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The association of hepatitis B virus screening and antiviral prophylaxis with adverse liver outcomes in Chinese cancer patients undergoing chemotherapy

A retrospective study

Lan-Ying He, MM[a], Yu-Lan Wang, MM[b], Xu Tian, MSN[a], Wei-Qing Chen, MD[a,*]

Abstract

Currently, the association of the initiation time of hepatitis B virus (HBV) screening and antiviral prophylaxis with adverse liver outcomes in cancer patients undergoing chemotherapy remains conflicting.

This retrospective study was designed to determine the association of HBV screening and antiviral prophylaxis with adverse liver outcomes, and then proposed optimal management strategies on HBV screening and antiviral prophylaxis.

We analyzed the medical data of Chinese cancer patients undergoing chemotherapy between 2000 and 2015. Descriptive statistics and Chi square tests were performed to analyze the basic characteristics of patients. Time-to-event analysis was used to determine incidence, and competing risk analysis was used to determine the hazard ratios (HRs) for outcomes.

A total of 12,158 patients (81.1% with solid tumors) were analyzed. Among solid tumors patients, late screening and late antiviral therapy of chronic HBV were associated with higher incidence of hepatitis flare (HR 3.29, 95% confidence interval [CI] 2.26–4.79; HR 6.79, 95% CI 4.42–10.41), hepatic impairment (HR 2.96, 95% CI 2.03–4.32; HR 8.03, 95% CI 4.78–13.48), liver failure (HR 2.19, 95% CI 1.41–3.40; HR 14.81, 95% CI 6.57–33.42), and HBV-related death (HR 3.29, 95% CI 2.26–4.79; HR 8.30, 95% CI 4.95–13.91) in comparison with early screening and early therapy.

Early HBV screening and antiviral therapy could reduce the risk of adverse liver outcomes among chronic HBV patients receiving chemotherapy. Hepatitis B surface antibody-positivity was associated with a decreased risk of liver failure and chronic HBV, late screening or late antiviral therapy were predictors of liver failure for patients with anti-tumor therapy. However, it should be applied cautiously into each types of solid tumors and hematologic malignancies because subgroup analysis according to type of cancer was not designed.

Abbreviations: anti-HBs = hepatitis B surface antibody, CI = confidence interval, HbsAg = hepatitis surface antigen, HBV = hepatitis B virus, HR = hazard ratio.

Keywords: antiviral therapy, chemotherapy, hepatitis B virus, hepatic impairment, hepatitis flare, liver failure

1. Introduction

Hepatitis B virus (HBV) infection remains an extensive healthare problem around the world, since approximately 240 million people show serological evidence of chronic infection (hepatitis B surface antigen [HBsAg] positive), especially in Asia.[1,2] Anti-tumor therapy (chemotherapy, radiotherapy or immunosuppressive therapy) has the potential to cause HBV reactivation through disrupting the immune balance, resulting in severe hepatitis, liver failure, even HBV-related death.[1–3]

HBV screening and antiviral prophylaxis are recommended for cancer patients undergoing chemotherapy to prevent HBV reactivation. These studies are more frequently in hematological tumors than solid tumors.[4–6] However, the guidelines about recommendations of HBV screening and prophylaxis which have no extensive applied still represent a challenge for specialists because of lacking of clinical outcome data.[7] Furthermore, for cancer patients receiving chemotherapy, especially solid tumors patients, the data on the incidence of adverse liver outcomes are very little. Thankfully, a study performed in a European country has demonstrated that early HBV screening correlates with early antiviral prophylaxis and reduces the incidence of liver failure and death in cancer patients receiving chemotherapy.[8,9] To our knowledge, the prevalence of chronic HBV infection in China

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Equal contributors (LYH, YLW and XT).

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[a] *Department of Gastroenterology, Chongqing University Cancer Hospital,* [b] *ChungKing General Hospital, Chongqing, China.*

[*] *Correspondence: Wei-Qing Chen, Department of Gastroenterology, Key Laboratory for Biorheological Science and Technology of Ministry of Education (Chongqing University), Chongqing University Cancer Hospital and Chongqing Cancer Institute and Chongqing Cancer Hospital, 181 Hanyu Road, Shapingba District, Chongqing 400044, China (e-mail: chenwq20140809@163.com).*

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is very high,[10] however, there has not been a study for systematically investigating the effect of timing of HBV screening and antiviral therapy on adverse liver outcomes among Chinese patients undergoing chemotherapy. Therefore, we designed this retrospective study to determine the effect of initiation timing of HBV screening and antiviral therapy on the development of adverse liver outcomes among Chinese cancer patients with chronic, resolved or past HBV infections, in order to design optimal management strategies on HBV screening and antiviral prophylaxis to be incorporated into cancer treatment guidelines.

2. Materials and methods

This study was approved by the Ethical Committee of Chongqing University Cancer Hospital. This was the retrospective design without providing the written informed consent to the patients in this study and the ethics committees approved this consent procedure.

2.1. Patients

We designed this retrospective cohort study in Chongqing University Cancer Hospital based on the medical data which were recorded between 2000 and 2015. Inclusion criteria:

(1) solid tumors or hematologic malignancies patients;
(2) Patients ≥18 years;
(3) Patients received the first administration of chemotherapy in hospital.

Exclusion criteria:

1) Patients with a history of antiviral treatment or chemotherapy;
2) Patients with hepatocellular carcinoma, liver cirrhosis, alcoholic hepatitis, autoimmune liver disease or fatty liver disease;
3) Patients concomitantly infected with hepatitis A virus, hepatitis D virus, hepatitis E virus, human immunodeficiency virus, or hepatitis C virus.

We conducted this study after approval by the Institutional Ethics Committee of Chongqing University Cancer Hospital. Clinical characteristics and data were retrieved from institutional medical record databases.

2.2. Definition of outcome

Chronic HBV infection was defined as HbsAg positive and hepatitis B core antibody (anti-HBc) positive or unknown. Resolved HBV infection was defined as HBsAg negative, anti-HBc positive, and hepatitis B surface antibody (anti-HBs) positive. Past HBV infection was defined as HBsAg negative, anti-HBc positive, and anti-HBs negative or unknown.[11]

Chemotherapy initiation period was defined as the time interval from 2 months before the beginning of the first cycle of chemotherapy to the day before the second cycle of chemotherapy. There was no doubt that the time interval from the first day of the second cycle of chemotherapy to the end of the study was the post-chemotherapy period. If HBV serological markers testing were made at Chongqing University Cancer Hospital before the post-chemotherapy period, we defined as early HBV screening, otherwise, as late screening. If antiviral therapy came into operation before the post-chemotherapy period without any adverse liver outcome, we defined as early antiviral therapy initiation, otherwise, as late therapy.

Adverse liver outcomes included hepatitis flare, hepatic impairment, liver failure, and HBV-related death. Hepatitis flare was defined as 3-fold or greater increase in serum alanine aminotransferase level that exceeded the reference range or an absolute increase of alanine aminotransferase to over 100 U/L during chemotherapy. Hepatitis impairment was defined as the total bilirubin level up to 2.5 mg/dL or an international normalized ratio up to 1.5 on the basis of hepatitis. Liver failure was defined as a hepatitis flare with ascites or hepatic encephalopathy. HBV-related death was defined as patients died with an adverse liver event.[12] We collected liver outcomes during the period from the first day of the second cycle of chemotherapy to 2 years after the last cycle of chemotherapy at Chongqing University Cancer Hospital, last follow-up, or death. If there were no outcomes during the period of studying, patients were censored.

2.3. Statistical analysis

Categorical items were expressed as number (%), and numerical items were expressed as the mean ± standard deviation or median (minimum, maximum; or interquartile range). Numerical data were analyzed using an independent-samples t test. Categorical data were analyzed using the chi square test. All analyses were performed using SPSS 22.0 (IBM, Armonk, NY). Time-to-event analysis was performed to analyze the possible liver outcomes among included patients in different conditions, and competing risk analysis for the hazard of possible liver outcomes was performed to explain the competing risks of death for those who died without any liver outcome with the Fine-Gray model using the software package Stata version 15.[13] In addition, multivariate sub-distribution hazard models were performed to separately determine predictors of liver failure among patients with chronic, resolved or past HBV infections. Covariates included age, sex, type of HBV infection, and timing of HBV screening or antiviral therapy. $P < .05$ was considered statistically significant.

3. Results

A total of 12,158 patients undergoing chemotherapy were included in the retrospective cohort study between 2000 and 2015 (Fig. 1), and female patients were more than male patients (n = 7051, 58.0%; n = 5107, 42%) (Table 1). The mean age of the patients was 54 years, with an age range of 18 to 88 years; 9856 (81.1%) and 2302 (18.9%) cases were solid tumors and hematologic malignancies, respectively. The mean follow-up duration of the patients was 28 months (range, 2.6 - 89.3 months). Overall, among included patients, 9558 (78.6%) had early HBV testing, 835 (6.3%) late. Hematologic malignancy patients showed higher rates of early antiviral therapy compared with those with solid tumors (4.6%, 94 of 2048; 2.3%, 192 of 8345; $P < .05$). Patients with chronic HBV in hematologic malignancies were associated with higher rates of early HBV testing (93.5%, 143 of 153; 91.5%, 479 of 525; $P > .05$), and early antiviral therapy (39.9%, 61 of 153; 30.9%, 162 of 525; $p < 0.05$) compared with those in solid tumors, the former had no statistical significance, while the latter had statistical significance. 327 of 525 chronic HBV patients in solid tumors had serum HBV DNA testing, of which 168 had detectable HBV DNA (>500 IU/mL), and 159 had undetectable HBV DNA (<500 IU/mL).83 of 153 chronic HBV patients in hematologic malignancies had serum HBV DNA testing (52 had detectable HBV DNA, and 31 had undetectable HBV DNA).

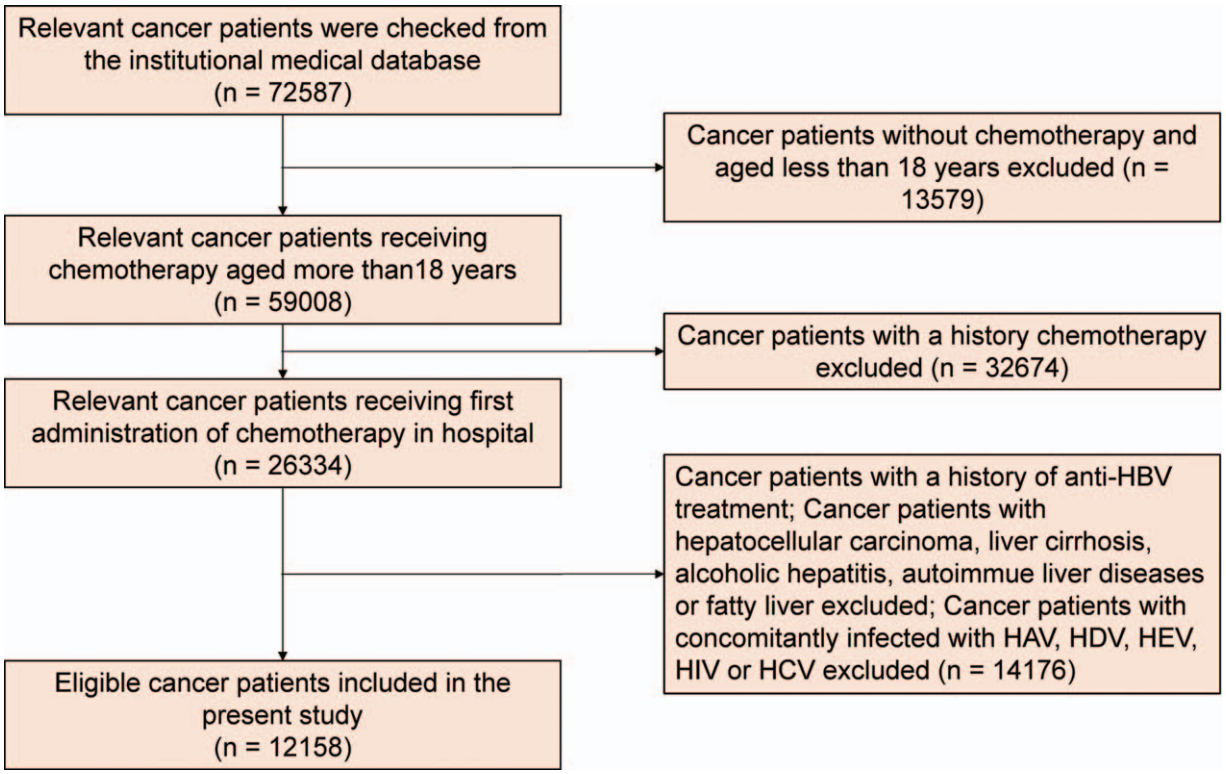

Figure 1. Flow chart showing selection of patients for study.

Overall, the incidence of liver outcomes were higher for HBV-positive patients (chronic HBV, resolved HBV and past HBV) compared with HBV-negative patients, and for patients with late HBV testing compared with those with early testing, but the untested patients either solid tumors or hematologic malignancies was the lowest (Table 2). Meantime, we found that liver outcomes were associated with higher incidence for HBV-positive patients with hematologic malignancy compared with those with solid tumors. For solid tumors or hematologic malignancy patients, the incidence of liver failure was 15.5%, 24.7%, and 6.5% when the HBV was tested early, late and without HBV infection, respectively.

Among the 8345 tested solid tumors patients, the incidence of chronic HBV, resolved HBV and past HBV infection was 6.3% (n = 525), 6.6% (n = 548) and 10.0% (n = 837), respectively. And hematologic malignancy patients had higher incidence of chronic HBV and past HBV infection (n = 153, 7.5%; n = 218, 10.6%), and lower resolved HBV infection (n = 126, 6.2%), compared with those with solid tumors, but there were all no statistical significance ($P > .05$) (Table 3). Among solid tumors patients, late testing of chronic HBV showed higher incidence of hepatitis flare (hazard ratio [HR] 3.29, 95% confidence interval [CI] 2.26–4.79), hepatic impairment (HR 2.96, 95% CI 2.03–4.32), liver failure (HR 2.19, 95% CI 1.41–3.40), and HBV-related death (HR 3.29, 95% CI 2.26–4.79) in comparison with early screening. However, we showed that there was no significant difference in hepatitis flare, hepatic impairment, liver failure, and HBV-related death between late and early screening of resolved HBV (HR 0.52, 95% CI 0.16–1.65; HR 0.79, 95% CI 0.33–1.89; HR 0.24, 95% CI 0.03–1.75; HR 0.52, 95% CI 0.18–1.65) or past HBV (HR 0.79, 95% CI 0.42–1.46; HR 0.91, 95% CI 0.51–1.61; HR 0.98, 95% CI 0.47–2.04; HR 0.79, 95% CI 0.42–1.46). Among 525 chronic HBV patients with solid tumors, 161 (30.7%) patients had liver failure.

For hematologic malignancies patients, we found that there was no significant difference in hepatitis flare, hepatic impairment, liver failure, and HBV-related death between late and early screening of chronic HBV (HR 1.13, 95% CI 0.47–2.73; HR 0.81, 95% CI 0.32–2.09; HR 0.80, 95% CI 0.29–2.22; HR 1.13, 95% CI 0.47–2.73) (Table 3). The effect of timing of HBV testing on liver failure could not be evaluated because of a lack of patients, and there was no significant difference in hepatitis flare, hepatic impairment and HBV-related death between late and early screening of resolved HBV (HR 3.14, 95% CI 0.64–15.38; HR 2.16, 95% CI 0.24–19.41; HR 3.14, 95% CI 0.64–15.38). But among past HBV patients, late screening showed a higher risk of hepatitis flare (HR 2.05, 95% CI 1.03–4.07), hepatic impairment (HR 2.60, 95% CI 1.27–5.34), liver failure (HR 2.83, 95% CI 1.08–7.42), and HBV-related death (HR 2.05, 95% CI 1.03–4.07) compared with those with early. Among the 153 chronic HBV patients with hematologic malignancy, 47 (30.7%) patients had liver failure.

Overall, late antiviral therapy of chronic HBV was significantly associated with a higher risk of hepatitis flare (HR 5.27, 95% CI 3.83–7.25), hepatic impairment (HR 6.65, 95% CI 4.43–9.99), liver failure (HR 10.08, 95% CI 5.64–18.01), and HBV-related death (HR 5.88, 95% CI 4.05–8.53) compared with early therapy (Table 4). However, there was no significant difference in hepatitis flare, hepatic impairment, and HBV-related death between late and early antiviral therapy of resolved HBV (HR

Table 1

Baseline characteristics and clinical data of patients included in the study.

Characteristic	All patients (n = 12158), No. (%)	Solid Tumors (n = 9856)			Hematologic malignancies (n = 2302)		
		HBV status identified (n = 8345), No. (% of All patients)	Total HBV+ (n = 1910), No. (% of Patients with HBV status identified)	Chronic HBV (n = 525), No. (% of patients with HBV status identified)	HBV status identified (n = 2048), No. (% of All patients)	Total HBV+ (n = 497), No. (% of patients with HBV status identified)	Chronic HBV (n = 153), No. (% of patients with HBV status identified)
Age							
18–45yr	3071 (25.2)	2015 (65.6)	363 (18.0)	93 (4.6)	578 (18.5)	113 (19.1)	37 (6.1)
46–55yr	3152 (25.9)	2195 (69.6)	484 (22.1)	161 (7.3)	599 (18.4)	168 (27.3)	53 (8.1)
56–65yr	3046 (25.1)	2051 (67.3)	551 (26.9)	182 (8.9)	505 (16.6)	139 (26.2)	47 (9.5)
66–75yr	2383 (19.6)	1885 (79.1)	474 (25.1)	83 (4.4)	301 (13.)	71 (26.3)	15 (6.8)
≧76y	506 (4.2)	199 (39.3)	38 (19.1)	6 (3.0)	65 (14.8)	6 (20.1)	1 (4.4)
Sex							
Female	7051 (58.0)	4727 (67.0)	894 (18.9)	194 (4.1)	932 (13.2)	198 (21.2)	52 (5.6)
Male	5107 (42.0)	3618 (70.8)	1016 (28.1)	331 (9.1)	1116 (21.9)	299 (26.8)	101 (9.1)
Residence							
Chongqing	9241 (76.0)	6964 (75.3)	1629 (23.4)	452 (6.5)	1465 (15.9)	352 (24.0)	118 (8.1)
Outside Chongqing	2917 (24.0)	1381 (47.3)	281 (20.3)	73 (5.3)	583 (20.0)	145 (24.9)	35 (6.0)
HBV-DNA screening*							
HBV-DNA+	NA	203	203 (100)	168 (82.8)	64	64 (100)	52 (81.3)
HBV-DNA-	NA	393	393 (100)	159 (40.5)	53	53 (100)	31 (58.5)
None	NA	7749	1314 (17.0)	198 (2.6)	1931	380 (19.7)	70 (3.6)
Timing of HBV screening†							
Early	9558 (78.6)	7634 (79.9)	1775 (23.3)	479 (6.3)	1924 (20.1)	462 (24.0)	143 (7.4)
Late	835 (6.9)	711 (85.1)	135 (19.0)	46 (6.5)	124 (14.9)	35 (28.2)	10 (8.1)
No HBV identified	1765 (14.5)	NA	NA	NA	NA	NA	NA
Timing of antiviral therapy initiation‡							
Early	NA	192	192 (100)	162 (84.4)	94	94 (100)	61 (64.9)
Late/None	NA	8153	1718 (21.1)	363 (4.5)	1954	403 (20.6)	92 (4.7)

HBV = hepatitis B virus, HBV+ = the total number of patients with chronic, resolved and past HBV infections, HBV-DNA = hepatitis B virus-desoxyribonucleic acid, IU = international unit, mL = milliampere, NA = not applicable.

* HBV-DNA+ was defined as a greater increase in serum HBV-DNA level that exceeded the reference range (>500 IU/mL); HBV-DNA- was defined as serum HBV-DNA level in the reference range (≤500 IU/mL).

† Early HBV screening was defined as HBV serological markers testing were made before or during the chemotherapy initiation period. Late HBV screening was defined as HBV serological markers testing were made after the chemotherapy initiation period.

‡ Early antiviral therapy initiation was defined as antiviral medications started before or during the chemotherapy initiation period and before any adverse liver outcome.

1.31, 95% CI 0.53–3.24; HR 3.57, 95% CI 0.50–25.30; HR 1.21, 95% CI 0.39–3.73) and the effect of timing of antiviral therapy on liver failure could not be evaluated because of a lack of patients. We also found that there was no significant difference in hepatitis flare, hepatic impairment, liver failure, and HBV-related death of past HBV (HR 1.52, 95% CI 0.86–2.67; HR 2.08, 95% CI 0.79–5.49; HR 4.61, 95% CI 0.66–32.03; HR 2.41, 95% CI 0.93–6.20).

Among solid tumors patients, late antiviral therapy of chronic HBV showed a higher rate of hepatitis flare (HR 6.79, 95% CI 4.42–10.41), hepatic impairment (HR 8.03, 95% CI 4.78–13.48), liver failure (HR 14.81, 95% CI 6.57–33.42), and HBV-related death (HR 8.30, 95% CI 4.95–13.91) compared with early therapy (Table 4). However, there was no significant difference in hepatitis flare and HBV-related death between late and early screening of resolved HBV or past HBV. For resolved HBV or past HBV patients, and the effect of timing of antiviral therapy on liver failure could not be evaluated because of a lack of patients.

For hematologic malignancies patients, we found that late antiviral therapy of chronic HBV showed a significantly higher risk of hepatitis flare (HR 3.54, 95% CI 2.14–5.86, hepatic impairment (HR 4.56, 95% CI 2.30–9.02), liver failure (HR 5.15, 95% CI 2.18–12.20), and HBV-related death (HR 3.53, 95% CI 1.99–6.25) compared with early therapy (Table 4). There was no significant differences in hepatitis flare, hepatic impairment, and HBV-related death between late and early screening of resolved HBV, and the effect of timing of antiviral therapy on liver failure could not be evaluated because of a lack of patients. However, among past HBV patients, we showed that the risk of hepatitis flare (HR, 2.83; 95% CI, 1.35–5.91), hepatic impairment (HR, 3.04; 95% CI, 1.00–9.23) and HBV-related death (HR, 4.52; 95% CI, 1.49–13.73) were significantly higher for late antiviral therapy patients compared with those with early therapy. Unfortunately, there was no obvious association between the timing of antiviral therapy and liver failure among past HBV.

For solid tumors in patients, past HBV infection showed a lower risk of liver failure than chronic HBV (HR 2.77, 95% CI 2.15–3.58), but higher for resolved HBV (HR 0.66, 95% CI 0.46–0.96) (Table 5). For patients with a HBV infection, late screening or antiviral therapy showed a higher risk of liver failure than early screening or therapy (HR 1.61, 95% CI 1.11–2.32; HR 6.26, 95% CI 2.79–14.02). Those between 18 to 45 years old had a lower risk of liver failure than those more than 65 years old (HR 0.44, 95% CI 0.29–0.65). For hematologic malignancy patients, past HBV infection showed a lower risk of liver failure than chronic HBV (HR 1.52, 95% CI

Table 2

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

HBV Status/Timing of HBV screening*	Total No.	Hepatitis flare			Hepatic impairment			Liver failure			Death (HBV-related)		
		No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†
All cancers													
HBV+/early	2237	831 (37.1)	4.94 (4.20–5.82)	<.01	529 (23.6)	5.70 (4.57–7.13)	<.01	347 (15.5)	6.10 (4.58–8.14)	<.01	575 (25.7)	4.73 (3.90–5.73)	<.01
HBV+/late	170	93 (54.7)	7.23 (5.56–9.41)	<.01	64 (37.6)	8.41 (6.07–11.65)	<.01	42 (24.7)	8.40 (5.56–12.70)	<.01	67 (39.4)	7.23 (5.29–9.88)	<.01
HBV−/early or late	7986	1371 (17.2)	1.83 (1.56–2.14)	<.01	812 (10.2)	2.10 (1.70–2.60)	<.01	521 (6.5)	2.31 (1.74–3.05)	<.01	845 (10.6)	1.59 (1.32–1.92)	<.01
HBV status unknown	1765	179 (10.1)	Ref		92 (5.1)	Ref		54 (3.1)	Ref		127 (7.2)	Ref	
Solid tumors													
HBV+/early	1775	592 (33.4)	4.03 (3.37–4.81)	<.01	386 (21.7)	4.85 (3.80–6.20)	<.01	261 (14.7)	5.18 (3.79–7.08)	<.01	392 (22.1)	3.66 (2.97–4.52)	<.01
HBV+/late	135	73 (54.1)	6.13 (4.60–8.18)	<.01	50 (37.0)	7.38 (5.15–10.56)	<.01	33 (24.4)	7.08 (4.48–11.19)	<.01	49 (36.6)	5.73 (4.02–8.16)	<.01
HBV−/early or late	6435	1045 (16.2)	1.65 (1.40–2.00)	<.01	547 (8.5)	1.69 (1.33–2.15)	<.01	367 (5.7)	1.87 (1.38–2.53)	<.01	699 (10.9)	1.53 (1.25–1.86)	<.01
HBV status unknown	1511	154 (10.2)	Ref		78 (5.2)	Ref		47 (3.1)	Ref		112 (7.4)	Ref	
Hematologic malignancies													
HBV+/early	462	239 (51.7)	12.30 (8.08–18.71)	<.01	143 (31.0)	12.03 (6.94–20.84)	<.01	86 (18.6)	13.27 (6.19–28.46)	<.01	183 (39.6)	14.90 (8.67–25.60)	<.01
HBV+/late	35	20 (57.1)	19.92 (10.45–38.0)	<.01	14 (40.0)	20.86 (9.65–45.10)	<.01	9 (25.7)	22.73 (8.51–60.69)	<.01	18 (51.4)	25.73 (12.46–53.1)	<.01
HBV−/early or late	1551	326 (21.0)	3.12 (2.08–4.69)	<.01	265 (17.1)	4.73 (2.77–8.08)	<.01	154 (9.9)	5.60 (2.64–11.89)	<.01	146 (9.4)	2.37 (1.38–4.08)	.002
HBV status unknown	254	25 (9.8)	Ref		14 (5.5)	Ref		7 (2.8)	Ref		15 (5.9)	Ref	

CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio, Ref = reference.

* Early HBV screening was defined as HBV serological markers testing were made before or during the chemotherapy initiation period. Late HBV screening was defined as HBV serological markers testing were made after the chemotherapy initiation period.

† From a univariate Fine-Gray model of the sub-distribution hazard with death for those who died without liver outcomes as a competing risk.

1.01–2.30), but higher for resolved HBV (HR 0.36, 95% CI 0.17–0.77). For patients with a HBV infection, late antiviral therapy showed a higher risk of liver failure than early therapy (HR 3.46, 95% CI 1.61–7.47).

4. Discussion

China is part of the major endemic countries of HBV in the world. The prevalence of chronic HBV infection in the Chinese population is as high as 7% to 15% when compared with 0.2% to 0.5% carrier rate in western countries.[14] With the increasing awareness of HBV reactivation during chemotherapy for cancer patients, incipient screening and antiviral prophylaxis have been recommended gradually in clinical practices.[2,15,16] However, up to now, there is still not an optimal management strategy because of insufficient evidence, especially for solid tumors.

Recent studies have confirmed that patients with HBsAg-positive may show a high risk (range from 15% to 60%) for HBV reactivation during cytotoxic chemotherapy and antiviral prophylaxis could reduce the risk for HBV reactivation, adverse liver event and chemotherapy disruption significantly.[17–19] In our study, we found that late HBV screening showed higher rates of adverse liver outcomes compared with early screening for chronic HBV patients with solid tumors. Additionally, we found that late/no antiviral therapy showed higher rates of adverse liver outcomes than early therapy for chronic HBV patients with solid tumors or hematologic malignancies. A previous study showed that early use of antiviral therapy could be related to early HBV testing, resulting in reducing the rate of liver failure among chronic HBV patients with early testing, which was consistent with our findings.[9] However, for chronic HBV patients in our study, the risk of liver failure was still high, we thought the reason was only a few patients with early HBV screening had early antiviral therapy and no patient receiving late screening. So, we suggest that we need close monitoring or early antiviral treatment as soon as patients with cytotoxic chemotherapy show serological evidence of chronic infection.

At present, no guidelines have recommended to perform universal HBV screening for patients with solid tumors during chemotherapy, because controversies still existed among different associations worldwide. Some studies demonstrated that it was necessary to have early testing and antiviral treatment for this population, even in European areas with a low HBV prevalence.[20–22] However, another study found that universal HBV screening was not cost-effective in patients with solid tumors.[20] Among the patients with solid tumors and chronic HBV in our study, late screening and late/no antiviral therapy showed higher rates of adverse liver outcomes, and the independent risk factors for liver failure were a chronic HBV infection, the late screening and late/no antiviral therapy. We suggest that appropriate HBV screening and antiviral prophylaxis strategy are also needed for patients with solid tumors before or during chemotherapy. In order to determine an optimal screening strategy, future studies should verify the cost-effectiveness of HBV screening before chemotherapy in patients with solid tumors.

In this study, we found that the rates of early HBV screening and antiviral therapy of hematologic malignancy patients were higher than solid tumors. Previous studies have reported that hematologic malignancy patients were more susceptible to HBV reactivation when treated with chemotherapy, likely because of the invading lymphocytes characteristic of HBV virus.[23–25] With

Table 3

Impact of the timing of HBV screening on adverse liver outcomes by cancer type.

Timing of HBV screening*	Total (n = 2407)	Hepatitis flare			Hepatic impairment			Liver failure			Death (HBV-related)		
		No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†	No. (% of Total)	HR (95% CI)	P†
All cancers													
Chronic HBV													
Early	622	295 (47.4)	Ref		236 (37.9)	Ref		180 (28.9)	Ref		248 (39.9)	Ref	
Late	56	47 (83.9)	2.85 (2.04–3.97)	<.01	38 (67.9)	2.41 (1.69–3.45)	<01	28 (50.0)	1.93 (1.28–2.92)	<.01	42 (75.0)	2.86 (2.01–4.07)	<.01
Resolved HBV													
Early	629	148 (23.5)	Ref		79 (12.6)	Ref		48 (7.6)	Ref		84 (13.4)	Ref	
Late	45	12 (26.7)	0.97 (0.55–1.71)	.92	6 (13.3)	0.84 (0.38–1.88)	0.68	1 (2.2)	0.22 (0.03–1.62)	0.14	5 (11.1)	0.68 (0.27–1.72)	0.42
Past HBV													
Early	986	388 (39.4)	Ref		214 (21.7)	Ref		119 (12.1)	Ref		243 (24.6)	Ref	
Late	69	34 (49.3)	1.00 (0.70–1.43)	.99	20 (29.0)	1.10 (0.70–1.73)	0.67	13 (18.8)	1.28 (0.72–2.27)	0.41	20 (29.0)	0.96 (0.60–1.54)	0.88
Solid tumors													
Chronic HBV													
Early	479	209 (43.6)	Ref		176 (36.7)	Ref		137 (28.6)	Ref		178 (37.2)	Ref	
Late	46	39 (84.8)	3.29 (2.26–4.79)	<01	33 (71.7)	2.96 (2.03–4.32)	<01	24 (52.2)	2.19 (1.41–3.40)	<01	35 (76.1)	3.29 (2.26–4.79)	<.01
Resolved HBV													
Early	513	111 (21.6)	Ref		64 (12.5)	Ref		40 (7.8)	Ref		61 (11.9)	Ref	
Late	35	10 (28.6)	0.52 (0.16–1.65)	.27	5 (14.3)	0.79 (0.33–1.89)	0.60	1 (2.9)	0.24 (0.03–1.75)	0.16	3 (8.8)	0.52 (0.18–1.65)	.27
Past HBV													
Early	783	272 (34.7)	Ref		146 (18.6)	Ref		84 (10.7)	Ref		153 (19.5)	Ref	
Late	54	24 (4.4)	0.79 (0.42–1.46)	.45	12 (22.2)	0.91 (0.51–1.61)	0.74	8 (14.8)	0.98 (0.47–2.04)	0.96	11 (20.4)	0.79 (0.42–1.46)	.45
Hematologic malignancies													
Chronic HBV													
Early	143	86 (60.1)	Ref		60 (42.0)	Ref		43 (30.1)	Ref		70 (49.0)	Ref	
Late	10	8 (80.0)	1.13 (0.47–2.73)	.79	5 (50.0)	0.81 (0.32–2.09)	0.67	4 (40.0)	0.80 (0.29–2.22)	0.67	7 (70.0)	1.13 (0.47–2.73)	.79
Resolved HBV													
Early	116	37 (31.9)	Ref		15 (12.9)	Ref		8 (6.9)	Ref		23 (19.8)	Ref	
Late	10	2 (20.0)	3.14 (0.64–15.38)	.16	1 (10.0)	2.16 (0.24–19.41)	0.49	0 (0.0)	NA		2 (20.0)	3.14 (0.64–15.38)	.16
Past HBV													
Early	203	116 (57.1)	Ref		68 (33.5)	Ref		35 (17.2)	Ref		90 (44.3)	Ref	
Late	15	10 (6.7)	2.05 (1.03–4.07)	.04	8 (53.3)	2.60 (1.27–5.34)	<.01	5 (33.3)	2.83 (1.08–7.42)	0.04	9 (60.0)	2.05 (1.03–4.07)	.04

CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio, NA = not applicable, Ref = reference.

* Early HBV screening was defined as HBV serological markers testing were made before or during the chemotherapy initiation period. Late HBV screening was defined as HBV serological markers testing were made after the chemotherapy initiation period.

† From a univariate Fine-Gray model of the sub-distribution hazard with death for those who died without liver outcomes as a competing risk.

Table 4

Impact of the timing of antiviral therapy on adverse liver outcomes by cancer type.

Timing of antiviral screening*	Total (n = 2407)	Hepatitis flare			Hepatic impairment			Liver failure			Death (HBV-related)		
		No. (% of total)	HR (95% CI)	P†	No. (% of total)	HR (95% CI)	P†	No. (% of total)	HR (95% CI)	P†	No. (% of total)	HR (95% CI)	P†
All cancers													
Chronic HBV													
Early	223	41 (18.4)	Ref		25 (11.2)	Ref		12 (5.4)	Ref		30 (13.5)	Ref	
Late	455	301 (66.2)	5.27 (3.83–7.25)	<.01	249 (54.7)	6.65 (4.43–9.99)	<.01	196 (43.1)	10.08 (5.64–18.01)	<.01	260 (57.1)	5.88 (4.05–8.53)	<.01
Resolved HBV													
Early	28	5 (17.9)	Ref		1 (3.6)	Ref		0 (0.0)	Ref		3 (10.7)	Ref	
Late	646	155 (24.0)	1.31 (0.53–3.24)	.56	84 (13.0)	3.57 (0.50–25.30)	0.20	49 (7.6)	NA		86 (13.3)	1.21 (0.39–3.73)	.75
Past HBV													
Early	35	10 (28.6)	Ref		4 (11.4)	Ref		1 (2.9)	Ref		4 (11.4)	Ref	
Late	1020	412 (40.4)	1.52 (0.86–2.67)	.15	230 (22.5)	2.08 (0.79–5.49)	0.14	131 (12.8)	4.61 (0.66–32.03)	0.12	259 (25.4)	2.41 (0.93–6.20)	.07
Solid tumors													
Chronic HBV													
Early	162	22 (13.6)	Ref		15 (9.3)	Ref		6 (3.7)	Ref		15 (9.3)	Ref	
Late/none	363	226 (62.3)	6.79 (4.42–10.41)	<.01	194 (53.4)	8.03 (4.78–13.48)	<.01	155 (42.7)	14.81 (6.57–33.42)	<.01	198 (54.5)	8.30 (4.95–13.91)	<.01
Resolved HBV													
Early	14	2 (14.3)	Ref		0 (0.0)	Ref		0 (0.0)	Ref		1 (7.1)	Ref	
Late/none	534	118 (22.1)	1.50 (0.38–5.94)	.56	69 (12.9)	NA		41 (7.7)	NA		63 (11.8)	1.65 (0.24–11.40)	.61
Past HBV													
Early	16	4 (25.0)	Ref		1 (6.3)	Ref		0 (0.0)	Ref		1 (6.3)	Ref	
Late/none	821	292 (35.6)	1.22 (0.51–2.94)	.65	157 (19.1)	2.74 (0.37–20.55)	0.33	92 (11.2)	NA		163 (19.9)	2.89 (0.44–19.16)	.27
Hematologic malignancies													
Chronic HBV													
Early	61	19 (31.1)	Ref		10 (16.4)	Ref		6 (9.8)	Ref		15 (24.6)	Ref	
Late/none	92	75 (81.5)	3.54 (2.14–5.86)	<01	55 (59.8)	4.56 (2.30–9.02)	<.01	41 (44.6)	5.15 (2.18–12.20)	<.01	62 (67.4)	3.53 (1.99–6.25)	<.01
Resolved HBV													
Early	14	3 (21.4)	Ref		1 (7.1)	Ref		0 (0.0)	Ref		2 (14.3)	Ref	
Late/none	112	36 (32.1)	1.60 (0.48–5.35)	.44	15 (13.4)	1.88 (0.26–13.39)	0.52	8 (7.1)	NA		23 (20.5)	1.60 (0.38–6.80)	.52
Past HBV													
Early	19	6 (31.6)	Ref		3 (15.8)	Ref		1 (5.3)	Ref		3 (15.8)	Ref	
Late/none	199	120 (60.3)	2.83 (1.35–5.91)	<.01	73 (36.7)	3.04 (1.00–9.23)	0.05	39 (19.6)	4.51 (0.64–31.88)	0.13	96 (48.2)	4.52 (1.49–13.73)	<.01

CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio, NA = not applicable, Ref = reference.

* Early antiviral therapy initiation was defined as antiviral medications started before or during the chemotherapy initiation period and before any adverse liver outcome.

† From a univariate Fine-Gray model of the sub-distribution hazard with death for those who died without liver outcomes as a competing risk.

Table 5

Risk of liver failure for 2407 patients with chronic, resolved or past HBV infections.

	Solid tumors (n = 1910)			Hematologic malignancies (n = 497)		
Parameter	HR (95% CI)	P*	P* for overall effects	HR (95% CI)	P*	P* for overall effects
Age						
18–46 yr	0.44 (0.29–0.65)	<.01	.07	1.05 (0.49–2.26)	0.89	.30
47–55 yr	0.77 (0.56–1.05)	.10		1.37 (0.68–2.77)	0.37	
56–65 yr	1.08 (0.81–1.44)	.59		1.84 (0.90–3.78)	0.10	
≧66y	Ref			Ref		
Sex						
Female	Ref			Ref		
Male	1.20 (0.95–1.51)	.12		0.98 (0.66–1.47)	0.94	
Type of HBV infection						
Chronic	2.77 (2.15–3.58)	<.01	<.01	1.52 (1.01–2.30)	0.04	.01
Resolved	0.66 (0.46–0.96)	.03		0.36 (0.17–0.77)	0.01	
Past	Ref			Ref		
Timing of HBV screening†						
Early	Ref			Ref		
Late	1.61 (1.11–2.32)	.01		1.66 (0.85–3.24)	0.14	
Initiation of antiviral therapy‡						
Early	Ref			Ref		
Late/none	6.26 (2.79–14.02)	<.01		3.46 (1.61–7.47)	<.01	

CI = confidence interval, HBV = hepatitis B virus, HR = hazard ratio, Ref = reference.

* From a multivariate Fine-Gray model of the sub-distribution hazard with death for those who died without liver outcomes as a competing risk.

† Early HBV screening was defined as HBV serological markers testing were made before or during the chemotherapy initiation period. Late HBV screening was defined as HBV serological markers testing were made after the chemotherapy initiation period.

‡ Early antiviral therapy initiation was defined as antiviral medications started before or during the chemotherapy initiation period and before any adverse liver outcome.

this high incidence, recurrence of HBV infection in this specific population has drawn global attention. According to the guidelines for the management of HBV infection, HBV incipient screening and antiviral therapy are recommended to prevent HBV reactivation for patients receiving anti-cancer therapy, especially rituximab or hematopoietic stem cell transplantation.[25,26] In our study, 94% were tested early among the hematologic malignancy patients who had HBV testing. However, among the 153 patients with chronic HBV, only 40% had early antiviral therapy, likely because of less dynamic monitoring and antiviral therapy in a timely manner. There was no obvious difference in outcomes between early and late HBV screening in chronic HBV patients. However, we found that late/no antiviral therapy showed higher risks of adverse liver outcomes for chronic HBV patients compared with early therapy. Besides, we found that chronic HBV infection, the late/no antiviral therapy was independent risk factors for liver failure among hematologic malignancy patients. We conclude that we should not only make early HBV testing, but also take early antiviral therapy actively among hematologic malignancy patients.

Patients with resolved or past HBV infection show a high risk of HBV reactivation, particularly those with hematologic malignancy when receiving rituximab-based chemotherapy with reactivation rates ranging from 4.1% to 23.8%.[11,27–29] In our study, a higher rate of adverse liver outcomes was also observed in late testing patients compared to early patients with resolved HBV and past HBV infection, but we could not fully evaluate the effect of the timing of HBV testing on any adverse liver outcome because of the small numbers of patients. So, randomized controlled trial with larger samples and longer term of outcome assessments are needed to detect a significant association. Previous studies have suggested that undetectable anti-HBs titers faced a significantly higher risk of HBV reactivation than did other patients in hematologic malignancies.[30,31] However, whether a positive antibody to anti-HBs protects against reactivation remains uncertain. In our study, we found that a 0.66 (95% CI, 0.46–0.96) times lower risk of liver failure for resolved HBV patients in comparison with those with past HBV infection in solid tumors and 0.36 (95% CI, 0.17–0.77) times in hematologic malignancies. It suggested that anti-HBs positive was associated with a decreased risk of reactivation. So, we suggest that we need close monitoring for patients with anti-HBs negative undergoing chemotherapy.

Our study has several strengths. First, to our knowledge, this is the first study which systematically investigated the impact of timing of HBV screening and antiviral therapy on the development of adverse liver outcomes among patients in a chemotherapeutic setting in a country with a high HBV prevalence. Second, our study included a large number of patients with solid tumors or hematologic malignancies. Furthermore, we provided more important clinical data to design optimal management strategies on HBV screening and antiviral prophylaxis for solid tumors patients undergoing chemotherapy. Lastly, patients were divided into with chronic HBV infection, resolved HBV infection and past HBV infection in our study, and we successfully demonstrated the importance of anti-HBs in HBV serological examination for patients receiving chemotherapy.

However, our study has several limitations. First, this was a retrospective design, we could not be sure of the real situation at that time. Second, included patients in our study might receive 1 or more chemotherapy drug during each course of chemotherapy, change chemotherapy regimens in the middle of the study or receive chemotherapy combined with radiotherapy, so we could not be able to analyze the effects of different chemotherapy regimens on adverse liver outcomes. Third, we could not be able

to analyze the correlation between liver outcomes and HBV reactivation, because HBV DNA screening was not performed for all patients. Finally, our study conducted in a single institution, eventually could affect the overall quality of our study.

In conclusion, our study demonstrated that among chronic HBV patients, early HBV screening reduced the risk of adverse liver outcomes for solid tumors patients, early antiviral therapy reduced adverse liver outcomes for solid tumors or hematologic malignancy patients. We also found that anti-HBs-positivity was associated with a decreased risk of liver failure and chronic HBV, late screening or late antiviral therapy were predictors of liver failure for solid tumors or hematologic malignancy patients. Therefore, we suggested that appropriate HBV screening strategy and antiviral prophylaxis before chemotherapy for patients with confirmed HBsAg positive or those with HBsAg negative, anti-HBc positive and anti-HBs negative. The study provided important knowledge about the risk of adverse liver outcomes in cancer patients with HBV infections who were receiving chemotherapy. Nevertheless, this retrospective cohort study was performed at a single center, prospective cohort studies with a larger sample and longer outcome assessments are needed to support our results. Moreover, the conclusion from the present study should be applied cautiously into each types of solid tumors and hematologic malignancies because subgroup analysis according to type of cancer was not designed.

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Author contributions

Conceptualization: Yu-Lan Wang, Wei-Qing Chen.
Data curation: Yu-Lan Wang, Xu Tian, Lan-Ying He.
Formal analysis: Lan-Ying He, Xu Tian, Yu-Lan Wang.
Investigation: Yu-Lan Wang, Xu Tian, Lan-Ying He.
Methodology: Yu-Lan Wang, Xu Tian.
Project administration: Xu Tian.
Resources: Xu Tian and Lan-Ying He.
Software: Yu-Lan Wang, Xu Tian, Lan-Ying He.
Supervision: Wei-Qing Chen.
Validation: Lan-Ying He and Xu Tian.
Writing – original draft: Xu Tian.
Writing – review & editing: Xu Tian, Wei-Qing Chen.

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