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# Multidisciplinary Approach to Prevent *de novo* Hepatitis B in Patients with Rheumatoid Arthritis

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The reactivation of hepatitis B virus (HBV) in patients with rheumatoid arthritis (RA) is currently a social problem. Our hospital has established a project team, which consisted of medical staff including doctors, nurses, pharmacists, and technicians, to prevent HBV reactivation and subsequent *de novo* hepatitis B in 2015. To verify the usefulness of the team, we aimed to examine the implementation rate of HBV screening tests in patients with RA in 2011, 2015, and 2018. We also examined the rate of HBV infection, as well as the rate of HBV reactivation during the course. In this study, medical records of patients who visited our hospital in 2011, 2015, and 2018 were retrospectively reviewed. HBV screening was completed when hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) were all examined. The prevalence of patients who completed HBV screening dramatically increased from 2.4% in 2011 to 79.1% in 2015 and 86.9% in 2018. Patients who completed the screening had significantly higher rates of liver dysfunction, methotrexate use, and use of biological disease-modifying antirheumatic drugs than those who did not. Of the 767 patients who completed HBV screening in 2018, 157 patients (20.5%) had previously resolved HBV infection (HBsAg-negative but HBsAb- and/or HBcAb-positive). During a mean follow-up of 41.0 months, reactivation of HBV was observed in 10 out of the 157 patients (6.4%); however, none developed *de novo* hepatitis B. In conclusion, our multidisciplinary approach to prevent *de novo* hepatitis B is considered useful.

**Keywords:** hepatitis B virus; previously resolved infection; reactivation; rheumatoid arthritis; screening
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## Introduction

The treatment of rheumatoid arthritis (RA) has progressed dramatically in recent years, and not only clinical but also structural and functional remissions are current achievable therapeutic goals in patients with RA (Smolen et al. 2016). This is mainly attributable to the treatment strategy known as a "treat-to-target" approach, whereby if patients have an inadequate response to treatment, the treatment should be intensified or switched until the patients are well controlled (Smolen et al. 2020). Methotrexate (MTX), biological disease-modifying antirheumatic drugs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) contributed greatly to this strategy (Smolen et al. 2020). In fact, multiple reports have already shown that early introduction of bDMARDs efficiently inhibits joint destruction in RA (Takeuchi et al. 2014; Koga et al. 2016). However, in parallel, the reactivation of hepatitis B virus (HBV) by these agents in patients with RA has become a growing social problem (Harigai et al. 2014). HBV can be reactivated not only from carriers of HBV but also from patients who have previously resolved HBV (prHBV) infection.

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Reactivation from patients with prHBV infection causes *de novo* hepatitis B, which has recently attracted attention because it has a high mortality rate (Tanaka and Urata 2012; Loomba and Liang 2017).

We have previously reported a retrospective multicenter survey showing that the infection rate of HBV in patients with RA was about 25% and that in systemic lupus erythematosus was about 14%, in the Tohoku area, an area in the northeast part of Japan (Watanabe et al. 2014, 2015). In Japan, hepatitis B immunoglobulin and HBV vaccines have been administered to prevent vertical transmission of HBV from hepatitis B surface antigen (HBsAg)-positive mothers to children; as a result, the infection rate of HBV in the younger generation has decreased (Inoue and Tanaka 2016). Although HBV vaccination induces hepatitis B surface antibody (HBsAb), it should be noted that some patients who do have past HBV infection are positive for HBsAb alone, making it difficult to distinguish these patients from vaccinated individuals. In addition, we encountered patients in which HBsAb decreased with the intensification of treatment (Watanabe et al. 2013). As mentioned above, we should be aware that there are still many pitfalls regarding HBV.

Osaki Citizen Hospital, located in the Tohoku area of Japan, established a project team to prevent HBV reactivation and subsequent *de novo* hepatitis B. The team is multidisciplinary and has consisted of medical staff such as doctors, nurses, pharmacists, and technicians, as well as medical safety promotion office and medical information management office staff since September 2015. The team performed the following functions: (1) HBsAg, HBsAb, and hepatitis B core antibodies (HBcAb) were set as HBV screening tests; (2) when a drug with a high risk of HBV reactivation is prescribed, an alert is displayed on the electronic medical record; (3) the results of HBV-DNA measurement were listed and distributed every 2 weeks to each department; and (4) the implementation status of the HBV screening test and HBV-DNA measurement was confirmed every 2 months and distributed to each department.

In this study, we examined the implementation rate of HBV screening tests in 2011, 2015, and 2018 in order to verify the usefulness of the team. We also compared the screening-completed group and with the non-completed group and investigated the reasons why not all patients underwent HBV screening in 2018. In addition, we examined the rate of HBV infection in cases where screening was performed in 2018, and compared clinical characteristics of HBV carriers, patients with prHBV infection, and HBV non-infected patients. Finally, we examined the rate of HBV-DNA reactivation during the clinical course in patients with prHBV infection.

## Materials and Methods

*Patient selection*

Patients with RA who visited our hospital from April 2011 to March 2012 (year 2011), those who visited from April 2015 to March 2016 (year 2015), and those who visited from April 2018 to March 2019 (year 2018) were enrolled in this study. Diagnosis of RA was based on the 2010 RA classification criteria (Aletaha et al. 2010). If patients continued to visit our hospital from 2011 to 2018, they were enrolled in 2011, 2015, and 2018. The protocol for this retrospective study was approved by the Ethics Committee of the Osaki Citizen Hospital (No. 20190807-15) and was performed in accordance with the Declaration of Helsinki. Written informed consent was not obtained; however, the study was approved by posting the opt-out on the hospital's website.

*Clinical data*

The medical records of patients were retrospectively reviewed, and clinical data were obtained with regard to age, sex, and the presence of bronchopulmonary involvement. Laboratory tests including rheumatoid factor (RF), liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR), and HBV screening tests (HBsAg, HBsAb, and HBcAb) were also obtained from medical records.

*Definition of HBV screening*

The screening was considered completed if all three HBsAg, HBsAb, and HBcAb were measured during or before the year the patients visited our hospital.

*Definition of HBV reactivation*

HBV reactivation in patients with previously resolved infection was defined when HBV-polymerase chain reaction (PCR) results converted from an undetectable to a detectable level (1.0 log copies (LC)/mL) or were increased compared with the previous value if they were already detectable. HBV-DNA measurements in patients with prHBV infection were followed up from the first examination of HBV-DNA tests until July 2019.

*Definition of organ damage*

Liver dysfunction was defined when liver function tests (either AST or ALT) exceeded the normal upper limit (AST 30 U/L and ALT 42 U/L), and renal dysfunction was defined when the eGFR was $< 60$ mL/min/1.73 $m^2$ at the last visit during the 1-year period. Bronchopulmonary involvement was determined on the basis of the description in medical records.

*Treatment*

We separately obtained data regarding use and amount of MTX, tacrolimus, prednisolone (PSL), other conventional synthetic DMARDs (csDMARDs), including salazosulfapyridine (SASP), bucillamine, iguratimod, and mizoribine, bDMARDs, and tsDMARDs at the last visit of the year.

*Definition of drugs with a high risk of HBV reactivation*

In our hospital, when MTX, tacrolimus, PSL, and all types of bDMARDs, including anti-tumor necrosis factor (TNF) $\alpha$ inhibitors, anti-IL-6 receptor antibodies, abatacept (Okazaki et al. 2020), and tsDMARDs such as Janus kinase (JAK) inhibitors were prescribed, an alert was displayed on the electronic medical record.

*Role of the project team against HBV reactivation and de novo hepatitis B*

Technicians, medical safety promotion office, and medical information management office examined HBV-DNA results every 2 weeks and the implementation of HBV screening every 2 months. Doctors, nurses, pharmacists selected drugs at high risk for HBV reactivation. All members shared the responsibility for confirming that appropriate management is being provided in each patient.

*Statistical analysis*

Statistical analysis was performed using GraphPad Prism 8 (San Diego, California, USA). Fisher's exact test was used for binary data, and Mann-Whitney *U*-test was used for continuous data, as described previously (Tomiyama et al. 2016; Yoshida et al. 2016). One-ANOVA with Tukey's multiple comparisons test was performed to compare three groups.

## Results

*Patients enrolled in the study*

In total, 377, 647, and 883 patients visited our hospital in 2011, 2015, and 2018, respectively (Kondo et al. 2019). Average age was 66.9, 65.8, and 64.9 years, and female were predominant in all years (297/377, 500/657, and 672/883, respectively). RF was positive in 703 out of 883 patients, while anti-citrullinated protein antibody (ACPA) was positive in 440 out of 617 patients measured in 2018.

*The implementation rate of HBV screening increased considerably from 2011 to 2018*

In 2011, the majority of the patients (59.9%) were examined for HBsAg alone (Fig. 1A). Only 9 out of 377 patients (2.4%) completed all HBV screening tests (HBsAg, HBsAb, and HBcAb) (Fig. 1A). On the other hand, 512 out of 647 patients in 2015 (79.1%) and 767 out of the 883 patients in 2018 (86.9%) were fully screened for HBV infection (Fig. 1B, C). When limited to the HBsAg test, almost all patients underwent screening (645/647 in 2015 and 880/883 in 2018). These results indicate that the HBV screening rate dramatically increased in 2015 and further improved until 2018. However, three patients (0.3%) were not screened at all, even in 2018 (Fig. 1C), indicating that there is still room for improvement.

*Comparison between patients who were fully screened for HBV tests in 2018 and those who were not*

We then compared the clinical characteristics between patients who were screened for HBV tests and those who were not. Patients who completed full HBV screening testing had significantly higher rates of liver dysfunction, MTX use, and bDMARDs use (Table 1). On the other hand, patients who were not fully screened for HBV had a tendency to use csDMARDs other than MTX and tacrolimus ($p = 0.08$). These results indicate that rheumatologists examine HBV screening tests when patients have liver dysfunc-

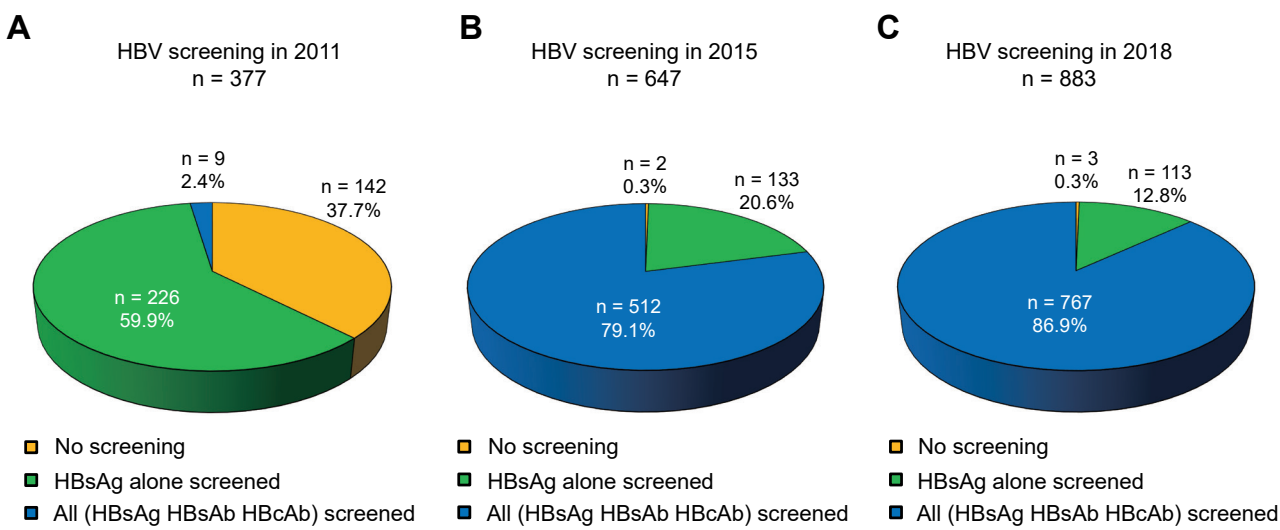


Fig. 1. Improvement in HBV screening rates between 2011 and 2018.
**(A)** HBV screening rate in 2011 (n = 377). **(B)** HBV screening rate in 2015 (n = 647). **(C)** HBV screening rate in 2018 (n = 883). Patients who were not tested for HBV infection were colored yellow. Patients who were examined for HBsAg alone were colored green. Blue represented patients who completed all HBV tests.
HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus.

Table 1. Comparison of clinical characteristics between patients who were fully screened for HBV tests and those who were not.

| | All patients | Screening completed | Screening not completed | p value |
|---|---|---|---|---|
| n | 883 | 767 | 116 | |
| Age (Mean ± SD) | 64.9 ± 13.0 | 65.0 ± 12.8 | 64.3 ± 14.7 | 0.86 |
| Female (n, %) | 672 (76.1%) | 580 (75.6%) | 92 (79.3%) | 0.42 |
| RF (n, %) | 704 (79.7%) | 617 (80.4%) | 87 (75%) | 0.17 |
| Liver dysfunction (n, %) | 186 (21.1%) | 172 (22.4%) | 14 (12.1%) | **0.01** |
| Renal dysfunction (n, %) | 224 (25.4%) | 199 (25.9%) | 25 (21.6%) | 0.36 |
| BP involvement (n, %) | 141 (16.0%) | 122 (15.9%) | 19 (16.3%) | 0.89 |
| MTX (n, %) | 455 (51.5%) | 418 (54.5%) | 37 (31.9%) | **< 0.0001** |
| Tacrolimus (n, %) | 225 (25.5%) | 202 (26.3%) | 23 (19.8%) | 0.14 |
| PSL (n, %) | 364 (41.2%) | 314 (40.9%) | 50 (43.1%) | 0.69 |
| other csDMARDs (n, %) | 257 (29.1%) | 215 (28.0%) | 42 (36.2%) | 0.08 |
| bDMARDs (n, %) | 300 (34.0%) | 274 (35.7%) | 26 (22.4%) | **0.0045** |
| tsDMARDs (n, %) | 29 (3.3%) | 25 (3.3%) | 4 (3.4%) | 0.79 |

bDMARDs, biological disease-modifying antirheumatic drugs; BP involvement, bronchopulmonary involvement; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HBV, hepatitis B virus; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; tsDMARDs, targetd synthetic disease-modifying antirheumatic drugs.

tion or before patients initiate MTX or bDMARDs. However, some patients who were prescribed MTX, bDMARDs, or tsDMARDs did not complete HBV screening tests, and these results require more attention.

*Results of HBV screening in 2018*

Of the 767 patients who completed full HBV screening in 2018 (Fig. 1C), HBV carriers (HBsAg+) accounted for 2.5% (19 patients), and 157 patients (20.5%) were recognized as having prHBV infection (HBsAb+ and/or HBcAb+) (Fig. 2A). Among them, the vast majority (68.8%) of patients with prHBV infection were double positive for HBsAb and HBcAb (Fig. 2B). In total, 23 patients (14.6%) were single positive for HBsAb, whereas 26 patients (16.6%) were positive for HBcAb alone. In total, 7 out of the 23 patients who were positive for HBsAb alone had a vaccination history. These results indicate that approximately 1 in 4 patients with RA in our hospital were previously exposed to HBV and that both HBsAb and HBcAb should be examined because some patients are only positive for one test.

*Comparison between HBV carriers, patients with previously resolved HBV infection and HBV non-infected patients*

Next, we compared the clinical characteristics between HBV carriers, patients with prHBV infection, and HBV non-infected patients. Compared with other groups, the age of patients with prHBV infection was significantly higher (Table 2). Opposite to our expectation, liver dysfunction was not observed in HBV carriers. Nucleoside analogues were used in 11 of 19 HBV carriers based on the risk of the drug administered. Liver dysfunction observed in 28 patients with prHBV infection was attributed to drug toxicities in 17 patients, whereas fatty liver in 9 patients, liver cirrhosis due to hepatitis C virus in 1 patient, and congestive heart failure in 1 patient were thought to be the causes of liver dysfunction. No case was considered *de novo* hepatitis B. Renal dysfunction and bronchopulmonary involvement were observed most commonly in HB carriers and patients with prHBV infection, respectively. MTX and bDMARDs tended to be prescribed less in HBV carriers. These results demonstrate that rheumatologists treat HBV carriers by considering liver function, whereas patients with prHBV infection are treated in the same manner as HBV non-infected patients using MTX and bDMARDs.

*Reactivation of HBV from patients with previously resolved infection*

Among the 157 patients with prHBV infection (Fig. 2A), all patients were routinely monitored by HBV-DNA PCR testing at least every 3 months. During a mean follow-up of 41.0 months, reactivation of HBV was observed in 10 out of 157 patients (6.4%) (Fig. 3A). In our hospital, when HBV-PCR results became 1.2 LC/mL or more, patients were treated with a nucleoside analogue. As a result, 5 out of 10 patients were treated with nucleoside analogues, and the others were followed up without treatment (Fig. 3B, C). Two patients had positive HBV-PCR results at baseline because they were already on therapy for RA (Fig. 3B). After initiating treatment with nucleoside analogues, the results of HBV-PCR tests in all cases improved immediately to an undetectable level and none developed *de novo* hepatitis B (Fig. 3B). On the other

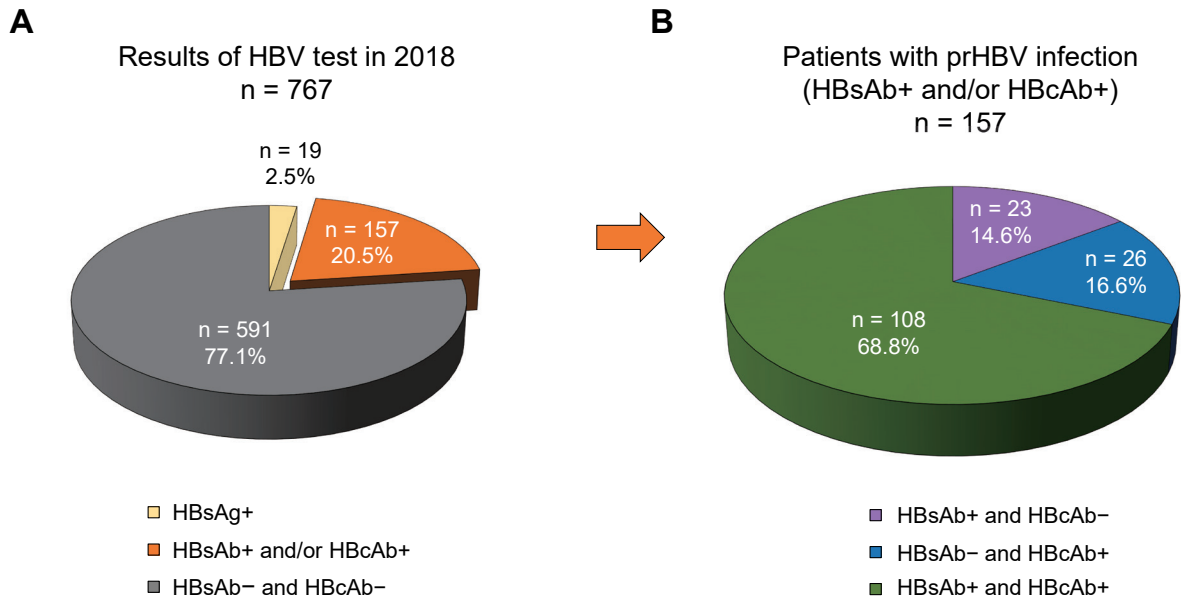


Fig. 2. Results of HBV screening in 2018.
**(A)** Results of HBV tests in 2018 (n = 767). In total, 157 patients (20.5%) were considered as having previously resolved HBV infection (HBsAg-negative, HBsAb-positive and/or HBcAb-positive) and colored orange. **(B)** Detailed analysis regarding HBsAb and HBcAb in patients with previously resolved HBV infection (n = 157). Green represented patients who were positive for HBsAb and HBcAb. Purple represented patients who were positive for HBsAb alone. Patients who were positive for HBcAb alone were colored blue.
HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; prHBV, previously resolved HBV.

Table 2. Comparison of clinical characteristics between HBV carriers, patients with previously resolved infection, and HBV non-infected patients.

| | Group 1<br>HBV carrier | Group 2<br>prHBV infection | Group 3<br>non-infected | p value<br>(1 vs. 2) | p value<br>(1 vs. 3) | p value<br>(2 vs. 3) |
|---|---|---|---|---|---|---|
| n | 19 | 157 | 591 | | | |
| Age (mean ± SD) | 64.0 ± 11.4 | 69.7 ± 10.4 | 63.8 ± 13.1 | 0.15 | 1 | **< 0.0001** |
| Female (n, %) | 15 (78.9%) | 115 (73.2%) | 450 (76.1%) | 0.85 | 0.96 | 0.73 |
| RF (n, %) | 18 (94.7%) | 131 (83.4%) | 468 (79.2%) | 0.47 | 0.21 | 0.46 |
| Liver dysfunction (n, %) | 0 (0%) | 28 (17.8%) | 144 (24.4%) | 0.18 | **0.03** | 0.19 |
| Renal dysfunction (n, %) | 9 (47.4%) | 50 (31.8%) | 140 (23.7%) | 0.31 | 0.05 | 0.09 |
| BP involvement (n, %) | 1 (5.3%) | 35 (22.3%) | 86 (14.6%) | 0.13 | 0.52 | **0.048** |
| MTX (n, %) | 7 (36.8%) | 79 (50.3%) | 332 (56.2%) | 0.51 | 0.22 | 0.39 |
| Tacrolimus (n, %) | 7 (36.8%) | 39 (24.8%) | 156 (26.4%) | 0.50 | 0.57 | 0.92 |
| PSL (n, %) | 9 (47.4%) | 73 (46.5%) | 232 (39.3%) | 0.93 | 0.97 | 0.23 |
| Other csDMARDs (n, %) | 7 (36.8%) | 43 (27.4%) | 165 (27.9%) | 0.66 | 0.67 | 0.99 |
| bDMARDs (n, %) | 2 (10.5%) | 55 (35.0%) | 217 (36.7%) | 0.089 | **0.049** | 0.92 |
| tsDMARDs (n, %) | 0 (0%) | 4 (2.5%) | 21 (3.6%) | 0.83 | 0.67 | 0.80 |

bDMARDs, biological disease-modifying antirheumatic drugs; BP involvement, bronchopulmonary involvement; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HBV, hepatitis B virus; MTX, methotrexate; prHBV, previously resolved HBV; PSL, prednisolone; RF, rheumatoid factor; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

hand, in the group that was followed up without treatment, the results of HBV-PCR fluctuated below 1.2 LC/mL (Fig. 3C). These results show that reactivation of HBV in patients with prHBV infection is not rare and early intervention with nucleoside analogue is effective in preventing *de novo* hepatitis B. On the other hand, if HBV-DNA fluctuates naturally without exceeding a certain level, it can be observed without intervention.

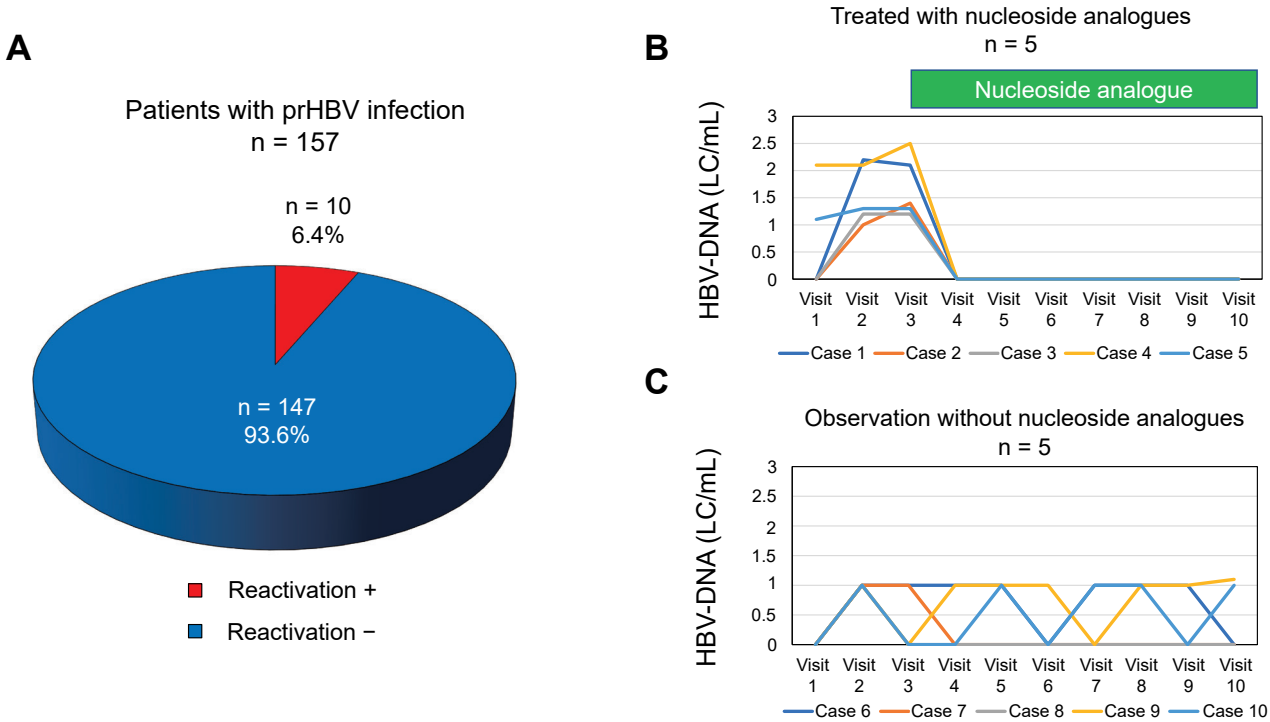


Fig. 3. Reactivation of HBV from patients with previously resolved infection.
**(A)** HBV reactivation rate in patients with previously resolved infection (HBsAg-negative and HBsAb-positive and/or HBcAb-positive, n = 157). Patients who developed HBV reactivation were colored red. **(B)** Results of HBV-DNA tests in patients treated with nucleoside analogues (n = 5). The timing when the nucleoside analogue was initiated was set to visit 3. **(C)** Results of HBV-DNA tests in patients followed up without treatment. The timing when HBV-DNA tests became detectable was set to visit 2.
HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; prHBV, previously resolved HBV.

Table 3. Clinical characteristics of the 10 patients who showed positive HBV-DNA results during the study.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 82 | 79 | 73 | 71 | 62 | 75 | 71 | 80 | 70 | 77 | 74.9 ± 5.9 |
| Sex | M | F | F | F | F | F | F | F | M | M | F 7/10 |
| HBsAb | + | + | + | + | + | + | – | – | + | + | 8/10 |
| HBcAb | – | + | + | + | + | + | + | + | + | + | 9/10 |
| HBV-DNA (LC/mL) | 2.2 | 1.4 | 1.2 | 2.5 | 1.3 | < 1.0 | < 1.0 | < 1.0 | 1.1 | < 1.0 | |
| Nucleoside analogue | + | + | + | + | + | – | – | – | – | – | 5/10 |
| RF | + | + | + | + | + | + | + | + | + | + | 10/10 |
| BP involvement | + | – | – | – | – | – | – | + | – | – | 2/10 |
| Renal dysfunction | + | + | – | – | – | – | – | – | – | + | 3/10 |
| MTX (mg/week) | – | – | – | 8 | 10 | 8 | 6 | – | 10 | – | 5/10 |
| PSL (mg/day) | 2 | 4 | 3 | – | 10 | 0.5 | – | 5 | 2 | – | 7/10 |
| Tac (mg/day) | 1 | – | – | – | – | 1 | – | 2 | 1 | – | 4/10 |
| bDMARDs | ABT | – | – | ABT | – | GLM | – | – | – | TCZ | 4/10 |
| tsDMARDs | – | – | TOF | – | – | – | – | – | – | – | 1/10 |

ABT, abatacept; bDMARDs, biological disease-modifying antirheumatic drugs; BP involvement, bronchopulmonary involvement; GLM, golimumab; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBV, hepatitis B virus; LC, log copies; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; Tac, tacrolimus; TCZ, tocilizumab; TOF, tofacitinib; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs.

*Clinical characteristics of the 10 patients who showed positive HBV-PCR results during the study*

Table 3 summarizes the clinical characteristics of 10 patients with HBV reactivation during the course of treatment. The average age of the 10 cases was 74.9 years, and 7 cases were female. Both HBsAb and HBcAb were positive in seven cases, and one case was positive for HBsAb alone (Case 1 in Table 3). As mentioned above, nucleoside analogues were prescribed in five cases because the highest HBV-DNA results exceeded 1.2 LC/mL or more (Cases 1-5). All cases were positive for RF, and bronchopulmonary involvement and renal dysfunction were observed in two and three cases, respectively. When HBV was reactivated, MTX was used in five cases and PSL was used in seven cases. Regarding bDMARDs and tsDMARDs, HBV reactivation was observed in all available drug types, including anti-TNF$\alpha$ inhibitors, IL-6 receptor antibodies, abatacept, and JAK inhibitors (Table 3). None of the 10 patients developed *de novo* hepatitis B. These results reconfirmed that any type of antirheumatic drug carries a risk of HBV reactivation. It is also noteworthy that MTX alone or PSL alone can reactivate HBV (Cases 2 and 7 in Table 3).

## Discussion

In this study, we retrospectively examined the implementation rate of HBV screening tests and found that the rate dramatically improved from 2011 to 2018. The complete HBV screening rate increased from 2.4% in 2011 to 86.9% in 2018 (Fig. 1). According to reports from other facilities, the overall HBV screening rate was 20.3% in the United States and 24.5% in Taiwan (Lin et al. 2018). Fujita et al. (2018) utilized the National Database of Japan, in which insurance claim data were accumulated from 2013 to 2014, and demonstrated that the screening rates of HBsAg, HBsAb, and HBcAb in 76,641 Japanese patients with RA were 28.23%, 12.52%, and 14.63%, respectively. Compared with these earlier reports, we can observe how high the HBV screening rate was at our hospital in 2018. In our hospital, HBsAg, HBsAb, and HBcAb were examined simultaneously before initiating treatment in most cases, which contributed to the increased HBV screening rate. Although it remains unclear whether the project team directly contributed to the increase of the implementation rate of HBV screening, the team was generally considered useful; however, many patients were still prescribed MTX and bDMARDs without HBV screening, indicating that there is still room for improvement in this process.

The HBV infection rate, including carriers and patients with previously resolved infection, in patients with RA was 23% in this study; this was similar not only to our previous reports but also to other reports from Japan (Mori 2011; Urata et al. 2011; Watanabe et al. 2014). Given that 75% of HBV-infected people reside in the Asia Pacific region (Lee 1997), this prevalence is not surprising. On the other hand, the prevalence of HBV infection in Western Europe and North America is estimated to be < 2% (Lin et al. 2018). Therefore, HBV screening before treatment should be more stringently performed in Japan. It has been reported that screening rates tend to be increasing in other facilities (Lin et al. 2018); however, further efforts should be made, particularly in Japan.

The incidence of HBV reactivation has been reported to range from 1.5% to 5% (Tamori et al. 2011; Fujita et al. 2018; Matsuzaki et al. 2018; Fukuda et al. 2019; Watanabe et al. 2019), and some studies also included patients who developed *de novo* hepatitis B (Matsuzaki et al. 2018). Although we cannot directly compare the incidence because the observation periods were different between studies, the incidence of HBV reactivation in our hospital was considered comparable to previous reports; however, no case developed *de novo* hepatitis B. A system has been established in which the results of the HBV-DNA tests are collected and distributed to each department every 2 weeks in our hospital; this means that HBV reactivation can be noticed earlier than usual, and the patients can be immediately referred to the Department of Gastroenterology. If the HBV-DNA test is high enough to initiate nucleoside analogue treatment, a telephone call is made and the patient might be seen early. This system contributed to the prevention of *de novo* hepatitis B in our hospital.

Essentially, all types of bDMARDs and tsDMARDs have a risk of HBV reactivation (Fukuda et al. 2019; Watanabe et al. 2019). It is also well known that drugs such as MTX, PSL, and tacrolimus can cause HBV reactivation (Duhart et al. 2003; Watanabe et al. 2012; Chen et al. 2017). Therefore, in our hospital, MTX, PSL, and tacrolimus, as well as bDMARDs and tsDMARDs, were defined as drugs carrying a high risk of HBV reactivation. Although there is a case report suggesting that other csDMARDs, such as SASP, can cause *de novo* hepatitis B (Akashi et al. 2016), the frequency is considered extremely low; thus, we excluded other drugs. However, according to the treat-to-target strategy, treatment is evaluated on a monthly basis, and if insufficient, a new drug should be given. Therefore, if HBV screening is performed before starting csDMARDs such as SASP, the screening rate may be further improved.

The limitations of this study are as follows. First, this study is a single center experience. Second, we did not take into account the gradual improvement in public awareness for the reactivation of HBV between 2011 and 2018. Third, although we conducted a survey on HBV screening, we did not collect detailed data on RA, such as disease activity, serological status of ACPA, and disease duration. Retrospective review of the medical records revealed that rheumatologist did not recommend strong treatment in the case of HBV carrier, even with high disease activity. When disease activity was extremely high, MTX and b/tsDMARDs were administered with a nucleoside analogue. ACPA should have been examined in all patients because ACPA is significantly associated to identify patients at risk of joint damage (Koga et al. 2017). Fourth, we did not take

the cost-effectiveness ratio into consideration. Changes in laboratory tests and treatment over the clinical course should also have been considered. We have used LC/mL as a unit of HBV-DNA results, which has traditionally been used in Japan. But in the near future, we should use the international unit, LIU/mL. Finally, and most importantly, although we examined the rate of HBV reactivation in patients who completed all HBV screening tests, the focus should be centered on patients who were not adequately screened for HBV. We are currently working on this limitation.

In conclusion, although our multidisciplinary efforts to prevent HBV reactivation were useful, there is still room for improvement, and further efforts should be made to improve the HBV screening rate.

## Author Contributions

R.W. conceived the study design, collected and analyzed the data, and wrote the manuscript. T.I., T.T., M.O., and M.G. were members of the project team. K.H., S.O., and M.K. participated in the study design and discussion. All authors reviewed and approved the manuscript.

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## Conflict of Interest

The authors declare no conflict of interest.

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