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Meta-Analysis

Hepatitis B reactivation linked to tumor necrosis factor-α inhibitors in rheumatoid arthritis: a systematic review and meta-analysis

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Abstract

This study aimed to evaluate the risk of hepatitis B virus reactivation (HBVr) in patients with HBV-related rheumatoid arthritis (RA) undergoing TNF inhibitor (TNFi) therapy. A systematic search of Embase, PubMed/MEDLINE, Scopus, Web of Science, ClinicalTrials.gov and the Cochrane Library was conducted, and pooled HBVr rates were calculated using random-effects models with subgroup analyses based on region, HBV serostatus, glucocorticoid use, antiviral prophylaxis, and TNFi type. Data from 15 studies, including 916 patients, were analyzed, revealing a pooled HBVr rate of 2% (95% CI: 0.01–0.03) with low heterogeneity (I^2 = 0.79%, p = 0.133). Regional variation was observed, with no HBVr cases in European studies (0.01; 95% CI: −0.01–0.03) and a 2% rate in Asian studies (95% CI: 0.01–0.04). HBsAg-positive patients demonstrated significantly higher HBVr rates (16%; 95% CI: 0.04–0.28) compared with HBsAg-negative patients (4%; 95% CI: −0.01–0.09), corresponding to an odds ratio (OR) of 12.60 (95% CI: 3.73–42.53). Patients receiving antiviral prophylaxis had a 6% HBVr rate compared to 3% in those without prophylaxis, though the difference was not statistically significant (OR: 1.30; p = 0.726). Similarly, glucocorticoid use did not significantly influence HBVr risk (6% vs. 5%; OR: 0.73; p = 0.563). HBVr rates also varied by TNFi type, with 4% for adalimumab, 3% for etanercept, and 2% for infliximab. Overall, TNFi therapy in HBV-related RA is associated with a low but clinically relevant risk of HBVr, with higher rates in HBsAg-positive patients and modest variation by region and drug type, while antiviral prophylaxis and glucocorticoid use appear to have no significant effect on risk.

Keywords: Hepatitis B reactivation, Tumor Necrosis Factor-α inhibitors, Rheumatoid arthritis, Systematic review, Meta-analysis.

1. Introduction

Tumor necrosis factor inhibitors (TNFi) and disease-modifying antirheumatic drugs (DMARDs) are widely used as effective therapies for autoimmune diseases such as rheumatoid arthritis (RA). Among these, TNF-α inhibitors, as biologic agents, play a crucial role in the treatment of RA [1]. TNF-α is a key pro-inflammatory cytokine involved in systemic inflammatory responses and the host defense against intracellular pathogens [2, 3]. TNF-α inhibitors can affect the replication and clearance of hepatitis B virus (HBV) by interfering with HBV-specific cytotoxic T lymphocyte (CTL) responses and reducing TNF-α expression. This interference may lead to the reactivation of latent HBV infections, a phenomenon known as hepatitis B virus reactivation (HBVr) [4, 5].

Given the critical therapeutic role of TNF-α inhibitors in rheumatic diseases and their potential influence on HBV replication and clearance, these inhibitors might promote viral replication escape. This, in turn, could result in the spread of HBV infection within hepatocytes and an increase in circulating viral load, thereby affecting the prognosis and treatment outcomes in patients with HBV-related RA [6, 7].

Upon reviewing recent studies, it was noted that the specific condition of RA combined with HBV infection limits the number of patients eligible for inclusion in such studies. Furthermore, HBVr is a relatively rare event (approximately 5%), which complicates the feasibility of study designs, the acquisition of large-scale data, and often results in small patient cohorts and inconsistent findings across studies [6]. In many cases, it is difficult to discern whether the low incidence of HBVr is due to insufficient sample sizes or the inherently low probability of HBVr occurring during TNFi treatment for RA [7].

High-quality meta-analyses can help address such rare events. However, previous systematic reviews in this field have long intervals between updates, include relatively older studies, and yield results that remain contentious, similar to observational studies [8]. Therefore, updating the data from systematic reviews and critically evaluating their findings to draw meaningful conclusions is essential.

This study aims to conduct a meta-analysis to evaluate HBVr in HBV-infected RA patients treated with TNF-α inhibitors, providing the following report.

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2. Materials and Methods

2.1. Search strategy

The search encompassed major literature databases, as well as clinical trial databases, including Embase, PubMed/MEDLINE, Scopus, Web of Science, ClinicalTrials.gov and the Cochrane Library. Search terms were developed according to the PICOS framework. The primary keywords included "rheumatoid arthritis", "hepatitis B", "hepatitis B virus reactivation", "TNF inhibitor", and designations of specific TNF inhibitors such as infliximab, adalimumab, etanercept, golimumab, and certolizumab. No search terms were specified for I (intervention) or S (study design) due to the inclusion of studies regardless of their control group or design. Boolean operators ("AND," "OR," "NOT") were used to combine terms, and search results were exported into EndNote 21 for preliminary screening. No language restrictions were applied. Both full-text articles and conference abstracts were considered, but grey literature beyond indexed conference proceedings was not included. Table 1 summarizes the list of queries used for searching PubMed/MEDLINE.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

- **Study types**: randomized controlled trials (RCTs), clinical controlled trials, cohort studies (prospective or retrospective), or case series.
- Studies investigating hepatitis B virus reactivation (HBVr) in rheumatoid arthritis (RA) patients receiving TNF-α inhibitors (TNFi).

Participants: RA patients diagnosed based on either the 1987 American College of Rheumatology (ACR) classification criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria [9, 10].

Patients had complete baseline data, follow-up information on HBV serological markers, and liver function tests, and were identified as chronic HBV carriers or having past HBV infection without active hepatitis, cirrhosis, hepatocellular carcinoma, or other chronic liver injuries.

Included studies involved at least one of the following TNFi: infliximab, adalimumab, golimumab, certolizumab, or etanercept. Other TNFi agents targeting similar pathways, such as Yisaipu (a recombinant human TNF receptor-II antibody fusion protein), were also eligible.

Studies where HBV-related RA subgroup data were separable were included due to limited data availability.

HBVr was defined as a sudden increase in HBV replication in inactive or resolved HBV infection cases, characterized by the appearance or elevation of HBV DNA in the serum of previously inactive or recovered patients [11].

2.2.2 Exclusion criteria

- Studies unrelated to RA patients or HBVr.
- Studies involving co-infection with hepatitis C virus (HCV) without detailed subgroup data on HBVr or studies solely including HCV-infected patients.

2.3. Study selection process

Two researchers independently screened studies based on inclusion and exclusion criteria. Titles and abstracts were reviewed for initial screening, followed by full-text reviews of selected papers. Any disagreements were resolved through discussion; unresolved disagreements were referred to a third researcher for resolution.

2.4. Quality assessment and data extraction

Data were extracted using a customized extraction sheet, including:

- Study type (RCT, controlled trial, cohort study, or case series),
- Study location,
- Sample size (including subgroup data),
- Mean age and gender distribution,
- Follow-up duration,
- HBV status (chronic infection, resolved infection, or occult infection),
- RA treatment regimen (e.g., glucocorticoids, DMARDs, biological DMARDs, specific TNFis),
- Use of prophylactic antiviral therapy and its protocol,
- Number or rate of HBVr events.

Since most included studies were cohort studies, often single-arm retrospective cohorts, the quality of studies was assessed using the Newcastle-Ottawa Scale (NOS) [12]. Each domain of the NOS was evaluated according to predefined criteria: representativeness of the cohort and ascertainment of exposure were judged by clarity of patient selection and HBV/RA diagnosis confirmation; comparability was assessed based on adjustment for major confounders such as HBV serostatus and use of antiviral prophylaxis; and adequacy of follow-up was judged by whether the study provided sufficient follow-up duration (≥6 months after initiation of TNFi therapy) and whether HBV reactivation was systematically monitored through serological or virological testing. Studies that lacked explicit follow-up reporting or routine monitoring were considered at higher risk of bias in this domain.

Table 1. List of queries used for searching PubMed/MEDLINE.

Row	Query	Results
#1	"rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms]	174,994
#2	"hepatitis b"[Title/Abstract] OR "HBV"[Title/Abstract] OR "HBVr"[Title/Abstract] OR "hepatitis b reactivation"[Title/Abstract] OR "hepatitis b"[MeSH Terms]	114,663
#3	"tumor necrosis factor alpha inhibitor"[Title/Abstract] OR "tumor necrosis factor inhibitor"[Title/Abstract] OR "tnf inhibitor"[Title/Abstract] OR "infliximab"[Title/Abstract] OR "adalimumab"[Title/Abstract] OR "etanercept"[Title/Abstract] OR "golimumab"[Title/Abstract] OR "certolizumab"[Title/Abstract] OR "tumor necrosis factor alpha"[MeSH Terms] OR "infliximab"[MeSH Terms] OR "adalimumab"[MeSH Terms] OR "etanercept"[MeSH Terms] OR "certolizumab pegol"[MeSH Terms]	166,676
#4	#1 AND #2 AND #3	94

2.5 Statistical analysis

The HBVr rate among RA patients receiving TNFi treatment was calculated along with its 95% confidence interval (CI). Data were stabilized using 1/2 continuity correction and the Freeman-Tukey double arcsine transformation [12]. Meta-analyses were conducted using RStudio version 4.3 (R Foundation for Statistical Computing, Vienna, Austria). The *meta* (version 6.5-0) and *metafor* (version 4.4-0) packages were used to estimate the overall reactivation rate and its 95% CI. Heterogeneity was evaluated using the Q test and I^2 statistic. Significant heterogeneity ($Q < 0.1$ or $I^2 > 50\%$) prompted the use of a random-effects model, while a fixed-effects model was applied when heterogeneity was negligible. Subgroup analyses were performed based on study region, use of prophylactic antiviral therapy, glucocorticoid use, and type of TNFi.

3. Results

3.1. Search results

The PRISMA flowchart of the systematic search is presented in Fig. 1. A total of 776 articles were identified. After importing the results into EndNote 21 and removing 24 duplicate records, titles and abstracts were screened to exclude articles that did not meet the inclusion criteria. This resulted in 31. Following a thorough review of full texts, articles not meeting the inclusion criteria regarding intervention, outcome measures, study population, or study design were excluded, leaving 15 eligible studies (13 in English and 2 in Chinese), encompassing 916 RA patients, that were ultimately included.

3.2. Study characteristics

Table 2 summarizes the characteristics of the included studies.

Among the 14 included studies, 2 were published in Chinese [14, 16], and the remaining 13 were in English. Six studies reported HBV reactivation (HBVr) cases, but to minimize reporting bias, studies without HBVr cases were also included. A 1/2 correction was applied to address zero-event issues, providing a more accurate reflection of the HBVr rate.

3.3. Quality assessment

The 15 included studies were assessed for their quality of evidence using the NOS tool, the results of which are presented in Table 3. One study (6.7%) scored 8 points, five studies (33.3%) scored 7 points, six (40%) scored 6 points, and three studies (20%) scored 5 points.

3.4. Overall prevalence

A total of 15 studies were included for data integration. Following 1/2 correction and Freeman-Tukey double arcsine transformation, the pooled HBV reactivation rate among patients with a history of HBV infection using TNFi therapy was 0.02 (95% CI: 0.01–0.03), with heterogeneity ($I^2 = 0.79\%$, $p = 0.133$) (Fig. 2), indicating a mean prevalence of 2%.

3.5. Subgroup analyses

3.5.1. Analysis based on region

Studies were categorized into Asian and European regions for subgroup analysis (Fig. 3). Among the 4 European studies, no HBV-positive cases were reported, with a pooled HBVr rate of 0.01 (95% CI: [−0.01, 0.03], $I^2 = 0\%$, $p = 0.884$), which was not statistically significant. In contrast, the 11 Asian studies yielded a pooled HBVr rate of 0.02 (95% CI: [0.01, 0.04], $I^2 = 0.03\%$, $p = 0.051$) with low heterogeneity and high statistical significance ($p < 0.001$).

Further analysis by country showed that the pooled HBVr rate was 0.07 (95% CI: [−0.04, 0.18], $I^2 = 92.96\%$, $p = 0.012$) in China; 0.02 (95% CI: [0.00, 0.04], $I^2 = 0\%$, $p = 0.691$) in Japan (Fig. 4), and 0.01 (95% CI: [−0.01, 0.03], $I^2 = 0\%$, $p = 0.819$) in Italy, of which only the latter was statistically significant.

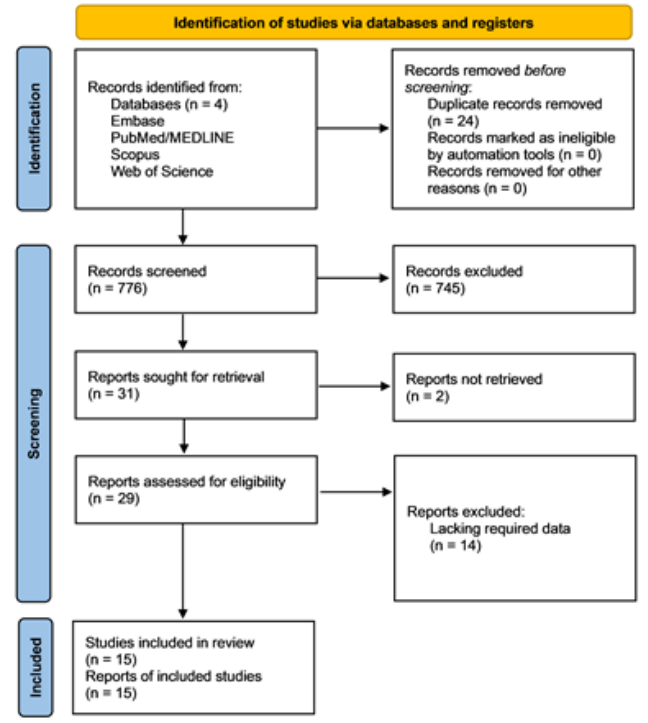

Fig. 1. PRISMA flowchart of the systematic search.

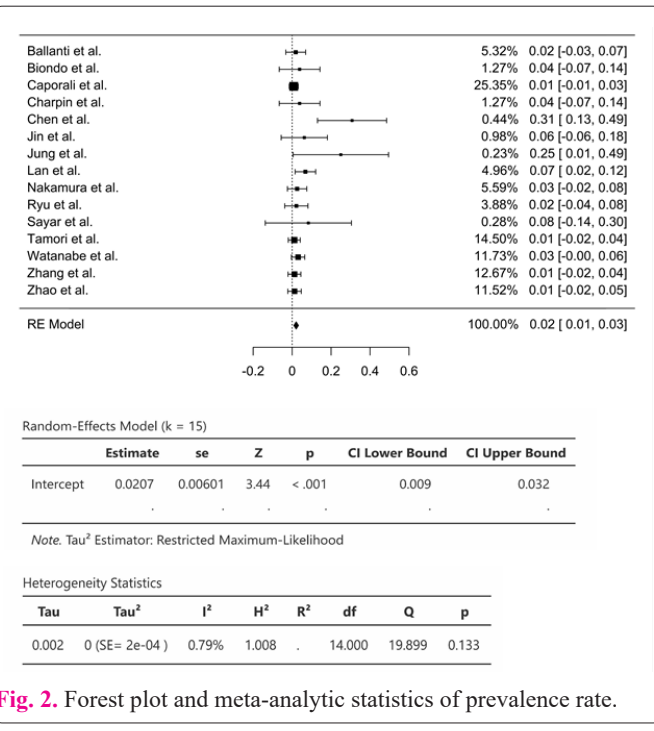

Fig. 2. Forest plot and meta-analytic statistics of prevalence rate.

Table 2. Characteristics of the included studies.

Study	Year	Country	Study Type	Sample Size (n)	Age	Female Sex (n, %)	Intervention	Ref.
Sayar et al.	2020	Turkey	Retrospective Observational	5	46.4 ± 5.9	3 (60%)	Adalimumab Certolizumab pegol Golimumab Etanercept	[5]
Watanabe et al.	2018	Japan	Retrospective Observational	152	68.00 ± 8.98	120 (78.9%)	Adalimumab Infliximab Certolizumab pegol Golimumab Etanercept	[13]
Zhao et al.	2017	China	Prospective Cohort	43	44.0 ± 10.0	32 (74.4%)	Etanercept (Yisaipu)	[14]
Chen et al.	2016	China	Retrospective Observational	123	49.5 ± 12.0	98 (79.7%)	TNFi (unspecified)	[15]
Jin et al.	2015	China	Prospective Cohort	156	32.7 ± 9.7	96 (61.5%)	Etanercept Infliximab Adalimumab	[16]
Ballanti et al.	2014	Italy	Retrospective Observational	32	63.3 ± 8.9	30 (93.7%)	Etanercept Adalimumab	[6]
Jung et al.	2014	South Korea	Retrospective Observational	12	–	–	Etanercept Infliximab Adalimumab	[17]
Nakamura et al.	2014	Japan	Retrospective Observational	57	59.3 ± 34.2	47 (82.5%)	Etanercept Infliximab Adalimumab	[18]
Biondo et al.	2013	Italy	Prospective Cohort	20	63.0 ± 9.5	13 (65%)	Etanercept Infliximab Adalimumab Golimumab	[19]
Zhang et al.	2013	China	Retrospective Observational	41	46.2 ± 2.7	34 (82.9%)	Infliximab	[20]
Ryu et al.	2012	South Korea	Retrospective Observational	49	40.2 ± 11.8	19 (38.8%)	Etanercept Infliximab Adalimumab	[21]
Lan et al.	2011	Taiwan	Retrospective Observational	88	50.1 ± 12.0	77 (87.5%)	Etanercept Adalimumab	[22]
Tamori et al.	2011	Japan	Prospective Cohort	50	59 (15 – 73)	41 (82%)	Etanercept Infliximab Adalimumab	[23]
Caporali et al.	2010	Italy	Prospective Cohort	67	57.4 ± 12.6	41 (61.2%)	Etanercept Infliximab Adalimumab	[24]
Charpin et al.	2009	France	Prospective Cohort	21	57.7 ± 2.7	13 (61.9%)	Etanercept Infliximab Adalimumab	[25]

Table 3. Results of quality assessment based on the NOS tool.

Study	Year	Antiviral Therapy (n, %)	Glucocorticoid Therapy (n, %)	HBV Reactivation	Follow-up Time (mo)*	NOS Score	Ref.
Sayar et al.	2020	0	2 (40%)	0	17.2 ± 9.2	6	[5]
Watanabe et al.	2018	0	107 (70%)	7	15 (4 – 34)	6	[13]
Zhao et al.	2017	0	0	0	12	6	[14]
Chen et al.	2016	0	51 (41.5%)	8	28.1	7	[15]
Jin et al.	2015	0	0	1	6	6	[16]
Ballanti et al.	2014	3 (9.4)	5 (15.6%)	0	27.2 ± 23.7	5	[6]
Jung et al.	2014	5 (41.7%)	0	3	–	5	[17]
Nakamura et al.	2014	0	0	3	18 (2 – 27)	6	[18]
Biondo et al.	2013	0	13 (65%)	0	45.0 ± 22.0	7	[19]
Zhang et al.	2013	0	0	0	7.5	6	[20]
Ryu et al.	2012	20 (40.8%)	0	0	14	8	[21]
Lan et al.	2011	10 (11.4%)	88 (100%)	6	12	5	[22]
Tamori et al.	2011	50 (100%)	0	0	23 (12 – 32)	7	[23]
Caporali et al.	2010	0	43 (64.2%)	0	42.5 ± 21.3	7	[24]
Charpin et al.	2009	0	0	0	27.2 (7 – 56)	7	[25]

*Follow-up time is reported is mean ± SD or median (IQR).

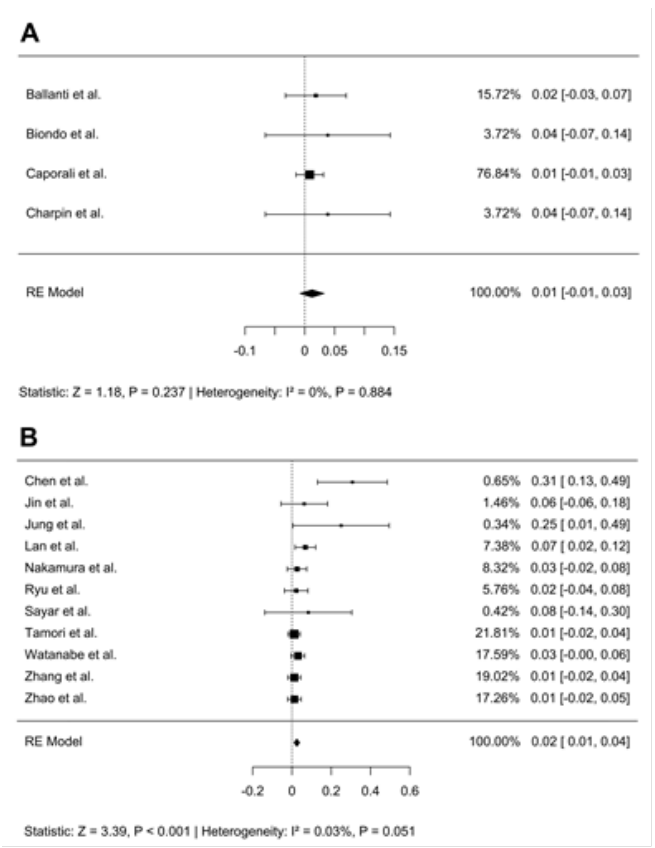

Fig. 3. Forest plots of HBVr prevalence based on region in Europe (A) and Asia (B).

3.5.2. Analysis based on Hepatitis B surface antigen (HBsAg) status

Due to limited data and the complexity of HBV antigen/antibody status, subgroup analysis was limited to HBsAg-positive and HBsAg-negative patients. Six studies reported HBVr rates in HBsAg-positive patients, while eight studies provided data on HBsAg-negative patients. The pooled HBVr rate was 0.16 (95% CI: [0.04, 0.28], I^2 = 37.45%, p = 0.122) in HBsAg-positive patients, and

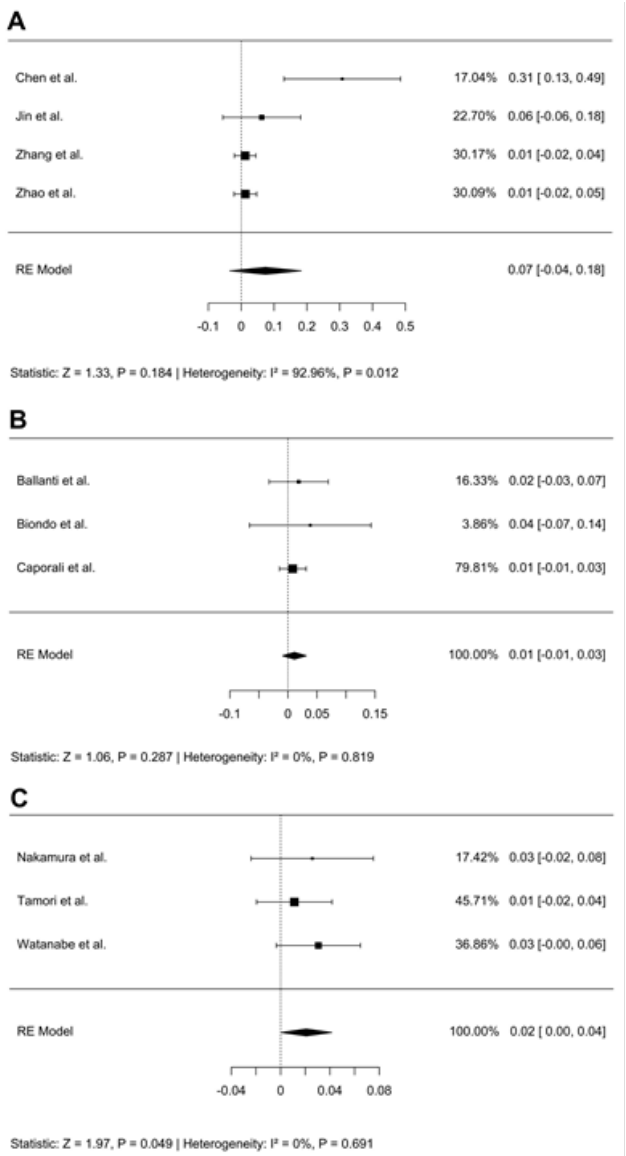

Fig. 4. Forest plots of HBVr based on region in China (A), Italy (B) and Japan (C).

0.04 (95% CI: [−0.01, 0.09], I^2 = 93.26%, p < 0.001) in HBsAg-negative patients (Fig. 5). As shown in the same figure, comparison of HBVr rate between HBsAg-positive and HBsAg-negative patients as dichotomous outcomes returned a significant OR of 12.60 (95% CI: [3.73, 42.53], I^2 = 0%, p = 0.706). In summary, the mean rate of HBVr in $HBsAg^+$ patients was 16%, who were 12.6 times more likely to develop HBVr compared with their $HBsAg^-$ counterparts.

3.5.3. Analysis based on use of antiviral prophylaxis

Five studies provided data on antiviral prophylaxis. As shown in Fig. 6, patients who received antiviral prophylaxis had a pooled HBVr rate of 0.06 (95% CI: [−0.01, 0.13], I^2 = 0, p = 0.950), whereas those without prophylaxis had a rate of 0.03 (95% CI: [0.00, 0.07], I^2 = 36.37%, p = 0.151). While both showed low heterogeneity, only the latter was found to be statistically significant (p < 0.05). Compared with patients not receiving antiviral prophylaxis, patients who received antiviral prophylaxis had an OR of 1.30 (95% CI: [−1.20, 1.72], I^2 = 0%, p = 0.725), but this was found to be statistically insignificant (Z = 0.350, p = 0.726). In summary, the mean rate of HBVr in patients not receiving antiviral prophylaxis was 3%.

3.5.4. Analysis based on glucocorticoid use

Among the included studies, 8 explicitly described whether glucocorticoids were used. Of these, one study reported a 100% glucocorticoid usage rate [22], while two studies reported no glucocorticoid usage [14, 16]. The study by Ballanti et al. [6] in 2014 included data only for patients using glucocorticoids at doses greater than 7.5 mg/day, and the study by Caporali et al. [24] in 2010 did not report data separately for RA patients based on glucocorticoid use. Consequently, these two studies were excluded

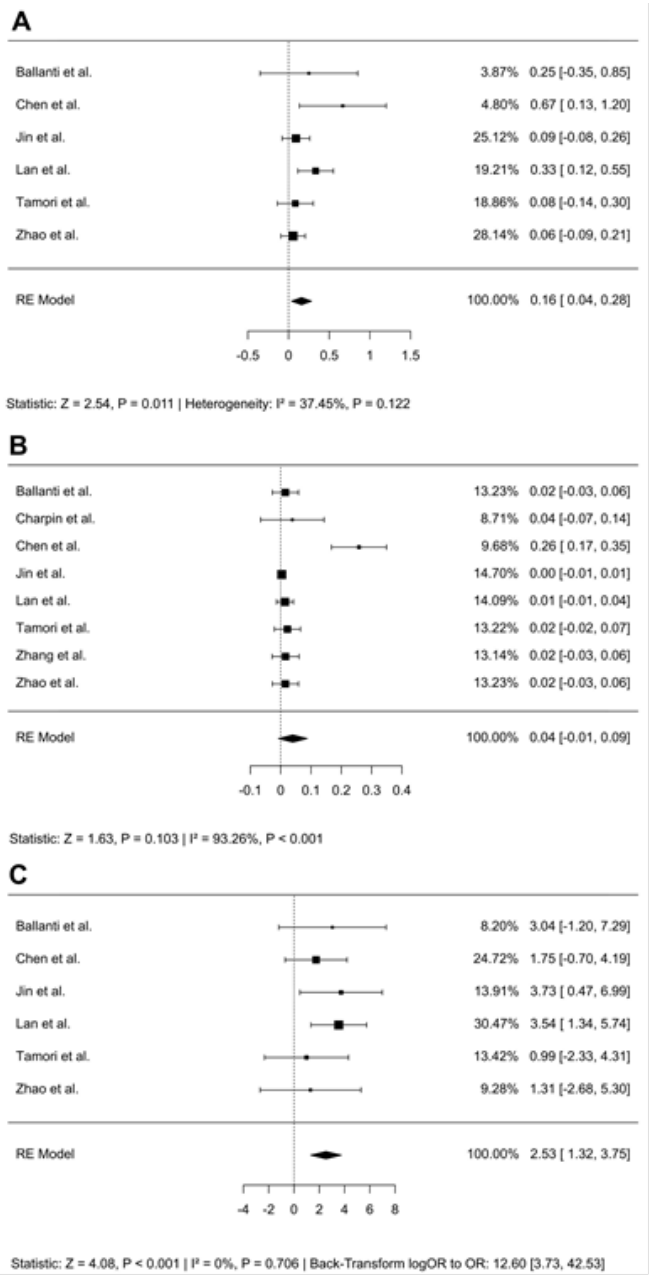

Fig. 5. Forest plots of the prevalence of HBVr among $HBsAg^+$ (A) and $HBsAg^-$ patients (B), as well as comparison of HBVr in $HBsAg^+$ vs. $HBsAg^-$ (C) patients.

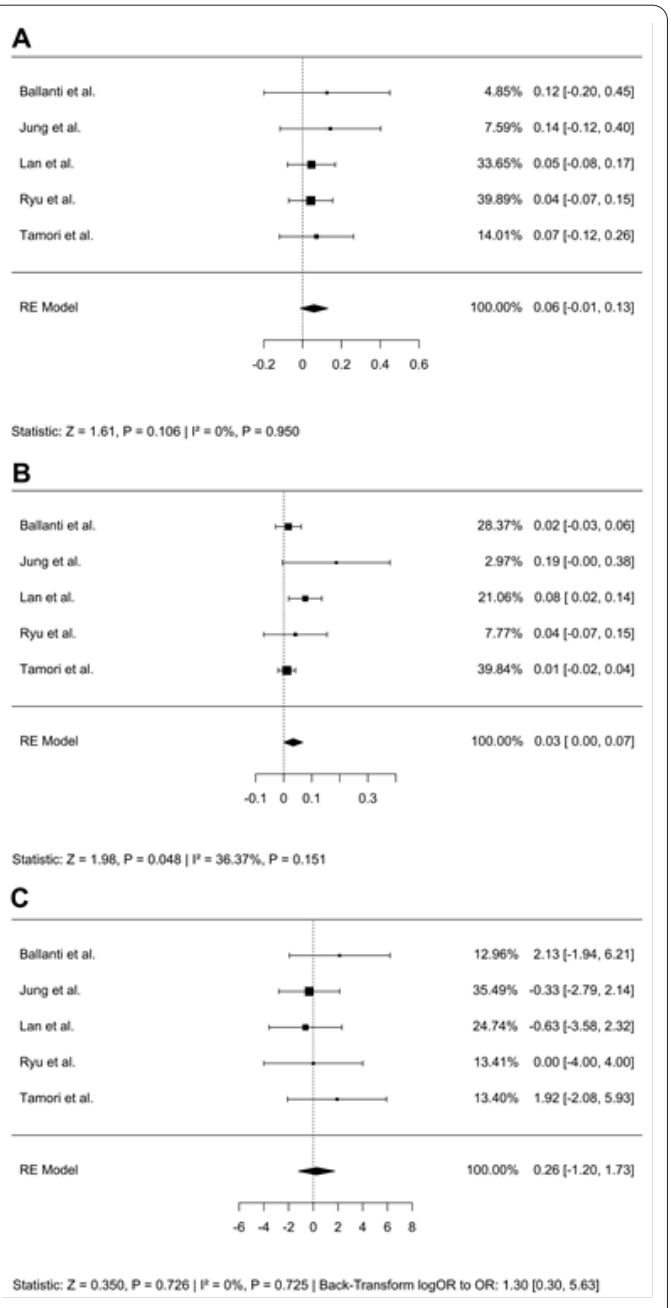

Fig. 6. Forest plots of HBVr rate among patients receiving antiviral prophylaxis (A) and patients not receiving antiviral prophylaxis (B), along with comparison of HBVr rate among patients receiving antiviral prophylaxis vs. those not receiving (C).

from the analysis. As visualized in Fig. 7, a meta-analysis of the remaining 6 studies, comprising 289 patients for whom glucocorticoid treatment data could be separated, revealed the following: HBVr rate among patients using glucocorticoids was 0.06 (95% CI: [0.03, 0.08]; I^2 = 0%, p = 0.937), while the HBVr rate among patients not receiving glucocorticoids was 0.05 (95% CI: [0.00, 0.09]; I^2 = 0%, p = 0.574), both of which were statistically significant (p < 0.05) with low heterogeneity. However, comparison of the HBVr rate between the two groups (excluding one study) showed an OR of 0.73 (95% CI: [0.26, 2.10]; I^2 = 0%, p = 0.710), which, despite showing low heterogeneity, was deemed as statistically insignificant (p = 0.563). In summary, the mean rates of HBVr in patients receiving glucocorticoids and those not receiving were 6% and 5%, respectively.

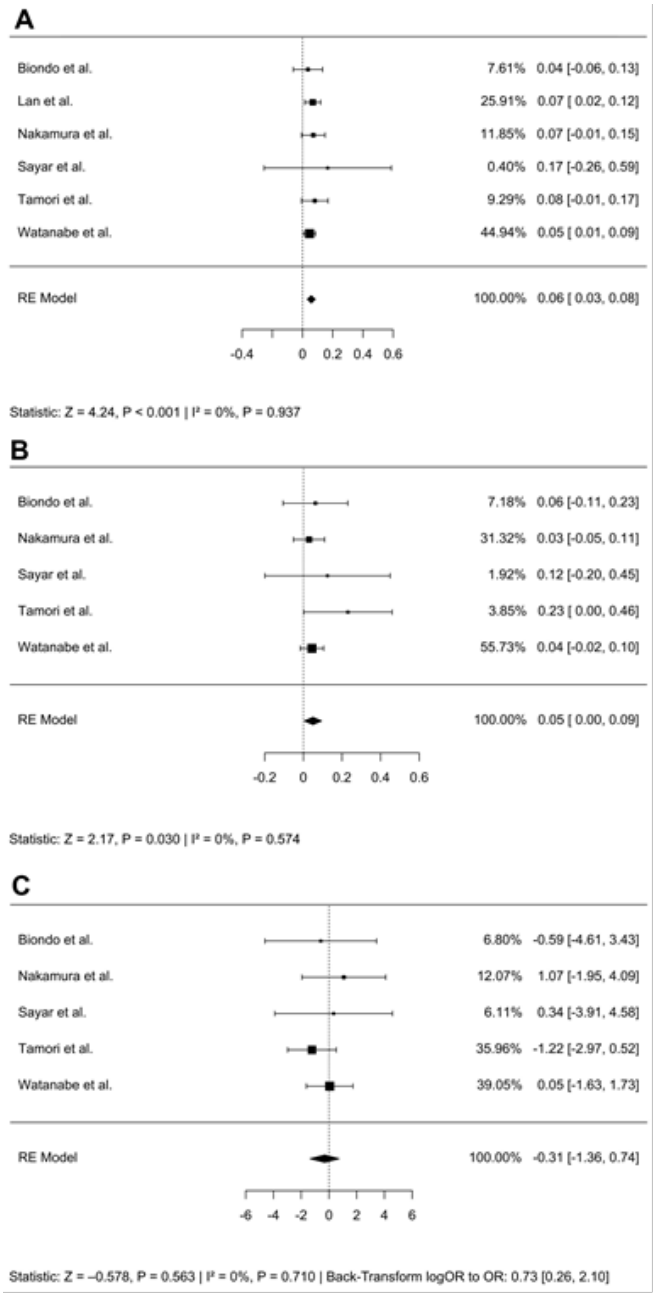

Fig. 7. Forest plots of HBVr rate among patients receiving glucocorticoids (A), patients not receiving glucocorticoids (B), along with the comparison of HBVr rate among patients receiving glucocorticoids vs. those not receiving (C).

3.5.5. Analysis based on TNF inhibitor (TNFi) type

The included studies evaluated six TNFi agents: etanercept and and Yisaipu, a biosimilar for etanercept [26], adalimumab, infliximab, golimumab and certolizumab pegol. No HBVr cases were identified in the subgroups for certolizumab pegol. In the case of golimumab, only two studies reported data, which rendered meta-analysis infeasible. As visualized in Fig. 8, pooled analysis of the original data yielded the following HBVr rates:

- **For adalimumab**: 0.04 (95% CI: [0.01, 0.08]; I^2 = 0.09%, p = 0.865)
- **For etanercept**: 0.03 (95% CI: [0.01, 0.05]; I^2 = 0%, p = 0.712)
- **For infliximab**: 0.02 (95% CI: [0.00, 0.04]; I^2 = 0%, p = 0.727)

In summary, the rates of HBVr among patients receiving adalimumab and etanercept were 4% and 2%, respectively, which were found to be statistically significant (p <

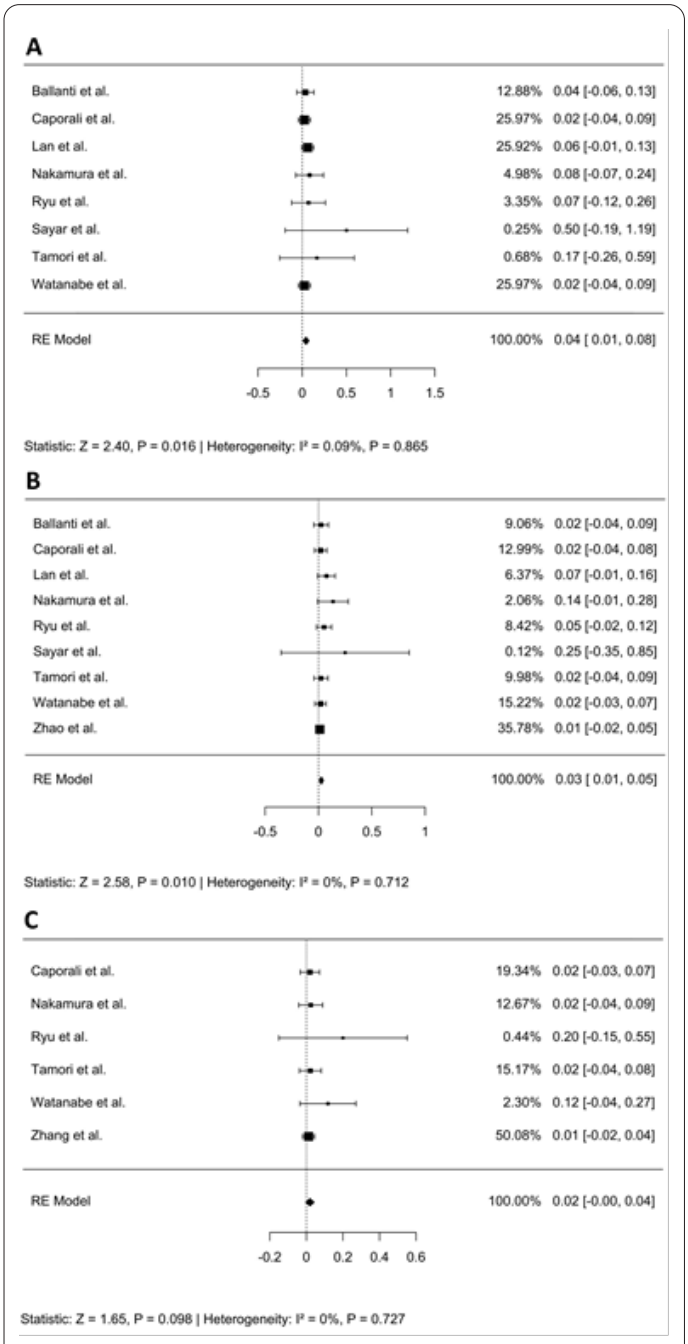

Fig. 8. Forest plots of HBVr rate among patients receiving adalimumab (A), etanercept (B) and infliximab (C).

0.05), while conferring low heterogeneity.

3.6. Publication bias

In clinical trials of this nature, studies without HBV-positive cases may be less likely to be published compared to those with HBV-positive cases, making publication bias inherent and difficult to eliminate. This could result in meta-analyses leaning toward positive conclusions.

Additionally, this study included both English and Chinese literature, which may have biased the results toward populations whose primary languages are English or Chinese. The inclusion of Chinese literature disproportionately increased the weight of HBVr rates observed in Chinese populations, potentially introducing further bias in the calculated HBVr rate.

4. Discussion

4.1. Overall reactivation rate

The findings of this study demonstrate an overall HBVr rate of 0.02 (95% CI: 0.01–0.03) among RA patients treated with TNFi therapy, consistent with low heterogeneity ($I^2 = 0.79\%$, $p = 0.133$). These results contrast with Cantini et al.'s 2014 study, which reported a higher HBVr rate of 0.042 (95% CI: 0.014–0.082) and moderate heterogeneity ($I^2 = 74.7\%$) [27]. Despite the low overall incidence, HBVr remains clinically significant, particularly in specific subgroups. In regions with sufficient healthcare resources, routine liver function monitoring and HBV serological testing may be prudent during and after TNFi therapy. Furthermore, prophylactic antiviral therapy could be considered for patients with a prior history of HBV infection, particularly HBsAg-positive patients, who exhibit significantly higher HBVr rates (16%). However, implementing such measures broadly may lead to resource overutilization, especially in low-risk populations.

In contrast, in resource-limited settings, extending the intervals between follow-ups or reducing the number of screening tests may be a more pragmatic approach. Antiviral treatment could instead be initiated when abnormalities in serum transaminase levels are detected. Some studies have suggested that regular screening for HBsAg and hepatitis B core antibody (HBcAb) in RA patients undergoing TNFi therapy is warranted, but do not recommend routine prophylaxis [7].

4.2. Subgroup analysis by geographic region

This study highlights regional variability in HBVr rates following TNFi therapy, aligning with the known geographic differences in HBV prevalence. Subgroup analysis revealed no reported HBVr cases in European studies, with a pooled rate of 0.01 (95% CI: −0.01 to 0.03, $I^2 = 0\%$, $p = 0.884$), compared to 0.02 (95% CI: 0.01–0.04, $I^2 = 0.03\%$, $p = 0.051$) in Asian studies. This discrepancy correlates with the higher baseline HBV prevalence in Asia (3%) compared to Europe (1.5%), as reported by the WHO [28]. These findings suggest that HBVr risk may partially stem from regional HBV endemicity, with higher reactivation potential in areas where re-exposure to HBV is more likely.

In Europe, the overall HBV infection rate is lower due to factors such as dietary habits, smaller population size, and stricter public health measures [29]. Additionally, lower population density in Europe results in a significantly lower density of HBV-infected individuals compared to Asia, and RA patients using TNFi are even less common. Consequently, collecting sufficient cases for research in Europe is more challenging, leading to fewer studies and a potential publication bias that could underestimate the true HBVr rate [30].

Moreover, national differences in HBV prevention and management protocols further influence HBVr rates. While some countries initiate antiviral therapy based on abnormal liver function tests, others rely on HBV DNA levels as the treatment threshold. These variations contribute to the observed discrepancies in HBVr rates between regions [31, 32]. In conclusion, the HBVr rate among RA patients with a history of HBV infection is lower in Europe than in Asia, although potential biases must be carefully considered when interpreting these findings.

4.3. Subgroup analysis by HBsAg status

The subgroup analysis of HBsAg-positive and HBsAg-negative patients indicates a potential association between HBsAg positivity and HBVr incidence. Studies investigating HBV reactivation (HBVr) in RA patients receiving DMARDs other than TNFi have identified a strong association between HBsAg positivity and HBVr risk. Kuo et al. (2024) reported that among RA patients treated with b/tsDMARDs, HBVr incidence was significantly higher in patients with negative baseline anti-HBs (<10 mIU/mL), with rituximab posing the highest risk, followed by abatacept [33]. Similarly, Lan et al. (2023) demonstrated that HBsAg-negative patients undergoing rituximab therapy for autoimmune diseases exhibited a higher HBVr rate when anti-HBc-positive and lacking protective anti-HBs levels [34]. These findings emphasize the critical role of HBsAg and anti-HBs status in HBVr risk stratification for RA patients receiving b/tsDMARDs. However, due to the limited sample sizes and interactions between various subgroup factors, this relationship should not be considered definitive. HBsAg is known to correlate with the severity of hepatitis B during its pathological course [35], but more robust and reliable evidence from large-scale clinical trials is necessary to confirm these findings. Future studies with larger samples will be critical to elucidating the role of HBsAg in HBVr risk.

4.4. Subgroup analysis based on antiviral drug use

Due to the lack of explicit descriptions regarding antiviral drug use in some of the included studies, the number of studies available for this subgroup analysis was limited. Consequently, the present study did not identify a statistically significant difference in the rate of HBV reactivation based on antiviral drug use.

From a clinical perspective, there is variability in the timing of antiviral prophylaxis implementation [36, 37]. Some clinicians initiate antiviral therapy before or at the onset of TNFi treatment, while others begin prophylaxis only when patients exhibit early warning signs, such as elevated transaminase levels [38]. This division introduces a degree of subjective bias attributable to clinical decision-making, thereby compromising the reliability of the study outcomes. Additionally, the type and dosage of antiviral drugs may also confound the HBV reactivation rate, a limitation not restricted to this subgroup but observed across other subgroup analyses as well.

The lack of a definitive conclusion may also stem from the relatively small number of patients in the antiviral

prophylaxis subgroup. Furthermore, applying continuity correction methods, such as the 1/2 correction, may have influenced the outcomes and introduced bias. To draw robust and credible conclusions, future studies will require larger sample sizes and more precise subgroup definitions.

Data from some of the included studies suggest that antiviral prophylaxis can reduce HBV reactivation rates [8, 39]. Research on the effectiveness of different antiviral regimens indicates that lamivudine may be less effective in preventing HBV reactivation compared to other antiviral agents, likely due to the development of resistance through YMDD motif mutations [40, 41]. However, a 2018 meta-analysis on a similar topic also failed to establish a clear association between antiviral prophylaxis and HBV reactivation [42].

The existing controversy in prior research highlights the ongoing challenges in this field. Given the availability of sufficient medical resources, we recommend the routine use of antiviral prophylaxis for patients receiving TNFi therapy to reduce the likelihood of HBV reactivation and associated adverse events.

4.5. Subgroup analysis based on glucocorticoid use

The subgroup analysis on glucocorticoid use suggests that glucocorticoids may increase the rate of HBV reactivation among the target population. This finding aligns with the conclusions of Grossi et al. [43]. In contrast, Cheng et al. reported that non-steroid chemotherapy reduced the rate and severity of HBV reactivation in HBsAg-positive lymphoma patients [44].

Glucocorticoids are critical therapeutic agents and are widely used in clinical practice, as reflected in treatment guidelines from various countries [45]. To mitigate the risk of HBV reactivation during glucocorticoid therapy, it is advisable to adjust the monitoring frequency of liver function and HBV serological markers. Concurrent antiviral prophylaxis during glucocorticoid treatment should also be considered to reduce the incidence of HBV reactivation [45].

4.6. Subgroup analysis based on drug type

The subgroup analysis by type of TNFi provided limited insights into differences HBVr rates among the agents evaluated. Four TNFi agents were assessed, including etanercept, its biosimilar Yisaipu, adalimumab and infliximab. No HBVr cases were reported for certolizumab pegol, and data on golimumab were insufficient for meta-analysis. The pooled HBVr rates were 4% for adalimumab, 3% for etanercept, and 2% for infliximab. While the differences in HBVr rates between adalimumab and etanercept were statistically significant, the overall analysis suggests that the risk of HBVr across these agents is generally low and similar, with minimal heterogeneity.

A study by Moghoofei et al. [46] in 2018 provided aggregated HBV reactivation data for subgroups of specific antiviral drugs but did not extract data for individual drugs, limiting the clinical applicability of their findings. Mori et al. [47] reported HBV reactivation rates of 2.4% for etanercept, 0.6% for adalimumab, 0% for infliximab, 8.6% for tocilizumab, and 3.3% for rituximab. However, these results lacked rigorous statistical validation, and their reliability is considered inferior to that of meta-analyses.

4.7. Further considerations

Ballanti et al. [6] conducted a follow-up study on 32 patients with RA and a history of HBV infection who were treated with etanercept or adalimumab. They observed no cases of HBVr, but approximately one-fifth of the patients exhibited elevated serum transaminase levels. These elevations were speculated to be related to the use of DMARDs, prophylactic antiviral therapy, or alcohol consumption.

Minozzi et al. performed a meta-analysis of 71 randomized controlled trials and concluded that there is insufficient evidence to suggest that the impact of TNFi on HBVr varies by disease type [48]. Consequently, the study did not perform subgroup analyses based on disease type but instead analyzed RA, ankylosing spondylitis, and psoriatic arthritis patients collectively. However, the study acknowledged a limitation: variations in medications used for different diseases across regions may introduce bias. To minimize confounding factors, restricting the analysis to a single disease type, where feasible, would likely yield more reliable conclusions.

In certain regions, clinical guidelines recommend the use of antiviral prophylaxis at the initiation of TNFi therapy to reduce HBVr rates. While this approach may result in some degree of healthcare resource overuse, it provides significant protection for patients. Allowing HBVr to occur without preventive measures is detrimental to patient outcomes and recovery. Therefore, HBVr represents a serious adverse clinical event, and clinicians must closely monitor liver function during treatment. Any abnormalities, such as elevated transaminase levels, should prompt adjustments to hepatoprotective medications or modifications to antiviral prophylaxis or treatment regimens [49].

From another perspective, current research data do not demonstrate an association between HBVr rates and the underlying diseases in TNFi users. Including patients with various diseases treated with TNFi introduces uncertainty regarding the concurrent use of other medications and their potential interactions, which may increase the risk of HBVr [50]. To avoid such bias, this study focused exclusively on RA patients treated with TNFi. However, this decision presents challenges, as narrowing the study population reduces the sample size and the statistical power required to analyze low-incidence events like HBVr, potentially compromising the reliability of the findings.

Future research should focus on individual patient data meta-analyses to enable more granular stratification of HBV reactivation risk. Such analyses would allow evaluation of outcomes by HBsAg, anti-HBc, and anti-HBs serostatus, baseline HBV DNA levels, antiviral drug class, and concomitant glucocorticoid dose. This level of resolution would provide more precise risk estimates and inform personalized prophylaxis and monitoring strategies in patients with RA receiving TNFi therapy.

4.8. Strengths and limitations

This study has some limitations. The small sample size of included studies, insufficient patient numbers, unclear subgroup classifications, and concurrent use of DMARDs and corticosteroids in most studies preclude the assessment of HBVr risk associated solely with TNFi. In clinical practice, it is challenging to eliminate the influence of other medications, underscoring the need for future clinical trials with appropriate controls. Furthermore, the small number of studies and patients included limits the strength

of the conclusions, necessitating larger and more comprehensive clinical trials.

Regarding data processing, we utilized 1/2 correction and Freeman-Tukey double arcsine transformations to analyze the data. However, due to the limited number of included studies and the relatively low HBVr rate, potential heterogeneity in the analysis cannot be excluded. Thus, increasing the sample size remains essential.

For the patient population with a history of HBV infection and RA treated with TNFi, obtaining large patient datasets is challenging. This issue might be addressed through multicenter studies. Research in this area typically involves small sample sizes; thus, we applied 1/2 correction and Freeman-Tukey transformation with inverse transformation comparisons to ensure data accuracy, enhancing the study's reliability and relevance.

5. Conclusion

In conclusion, this study highlights that rheumatoid arthritis patients with a history of hepatitis B virus infection face a measurable risk of HBV reactivation following tumor necrosis factor inhibitor therapy, although the overall incidence remains relatively low. Subgroup analyses revealed significant regional variations in HBVr rates, suggesting that geographic and possibly healthcare-related factors may influence outcomes. Additionally, patients using corticosteroids in combination with TNFi exhibited a higher risk of HBVr compared to non-users, emphasizing the role of adjunct therapies in modulating reactivation risks. These findings underline the necessity for clinicians to closely monitor liver function and HBV status in RA patients receiving TNFi therapy, particularly in high-risk subgroups such as corticosteroid users. Future research should focus on large-scale, multicenter studies with robust sample sizes to confirm these findings, while also addressing confounding factors such as concomitant drug use and underlying comorbidities. Furthermore, precise clinical trial subgroup data and standardized protocols are essential for developing tailored preventive and therapeutic strategies to mitigate HBVr risk in this vulnerable population.

Abbreviations

HBV (Hepatitis B Virus), HBVr (Hepatitis B Virus Reactivation), RA (Rheumatoid Arthritis), TNFi (Tumor Necrosis Factor Inhibitor), TNF-α (Tumor Necrosis Factor-alpha), DMARDs (Disease-Modifying Antirheumatic Drugs), CTL (Cytotoxic T Lymphocyte), HBsAg (Hepatitis B Surface Antigen), HBcAb (Hepatitis B Core Antibody), ACR (American College of Rheumatology), EULAR (European League Against Rheumatism), RCT (Randomized Controlled Trial), NOS (Newcastle-Ottawa Scale), PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), OR (Odds Ratio), CI (Confidence Interval), SD (Standard Deviation), IQR (Interquartile Range), HCV (Hepatitis C Virus), b/tsDMARDs (Biologic/Targeted Synthetic Disease-Modifying Antirheumatic Drugs).

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publications

All authors confirm that they have read and approved the final version of the manuscript for publication.

Ethics approval and consent to participate

Not applicable. This study is a systematic review and meta-analysis based on previously published studies; no new human or animal data were collected.

Informed consent

Not applicable. No individual participant data are included in this article.

Availability of data and material

The data supporting this study's findings are available from the corresponding author upon reasonable request.

Authors' contributions

P.S. and F.Y. conceived and designed the study. P.S. and A.S. performed the literature search and data extraction. F.Y. and P.S. conducted the statistical analyses and interpreted the results. F.Y. drafted the initial manuscript. P.S. and A.S. critically revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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References

1. Radu AF, Bungau SG (2021) Management of rheumatoid arthritis: An overview. Cells 10 (11): 2857. doi: 10.3390/cells10112857
2. Mehta P, Manson JJ (2020) What Is the Clinical Relevance of TNF Inhibitor Immunogenicity in the Management of Patients With Rheumatoid Arthritis? Front Immunol 11: 589. doi: 10.3389/fimmu.2020.00589
3. Zamri F, de Vries TJ (2020) Use of TNF Inhibitors in Rheumatoid Arthritis and Implications for the Periodontal Status: For the Benefit of Both? Front Immunol 11: 591365. doi: 10.3389/fimmu.2020.591365
4. Fidan S, Capkın E, Arıca DA, Durak S, Okatan IE (2021) Risk of hepatitis B reactivation in patients receiving anti-tumor necrosis factor-α therapy. Int J Rheum Dis 24 (2): 254-259. doi: 10.1111/1756-185X.14034
5. Sayar S, Kürbüz K, Kahraman R, Öztürk O, Çalışkan Z, Levent Doğanay H, Özdil K (2020) Risk of hepatitis B reactivation during anti-TNF therapy; evaluation of patients with past hepatitis B infection. Turk J Gastroenterol 31 (7): 522-528. doi: 10.5152/TJG.2020.19295
6. Ballanti E, Conigliaro P, Chimenti MS, Kroegler B, Di Muzio G, Guarino MD, Triggianese P, Gigliucci G, Novelli L, Barbato C, Perricone R (2014) Use of Anti-Tumor Necrosis Factor Alpha Therapy in Patients with Concurrent Rheumatoid Arthritis and Hepatitis B or Hepatitis C: A Retrospective Analysis of 32 Patients. Drug Dev Res 75: S42-S45. doi: 10.1002/ddr.21193
7. Lee YH, Bae SC, Song GG (2013) Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumour necrosis factor therapy. Clin Exp Rheumatol 31 (1): 118-121. doi:
8. Lin TC, Yoshida K, Tedeschi SK, de Abreu MM, Hashemi N, Solomon DH (2018) Risk of Hepatitis B Virus Reactivation in Patients With Inflammatory Arthritis Receiving Disease-Modifying Antirheumatic Drugs: A Systematic Review and Meta-Analysis. Arthritis Care Res 70 (5): 724-731. doi: 10.1002/acr.23346
9. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Coo-

per NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, Medsger TA, Mitchell DM, Neustadt DH, Pinals RS, Schaller JG, Sharp JT, Wilder RL, Hunder GG (1988) The american rheumatism association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31 (3): 315-324. doi: 10.1002/art.1780310302

10. Kay J, Upchurch KS (2012) ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford) 51 (SUPPL. 6): vi5-vi9. doi: 10.1093/rheumatology/kes279
11. Ekpanyapong S, Reddy KR (2020) Hepatitis B Virus Reactivation: What Is the Issue, and How Should It Be Managed? Clin Liver Dis 24 (3): 317-333. doi: 10.1016/j.cld.2020.04.002
12. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25 (9): 603-605. doi: 10.1007/s10654-010-9491-z
13. Watanabe T, Fukae J, Fukaya S, Sawamukai N, Isobe M, Matsuhashi M, Shimizu M, Akikawa K, Tanimura K, Atsumi T, Koike T (2019) Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 22 (4): 574-582. doi: 10.1111/1756-185X.13401
14. Zhao Y, Wang Y, Wang X, Guo W, Zhao Z, Wang Z (2017) Hepatic safety of recombinant human type II tumor necrosis factor receptor-antibody fusion protein injection in the treatment of rheumatoid arthritis patients with chronic hepatitis B. Journal of Practical Medical Techniques 24 (10): 1109-1111. doi: 10.19522/j.cnki.1671-5098.2017.10.029
15. Chen MH, Chen MH, Liu CY, Tsai CY, Huang DF, Lin HY, Lee MH, Huang YH (2017) Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis 215 (4): 566-573. doi: 10.1093/infdis/jiw606
16. Jin De, Tie N, Liu J, Zhao L, Hao D, Zhao Y (2015) Study of Hepatitis B Virus Activity After Tumor Necrosis Factor α Antagonist Treatment in Patients With Inflammatory Arthropathy. Chinese Journal of Internal Medicine 54 (4): 313-316. doi: 10.3760/cma.j.issn.0578-1426.2015.04.008
17. Jung SM, Kang JY, Min HK, Koh JH, Suh YS, Lee JH, Lee J, Lee JY, Kim JM, Kwok SK, Ju JH, Park KS, Kim HY, Park SH (2014) Reactivation of Hepatitis B Virus in Patients Treated with Anti-TNF Therapy. Ann Rheum Dis 73 (Suppl 2): 482.482. doi: 10.1136/annrheumdis-2014-eular.5251
18. Nakamura J, Nagashima T, Nagatani K, Yoshio T, Iwamoto M, Minota S (2016) Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 19 (5): 470-475. doi: 10.1111/1756-185X.12359
19. Biondo MI, Germano V, Pietrosanti M, Canzoni M, Marignani M, Stroffolini T, Salemi S, D'Amelio R (2014) Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. Eur J Intern Med 25 (5): 482-484. doi: 10.1016/j.ejim.2013.11.014
20. Zhang X, Zhang F, Wu D, Bao C, Zhu P, Zhang X, Huang C, He D, Tao Y, Fang Y, Gu J, Wu H, Sun L, Yang X, Huang F, Xu H, Zhao D, Zhang M, Zheng Y, Li Z (2013) Safety of infliximab therapy in rheumatoid arthritis patients with previous exposure to hepatitis B virus. Int J Rheum Dis 16 (4): 408-412. doi: 10.1111/1756-185X.12125
21. Ryu HH, Lee EY, Shin K, Choi IA, Lee YJ, Yoo B, Park MC, Park YB, Bae SC, Yoo WH, Kim SI, Lee EB, Song YW (2012) Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNFα agents: A retrospective analysis of 49 cases. Clin Rheumatol 31 (6): 931-936. doi: 10.1007/s10067-012-1960-1
22. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, Yang SS (2011) Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis 70 (10): 1719-1725. doi: 10.1136/ard.2010.148783
23. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, Enomoto M, Inaba M, Nakatani T, Hino M, Kawada N (2011) Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: Evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol 46 (4): 556-564. doi: 10.1007/s00535-010-0367-5
24. Caporali R, Bobbio-Pallavicini F, Atzeni F, Sakellariou G, Caprioli M, Montecucco C, Sarzi-Puttini P (2010) Safety of tumor necrosis factor α blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res 62 (6): 749-754. doi: 10.1002/acr.20130
25. Charpin C, Guis S, Colson P, Borentain P, Mattéi JP, Alcaraz P, Balandraud N, Thomachot B, Roudier J, Gérolami R (2009) Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: Results from a cohort of 21 patients. Arthritis Res Ther 11 (6): R179. doi: 10.1186/ar2868
26. Lu H, Wang Y, Wang X, Wu X, Zhou L, Lin L, Sheng R, Tian H, Li T, Xu H (2021) Yisaipu® Provide AS Patients With an Economical Therapeutic Option While Original Biologicals are More Advantageous in the COVID-19 Epidemic Situation. Front Pharmacol 12: 692768. doi: 10.3389/fphar.2021.692768
27. Cantini F, Boccia S, Goletti D, Iannone F, Leoncini E, Panic N, Prignano F, Gaeta GB (2014) HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF- α) agents for rheumatic and dermatologic conditions: A systematic review and meta-analysis. Int J Rheumatol 2014: 926836-926836. doi: 10.1155/2014/926836
28. World Health O (2022) Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030. World Health Organization,
29. Alberts CJ, Clifford GM, Georges D, Negro F, Lesi OA, Hutin YJF, de Martel C (2022) Worldwide prevalence of hepatitis B virus and hepatitis C virus among patients with cirrhosis at country, region, and global levels: a systematic review. Lancet Gastroenterol Hepatol 7 (8): 724-735. doi: 10.1016/S2468-1253(22)00050-4
30. Hsu YC, Huang DQ, Nguyen MH (2023) Global burden of hepatitis B virus: current status, missed opportunities and a call for action. Nat Rev Gastroenterol Hepatol 20 (8): 524-537. doi: 10.1038/s41575-023-00760-9
31. Wong Grace LH (2024) Updated Guidelines for the Prevention and Management of Chronic Hepatitis B—World Health Organization 2024 Compared With China 2022 HBV Guidelines. J Viral Hepat 31 Suppl 2: 13-22. doi: 10.1111/jvh.14032
32. Yardeni D, Chang KM, Ghany MG (2023) Current Best Practice in Hepatitis B Management and Understanding Long-term Prospects for Cure. Gastroenterology 164 (1): 42-60.e46. doi: 10.1053/j.gastro.2022.10.008
33. Kuo MH, Tseng CW, Ko PH, Wang ST, Lu MC, Tung CH, Tseng KC, Huang KY, Lee CH, Lai NS (2024) HBV reactivation in HBsAg−/HBcAb+ rheumatoid arthritis patients receiving biologic/targeted synthetic DMARDs. Liver Int 44 (2): 497-507. doi: 10.1111/liv.15793
34. Lan TY, Lin YC, Tseng TC, Yang HC, Kao JH, Cheng CF, Lee TJ, Huang SC, Lu CH, Li KJ, Hsieh SC (2023) Risk of Hepatitis B Virus (HBV) Reactivation in HBsAg-Negative, Anti-HBc-Negative Patients Receiving Rituximab for Autoimmune Diseases in

HBV Endemic Areas. Gut Liver 17 (2): 288-298. doi: 10.5009/GNL210551

35. Cholongitas E, Haidich AB, Apostolidou-Kiouti F, Chalevas P, Papatheodoridis GV Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. Ann Gastroenterol(1108-7471 (Print)). doi:
36. Celsa C, Rizzo GEM, Di Maria G, Enea M, Vaccaro M, Rancatore G, Graceffa P, Falco G, Petta S, Cabibbo G, Calvaruso V, Craxì A, Cammà C, Di Marco V, Rizzo C, Destro Castaniti GM, Di Stefano V, Madonia G, Tilotta G, Agliastro G (2024) What is the benefit of prophylaxis to prevent HBV reactivation in HBsAg-negative anti-HBc-positive patients? Meta-analysis and decision curve analysis. Liver Int 44 (11): 2890-2903. doi: 10.1111/liv.16064
37. Yamauchi N, Maruyama D, Choi I, Atsuta Y, Sakai R, Miyashita K, Moriuchi Y, Tsujimura H, Kubota N, Yamamoto G, Igarashi T, Izutsu K, Yoshida S, Kojima K, Uchida T, Inoue Y, Tsukamoto N, Ohtsuka E, Suzuki S, Inaguma Y, Ichikawa S, Gomyo H, Ushijima Y, Nosaka K, Kurata M, Tanaka Y, Ueda R, Mizokami M, Kusumoto S (2021) Prophylactic antiviral therapy for hepatitis B virus surface antigen-positive patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy. Cancer Sci 112 (5): 1943-1954. doi: 10.1111/cas.14846
38. Lau GKK, Yiu HHY, Fong DYT, Cheng HC, Au WY, Lai LSF, Cheung M, Zhang HY, Lie A, Ngan R, Liang R (2003) Early Is Superior to Deferred Preemptive Lamivudine Therapy for Hepatitis B Patients Undergoing Chemotherapy. Gastroenterology 125 (6): 1742-1749. doi: 10.1053/j.gastro.2003.09.026
39. Hsu C, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, Lin TH, Hsiao HH, Young JH, Chang MC, Liao YM, Li CC, Wu HB, Tien HF, Chao TY, Liu TW, Cheng AL, Chen PJ (2008) A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: A randomized trial. Hepatology 47 (3): 844-853. doi: 10.1002/hep.22106
40. Su J, Long L, Zou K (2018) Antiviral prophylaxis for preventing reactivation of hepatitis B virus in rheumatic patients: a systematic review and meta-analysis. Clin Rheumatol 37 (12): 3201-3214. doi: 10.1007/s10067-018-4096-0
41. Utku AC, Karabay O (2016) Treatment of chronic hepatitis B patients with tyrosine-methionine-aspartate-aspartate mutations. World J Gastroenterol 22: 1727-1728. doi: 10.3748/WJG.V22.I4.1727
42. Su YC, Lin PC, Yu HC, Wu CC (2018) 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 74 (9): 1111-1119. doi: 10.1007/s00228-018-2487-4
43. Grossi O, Généreau T (2013) Corticoïdes et... infections, dopage, chirurgie et sexualité. Rev Med Interne 34 (5): 269-278. doi: 10.1016/j.revmed.2012.12.008
44. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, Kao WY, Uen WC, Hsu CH, Tien HF, Chao TY, Chen LT, Whang-Peng J (2003) Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology 37 (6): 1320-1328. doi: 10.1053/jhep.2003.50220
45. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, Vaysbrot E, McNaughton C, Osani M, Shmerling RH, Curtis JR, Furst DE, Parks D, Kavanaugh A, O'Dell J, King C, Leong A, Matteson EL, Schousboe JT, Drevlow B, Ginsberg S, Grober J, St.Clair EW, Tindall E, Miller AS, McAlindon T (2016) 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res 68 (1): 1-26. doi: 10.1002/art.39480
46. Moghoofei M, Mostafaei S, Ashraf-Ganjouei A, Kavosi H, Mahmoudi M (2018) HBV reactivation in rheumatic diseases patients under therapy: A meta-analysis. Microb Pathog 114: 436-443. doi: 10.1016/j.micpath.2017.12.014
47. Mori S, Fujiyama S (2015) Hepatitis B virus reactivation associated with antirheumatic therapy: Risk and prophylaxis recommendations. World J Gastroenterol 21 (36): 10274-10289. doi: 10.3748/wjg.v21.i36.10274
48. Minozzi S, Bonovas S, Lytras T, Pecoraro V, González-Lorenzo M, Bastiampillai AJ, Gabrielli EM, Lonati AC, Moja L, Cinquini M, Marino V, Matucci A, Milano GM, Tocci G, Scarpa R, Goletti D, Cantini F (2016) Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: A systematic review and meta-analysis. Expert Opin Drug Saf 15 (sup1): 11-34. doi: 10.1080/14740338.2016.1240783
49. Perrillo RP, Gish R, Falck-Ytter YT (2015) American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis b virus reactivation during immunosuppressive drug therapy. Gastroenterology 148 (1): 221-244.e223. doi: 10.1053/j.gastro.2014.10.038
50. Aygen B, Demir AM, Gümüş M, Karabay O, Kaymakoğlu S, Köksal AŞ, Köksal İ, Örmeci N, Tabak F (2018) Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report. Turk J Gastroenterol 29 (3): 259-269. doi: 10.5152/tjg.2018.18263