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ВИРУСОЛОГИЧЕСКИЙ РЕЦИДИВ У ПАЦИЕНТОВ С ОТМЕНОЙ ПРОТИВОВИРУСНОГО ЛЕЧЕНИЯ ХРОНИЧЕСКОГО ГЕПАТИТА В: СИСТЕМАТИЧЕСКИЙ ОБЗОР И МЕТА-АНАЛИЗ

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SYSTEMIC REVIEW AND META-ANALYSIS OF VIROLOGICAL RELAPSE RATE IN PATIENTS WITH DISCONTINUATION OF HEPATITIS B TREATMENT

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Резюме. Хронический гепатит В остается актуальной проблемой здравоохранения, одним из основных подходов лечения которого является назначение нуклеоз(-т)идных аналогов (НА) как правило на длительный срок. Клинические руководства допускают отмену НА, тем не менее долгосрочные результаты их отмены недостаточно изучены. Целью данного исследования оценка безопасности отмены НА у пациентов с хроническим гепатитом В.

Ключевые слова: хронический гепатит В, нуклеоз(-т)идные аналоги, отмена лечения, мета-анализ.

Resume. Chronic Hepatitis B (CHB) remains a major global health concern, with long-term use ofnucleos(t)ide analogues (NA) being the mainstay of antiviral therapy Current guidelines provide stopping criteria for NA therapy, but concerns about virological relapse and long-term outcomes persist. Thissystemic review and meta-analysis aim to evaluate the safety of discontinuing nucleos(t)ide analogues in chronic hepatitis B patients who meet the stopping criteria.

Keywords: chronic Hepatitis B, nucleos(t)ide analogues, treatment discontinuation, meta-analysis.

Relevance. The long-term management of CHB is crucial in reducing disease progression and preventing hepatocellular carcinoma. While NA therapy effectively suppresses viral replication, indefinite treatment poses economic burdens and potential adverse effects. Understanding the safety of NA discontinuation is essential for optimizing treatment strategies.

Aim: this study aims to assess the risk of virological relapse in CHB patients who meet the stopping criteria.

Objectives:

1. Screen medical databases PubMed, Google Scholar and Science Direct for original researches that report the outcomes of NA discontinuation.
2. Conduct a systematic review and meta-analysis of studies assessing NA discontinuation in CHB patients.
3. Determine the incidence of virological post-NA discontinuation.

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Materials and methods. A systematic search was conducted in PubMed, Google Scholar and Science Direct databases using predefined keywords. Studies reporting relapse rates following nucleos(t)ide analogue (NA) discontinuation in patients with chronic hepatitis B (CHB) were included in this meta-analysis. A total of 62 full-text articles were retrieved; after removing 35 duplicates, 27 studies met the eligibility criteria and were included in the final analysis.

The inclusion criteria were as follows: patients aged 18 years or older, infected solely with hepatitis B virus (HBV), treated exclusively with nucleos(t)ide analogues, a minimum follow-up duration of 12 months and papers which reported random control trials, observational studies and case control studies. Exclusion criteria included the presence of cirrhosis, co-infection with other hepatitis viruses, significant comorbidities, or treatment involving pegylated interferon.

Data extraction included study characteristics, patient demographics, NA used,HBeAg status, stopping criteria, and relapse outcomes. Meta-analysis was performed using R (ver. 4.4.1) with packages meta, metaphor, calculating pooled estimates and confidence intervals of virological and clinical relapse post NA discontinuation. Heterogeneity was assessed using I^2 statistics, and meta-regression was applied to explore influencing factors.

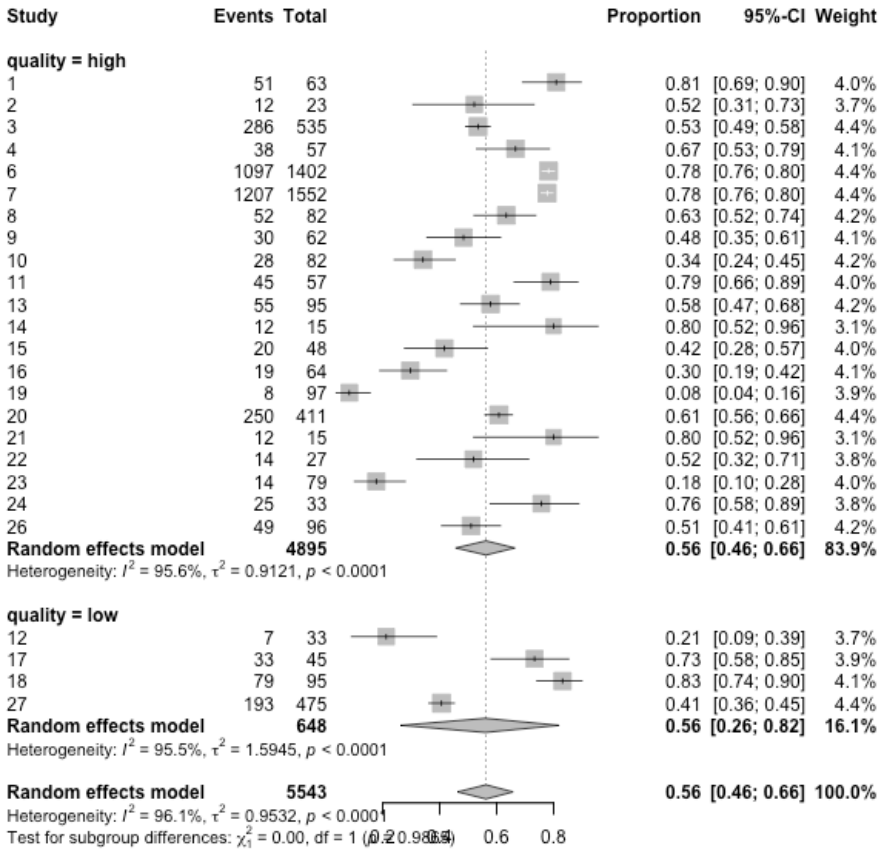

Fig. 1 – Forest plot with subgroups by NOS

Results and their discussion. The analysis included 27 studies with a total of 6503patients. The heterogenicity was (97.3%), thus we used random effect model to

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estimate effect. The pooled virological relapse rate was 56.3%, the results are depicted in a forest plot (Fig. 1).

We evaluated the presence of publication bias among the included studies, and the findings from this assessment are reported in the following figure (Fig. 2).

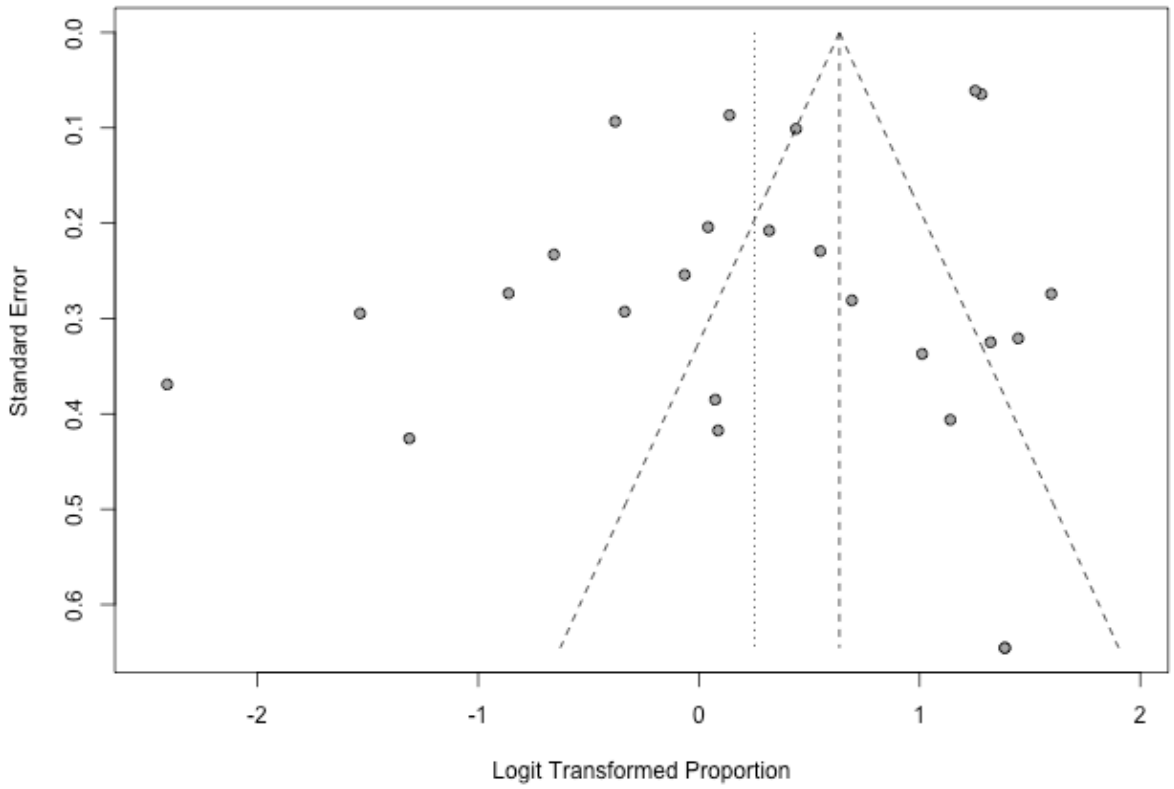

Fig. 2 – Funnel plot representing the publication bias

Publication bias was assessed graphically using a funnel plot. In an unbiased distribution, studies are expected to fall symmetrically within the funnel or along the reference lines. However, the plot demonstrated a lack of such symmetry, indicating potential publication bias. Specifically, there was an overrepresentation of studies with intermediate standard errors reporting lower relapse rates, while smaller studies with higher relapse rates appeared to be underrepresented. This suggests that smaller studies yielding higher relapse rates – likely considered expected outcomes – may be less frequently published, potentially due to cognitive or selective reporting biases. Conversely, studies reporting lower relapse rates may be preferentially published.

To address the potential publication bias, we applied the trim-and-fill method to simulate the presence of smaller studies with higher standard errors and elevated relapse rates, which may have been underreported. This approach allowed us to estimate the impact of these missing studies on the overall effect size. The adjusted analysis, accounting for this simulated data and assuming high heterogeneity, increased the pooled relapse rate from 56% to 70%. The detailed results of this adjusted model are provided below (Fig.3).

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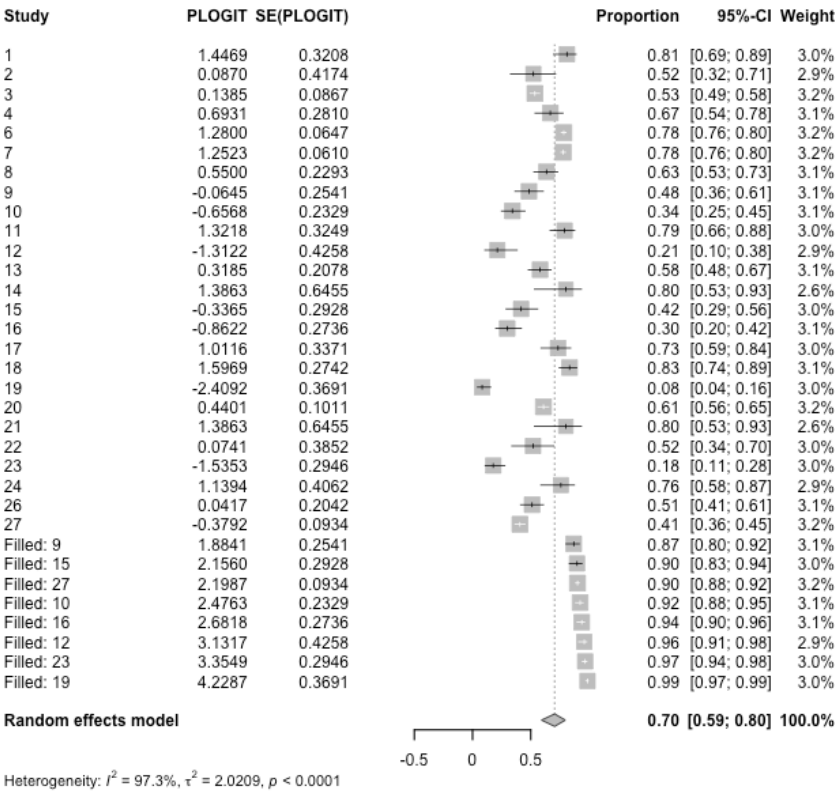

Fig. 3 – Trim-fill forest plot

To further explore the sources of heterogeneity, we conducted a meta-regression analysis using the Newcastle-Ottawa Scale (NOS) score, geographic region, and publication year as potential moderators. Despite incorporating these predictors, substantial heterogeneity remained unexplained. The results were as follows (table 1):

Tbl. 1. Results of meta regression

Moderator	Logit (β)	p-value	Probability [95% CI] *
Intercept	–0.108	0.947	47% [4%–96%]
Year: Pre-2020 (vs. Post)	–0.371	0.452	38% [19%–65%]
Region: Europe (vs. others)	+0.044	0.933	48% [27%–75%]
NOS	+0.076	0.741	-

There was considerable variability across the studies included in the analysis, as indicated by a high I^2 value of 97%, suggesting substantial heterogeneity in the effect sizes. Additionally, the between-study variance was substantial, with a τ^2 value of 1.09, further supporting the presence of significant differences among the studies. Notably, the moderators included in the analysis failed to explain any of this observed heterogeneity, as reflected by an R^2 value of 0%.

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These findings suggest that the high degree of heterogeneity could not be attributed to study quality, geographic region, or year of publication.

Conclusion. Our findings indicate that 56.3% of patients experienced relapse following the discontinuation of nucleos(t)ide analogues (NAs), raising concerns about the current practice of stopping antiviral therapy in chronic hepatitis B management. Given the substantial heterogeneity observed across studies, it is essential to conduct further research to strengthen the evidence base and identify potential influencing factors.

Egger's test revealed signs of publication bias, suggesting an underrepresentation of small-sample studies reporting high relapse rates. To investigate the sources of heterogeneity, we performed a meta-regression using the Newcastle-Ottawa Scale, geographic region, and publication year as predictors. However, none of these variables demonstrated statistical significance, and thus did not account for the observed heterogeneity. As a result, we plan to extend our analysis using additional predictors that may better explain the variability in relapse rates.

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