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Incidence of Hepatitis B Virus Reactivation in Patients Treated With Immunosuppressive and Chemotherapeutic Agents

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ABSTRACT

Background: Data on the incidence of hepatitis B virus reactivation (HBVr) remain limited. In Japan, patients who are HBsAg-negative and anti-HBc-positive with undetectable HBV DNA are monitored without antiviral prophylaxis, allowing the estimation of HBVr incidence.

Methods: Using administrative claims data from Japan (2008–2022), we included patients receiving immunosuppressive or chemotherapeutic agents who were HBV DNA-negative at baseline, underwent at least two HBV DNA tests, and did not receive antiviral therapy. HBVr incidence was estimated and stratified according to AGA guideline–based risk categories.

Results: We analysed 9422 patients. In the high-risk category, HBVr incidence was 52.3 per 1000 person-years (PY) (95% CI: 37.7–70.7) after anti-CD20 therapy and 46.5 per 1000 PY (95% CI: 15.1–108.5) after other high-risk agents. In the moderate-risk category, incidence was 21.0 per 1000 PY (95% CI: 8.4–43.2) after anthracycline derivatives, 12.1 per 1000 PY (95% CI: 4.9–25.0) after tyrosine kinase inhibitors, and 21.0 per 1000 PY (95% CI: 11.5–35.2) after moderate- to high-dose corticosteroids for ≥ 4 weeks. Low-dose or short-term corticosteroids were also associated with HBVr (12.4 per 1000 PY; 95% CI: 9.0–16.6). HBVr also occurred at 12.5 per 1000 PY (95% CI: 2.6–36.6) following other uncertain-risk immunosuppressive agents, including calcineurin inhibitors.

Conclusions: HBVr incidence was quantified across a broad range of immunosuppressive and chemotherapeutic therapies, including those with previously limited incidence data. The observed incidence patterns were broadly consistent with current guideline-based risk stratification, while also highlighting measurable risk in some therapies traditionally considered lower risk.

Abbreviations: AGA, American Gastroenterological Association; ALT, alanine aminotransferase; APASL, Asian-Pacific Association for the Study of the Liver; CAR T, chimeric antigen receptor T cell; cccDNA, covalently closed circular DNA; CI, confidence interval; DPC, Diagnosis Procedure Combination; EASL, European Association for the Study of the Liver; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation; HSCT, haematopoietic stem cell transplantation; ICD-10, International Classification of Diseases, 10th Revision; IQR, interquartile range; JAK, Janus kinase; NUC, nucleotide analog; PCR, polymerase chain reaction; PSL, prednisolone; PY, person-years; SOT, solid organ transplantation; TKI, tyrosine kinase inhibitor; TNF, tumour necrosis factor.

1 | Introduction

The World Health Organization estimated that 254 million people worldwide were living with chronic hepatitis B virus (HBV) infection in 2022 [1]. Beyond active HBV carriers, HBV reactivation (HBVr) can occur even in individuals with resolved HBV infection during or after immunosuppressive therapies, sometimes resulting in severe or fatal hepatitis flares [2]. This risk persists because once HBV enters hepatocytes, its circular DNA is converted into covalently closed circular DNA (cccDNA), making complete viral eradication difficult.

The risk of HBVr varies substantially across immunosuppressive agents [2–5], with B cell–depleting therapies such as rituximab associated with the highest risks [6, 7]. HBV serostatus further modifies this risk, as individuals who are HBsAg-positive are more vulnerable than those who are HBsAg-negative. In 2025, the American Gastroenterological Association (AGA) updated its HBVr guidelines for the first time since 2014, classifying immunosuppressive and anticancer agents into three risk categories: high (> 10%), moderate (1%–10%), and low (< 1%) for HBsAg-positive and HBsAg-negative patients separately [3]. Antiviral prophylaxis is recommended for high- and moderate-risk groups, while HBV DNA monitoring is advised for low-risk patients. Similarly, the European Association for the Study of the Liver (EASL) and the Asian-Pacific Association for the Study of the Liver (APASL) recommend antiviral prophylaxis with nucleoside/nucleotide analogs (NUCs) in high-risk cases [4, 8]. For HBsAg-negative patients in the moderate- to low-risk groups without advanced fibrosis or cirrhosis, alanine aminotransferase (ALT) levels are monitored every 3 months [8].

In contrast, the Japanese HBV reactivation guidelines adopt a distinct approach, recommending antiviral therapy for all patients who are HBsAg-positive, regardless of risk category. For patients who are HBsAg-negative, even in the high-risk group, regular HBV DNA monitoring every 1–3 months and preemptive antiviral therapy are advised [9]. Notably, the Japanese guidelines also include immunosuppressive agents and chemotherapies classified as having uncertain HBVr risk.

Although HBVr risk has been well characterized in patients receiving rituximab or tumour necrosis factor (TNF) inhibitors [3, 6, 7, 10], data remain limited for many other agents, including corticosteroids and newer immunosuppressants. Against this background, data from Japan can provide a comprehensive assessment of the incidence of HBVr in HBsAg-negative patients who did not receive antiviral prophylaxis. Moreover, most previous studies have reported HBVr risk as a proportion, which may be appropriate for short-term treatments such as chemotherapy, whereas incidence-based measures are more suitable for long-term immunosuppressive therapy in chronic conditions such as connective tissue diseases. In addition, because multiple immunosuppressive agents are often used concurrently, evaluating risk periods and estimating incidence for individual agents may yield more precise risk assessments.

This study aimed to evaluate the incidence of HBVr associated with a broad range of immunosuppressive and anticancer agents, including those classified as having uncertain-risk, in patients not receiving antiviral prophylaxis using a nationwide large-scale hospital-based administrative claims database in Japan.

2 | Methods

2.1 | Study Populations

This study adhered to the RECORD guidelines [11]. We conducted a retrospective cohort study using administrative claims data from the Medical Data Vision [12]. This database includes data from 432 hospitals, representing approximately 27% of Japan's Diagnosis Procedure Combination (DPC) hospitals. Between April 1, 2008, and December 31, 2022, 42.32 million people had visit records in these hospitals. The DPC system is a case-mix reimbursement system, and DPC hospitals are typically medium- to large-sized centers providing most inpatient care in Japan. The database contains both inpatient and outpatient information, including diagnoses, prescribed medications, procedures, and laboratory tests. Records are generated for reimbursement claims, which helps ensure data accuracy. Laboratory results, such as HBV DNA and alanine aminotransferase (ALT) levels, are available for approximately 10% of hospitals. However, patient tracking is limited to a single institution, and follow-up ends when patients transfer to another facility.

We analysed the data from patients with available laboratory results. The inclusion criteria were as follows: (1) receipt of at least two HBV DNA tests, and (2) a negative result at the first HBV DNA test. Patients who received antiviral therapy before HBV DNA positivity were excluded. We also excluded individuals whose treatment risk periods did not overlap with the observation window.

2.2 | Definition of HBV Reactivation, Related Hepatitis, and Appropriate Monitoring

HBV DNA levels were quantified using real-time polymerase chain reaction (PCR), with positivity defined as > 20 IU/mL [9]. HBVr was defined as the first occurrence of a positive HBV DNA test during the observation period. For patients with HBVr, we examined whether subsequent antiviral treatment was initiated and whether hepatitis had occurred. Hepatitis was defined as an ALT level of ≥ 100 IU/L in the absence of alternative causes of baseline elevation. This threshold has been commonly used in prior studies and is broadly consistent with guideline-based definitions, in which a hepatitis flare due to HBVr is defined as an elevation in serum ALT to at least three times the baseline level [3], despite variability across studies and among institutions. Because assessment of the temporal relationship between HBVr and ALT elevation may require clinical judgment, all cases of hepatitis were reviewed and independently confirmed by both a board-certified hepatologist (KO) and an infectious disease specialist (KI).

In addition, we performed exploratory sensitivity analyses using higher HBV DNA thresholds to evaluate the robustness of our primary definition. Because preemptive antiviral therapy is

commonly initiated at low-level HBV DNA positivity (≥20 IU/mL) in Japan, we used composite definitions incorporating HBV DNA thresholds (>100 and >1000 IU/mL) or initiation of antiviral therapy.

2.3 | Risk Classification of Each Treatment Agent

HBsAg test results were unavailable in the database. However, in a large blood donor study using highly sensitive nucleic acid amplification testing with confirmatory assays, only 2 of 272 HBsAg-positive individuals (0.7%) had undetectable HBV DNA, indicating that HBsAg positivity among HBV DNA–negative individuals is rare and likely negligible for the purposes of this analysis [13]. Furthermore, because the Japanese HBV treatment guidelines recommend preemptive antiviral therapy for all patients who are HBsAg-positive and undergoing immunosuppressive therapy [9], we assumed that most patients included in this study were HBsAg-negative. Accordingly, risk categories were defined based on the 2025 AGA guidelines for HBsAg-negative patients [3] (Table S2).

The high-risk category (Group A) comprised patients receiving B-cell-depleting therapies, with anti-CD20 antibodies (e.g., rituximab and obinutuzumab) evaluated separately from other high-risk agents (e.g., belimumab and daratumumab).

The moderate-risk category (Group B) included anthracycline derivatives, anti-T cell therapies (e.g., abatacept); tyrosine kinase inhibitors (TKIs) (e.g., imatinib, sunitinib); cytokine/integrin inhibitors (e.g., ustekinumab, secukinumab); anti-IL-6 antibodies (e.g., tocilizumab); chimeric antigen receptor T-cell (CAR-T) therapy; and Janus kinase (JAK) inhibitors (e.g., tofacitinib, baricitinib). In addition, moderate- or high-dose corticosteroid therapy administered for more than 4 weeks was classified as moderate risk. Prednisolone (PSL) equivalents of <10 mg/day were defined as low dose, 10–20 mg/day as moderate dose, and ≥20 mg/day as high dose.

The low-risk category (Group C) included anti-TNF agents (e.g., infliximab), immune checkpoint inhibitors (ICIs), low-dose corticosteroids or corticosteroids administered for ≤4 weeks, including intra-articular corticosteroids, and antimetabolites (methotrexate, 6-mercaptopurine, and azathioprine).

The uncertain-risk category (Group D) included other immunosuppressive agents (e.g., tacrolimus and cyclosporine), chemotherapeutic agents, and monoclonal antibodies (e.g., mogamulizumab). In the 2025 AGA guidelines, transarterial chemoembolization is classified as a moderate-risk therapy, and direct-acting antivirals are classified as low risk for HBV reactivation [3]. However, because these therapies were not managed under the same framework as immunosuppressive agents in earlier AGA guidelines [14] or in the Japanese guidelines [9], they were excluded from the current analysis.

In accordance with the AGA guidelines [14], immunosuppression related to solid organ transplantation (SOT) and haematopoietic stem cell transplantation (HSCT) was not included in the risk classification. Patients were censored at the time a diagnosis or procedure code indicating SOT or HSCT first appeared in the database.

2.4 | Definitions of the Observation Period of Each Patient and the Risk Period for Each Agent

The observation period was defined as the time from the first HBV DNA test to the last HBV DNA test, or the time when HBV DNA became positive, whichever came first.

During follow-up, the risk period for HBVr was defined according to the treatment risk category, extending to 365 days after the last administration for Group A (high-risk, anti-CD20–based therapy) [15] and to 182 days for Groups B–D (moderate-, low-, and uncertain-risk therapies) [3, 9]. Overlapping periods were assigned to the highest-risk category (Figure 1).

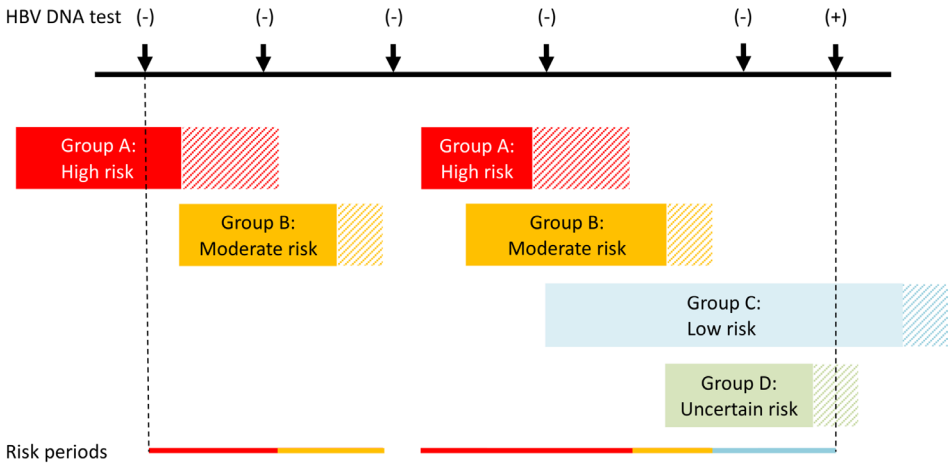

FIGURE 1 | Example timeline for classifying risk periods. Black arrows indicate HBV DNA test results; coloured bars indicate the administration of the risk agents; shaded coloured bars indicate the follow-up period at risk of HBV reactivation. The observation period for each patient was defined as the period from the date of the first HBV DNA test to the date of the last test or the date of HBV reactivation, whichever came first. When multiple immunosuppressive agents with different risk categories were administered concurrently, the observation period was classified according to the highest applicable risk category.

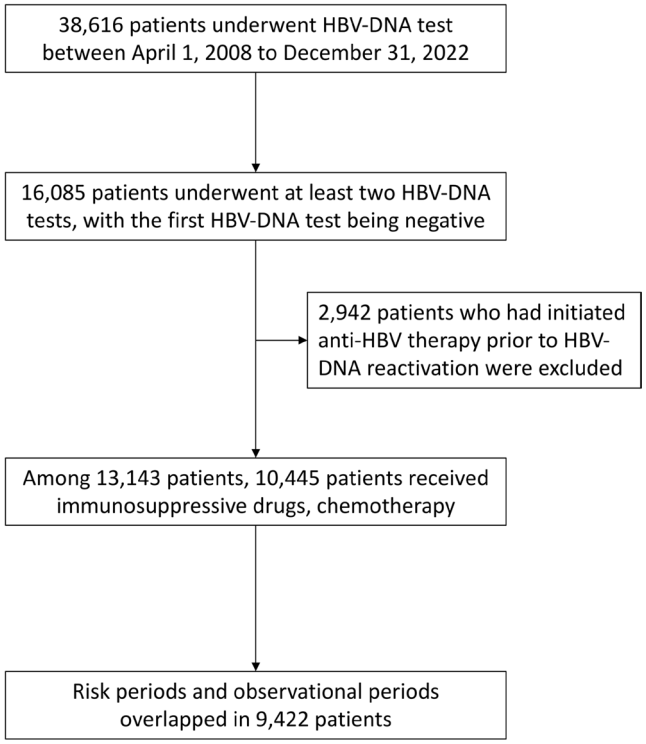

FIGURE 2 | Study flow chart. HBV, hepatitis B virus.

TABLE 1 | Patient characteristics.

Baseline characteristics	*n* = 9422
Age, year	71 (64–77)
Male	52.9% (4980)
Observation period, day	272 (119–567)
Total times of HBV DNA testing	4 (2–9)
Underlying diseases	
Solid tumour	56.2% (5296)
Hepatocellular carcinoma	2.1% (199)
Lymphoma	12.4% (1165)
Leukaemia	7.2% (683)
Collagen diseases	22.3% (2100)
Inflammatory bowel diseases	1.5% (146)
Multiple myeloma and NMOSD	0.1% (10)
Liver cirrhosis	1.9% (176)
HCV co-infection	4.2% (393)

Note: Categorical variables: proportions (number); continuous variables: median (interquartile range).
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NMOSD, neuromyelitis optica spectrum disorder.

Exposure was treated as time-varying, with person-time classified according to the agents administered during each period. When multiple agents were used concurrently, exposure was assigned to the highest-risk category. When two or more agents within the same risk category were used, these periods were grouped and analysed as concurrent exposure within that category (e.g., more than two low risk exposures).

2.5 | Outcomes and Variables

The primary outcome was the estimated incidence of HBVr in each risk category. The incidence was also estimated for each subgroup (e.g., IL-6 inhibitors and TKIs). When multiple subgroups with the same risk level overlapped, the observation period was estimated separately as a period with concurrent exposure to two or more agents of the same risk category. Underlying diseases were identified using International Classification of Diseases, Tenth Revision (ICD-10) codes (Table S1).

To assess adherence to monitoring guidelines, we calculated the frequency of HBV DNA testing for patients whose risk periods extended ≥ 90 days by determining the number of HBV DNA tests performed per month during each risk period.

2.6 | Statistical Analysis

Data are presented as medians and interquartile ranges (IQR) for quantitative variables and as numbers and percentages for qualitative variables. The incidence and 95% confidence intervals (CI) of HBVr for each risk category or subgroup were calculated using the Poisson model. Statistical analyses were performed utilizing Stata version 18.0.

2.7 | Ethics

This study was approved by the Institutional Committee on Research Ethics of The University of Tokyo (approval number: 2023143NI). The requirement for informed consent was waived because the data were fully anonymized and not traceable. The study was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision).

3 | Results

3.1 | Background Characteristics

Of the 38,616 patients who underwent HBV DNA testing during the study period, 9422 (24.4%) met the inclusion criteria and were included in the final analysis (Figure 2). The baseline characteristics of the cohort are shown in Table 1. Male was 52.9% (4980/9422), and the median age was 71 years old (IQR, 64–77). The median observation period was 272 days (IQR, 119–567 days), and patients underwent a median of four HBV DNA tests during the observation period (IQR, 2–9).

3.2 | Incidence of HBV Reactivation by Risk Level and Drug Class

The risk periods and numbers of HBVr cases are listed in Table 2. In total, 132 patients were diagnosed with HBVr.

TABLE 2 | Incidence of HBV reactivation.

	Number of patients	Total risk periods (years)	HBVr events	Incidence per 1000PY
Group A	1039	912.8	47	51.5 (37.8–68.5)
Anti-CD20 therapy	916	802.9	42	52.3 (37.7–70.7)
Other high-risk agents	123	107.5	5	46.5 (15.1–108.5)
More than two high risk exposures	3	2.4	0	0.0 (0.0–1519.0)
Group B	2978	1976.8	30	15.2 (10.2–21.7)
Anthracycline derivatives	1078	333.8	7	21.0 (8.4–43.2)
Anti-T cell therapies	48	49.5	0	0.0 (0.0–74.5)
TKIs	510	576.5	7	12.1 (4.9–25.0)
Cytokine/integrin inhibitors	60	88.5	0	0.0 (0.0–41.7)
Anti-IL6 agents	90	88.8	1	11.3 (0.3–62.8)
JAK inhibitors	108	111.5	0	0.0 (0.0–33.1)
CAR-T cell therapies	0	0.0	0	NA
Corticosteroid therapies in moderate or high dose for ≧4 weeks	1126	667.4	14	21.0 (11.5–35.2)
More than two moderate risk exposures	174	60.8	1	16.4 (0.4–91.6)
Group C	6888	5274.5	50	9.5 (7.0–12.5)
Anti–TNF agents	66	68.2	0	0.0 (0.0–54.1)
Antimetabolites	602	792.3	3	3.8 (0.8–11.1)
Immune checkpoint inhibitors	304	167.1	0	0.0 (0.0–22.1)
Corticosteroid therapies low dose or <4 weeks	5667	3553.6	44	12.4 (9.0–16.6)
More than two low risk exposures	1506	1485.5	3	2.0 (0.4–5.9)
Group D	1563	957.6	5	5.2 (1.7–12.2)
Other chemotherapies	1319	700.9	2	2.9 (0.3–10.3)
Other immunosuppressive therapies	240	239.4	3	12.5 (2.6–36.6)
Other monoclonal antibodies	11	10.6	0	0.0 (0.0–347.3)
More than two unknown risk exposures	15	6.8	0	0.0 (0.0–545.7)

Note: Group A, high risk; Group B, moderate risk; Group C, low risk; Group D, uncertain risk, according to the 2025 American Gastroenterological Association guideline for HBsAg-negative patients.
Abbreviations: CAR-T, chimeric antigen receptor T-cell; CD20, cluster of differentiation 20; HBVr, hepatitis b virus reactivation; IL6, interleukin-6; JAK, Janus kinase; NA, not applicable; PY, person-years; TKI, tyrosine kinase inhibitor; TNF, tumour necrosis factor.

Sex, age, and drug details related to HBVr are provided in Table S3. Figure 3 illustrates the incidence of HBVr across treatment-specific risk periods, showing point estimates and 95% confidence intervals according to the guideline-defined risk groups.

Overall, the incidence was highest during Group A risk periods (51.5 per 1000 PY; 95% CI: 37.8–68.5), followed by Group B risk periods (15.2 per 1000 PY; 95% CI: 10.2–21.7), Group C risk periods (9.5 per 1000 PY; 95% CI: 7.0–12.5), and Group D risk periods (5.2 per 1000 PY; 95% CI: 1.7–12.2).

Within the Group A risk periods, the incidence of HBVr was similarly high following anti-CD20 therapy (52.3 per 1000 PY; 95% CI: 37.7–70.7) and other high-risk agents (46.5 per 1000 PY; 95% CI: 15.1–108.5). In the Group B risk periods, measurable HBVr incidence was observed following anthracycline derivatives (21.0 per 1000 PY; 95% CI: 8.4–43.2), TKIs (12.1 per 1000 PY; 95% CI: 4.9–25.0), and moderate or high-dose corticosteroid therapy for ≥4 weeks (21.0 per 1000 PY; 95% CI: 11.5–35.2).

Notably, within the Group C risk periods, a measurable HBVr incidence was observed following corticosteroid therapy at low doses or for less than 4 weeks (12.4 per 1000 PY; 95% CI: 9.0–16.6). HBVr also occurred following antimetabolite therapy, with a lower incidence (3.8 per 1000 PY; 95% CI: 0.8–11.1). In addition, in the Group D risk periods, HBVr was also observed after other immunosuppressive agents (12.5 per 1000 PY; 95%

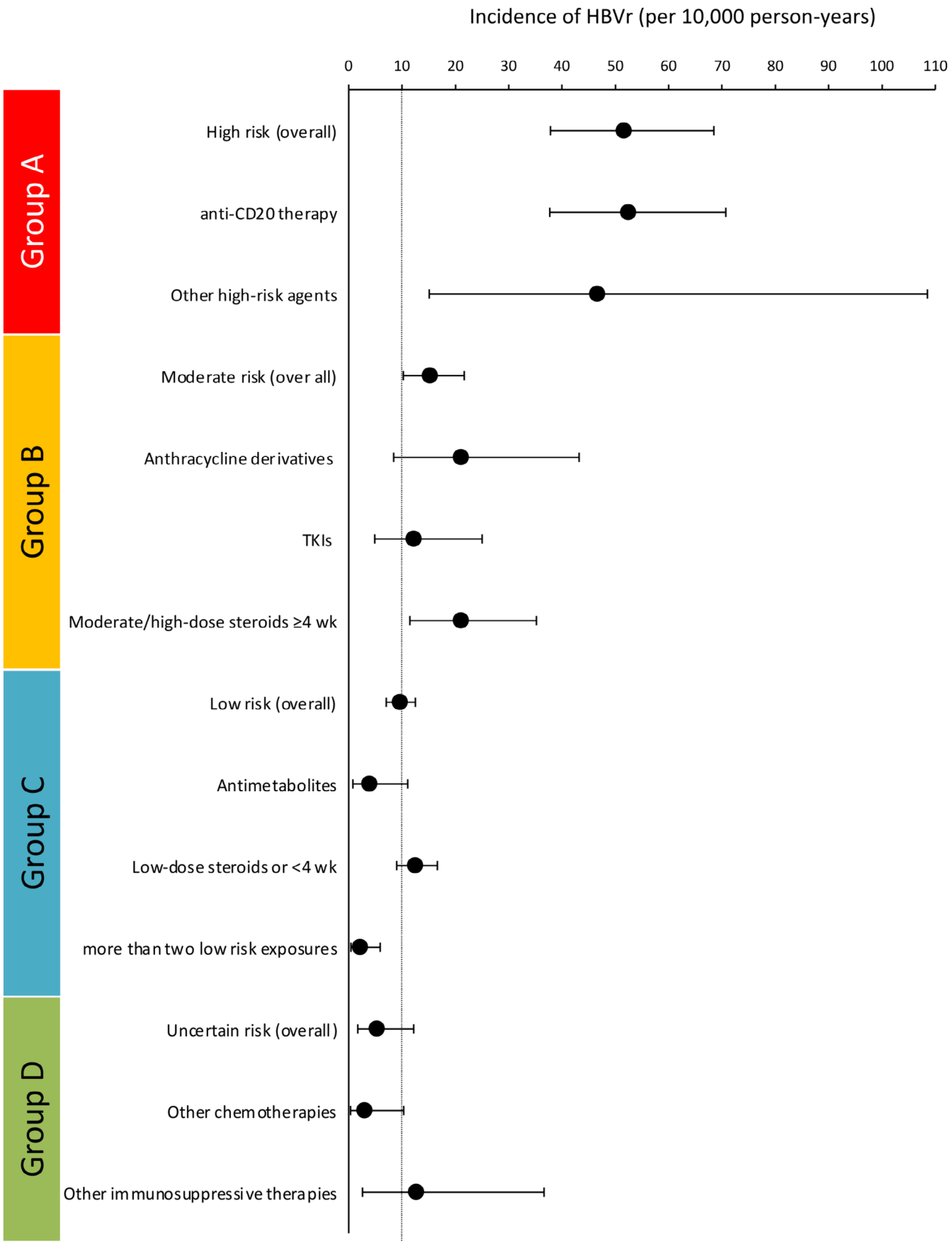

FIGURE 3 | Legend on next page.

FIGURE 3 | Incidence of HBV reactivation by treatment category. Dots indicate incidence rates of HBV reactivation per 1000 person-years, and horizontal bars represent 95% confidence intervals. The vertical dotted line indicates an incidence of 10 per 1000 person-years, corresponding to the threshold separating moderate- and low-risk categories in the AGA guideline. Risk categories correspond to guideline-defined groups: Group A, high risk; Group B, moderate risk; Group C, low risk; and Group D, uncertain risk. Categories with zero or one HBV reactivation event were excluded from this figure because incidence estimates were unstable with extremely wide confidence intervals; these data are provided in Table 2. HBVr, hepatitis B virus reactivation; TKI, tyrosine kinase inhibitor.

CI: 2.6–36.6), including cyclosporine ($n=2$) and a combination of hydroxychloroquine and tacrolimus ($n=1$).

3.3 | Sensitivity Analyses Using Alternative HBV DNA Thresholds

Among the 132 patients with HBVr defined as HBV DNA > 20 IU/mL, 108 (81.8%) met the alternative definition of HBV DNA > 100 IU/mL or initiation of antiviral therapy, and 89 (67.4%) met the definition of HBV DNA > 1000 IU/mL or initiation of antiviral therapy. These proportions were broadly consistent across risk categories, suggesting that the main findings were not driven solely by very low-level HBV DNA positivity. Detailed results are provided in Table S1.

3.4 | Clinical Course and Outcomes in Patients With HBVr

Hepatitis occurred in 17 patients (0.18% [17/9422] of the total; 12.9% [17/132] of HBVr): seven during Group A risk periods (14.9% [7/47] of HBVr), six during Group B risk periods (20.0% [6/30] of HBVr), four even during Group C risk periods (8.0% [4/50] of HBVr). No cases were observed during the Group D risk periods (0% [0/5] of HBVr) (Table S4).

3.5 | Frequency of HBV DNA Monitoring

For risk periods longer than 90 days, the median frequency of HBV DNA testing was highest among Group A (0.73 [IQR: 0.51–0.93] tests/month, $n=838$), and gradually decreased across Group B (0.50 [0.30–0.80] tests/month, $n=1998$), Group C (0.49 [0.30–0.69] tests/month, $n=4850$), and Group D (0.43 [0.23–0.67] tests/month, $n=961$). The proportion of patients who underwent HBV testing less frequently than once every 90 days was 11.3% (95/838), 29.9% (598/1998), 30.5% (1478/4850), and 37.4% (359/961), respectively.

4 | Discussion

In this nationwide, large-scale claims-based study, we quantified the incidence of HBVr across a broad spectrum of immunosuppressive and chemotherapeutic agents in patients with undetectable HBV DNA at baseline who did not receive antiviral prophylaxis and were presumed to be predominantly HBsAg-negative, including several agents for which incidence data have previously been limited. These incidence estimates may also support current guideline-based risk stratification frameworks. Importantly, we also identified clinically meaningful HBVr associated with corticosteroid use, including low-dose or short-term administration, as well as with other agents traditionally considered to carry a lower risk. Notably, most HBVr cases defined by HBV DNA > 20 IU/mL also met higher thresholds or required antiviral treatment, supporting the clinical relevance of our primary definition.

B-cell-depleting therapy, particularly anti-CD20 antibodies, is the well-established risk factor for HBVr. Previous prospective studies in HBsAg-negative patients treated with anti-CD20 therapy have reported HBVr rates of approximately 8%–11% within 1 year [6, 7]. In our study, the incidence during anti-CD20 risk periods was similarly high, and notably, other high-risk agents showed a comparable incidence of HBVr. Data on HBVr associated with other high-risk agents, such as daratumumab, remain limited. However, these agents share mechanisms that impair humoral immunity, including depletion of B cells or plasma cells, and our findings suggest that they may also confer a clinically relevant risk of HBVr, underscoring the need for careful monitoring. Importantly, despite treatment at large hospitals, a substantial proportion of HBVr cases progressed to hepatitis, likely reflecting delays in HBV DNA monitoring and initiation of antiviral therapy. If proper monitoring cannot be performed, prophylactic anti-HBV therapy may be a safer approach during the high-risk periods.

Within the moderate-risk category, anthracycline derivatives and TKIs accounted for a large proportion of exposures in our cohort. Previous studies evaluating these agents have often been limited by small sample sizes [16] or have focused primarily on HBsAg-positive populations [17]. In contrast, our study provides incidence-based estimates in a large cohort of presumed HBsAg-negative patients, thereby offering important evidence supporting current guideline-based risk stratification. Notably, HBVr was observed across multiple TKI subclasses, including multikinase inhibitors, epidermal growth factor receptor inhibitors, and Bruton tyrosine kinase inhibitors, suggesting that HBVr risk is not confined to a single TKI class.

Corticosteroids, categorized according to their dose and duration, are widely used as immunosuppressive agents. In HBsAg-positive patients, corticosteroids have long been associated with an increased risk of HBVr, with higher doses and longer durations further increasing the risk [18–20]. However, data on patients who are HBsAg-negative are limited. One large-scale cohort study found that PSL > 20 mg for > 7 days is a risk factor for HBsAg seroconversion [21], though HBV DNA was not assessed. Our study is one of the largest incidence-based evaluations of HBVr after corticosteroid therapy in patients presumed to be HBsAg-negative. Importantly, measurable HBVr incidence was observed even after low-dose or short-term corticosteroid administration, and cases of hepatitis occurred even within

these guideline-defined low-risk periods. Because many patients receiving low-dose corticosteroids also received concomitant immunosuppressive therapies within the same or lower risk categories, the observed risk may not be attributable to corticosteroids alone. Nevertheless, these findings likely reflect real-world clinical practice and underscore the need for careful HBV monitoring during corticosteroid therapy, including low-dose or short-term use. Not all HBVr cases were associated with clinically significant hepatitis, and further studies are needed to clarify the clinical significance of low-level HBV reactivation detected during routine monitoring.

Antimetabolites, such as methotrexate, are classified as low-risk according to the AGA guidelines. Consistent with this finding, a previous study from Thailand reported no HBV reactivation in 65 anti-HBc-positive patients receiving long-term methotrexate therapy [22]. In our cohort, a small number of HBVr events were observed during antimetabolite exposure; however, the incidence remained low, supporting the guideline classification of these agents as low-risk.

Regarding the uncertain risk group, conventional immunosuppressive therapies and chemotherapies are included in the Japanese HBV guidelines for monitoring [9]. In our study, although SOT and HSCT were censored, HBVr was observed during exposure to calcineurin inhibitors such as tacrolimus and cyclosporine. These agents are not explicitly categorized according to current AGA guidelines. Our findings suggest that HBVr can occur during calcineurin inhibitor therapy and highlight the need for further investigation and careful clinical monitoring in this setting.

Despite the many strengths of our study, it has some limitations. First, as shown in Table S3, many patients received multiple immunosuppressive or chemotherapeutic agents. We categorized exposure according to the highest-risk agent; however, in the presence of concomitant therapies, the observed risk may not be attributable to a single drug, particularly in patients with hematologic malignancies receiving multidrug immunosuppressive regimens. Additionally, the frequency of HBV DNA testing in routine clinical practice may be lower than that in prospective studies, potentially leading to an underestimation of the incidence of HBVr. Variability in monitoring frequency across risk categories may also have influenced the detection of HBVr. Nevertheless, we believe that the observed incidence of HBVr associated with low-dose or short-term corticosteroids and conventional immunosuppressive agents is unlikely to be fully explained by these biases.

Second, the proportion of hepatitis cases among HBVr cases may have been overestimated owing to insufficient HBV DNA monitoring, as asymptomatic HBVr without hepatitis may have been missed. The clinical relevance of detecting low-level viraemia through more intensive monitoring remains uncertain. However, sensitivity analyses using higher HBV DNA thresholds yielded similar results, suggesting that our findings are robust to the definition of HBVr. As shown in Table S3, the interval from HBVr detection to treatment was prolonged in some cases, and several patients developed clinically significant hepatitis. These findings highlight the complexity of optimal monitoring strategies, and the appropriate frequency of HBV DNA testing warrants further investigation. Moreover, patients with de novo hepatitis may be referred to specialized centers, and outcomes such as clinical course and mortality may not be fully captured if care is transferred. Therefore, detailed evaluation of the prognosis of de novo hepatitis was limited in this study.

Third, we could not assess indication-specific differences in HBVr risk (e.g., anti-CD20 therapy for lymphoma vs. autoimmune diseases) because of the limited number of events and potential confounding by treatment intensity. Current AGA guidelines stratify HBVr risk primarily according to drug class rather than underlying disease indication, and our analytic framework was aligned with this approach.

Fourth, although we evaluated a wide range of immunosuppressive and chemotherapeutic agents, the number of HBVr events was limited for some agents, resulting in imprecise estimates with wide confidence intervals that should be interpreted with caution.

Fifth, HBsAg status was not available in this study. Because HBVr risk stratification fundamentally differs between HBsAg-positive and HBsAg-negative individuals in current guidelines, this represents an important limitation. However, all patients included in this study were confirmed to have undetectable HBV DNA at baseline and did not receive antiviral therapy prior to HBV DNA positivity. Previous data using highly sensitive nucleic acid testing have shown that the proportion of HBsAg-positive individuals among HBV DNA–negative persons is very low (2/272, 0.7%) [13]. Furthermore, in Japan, antiviral prophylaxis is recommended for all HBsAg-positive patients undergoing immunosuppressive or chemotherapeutic therapy regardless of HBV DNA status [9], suggesting that the proportion of such patients in our untreated cohort is likely to be even lower. Even assuming that 1% of patients were actually HBsAg-positive despite being classified as HBsAg-negative, and that their risk of HBVr was 10-fold higher than that of truly HBsAg-negative individuals, the overall incidence would be overestimated by approximately 9% (e.g., from 13.9 to 15.2 per 1000 person-years in the moderate risk category). In addition, the proportion of HBsAg-positive patients is unlikely to differ substantially across treatment categories. Therefore, such misclassification is unlikely to materially affect comparisons between risk groups or alter the main conclusions of this study.

Finally, anti-HBs status was not available in our dataset. Because anti-HBs positivity, particularly at higher titers, has been associated with a lower risk of HBV reactivation in HBsAg-negative individuals, the inability to account for this factor may have influenced our incidence estimates.

In conclusion, this large-scale study described the incidence of HBVr in patients treated with immunosuppressive and chemotherapeutic agents who had undetectable HBV DNA at baseline and were presumed to be predominantly HBsAg-negative, and who did not receive antiviral prophylaxis. Our findings provide important evidence for the use of immunosuppressive agents and clinical settings in which data are limited in the current guidelines. In addition, we demonstrated that HBVr can occur even with low-dose or short-term corticosteroids and conventional immunosuppressive agents. Given that HBVr can lead to severe hepatitis if left untreated, appropriate prevention or monitoring strategies are crucial, even for drugs classified as low or uncertain risk.

Author Contributions

Kyoji Moriya: writing – review and editing, supervision. **Kazuhiko Koike:** writing – review and editing, supervision. **Kazuhiko Ikeuchi:** conceptualization, methodology, formal analysis, data curation, writing – original draft, writing – review and editing, validation, funding acquisition. **Kazuya Okushin:** conceptualization, methodology, writing – review and editing, writing – original draft, validation. **Toshiyuki Kishida:** writing – review and editing. **Hiroshi Yotsuyanagi:** conceptualization, methodology, supervision, funding acquisition, writing – review and editing. **Akira Kado:** writing – review and editing. **Takeya Tsutsumi:** writing – review and editing, supervision, conceptualization, methodology. **Makoto Saito:** writing – review and editing, methodology, supervision.

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Disclosure

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: ChatGPT (OpenAI, USA) was used to assist with English language editing and phrasing improvements. This tool was not used to generate scientific content, perform analyses, or draft the manuscript. All the scientific content was developed by the authors. Data Transparency Statement: The data used in this study were obtained from Medical Data Vision Co. Ltd., and are not publicly available because of contractual and privacy restrictions. Relevant analytic data are available from the corresponding author upon reasonable request at kazuyaokushin@g.ecc.u-tokyo.ac.jp. Writing Assistance: English language editing assistance was provided by Editage (www.editage.jp). This assistance was funded by the authors.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from MDV. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of MDV.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** ICD-10 codes for case definition. **Table S2:** List of immunosuppressive and chemotherapeutic agents classified by HBV reactivation risk. **Table S3:** Characteristics of patients with hepatitis B virus reactivation. **Table S4:** Characteristics of patients who developed hepatitis due to HBV reactivation.