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\textsuperscript{a}, Yu-Lan Wang, MM\textsuperscript{b}, Xu Tian, MSN\textsuperscript{c}, Wei-Qing Chen, MD\textsuperscript{a,}\textsuperscript{∗}

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 4.42–10.14), hepatic impairment (HR 2.96, 95\% CI 2.03–4.32; HR 9.03, 95\% CI 4.78–13.49), 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 healthcare problem around the world, since approximately 240 million people show serological evidence of chronic infection (hepatitis B surface antigen [HbsAg] positive), especially in Asia.\textsuperscript{[1–3]} 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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[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.\textsuperscript{[8,9]} To our knowledge, the prevalence of chronic HBV infection in China
is very high, 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 100U/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; 9836 (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, 9358 (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; \( p < .05 \)) 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).
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

---

**Figure 1.** Flow chart showing selection of patients for study.
Among solid tumors patients, late antiviral therapy of chronic HBV showed a higher rate of hepatitis flare, hepatic impairment, liver failure, and HBV-related death than chronic HBV (HR 1.52, 95% CI 0.50–25.30; HR 0.44, 95% CI 0.29–0.65). For hematologic malignancies patients, past HBV infection showed a lower rate of liver failure than chronic HBV (HR 2.77, 95% CI 1.00–9.23) but higher for resolved HBV (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 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).

### Table 1
Baseline characteristics and clinical data of patients included in the study.

| Characteristic | All patients (n = 12158), No. (%) | Hematologic malignancies (n = 2302) |
|---------------|---------------------------------|-----------------------------------|
| Age           |                                 |                                   |
| 18–45yr       | 5071 (25.2)                     | 112 (4.9)                         |
| 46–55yr       | 3152 (25.9)                     | 99 (4.8)                          |
| 56–65yr       | 3046 (25.1)                     | 81 (4.0)                          |
| 66–75yr       | 2383 (19.6)                     | 58 (2.6)                          |
| Å76y          | 506 (4.2)                       | 12 (0.5)                          |
| Sex           |                                 |                                   |
| Female        | 7051 (58.0)                     | 156 (6.8)                         |
| Male          | 5107 (42.0)                     | 175 (7.6)                         |
| Residence     |                                 |                                   |
| Chongqing     | 9241 (76.0)                     | 192 (8.4)                         |
| Outside Chongqing | 2917 (24.0)       | 220 (9.6)                         |
| HBV-DNA screening† |                            |                                   |
| HBV-DNA+      | NA                              | 203 (100)                         |
| HBV-DNA-      | 393 (39.0)                      | 100 (50.0)                        |
| None          | 7749 (75.3)                     | 100 (50.0)                        |
| Timing of HBV screening† |                      |                                   |
| Early         | 9558 (78.6)                     | 7634 (79.9)                       |
| Late          | 835 (6.9)                       | 711 (85.1)                        |
| No HBV identified | 1765 (14.5)       | NA                                |
| Timing of antiviral therapy initiation‡ |                    |                                   |
| Early         | NA                              | 192 (100)                         |
| Late/None     | 8153 (67.0)                     | 1718 (21.1)                       |

### Table 2
Baseline characteristics and clinical data of patients included in the study.

| Characteristic | All patients (n = 8345), No. (%) | Hematologic malignancies (n = 2048) |
|---------------|---------------------------------|-----------------------------------|
| Age           |                                 |                                   |
| 18–45yr       | 5071 (25.2)                     | 112 (4.9)                         |
| 46–55yr       | 3152 (25.9)                     | 99 (4.8)                          |
| 56–65yr       | 3046 (25.1)                     | 81 (4.0)                          |
| 66–75yr       | 2383 (19.6)                     | 58 (2.6)                          |
| Å76y          | 506 (4.2)                       | 12 (0.5)                          |
| Sex           |                                 |                                   |
| Female        | 7051 (58.0)                     | 156 (6.8)                         |
| Male          | 5107 (42.0)                     | 175 (7.6)                         |
| Residence     |                                 |                                   |
| Chongqing     | 9241 (76.0)                     | 192 (8.4)                         |
| Outside Chongqing | 2917 (24.0)       | 220 (9.6)                         |
| HBV-DNA screening† |                            |                                   |
| HBV-DNA+      | NA                              | 203 (100)                         |
| HBV-DNA-      | 393 (39.0)                      | 100 (50.0)                        |
| None          | 7749 (75.3)                     | 100 (50.0)                        |
| Timing of HBV screening† |                      |                                   |
| Early         | 9558 (78.6)                     | 7634 (79.9)                       |
| Late          | 835 (6.9)                       | 711 (85.1)                        |
| No HBV identified | 1765 (14.5)       | NA                                |
| Timing of antiviral therapy initiation‡ |                    |                                   |
| Early         | NA                              | 192 (100)                         |
| Late/None     | 8153 (67.0)                     | 1718 (21.1)                       |

### Table 3
Baseline characteristics and clinical data of patients included in the study.

| Characteristic | All patients (n = 8345), No. (%) | Hematologic malignancies (n = 2048) |
|---------------|---------------------------------|-----------------------------------|
| Age           |                                 |                                   |
| 18–45yr       | 5071 (25.2)                     | 112 (4.9)                         |
| 46–55yr       | 3152 (25.9)                     | 99 (4.8)                          |
| 56–65yr       | 3046 (25.1)                     | 81 (4.0)                          |
| 66–75yr       | 2383 (19.6)                     | 58 (2.6)                          |
| Å76y          | 506 (4.2)                       | 12 (0.5)                          |
| Sex           |                                 |                                   |
| Female        | 7051 (58.0)                     | 156 (6.8)                         |
| Male          | 5107 (42.0)                     | 175 (7.6)                         |
| Residence     |                                 |                                   |
| Chongqing     | 9241 (76.0)                     | 192 (8.4)                         |
| Outside Chongqing | 2917 (24.0)       | 220 (9.6)                         |
| HBV-DNA screening† |                            |                                   |
| HBV-DNA+      | NA                              | 203 (100)                         |
| HBV-DNA-      | 393 (39.0)                      | 100 (50.0)                        |
| None          | 7749 (75.3)                     | 100 (50.0)                        |
| Timing of HBV screening† |                      |                                   |
| Early         | 9558 (78.6)                     | 7634 (79.9)                       |
| Late          | 835 (6.9)                       | 711 (85.1)                        |
| No HBV identified | 1765 (14.5)       | NA                                |
| Timing of antiviral therapy initiation‡ |                    |                                   |
| Early         | NA                              | 192 (100)                         |
| Late/None     | 8153 (67.0)                     | 1718 (21.1)                       |
### Table 2

| Impact of the HBV status on adverse liver outcomes by cancer type. |
|---------------------------------------------------------------|
| **Hepatitis are Hepatic impairment Liver failure Death (HBV-related)** |
| **Total** | **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)** |
| All cancers | HBV+/early | 2237 | 831 (37.1) | 4.94 (4.20–5.82) | <.01 | 7.13 (4.58–11.65) | 6.01 (4.02–9.36) | <.01 | 575 (25.7) | 4.73 (3.90–5.73) | <.01 | 347 (15.5) | 6.10 (4.58–8.14) | <.01 |
| | HBV+/late | 1775 | 592 (33.4) | 4.03 (3.37–4.69) | <.01 | 395 (21.7) | 4.85 (3.86–6.00) | <.01 | 261 (14.7) | 5.18 (3.79–7.11) | <.01 | 143 (8.5) | 2.30 (1.11–4.83) | .01 |
| | HBV status unknown | 1765 | 179 (10.1) | Ref | | 92 (5.1) | Ref | | 54 (3.1) | Ref | | 127 (7.2) | Ref | |
| Hematologic malignancies | HBV+/early | 462 | 239 (51.7) | 12.30 (6.09–23.71) | <.01 | 142 (31.0) | 12.03 (6.29–22.18) | <.01 | 68 (14.6) | 13.37 (6.12–30.64) | <.01 | 81 (18.1) | 14.39 (3.93–56.09) | <.01 |
| | HBV+/late | 35 | 20 (57.1) | 19.92 (10.45–38.04) | <.01 | 9 (25.7) | 22.73 (8.55–64.69) | <.01 | 18 (51.4) | 25.73 (11.83–56.69) | <.01 | 14 (4.3) | 18.81 (4.46–83.64) | .01 |
| | HBV status unknown | 1551 | 296 (19.1) | 3.12 (2.08–4.69) | <.01 | 125 (7.9) | 4.73 (2.77–8.08) | <.01 | 154 (9.9) | 5.60 (2.64–11.89) | <.01 | 19 (11.9) | 2.37 (1.38–4.08) | <.01 |

**Q**-coefficient indicates HBV positivity. R-coefficient indicates HBV-related or related to the chemotherapy initiation period.

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. With the increasing awareness of HBV reactivation during chemotherapy for cancer patients, incipient screening and antiviral prophylaxis have been recommended gradually in clinical practices. 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. 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. 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. However, another study found that universal HBV screening was not cost-effective in patients with solid tumors.

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 antiviral prophylaxis could reduce the risk for HBV reactivation, adverse liver event and chemotherapy disruption significantly. 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. With
| Timing of HBV screening | Total (n = 2407) | Hepatitis flare | Hepatic impairment | Liver failure | Death (HBV-related) |
|------------------------|-----------------|-----------------|-------------------|-------------|------------------|
|                        | No. (% of Total) | HR (95% CI)     | No. (% of Total)  | HR (95% CI) | No. (% of Total)  | HR (95% CI) |
| All cancers            |                 |                 |                   |             |                 |             |
| Chronic HBV            |                 |                 |                   |             |                 |             |
| Early                  | 622             | 295 (47.4)      | 236 (37.9)        | 180 (28.9)  | 248 (39.9)      |
| Late                   | 56              | 47 (83.9)       | 37 (67.9)         | 28 (50.0)   | 42 (75.0)       |
| Resolved HBV           |                 |                 |                   |             |                 |             |
| Early                  | 629             | 148 (23.5)      | 79 (12.6)         | 48 (7.6)    |                 |
| Late                   | 45              | 12 (26.7)       | 6 (13.3)          | 1 (2.2)     |                 |
| Past HBV               |                 |                 |                   |             |                 |             |
| Early                  | 986             | 388 (39.4)      | 214 (21.7)        | 119 (12.1)  | 243 (24.6)      |
| Late                   | 69              | 34 (49.3)       | 20 (29.0)         | 13 (18.3)   | 20 (29.0)       |
| Solid tumors           |                 |                 |                   |             |                 |             |
| Chronic HBV            |                 |                 |                   |             |                 |             |
| Early                  | 479             | 203 (42.6)      | 176 (36.7)        | 137 (28.6)  | 178 (37.2)      |
| Late                   | 46              | 33 (68.4)       | 33 (71.7)         | 24 (52.2)   | 35 (76.1)       |
| Resolved HBV           |                 |                 |                   |             |                 |             |
| Early                  | 513             | 111 (21.6)      | 64 (12.3)         | 40 (7.8)    |                 |
| Late                   | 35              | 10 (23.6)       | 5 (14.3)          | 1 (2.9)     |                 |
| Past HBV               |                 |                 |                   |             |                 |             |
| Early                  | 783             | 272 (34.7)      | 146 (18.6)        | 84 (10.7)   | 153 (19.5)      |
| Late                   | 54              | 24 (44.3)       | 12 (22.2)         | 8 (14.8)    | 11 (20.4)       |
| Hematologic malignancies|                |                 |                   |             |                 |             |
| Chronic HBV            |                 |                 |                   |             |                 |             |
| Early                  | 143             | 86 (60.1)       | 60 (42.0)         | 43 (30.1)   | 70 (49.0)       |
| Late                   | 10              | 8 (80.0)        | 5 (50.0)          | 4 (40.0)    | 7 (70.0)        |
| Resolved HBV           |                 |                 |                   |             |                 |             |
| Early                  | 116             | 37 (31.9)       | 15 (12.9)         | 8 (6.9)     | 23 (19.8)       |
| Late                   | 10              | 2 (20.0)        | 1 (10.0)          | 0 (0.0)     | 2 (20.0)        |
| Past HBV               |                 |                 |                   |             |                 |             |
| Early                  | 203             | 116 (57.1)      | 68 (33.9)         | 35 (17.2)   | 90 (44.3)       |
| Late                   | 15              | 10 (6.7)        | 8 (53.3)          | 5 (33.3)    | 9 (60.0)        |

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

1Early 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.

2From a univariate Fine-Gray model of the sub-distribution hazard with death 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) |  |  |  |  |  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 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 | (11.2) | Ref | <.01 | 25 | (11.2) | Ref | <.01 | 12 | (5.4) | Ref | <.01 | 30 | (12.5) | Ref | <.01 |
| Late | 455 | (66.2) | 5.27 (3.83–7.25) | <.01 | 249 | (54.7) | 6.65 (4.43–9.90) | <.01 | 249 | (54.7) | 6.65 (4.43–9.90) | <.01 | 240 | (55.7) | 5.28 (3.81–7.37) | <.01 |
| Resolved HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 28 | (17.9) | Ref | .56 | 4 | (11.4) | Ref | .56 | 1 | (2.9) | Ref | .56 | 4 | (11.4) | Ref | .56 |
| Late | 1020 | (40.4) | 1.52 (0.86–2.67) | .15 | 230 | (22.9) | 2.08 (0.79–5.49) | .15 | 131 | (12.8) | 4.61 (0.66–32.03) | .15 | 259 | (25.4) | 2.41 (0.93–6.20) | .15 |
| Past HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 35 | (28.6) | Ref | .56 | 4 | (11.4) | Ref | .56 | 1 | (2.9) | Ref | .56 | 4 | (11.4) | Ref | .56 |
| Late | 1020 | (40.4) | 1.52 (0.86–2.67) | .15 | 230 | (22.9) | 2.08 (0.79–5.49) | .15 | 131 | (12.8) | 4.61 (0.66–32.03) | .15 | 259 | (25.4) | 2.41 (0.93–6.20) | .15 |
| Solid tumors |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chronic HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 162 | (13.6) | Ref | <.01 | 15 | (9.3) | Ref | <.01 | 6 | (3.7) | Ref | <.01 | 15 | (9.3) | Ref | <.01 |
| Late/none | 363 | (29.2) | 6.79 (4.42–10.41) | <.01 | 194 | (53.4) | 8.03 (4.78–13.48) | <.01 | 194 | (53.4) | 8.03 (4.78–13.48) | <.01 | 198 | (54.5) | 8.30 (4.95–13.91) | <.01 |
| Resolved HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 14 | (14.3) | Ref | .56 | 0 | (0.0) | Ref | .56 | 0 | (0.0) | Ref | .56 | 1 | (7.1) | Ref | .56 |
| Late/none | 534 | (22.1) | 1.50 (0.38–5.94) | .56 | 69 | (12.9) | NA | .56 | 69 | (12.9) | NA | .56 | 62 | (11.8) | 1.65 (0.24–11.40) | .61 |
| Past HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 16 | (25.0) | Ref | .56 | 1 | (6.3) | Ref | .56 | 1 | (6.3) | Ref | .56 | 1 | (6.3) | Ref | .56 |
| Late/none | 821 | (35.6) | 1.22 (0.51–2.94) | .65 | 157 | (19.1) | 2.74 (0.37–20.55) | .65 | 92 | (11.2) | NA | .65 | 163 | (19.9) | 2.89 (0.44–19.16) | .27 |
| Hematologic malignancies |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chronic HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 61 | (31.1) | Ref | <.01 | 10 | (16.4) | Ref | <.01 | 6 | (9.8) | Ref | <.01 | 15 | (24.6) | Ref | <.01 |
| Late/none | 92 | (58.9) | 3.54 (2.14–5.86) | <.01 | 53 | (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 | (31.4) | Ref | .44 | 1 | (7.1) | Ref | .44 | 0 | (0.0) | Ref | .44 | 2 | (14.3) | Ref | .44 |
| Late/none | 112 | (32.1) | 1.60 (0.48–5.35) | .44 | 15 | (13.4) | 1.88 (0.56–6.39) | .44 | 8 | (7.1) | NA | .44 | 23 | (20.5) | 1.60 (0.38–6.80) | .52 |
| Past HBV |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Early | 19 | (31.6) | Ref | <.01 | 3 | (15.8) | Ref | <.01 | 1 | (5.3) | Ref | <.01 | 3 | (15.8) | Ref | <.01 |
| Late/none | 199 | (60.3) | 2.83 (1.35–5.91) | <.01 | 73 | (36.7) | 3.04 (1.00–9.23) | <.01 | 39 | (19.6) | 4.51 (0.64–31.88) | <.01 | 90 | (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.
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 range from 4.1% to 2.3%. [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 chemotherapy 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

### Table 5

| Parameter                  | Solid tumors (n = 1910) | Hematologic malignancies (n = 497) |
|----------------------------|------------------------|-----------------------------------|
|                            | HR (95% CI)            | P for overall effects              | HR (95% CI)            | P for overall effects              |
| Age                        |                        |                                   |                        |                                   |
| 18–46 yr                   | 0.44 (0.29–0.65)       | <.01                              | 1.05 (0.49–2.26)       | 0.89                              |
| 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                              |
| ≥66 yr                     | Ref                    |                                   | Ref                    |                                   |
| Sex                        |                        |                                   |                        |                                   |
| Female                     | 1.20 (0.95–1.51)       | .12                               | 0.90 (0.66–1.47)       | 0.94                              |
| Male                       | Ref                    |                                   | Ref                    |                                   |
| Type of HBV infection      |                        |                                   |                        |                                   |
| Chronic                    | 2.77 (2.15–3.58)       | <.01                              | 1.52 (1.01–2.30)       | 0.04                              |
| 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‡ | 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.
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.

Acknowledgments

All authors would like to thank the patients and the supporting staff members in this study.

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.

References

[1] Illidan R. The summarized of EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Turk J Gastroenterol 2017;28:412–6.
[2] Paul S, Saxena A, Terrin N, et al. Hepatitis B virus reactivation and prophylaxis during solid tumor chemotherapy: a systematic review and meta-analysis. Ann Intern Med 2016;164:30–40.
[3] Su YC, Lin PC, Yu HC, et al. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. Eur J Clin Pharmacol 2018;74:1111–9.
[4] Jaillais A, Herber-Mayne A, D’Alteroche L, et al. HBV infection: screening and treatment for oncology patients. Bull Cancer 2018;105:162–70.
[5] Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology 2017;152:1297–309.
[6] Wu YT, Li X, Liu ZL, et al. Hepatitis B virus reactivation and antiviral prophylaxis during lung cancer chemotherapy: a systematic review and meta-analysis. PLoS One 2017;12:e0179680.
[7] Bessone F, Dorfman M. Management of hepatitis B reactivation in immunosuppressed patients: An update on current recommendations. World J Hepatol 2016;8:385–94.
[8] Genc L, Casillas A, Seregard CA, et al. Hepatitis B prevalence, risk factors, infection awareness and disease knowledge among inmates: a cross-sectional study in Switzerland’s largest pre-trial prison. J Glob Health 2018;8:020407.
[9] Hwang JP, Suarez-Almazor ME, Cantor SB, et al. 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. Cancer 2017;123:3367–76.
[10] Wembaum CM, Williams I, Matt EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008;57(RR-8):1–20.
[11] Paul S, Dickstein A, Saxena A, et al. Role of surface antibody in hepatitis B reactivation in patients with resolved infection and hematologic malignancy: A meta-analysis. Hepatology (Baltimore, Md) 2017;66:378–88.
[12] Yeo W, Chan PK, Zhong S, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000;62:299–307.
[13] Beyersmann J, Schumacher M. Time-dependent covariates in the proportional subdistribution hazards model for competing risks. Biostatistics 2008;9:765–76.
[14] Lv JW, Chen YP, Huang XD, et al. Hepatitis B virus screening and reactivation and management of patients with nasopharyngeal carcinoma: a large-scale, big-data intelligence platform-based analysis from an endemic area. Cancer 2017;123:3540–9.
[15] Liu Z, Jiang L, Liang G, et al. Hepatitis B virus reactivation in breast cancer patients undergoing chemotherapy: a review and meta-analysis of prophylaxis management. J Viral Hepat 2017;24:561–72.
[16] Ludwig E, Cohen N, Papanicolaou GA, et al. Screening and prevention of hepatitis B virus reactivation during chemotherapy. Oncology (Williston Park) 2015;29:937.
[17] Coluccio G, Begini P, Marzano A, et al. Hepatitis B in patients with hematological diseases: an update. World J Hepatol 2017;9:1043–53.
[18] Karaca M, Tural D, Akar E, et al. Hepatitis B reactivation rate is higher among HBsAg positive patients undergoing chemotherapy and hematologic malignancies: a network meta-analysis. PloS One 2017;12:e0179680.
[19] Li H, Zhang HM, Chen LF, et al. Prophylactic lamivudine to improve the outcome of HBsAg-positive lymphoma patients during chemotherapy: a systematic review and meta-analysis. Clin Res Hepatol Gastroenterol 2015;39:80–92.
[20] Day FL, Link E, Thursky K, et al. Current hepatitis B screening practices and clinical experience of reactivation in patients undergoing chemotherapy for solid tumors: a nationwide survey of medical oncologists. J Oncol Pract 2011;7:141–7.
[21] Federico A, Brancaccio G, Dalloro M, et al. Reactivation of hepatitis B virus in cancer patients treated with chemotherapy for solid tumors. Is the prophylaxis really required? Dig Liver Dis 2017;49:197–201.
[22] Xu Z, Dai W, Wu YT, et al. Prophylactic effect of lamivudine on chemotherapy-induced hepatitis B virus reactivation in patients with solid tumour: A meta-analysis. Eur J Cancer Care 2018;27:e12799.
[23] Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. Ann Oncol 2011;22:1170–80.
[24] Law MF, Lai HK, Chan HN, et al. The impact of hepatitis B virus (HBV) infection on clinical outcomes of patients with diffuse large B-cell lymphoma. Eur J Cancer Care (Engl) 2015;24:117–24.
[25] Lu S, Xu Y, Mu Q, et al. The risk of hepatitis B virus reactivation and the role of antiviral prophylaxis in hepatitis B surface antigen negative/ hepatitis B core antibody positive patients with diffuse large B-cell lymphoma receiving rituximab-based chemotherapy. Leuk Lymphoma 2015;56:1027–32.
[26] Zhang MY, Zhu GQ, Zheng JN, et al. Nucleos(t)ide analogues for prophylaxis really required? Dig Liver Dis 2017;49:197–201.
[27] Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus infection.
reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765–72.

[28] Matsubara T, Nishida T, Shimoda A, et al. The combination of anti-HBc and anti-HBs levels is a useful predictor of the development of chemotherapy-induced reactivation in lymphoma patients with resolved HBV infection. Oncol Lett 2017;14:6343–52.

[29] Zappulo E, Nicolini LA, Di Grazia C, et al. Efficacy of lamivudine prophylaxis in preventing hepatitis B virus reactivation in patients with resolved infection undergoing allogeneic SCT and receiving rituximab. Infection 2019;47:59–65.

[30] Cho Y, Yu SJ, Cho EJ, et al. High titers of anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patient with non-Hodgkin’s lymphoma. J Med Virol 2016;88:1010–7.

[31] Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. J Clin Oncol 2014;32:3736–43.