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ORIGINAL ARTICLE

High hepatitis B virus screening rate among patients receiving systemic anticancer treatment in Japan

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Abstract

Background Patients with hepatitis B virus (HBV) infection have a risk of reactivation after chemotherapy. All patients undergoing chemotherapy should be screened for HBV infection. No large-scale studies have been conducted to examine HBV screening practice in Japan.

Methods We analyzed health insurance claims equivalent data linked with a nationwide hospital-based cancer registry. Patients diagnosed with cancer in 2014, who were aged 20 years and older and those who underwent systemic anticancer treatment in 2014–15 were included. We assessed the HBV screening rates by the HBsAg or anti-HBc tests, HBV-DNA tests, and entecavir prescriptions. Multiple logistic regression models were used to identify factors related to the receipt of screening.

Results Of 177,597 patients (mean [SD] age, 65.6 [12.2] years), 82.6% and 12.9% patients had a solid tumor and hematologic malignancy, respectively. Among them, 88.1%, 6.3%, and 5.5% received cytotoxic chemotherapy, targeted therapy, and anti-CD20 antibodies, respectively. Overall, 70.6% of patients were screened. The positive predictor of HBV screening was receiving anti-CD20 antibodies [odds ratio (OR); 2.23, 95% confidence interval (CI) 2.06–2.41, $p < 0.001$] and negative predictors were age ≥ 85 (OR 0.76, 95% CI 0.71–0.81), age 75–84 (OR 0.77, 95% CI 0.75–0.79) and targeted therapy (OR 0.69, 95% CI 0.67–0.72). Among the screened patients, 13.2% were tested for HBV-DNA, and 1.49% were prescribed entecavir.

Conclusions The HBV screening rate in Japan is higher than in other countries. Further improvement of the HBV screening rate is needed to prevent reactivation and avoidable deaths of patients with HBV infection.

Keywords Universal screening · Hepatitis B virus · Entecavir · Hepatitis B reactivation

Introduction

Patients with hepatitis B virus (HBV) infection have a risk of reactivation when receiving systemic anticancer treatment. The incidence of reactivation after chemotherapy is 20–50% in patients with chronic HBV infection (positive hepatitis B surface antigen [HBsAg]) and 0.3–9.0% in patients with resolved HBV infection (negative HBsAg and positive hepatitis B core antibody [anti-HBc]) [1–3]. The reactivation of HBV may delay systemic anticancer therapy and lead to severe hepatitis, liver failure, and death. After the development of serious hepatitis B due to reactivation, the mortality was high at 16–47%, even though antiviral therapy was used [2, 4]. The efficacy of antiviral prophylaxis before chemotherapy has been established. A recent meta-analysis has shown that prophylactic antiviral reduced reactivation by 88% in patients with chronic HBV infection receiving solid tumor chemotherapy [3]. Antiviral prophylaxis can be started only after we identify HBV-infected patients and about 40% of patients with HBV infection were unaware of their infection at the time of cancer diagnosis [5]. Therefore, appropriate screening is the most crucial step to prevent death from HBV reactivation.

The guideline published in 2013 by the Japanese Society of Hepatology recommended that all patients receiving chemotherapy should be screened for HBV infection [6]. For prophylactic administration of antivirals, entecavir is recommended for HBsAg positive patients. Patients with a negative HBsAg screening and positive anti-HBc should be screened using HBV-DNA levels, and prophylactic antivirals

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should be administered if HBV-DNA levels are ≥ 2.1 log copies/mL on pretreatment screening. These recommendations are consistent with other national and international guidelines [7–9].

Despite the national and international recommendations, previous reports showed that the HBV screening rate was as low as 14–16% in Western countries [10–12]. Although the prevalence of HBV infection is higher in Asia than in Western countries, only 17–27% of patients received HBV screening in Asian countries [13, 14]. Because it is well known that the prevalence of HBV infection is higher in Asia [15], practice patterns may be different from those in Western countries. Our study aimed to investigate the HBV screening rate in patients who received systemic anticancer therapy using a Japanese nationwide database including data from designated cancer hospitals.

Patients and methods

Data source

We extracted the data from the national database of a hospital-based cancer registry combined with the health insurance claims equivalent data. This data was collected for evaluating the quality of care for patients with cancer. A total of 424 hospitals joined the project and most of the participating hospitals were among cancer care hospitals designated by the Ministry of Health, Labour and Welfare, Tokyo, Japan. This National Database of the Hospital-based Cancer Registries is estimated to cover 67% of the new cancer cases in 2011 [16]. The health insurance claims equivalent data were derived from Diagnosis-Procedure Combination survey data. This survey data are not insurance claims per se, but collect all the information on all billable health services provided to the patients in parallel with the per-diem reimbursement insurance claims. We call the data "claims equivalent", because the survey data mimics the fee-for-service claims. Data for patients diagnosed with cancer in 2014 and the health services provided from October 1, 2013 through December 31, 2015 were used in this study. Patients diagnosed with cancer who were aged 20 and older and received at least one dose of systemic cancer treatment were analyzed. Age, sex, cancer type, and regions were obtained from a hospital-based cancer registry.

We categorized the cancer type into non-hepatocellular carcinoma (HCC) solid tumor, hematologic malignancy, and HCC using the International Classification of Diseases for Oncology, third edition (ICD-O-3) code. We identified claims for systemic anticancer agents. The list of these agents in this study is shown in Table 1. We classified systemic anticancer agents as cytotoxic chemotherapy, targeted therapy, anti-CD20 antibody, and immunotherapy.

Table 1 List and classification of systemic anticancer agents

Classification	Drugs
Cytotoxic chemotherapy	Tegafur, etoposide, fluorouracil, tegafur/gimeracil/oteracil, tegafur/uracil, capecitabine, melphalan, carbuquone, cyclophosphamide, procarbazine, mitobronitol/dbm, carmofur, methotrexate, doxilfluridine, busulfan, mercaptopurine, hydroxycarbamide, cytarabine, sobuzoxane, carboplatin, cisplatine, nedaplatin, mitomycin c, vinblastine, zinostatin stimalamer, oxaliplatin, fludarabine, epirubicin, l-asparaginase, doxorubicine, idarubicin, amurubicin, mitoxantrone, nimustine, enocitabine, ifosfamide, vindesine sulfate, cylocide, dacarbazine, ranimustine, paclitaxel, pirarubicin, bleomycin, temozolomide, pemetrexed, fludarabine, aclarubicin, daunorubicin, nogitecan, peplomycin, nelarabine, irinotecan, actinomycin d, pentostatin, enocitabine, docetaxel, miriplatin, vinorelbine, gemcitabine, bendamustine, azacitidine, eribulin, tipiracil hydrochloride, cabazitaxel, streptozocin, trabectedin, cladribine, nitrogen mastard, thiotepa, zinostatin, carmustine, trastuzumab emtansine, brentuximab vedotin, gemtuzumab ozogamicin
Targeted therapy	Tretinoin, imatinib, gefitinib, erlotinib, afatinib, sorafenib, sunitinib, cetuximab, panitumumab, thalidomide, vorinostat, dasatinib, nilotinib, bosutinib, trastuzumab, pertuzumab, lapatinib, tamibarotene, bortezomib, bevacizumab, ramucirumab, lenalidomide, pomalidomide, everolimus, temsirolimus, sirolimus, mogamulizumab, crizotinib, alectinib, axitinib, pazopanib, regorafenib, ruxolitinib, alemtuzumab, vemurafenib, lenvatinib, vandetanib, panobinostat
Anti-CD20 antibody	Rituximab, ofatumumab
Immunotherapy	Ipilimumab, nivolumab, celmoleukin, teceleukin

Low-molecular-weight compounds and antibody drugs were included in targeted therapy. Immunotherapy included ipilimumab, nivolumab, celmoleukin, and teceleukin. We excluded hormone therapy. When a patient received more than one systemic anticancer agents concurrently within 30 days from the first date of systemic treatment, we determined the group based on the anti-cancer drug with the highest risks for reactivation. We consider that the risk of reactivation is highest for anti-CD20 antibody, followed by cytotoxic chemotherapy, targeted therapy, and immunotherapy in order. This study was approved by the institutional review board at the National Cancer Center in Japan.

Owing to the retrospective nature of the database analysis, the requirement for informed consent was waived.

Statistical analysis

The primary outcome was the HBV screening rates among all patients receiving at least one dose of systemic anticancer treatment. We defined patients who underwent HBV screening as those who were tested for HBsAg or anti-HBc from 8 weeks before to 4 weeks after the first dose of systemic anticancer treatment. We also assessed the proportion of HBV-DNA tests and entecavir prescriptions to patients who received HBV screening tests during the appropriate period. To compare the characteristics of patients who were screened with those who were not, we used *t* tests for continuous values and the Chi-squared exact test for categorical variables. Logistic regression models were used to assess the relationship of the HBV test with age (< 65 vs. 65–74 vs. 75–84 vs. > 85), sex (male vs. female), cancer type (non-HCC solid tumor vs. hematologic malignancy vs. HCC), treatment type (cytotoxic chemotherapy vs. targeted therapy vs. anti-CD20 antibody vs. immunotherapy), hospital type (prefecture designated hospitals vs. others), and regions (Hokkaido vs. Tohoku vs. Kanto vs. Koshinetsu vs. Hokuriku vs. Tokai vs. Kinki vs. Chugoku vs. Shikoku vs. Kyusyu) in Japan. All tests were considered significant if the two-sided *p* value was < 0.05. Analyses were performed with Stata software (version; 15.1; StataCorp, College Station, TX).

Results

Overall, 177,597 patients who received at least one dose of systemic anticancer treatment were identified (Table 2). The mean [standard deviation, SD] age was 65.6 [12.2] years and 99,164 (55.8%) were men. For cancer type, 146,671 (82.6%), 22,936 (12.9%), and 7990 (4.5%) patients had non-HCC solid tumor, hematologic malignancy, and HCC, respectively. Among them, 156,418 (88.1%), 11,202 (6.3%), 9,757 (5.5%), and 184 (0.1%) received cytotoxic chemotherapy, targeted therapy, anti-CD20 antibodies, and immunotherapy, respectively.

HBV screening rate and prescription of entecavir

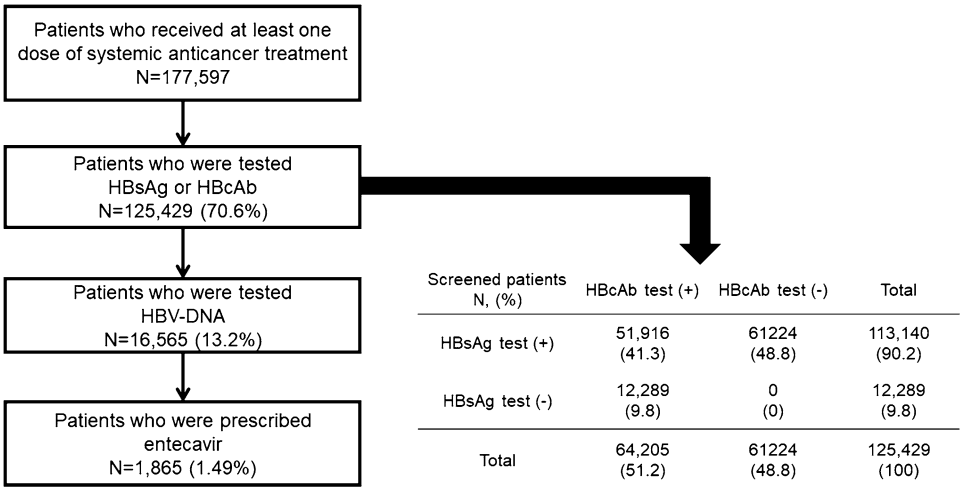
Of the 177,597 patients who underwent systemic anticancer treatment, 125,429 (70.6%) received either HBsAg or anti-HBc screening. The patients with hematologic malignancy and patients treated with anti-CD20 antibody had high screening rates (84.4% and 90.2%, respectively). Among the patients who received screening tests, 13.2% (16,565 of 125,429) were tested for HBV-DNA, which suggests screening tests were positive (HBsAg-positive or HBsAg-negative/anti-HBc-positive). Moreover, 1.49% (1865 of 125,429) of patients were prescribed entecavir, which is a prophylactic antiviral treatment. These patients were considered to be at high risk of reactivation (HBsAg-positive or HBsAg-negative/anti-HBc-positive/HBV-DNA-positive).

Among the patients who received HBV screening tests, 41.3% (51,916 of 125,429) were screened using both HBsAg and anti-HBc (Fig. 1). The use of HBsAg alone and anti-HBc alone was 48.8% (61,224 of 125,429) and 9.8% (12,289 of 125,429), respectively. Of patients who had the HBsAg test, 45.9% (51,916 of 113,140) received an anti-HBcAb test. Among patients who had an HBcAb test, 80.8% (51,916 of 64,205) received an HBsAg test.

Table 2 Patient characteristics

	Screening (−)	Screening (+)	*p* value
Number, (%)	52,168 (29.4)	125,429 (70.6)	
Age, *n* (%)			
< 65	19,330 (27.3)	51,565 (72.7)	< 0.001
65–74	19,229 (30.0)	44,970 (70.0)	
75–84	12,094 (32.1)	25,561 (67.9)	
> 85	1515 (31.3)	3333 (68.7)	
Sex, *n* (%)			
Male	28,434 (28.7)	70,730 (71.3)	< 0.001
Female	23,734 (30.3)	54,669 (69.7)	
Cancer type, *n* (%)			
Non-HCC solid tumor	45,752 (31.2)	100,919 (68.8)	< 0.001
Hematologic malignancy	3587 (15.6)	19,349 (84.4)	
HCC	2829 (35.4)	5161 (64.6)	
Treatment type, *n* (%)			
Cytotoxic chemotherapy	47,051 (30.1)	109,367 (69.9)	< 0.001
Targeted therapy	4076 (36.4)	7126 (63.6)	
Anti-CD20 antibody	959 (9.8)	8798 (90.2)	
Immunotherapy	50 (27.2)	134 (72.8)	
Hospital type, *n* (%)			
Prefecture designated hospitals	9564 (28.0)	24,622 (72.0))	< 0.001
Others	42,604 (29.7)	100,807 (70.3	
Region, *n* (%)			
Hokkaido	2090 (28.6)	5216 (71.4)	< 0.001
Tohoku	4643 (29.9)	10,912 (70.2)	
Kanto	15,962 (30.9)	35,684 (69.1)	
Koshinetsu	2852 (34.4)	5433 (65.6)	
Hokuriku	1885 (32.4)	3929 (67.6)	
Tokai	4477 (26.5)	12,414 (73.5)	
Kinki	8465 (27.8)	21,981 (72.2)	
Chugoku	4025 (29.0)	9840 (71.0)	
Shikoku	2496 (29.7)	5900 (70.3)	
Kyusyu	5269 (27.2)	14,106 (72.8)	

HCC hepatocellular carcinoma



Screened patients N, (%)	HBcAb test (+)	HBcAb test (-)	Total
HBsAg test (+)	51,916 (41.3)	61224 (48.8)	113,140 (90.2)
HBsAg test (-)	12,289 (9.8)	0 (0)	12,289 (9.8)
Total	64,205 (51.2)	61224 (48.8)	125,429 (100)

Fig. 1 Hepatitis B virus serologic tests used for screening among patients who received systemic anti-cancer treatment. *HBsAg* hepatitis B surface antigen, *anti-HBc* hepatitis B core antibody

Predictors of HBV screening

In the multiple logistic regression analysis (Table 3), the treatment of anti-CD20 antibodies was the strongest positive predictor for HBV screening [odds ratio (OR); 2.23, 95% confidence interval (CI) 2.06–2.41, $p < 0.001$]. Hematologic malignancy (compared to non-HCC solid tumor, OR; 1.98, 95% CI 1.89–2.06, $p < 0.001$) and prefecture-designated cancer care hospitals (compared to other hospitals, OR; 1.11, 95% CI 1.08–1.14, $p < 0.001$) were also positively associated with HBV screening. Targeted therapy (compared to cytotoxic chemotherapy, OR; 0.69, 95% CI 0.67–0.72, $p < 0.001$) and HCC (compared to non-HCC solid tumor, OR; 0.85, 95% CI 0.81–0.89, $p < 0.001$) were negatively associated with screening. The odds of HBV screening decreased with increasing patient age (compared with age < 65 years, age 65–74, OR 0.87, 95% CI 0.85–0.89, $p < 0.001$; age 75–84, OR 0.77, 95% CI 0.75–0.79, $p < 0.001$; age ≥ 85, OR 0.76, 95% CI 0.71–0.81, $p < 0.001$). A regional difference in HBV screening was observed. Compared with the Kanto area, the odds of screening were lowest in the Koshinetu area (OR; 0.84, 95% CI 0.80–0.89, $p < 0.001$) and highest in the Tokai area (OR; 1.25, 95% CI 1.20–1.30, $p < 0.001$).

Discussion

To our knowledge, this is the largest study to describe HBV screening practice in Japan. In our study, 70.6% of patients underwent HBV screening before receiving systemic anticancer treatment. Patients with hematologic malignancy were more likely to be screened than those with solid tumors. In contrast, patients who received targeted therapy were less likely to be screened than patients who received cytotoxic chemotherapy.

The HBV screening rate in our study was consistent with that of a previous report using the claims database of Japan Medical Data Center. Ikeda et al. showed that 66.3% of patients received an HBsAg test before chemotherapy [17]. However, patients aged ≥ 60 years were only 26% of total patients, because the database of Japan Medical Data Center consists of only current workers and families. Sixty percent of patients included in our study were over 65 years old, which was based on the actual situation in Japan. Moreover, in our study, the diagnosis of cancer was derived from cancer registries. Since the reportability to cancer registries is strictly defined by the registry rules, the diagnoses are expected to be much more accurate than diagnoses on insurance claims.

The screening rate in Japan was higher than that reported in other countries. At the MD Anderson Cancer Center in the USA, only 16.2% of patients were screened at the onset of chemotherapy [18]. The rate of screening was similarly low even in reports from the Mayo Clinic (16%) [10] and the University of Toronto (14%) [11]. Although the prevalence of HBV infection is higher in Asia than in Western countries, low screening rates have been reported. Only 17% of patients received HBV screening in China [14], and 27% in Taiwan [13]. The definition of HBV screening was different for each study, although the majority of guidelines recommended screening with HBsAg and anti-HBc. Even if we use the definition of HBV screening as tests for both HBsAg and anti-HBc, 29.2% (51,916 of 177,597) of patients were screened, and this is still higher than the previous report [12–14].

One possible explanation for the high screening rate is the awareness of the high prevalence of chronic or resolved HBV infection in Japan, as well as in other Asian countries. In Japan, 1–3% of patients receiving chemotherapy are HBsAg positive, and 17–25% are anti-HBc- and/or anti-HBs-positive [2]. While in the United States, the infection rate is less

Table 3 Predictors of HBV screening test in logistic regression analysis

	Univariate analysis OR	95% CI	*p* value	Multivariate analysis OR	95% CI	*p* value
Age,						
< 65	Ref	–	–	Ref	–	–
65 – 74	0.88	0.86–0.90	< 0.001	0.87	0.85–0.89	< 0.001
75 – 84	0.79	0.77–0.81	< 0.001	0.77	0.75–0.79	< 0.001
> 85	0.82	0.77–0.88	< 0.001	0.76	0.71–0.81	< 0.001
Sex						
Male	Ref	–	–	Ref	–	
Female	0.93	0.91–0.95	< 0.001	0.90	0.88–0.92	< 0.001
Cancer type						
Non-HCC solid tumor	Ref	–	–	Ref	–	–
Hematologic malignancy	2.44	2.36–2.54	< 0.001	1.98	1.89–2.06	< 0.001
HCC	0.83	0.79–0.87	< 0.001	0.85	0.81–0.89	< 0.001
Treatment type						
Cytotoxic chemotherapy	Ref	–	–	Ref	–	–
Targeted therapy	0.75	0.72–0.78	< 0.001	0.69	0.67–0.72	< 0.001
Anti-CD20 antibody	3.95	3.69–4.33	< 0.001	2.23	2.06–2.41	< 0.001
Immunotherapy	1.15	0.83–1.60	0.391	1.20	0.87–1.67	0.269
Hospital type						
Prefecture designated hospitals	1.09	1.06–1.12	< 0.001	1.11	1.08–1.14	< 0.001
Others	Ref	–	–	Ref	–	–
Region						
Hokkaido	1.12	1.06–1.18	< 0.001	1.16	1.09–1.22	< 0.001
Tohoku	1.05	1.01–1.09	0.012	1.05	1.00–1.09	0.028
Kanto	Ref	–	–	Ref	–	–
Koshinetsu	0.85	0.81–0.89	< 0.001	0.84	0.80–0.89	< 0.001
Hokuriku	0.93	0.88–0.99	0.018	0.92	0.87–0.98	0.09
Tokai	1.24	1.19–1.29	< 0.001	1.25	1.20–1.30	< 0.001
Kinki	1.16	1.13–1.20	< 0.001	1.20	1.16–1.24	< 0.001
Chugoku	1.09	1.05–1.14	< 0.001	1.09	1.05–1.14	< 0.001
Shikoku	1.06	1.01–1.11	0.030	1.05	0.99–1.10	0.083
Kyusyu	1.20	1.15–1.24	< 0.001	1.19	1.14–1.23	< 0.001

HCC, Hepatocellular carcinoma; OR, odds ratio; CI, confidence interval

than 1% for chronic HBV infection (HBsAg-positive) and 5–8% for resolved HBV infection (HBsAg-negative/anti-HBc-positive) [12]. Another explanation is that universal screening of HBV for patients with cancer is routine in our daily practice, unlike in the USA [5]. We routinely order the HBsAg test for patients with cancer on their first visit to the hospital. This practice pattern also explains why only 46% of patients who had the HBsAg test received the anti-HBcAb test. These patients might not have received the HBsAg test as appropriate screening.

We found that 13.2% of patients with HBV screening were tested for HBV-DNA. Japanese guidelines recommend that HBV-DNA should be measured in patients who are HBsAg-positive or HBsAg-negative/anti-HBc-positive. According to the prevalence of chronic and resolved HBV infection in Japan, around 20% of patients are expected to receive HBV-DNA testing before chemotherapy. Our results were not far from this assumption. Moreover, our guidelines recommend that antiviral drugs should be administered for patients who are HBsAg-positive or HBs-negative/anti-HBc-positive/HBV-DNA-positive. Given that 1–3% of patients with cancer are HBsAg-positive in Japan, the rate of 1.49% for prophylactic entecavir prescription in our study was reasonable.

For cancer type, the odds of screening were about 2.0 times greater for patients with hematologic malignancy than for those with non-HCC solid tumor in multivariate analysis. Previous reports also showed this trend [10–12, 17]. This may be related to the fact that oncologists are aware of the high risk of reactivation in patients with hematologic

malignancy, because anti-CD20 antibody and high-dose glucocorticoids are frequently used for these patients.

For treatment type, the odds of screening for patients who received targeted therapy were 30% lower than that of patients who received cytotoxic chemotherapy. Because the evidence is lacking about the risk of HBV reactivation with targeted therapy, oncologists are less aware of the potential risk of reactivation. However, HBV reactivation has been reported in patients who received everolimus, mammalian target of rapamycin (mTOR) inhibitor [19, 20], or tyrosine kinase inhibitors (TKIs) including imatinib [21], erlotinib [22], and ibrutinib [23]. Although the mechanism and prevalence of HBV reactivation induced by these targeted therapies remain unclear, an HBV screening test is endorsed in patients receiving targeted treatment [24].

We also found that the odds of screening were decreased with increasing patient age. This may be related to a decrease in the screening rate, because aggressive systemic chemotherapy is not performed in elderly patients. Although a previous report showed that HBV reactivation was less likely to develop in older patients [25], it remains inconclusive. More careful screening is desired for elderly patients. Interestingly, although no huge difference in HBV screening rates was observed between prefecture designated hospitals and others, the HBV screening rate differed according to region. We must promote the equal improvement of the quality of medical care throughout Japan.

There are limitations to our study. First, medical information at other facilities was not included in our data. If the patient received their HBV screening test at an institution different from the data extraction institution, we could not capture the data of the HBV screening test. Second, the claims data do not contain the results of the HBV screening test and HBV-DNA test. Therefore, we did not evaluate whether entecavir was appropriately prescribed for patients with a high risk of reactivation (HBsAg-positive or HBsAg-negative/anti-HBc-positive/HBV-DNA-positive) and whether the HBV-DNA test was correctly ordered for patients with positive HBV screening results. Finally, we could not assess the impact of national and Japanese guidelines, because we extracted data for 1 year after the guidelines were published.

In conclusion, this study showed a high HBV screening rate before systemic anticancer treatment in Japan. This result is in sharp contrast to previous reports in other countries. Further improvement of the HBV screening rate especially in Asia is needed to prevent reactivation and avoidable deaths of patients with HBV infection.

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Compliance with ethical standards

Conflict of interest The authors received no funding support. There are no conflicts of interest to report.

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