3)	Ref	

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; Ref, reference.

[a] Early identification was defined as positive findings on HBsAg or anti-HBc tests performed before or during the chemotherapy initiation period or anti-HBV therapy before first chemotherapy. Late identification was defined as HBsAg or anti-HBc tests performed after the chemotherapy initiation period.

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

[c] Four patients had invalid times to event and were excluded from the analysis.

TABLE 3. Impact of the Timing of HBV Identification on Adverse Liver Outcomes by Cancer Type

Timing of HBV Identification[a]	Total (n = 402)	Hepatitis Flare			Hepatic Impairment			Liver Failure			Death (All Causes)		
		No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b
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)	<.01	10 (76.9)	7.28 (2.85-18.60)	<.01	6 (46.2)	5.40 (1.71-17.00)	<.01	10 (76.9)	4.55 (1.99-10.40)	<.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)	.70	21 (23.3)	1.31 (0.78-2.21)	.31	6 (6.7)	0.85 (0.34-2.12)	.73	37 (41.1)	0.75 (0.53-1.07)	.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)	.02	9 (75.0)	8.48 (1.86-38.66)	<.01	5 (41.7)	9.38 (1.50-58.86)	.02	9 (75.0)	3.90 (1.19-12.83)	.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)	.07	14 (20.0)	2.77 (1.00-7.67)	.05	5 (7.1)	1.15 (0.32-4.14)	.83	28 (40.0)	0.73 (0.43-1.23)	.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)	<.01	1 (100.0)	N/A	N/A	1 (100.0)	N/A	N/A	1 (100.0)	23.49 (3.38-163.5)	<.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)	.11	1 (5.0)	0.63 (0.08-4.97)	.66	9 (45.0)	1.02 (0.56-1.84)	.96

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; N/A, not applicable (statistically meaningful comparisons not possible because of an insufficient sample size); Ref, reference.

[a] Early identification was defined as positive findings on HBsAg or anti-HBc tests performed before or during the chemotherapy initiation period or anti-HBV therapy before first chemotherapy. Late identification was defined as HBsAg or anti-HBc tests performed after the chemotherapy initiation period.

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

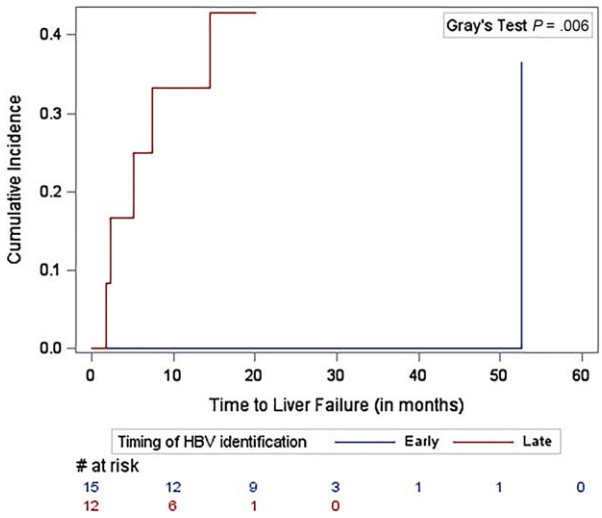

Figure 2. Cumulative incidence of liver failure in chronic HBV patients with solid tumors by the timing of HBV identification. HBV indicates hepatitis B virus.

There was no significant association between the timing of anti-HBV therapy and liver failure (Table 4). However, we found that the timing of HBV identification and the timing of anti-HBV therapy were 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, whereas all 13 chronic HBV patients who had late identification had late/no anti-HBV therapy. Among patients with hematologic malignancies, the risk of a hepatitis flare (HR, 3.13; 95% CI, 1.24-7.92) or hepatic impairment (HR, 5.09; 95% CI, 1.19-21.74) for past HBV patients and the risk of death for chronic HBV patients (HR, 7.82; 95% CI, 1.73-35.27) were significantly higher for persons with late anti-HBV therapy initiation in comparison with those with early anti-HBV therapy initiation (Table 4). Among patients who received rituximab, all 12 with chronic HBV and 31 of 103 with past HBV had early initiation of anti-HBV therapy. For patients with solid tumors, we could not fully evaluate the effect of the timing of anti-HBV therapy on liver failure because of the small numbers of patients.

Among patients with solid tumors, those with chronic HBV had a higher risk of liver failure than those with past HBV (HR, 4.94; 95% CI, 1.82-13.45), and those with late identification of an HBV infection had a higher risk of liver failure than those with early identification (HR, 2.86; 95% CI, 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; 95% CI, 1.10-10.17; Table 5).

DISCUSSION

In this analysis of a large cohort of patients receiving anticancer therapy, we found that late identification of chronic HBV after chemotherapy initiation for solid tumors led to higher risks of adverse liver outcomes in comparison 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. The timing of the identification of an HBV infection was correlated with the timing of anti-HBV therapy, and this suggests that the benefits of early HBV identification could be related to the early use of anti-HBV therapy or to close monitoring and early anti-HBV treatment at the first sign of a hepatitis flare.

Among the more than 15,000 patients in our study who had solid tumors, a chronic HBV infection and the late identification of a chronic or past HBV infection were independent risk factors for liver failure. The late identification of a 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 testing versus late testing on adverse liver outcomes in patients with solid tumors. In one study in which breast, colon, or lung cancer patients were screened before chemotherapy, there were no cases of liver failure among 30 patients with a chronic HBV infection with early HBV testing, of whom 28 had undergone early anti-HBV therapy.[14] In contrast, the rate of liver failure in our study was 6.7% for solid tumor patients with chronic HBV, and it was likely higher because none had early anti-HBV therapy.

Among patients with hematologic malignancies who had HBV testing, more than 90% were tested early. Because of the low numbers for late testing, we did not observe any difference in outcomes between patients with early HBV infection identification and patients with late identification. However, we found a 7.82 (95% CI, 1.73-35.27) times higher risk of death for chronic HBV patients with late/no anti-HBV therapy in comparison with 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 of 15 patients in the prophylaxis group and 1 of 15 in the group that was closely monitored with anti-HBV medication initiated upon an 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 because of less

TABLE 4. Impact of the Timing of Anti-HBV Therapy Initiation on Adverse Liver Outcomes by Cancer Type

Timing of Anti-HBV Therapy Initiation[a]	Total (n = 402)	Hepatitis Flare			Hepatic Impairment			Liver Failure			Death (All Causes)		
		No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b	No. (% of Total)	HR (95% CI)	P^b
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)	.01	13 (44.8)	2.32 (0.87-6.20)	.09	8 (27.6)	1.99 (0.54-7.38)	.30	19 (65.5)	3.28 (1.25-8.59)	.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)	.09	58 (19.2)	2.89 (0.90-9.30)	.08	22 (7.3)	3.12 (0.42-23.37)	.27	123 (40.7)	1.04 (0.63-1.74)	.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)	.09	10 (47.6)	3.42 (0.47-25.03)	.23	6 (28.6)	N/A	N/A	13 (61.9)	1.46 (0.30-7.26)	.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)	.67	18 (12.4)	0.88 (0.14-5.42)	.89	9 (6.2)	N/A	N/A	55 (37.9)	1.20 (0.26-5.55)	.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)	.11	3 (37.5)	1.73 (0.38-7.94)	.48	2 (25.0)	1.40 (0.23-8.56)	.71	6 (75.0)	7.82 (1.73-35.27)	<.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)	.02	40 (25.5)	5.09 (1.19-21.74)	.03	13 (8.3)	2.95 (0.38-22.68)	.30	68 (43.3)	1.16 (0.67-2.00)	.61

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; N/A, not applicable (statistically meaningful comparisons not possible because of an insufficient sample size); Ref, reference.
[a] Early initiation occurred during the chemotherapy initiation period before any adverse liver outcome. Late initiation occurred after the chemotherapy initiation period before or after an adverse liver outcome.
[b] From a univariate Fine and Gray model of the subdistribution hazard with death as a competing risk.

TABLE 5. Model of the Risk of Liver Failure for 402 Patients With Chronic or Past HBV Infections

Parameter	Solid Tumors (n = 181)			Hematologic Malignancies (n = 221)		
	HR (95% CI)	P[a]	P for Overall Effects[a]	HR (95% CI)	P[a]	P for Overall Effects[a]
Age						
18-46 y	4.51 (0.51-40.15)	.18	.13	1.60 (0.30-8.52)	.58	.50
47-55 y	6.27 (0.79-50.06)	.08		2.20 (0.44-11.01)	.34	
56-64 y	0.91 (0.06-14.24)	.95		0.85 (0.13-5.38)	.86	
≥65 y	Ref			Ref		
Sex						
Female	Ref					
Male	10.25 (2.21-47.59)	<.01	<.01			
Type of HBV infection						
Chronic	4.94 (1.82-13.45)	<.01	<.01	3.34 (1.10-10.17)	.03	.03
Past	Ref			Ref		
Timing of HBV identification[b]						
Early	Ref			Ref		
Late	2.86 (0.99-8.24)	.05	.05	1.23 (0.26-5.89)	.79	.79
Initiation of anti-HBV therapy[c]						
Early				Ref		.26
Late/none				1.93 (0.61-6.07)	.26	

Abbreviation: CI, confidence interval; HBV, hepatitis B virus; HR, hazard ratio; Ref, reference.
[a] From a multivariate Fine and Gray model of the subdistribution hazard with death as a competing risk.
[b] Early identification was defined as positive findings on HBsAg or anti-HBc tests performed before or during the chemotherapy initiation period or anti-HBV therapy before first chemotherapy. Late identification was defined as HBsAg or anti-HBc tests performed after the chemotherapy initiation period.
[c] Early initiation occurred during the chemotherapy initiation period before any adverse liver outcome. Late initiation occurred after the chemotherapy initiation period before or after an adverse liver outcome.

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 is the retrospective design, which limited our ability to ascertain whether patients meeting our criteria for liver failure truly had liver failure, to identify the exact etiology of adverse liver outcomes, and to assess adherence to anti-HBV therapy. We were unable to determine the effects of specific chemotherapy on adverse liver outcomes because many patients received more than 1 chemotherapy drug simultaneously or changed treatment regimens over time. Also, HBV DNA testing was not routinely performed, and thus liver outcomes could not be attributed to HBV reactivation. In addition, baseline hepatitis B e antigen and HBV DNA testing was not performed for all patients with a chronic HBV infection, and this limited the impact of the chronic HBV phase on the risk of adverse liver outcomes. Finally, our study represents practice patterns of a single institution, and the findings may not be representative.

In summary, our study demonstrated that among chronic HBV patients, early identification reduced the risk of liver failure for patients with solid tumors, and early anti-HBV therapy reduced all-cause mortality for 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 antivirals in patients with solid tumors.

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AUTHOR CONTRIBUTIONS

Jessica P. Hwang: Conceptualization, methodology, investigation, writing–original draft, and funding acquisition. **Maria E. Suarez-Almazor:** Conceptualization, methodology, investigation, and

writing–review and editing. **Scott B. Cantor:** Writing–review and editing. **Andrea Barbo:** Formal analysis, data curation, and writing–original draft. **Heather Y. Lin:** Formal analysis and writing–review and editing. **Sairah Ahmed:** Investigation and writing–review and editing. **Mariana Chavez-MacGregor:** Writing–review and editing. **Christian Donato-Santana:** Investigation and writing–review and editing. **Cathy Eng:** Writing–review and editing. **Alessandra Ferrajoli:** Writing–review and editing. **Michael J. Fisch:** Writing–review and editing. **Peter McLaughlin:** Writing–review and editing. **George R. Simon:** Writing–review and editing. **Gabriela Rondon:** Writing–review and editing and resources. **Elizabeth J. Shpall:** Writing–review and editing and resources. **Anna S. Lok:** Conceptualization and writing–original draft.

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