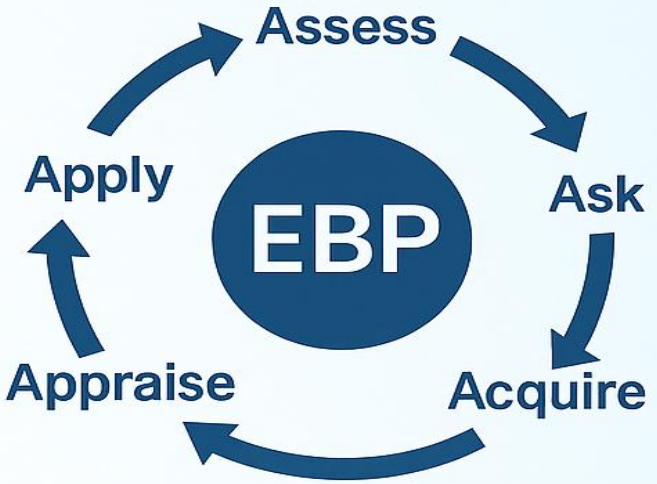
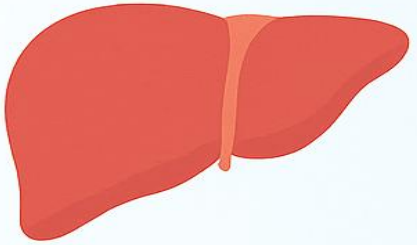
Evidence-Based Medicine in Action:



How Critical Appraisal Transforms Clinical Decisions

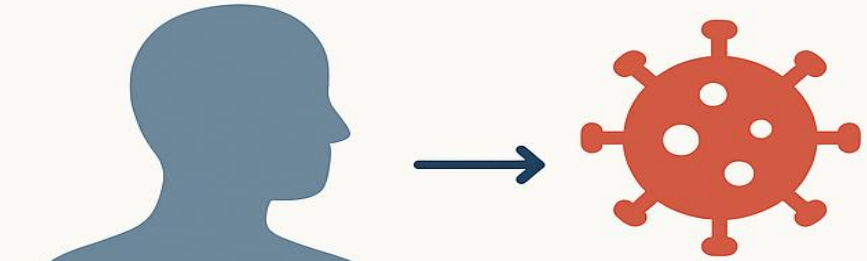


The Case of Hepatitis B Reactivation with Novel Immunosuppressives

Marouf Alhalabi & Hussam Aldeen Alshiekh

Department of Gastroenterology, Damascus Hospital & Iben Al-Nafees Hospital, Syria

A Clinician’s Dilemma at the Bedside



A patient with PsA and chronic HBV needs secukinumab (IL-17).

Answer determines: antivirals for years vs. careful monitoring

What is the true reactivation risk?

IL-17 / secukinumab

Clinician turns to the literature:
“Surely there’s a meta-analysis...

RHEUMATOLOGY

British Society for Rheumatology

Volume 64, Issue 3
March 2025

JOURNAL ARTICLE

Hepatitis B reactivation in PsA patients: an SLR and meta-analysis for IL-17, IL-23 and JAK inhibitors

FREE

Theodoros Androutsakos , Konstantinos Dimitriadis , Maria-Loukia Koutsompina , Konstantinos D Vassilakis , Avraam Pouliakis , George E Fragoulis ✉

Rheumatology, Volume 64, Issue 3, March 2025, Pages 935–942,
https://doi.org/10.1093/rheumatology/keae445

Article Contents

Meta-Analysis: Reassuringly Low Risk

(Androutsakos 2025)

IL-17 4%

IL-12/23 2%

JAKi 4%

All drugs look equally safe

Monitoring may be enough

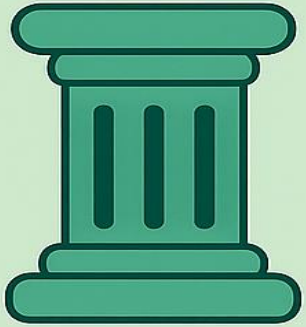
The story could have ended here...

but should it?

WHY IS CRITICAL APPRAISAL IMPORTANT?

* *even* **IF** *you download medical articles from peer-reviewed journals of well-known societies and* **WITH** *high level of evidence*

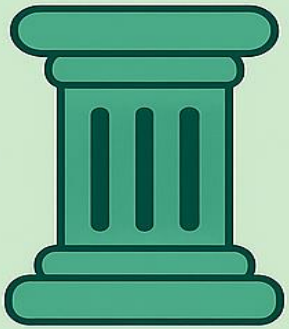
Evidence-Based Medicine: Trust, But Verify



VALIDITY

Is this study valid?

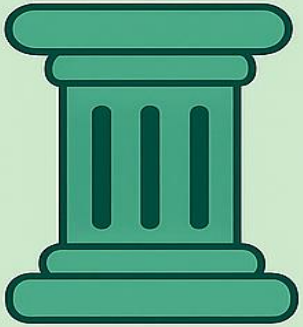
- methods
- search
- analysis



RESULTS

What are the true results?

- effect size, CIs, τ^2, I, Q, sensitivity, Doi + LFK



APPLICABILITY

Are they applicable to my patient?

Good science requires more than headlines—it requires critical appraisal.

Flaws in Previous Search Strategy for HBV Reactivation Risk

Incomplete

- ✗ Anti-IL17
- ✗ Anti-IL23
  JAK inhibitors
- ✓ HBV
- ✗ PsA
- ✗ Psoriasis
- ✓ Autoimmune diseases

Important diseases not captured

Crohn's disease

Polycythemia vera

✗ **Pareneteses/ logic errors** (OR leaking into AND)

✗ **lopers**

Complete & robust

Population
PsA, RA, Psoriasis, Is, Crohn's, PV

Intervention
IL-17, IL-23, IL-12/23, JAK inhibitors

Comparator
No treatment

Outcome
HBV reactivation

A flawed search can lead to missed evidence → corrected search ensures inclusion of Crohn's disease

Common Incorrect Approach

Used pooled mean estimates instead of proportion data

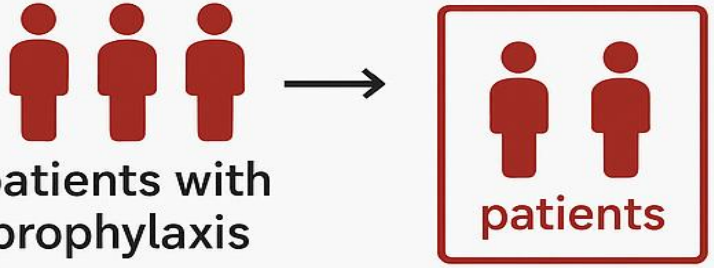
Converted median and interquartile range to mean ± SD using Hozo et *al*. and Wan et *al*. formulas

Used Deep Meta Tool, Version 1 for mean estimation

Not suitable for incidence or prevalence meta-analysis (distorts rare event estimates)

Errors in Current Risk Assessment of Reactivation

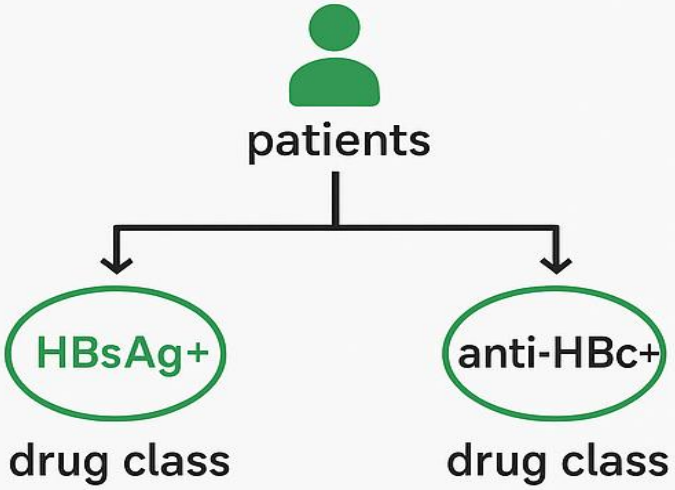
Why current analysis misleading



Diluted risk → artificially safer

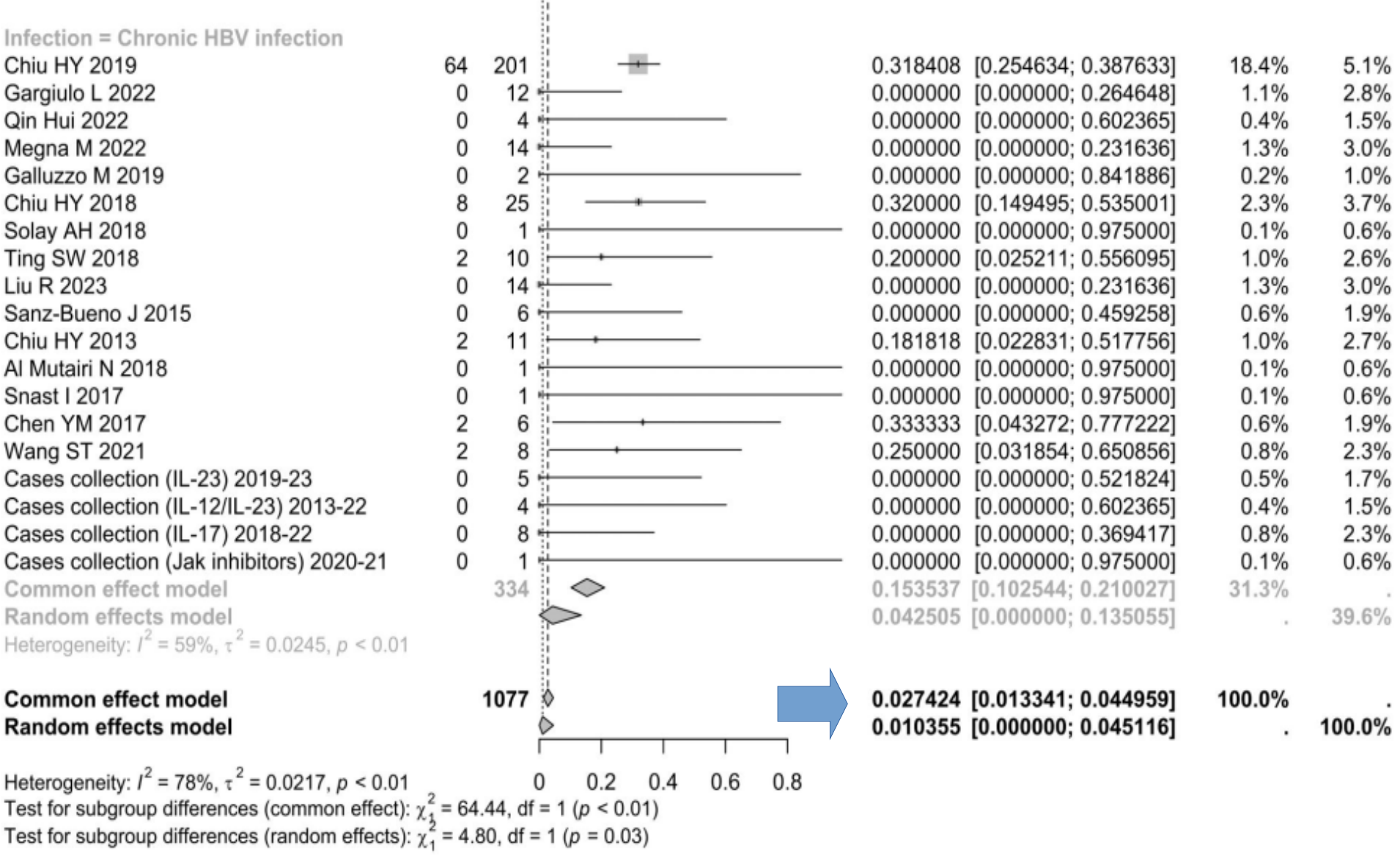
1. **Error #1:** Lumping all drug classes as a single group according to HBsAg status
2. **Error #2:** Calculating per drug class without HBsAg status (mixes HBsAg+ and anti-HBc+)

Correct method: Stratify first by HBsAg status

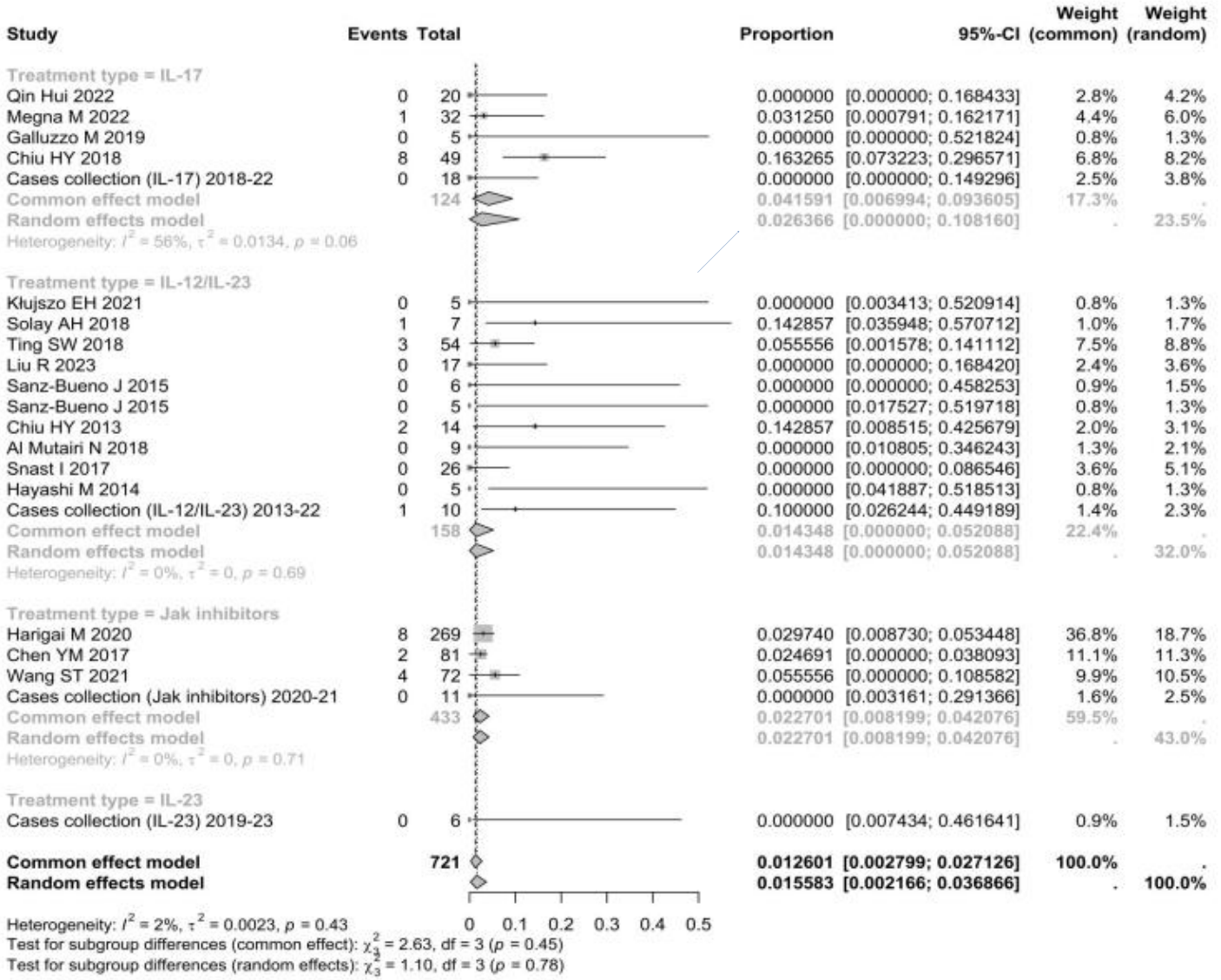


This preserves true risk signals and avoids dilution

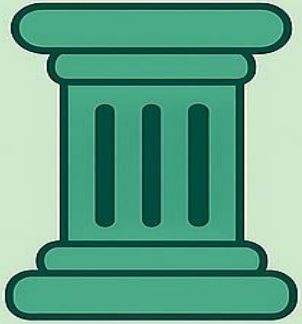
High-risk groups appear safer than they are


Infection = Chronic HBV infection
Chiu HY 2019 64 201 0.318408 [0.254634; 0.387633] 18.4% 5.1%
Gargiulo L 2022 0 12 0.000000 [0.000000; 0.264648] 1.1% 2.8%
Qin Hui 2022 0 4 0.000000 [0.000000; 0.602365] 0.4% 1.5%
Megna M 2022 0 14 0.000000 [0.000000; 0.231636] 1.3% 3.0%
Galluzzo M 2019 0 2 0.000000 [0.000000; 0.841886] 0.2% 1.0%
Chiu HY 2018 8 25 0.320000 [0.149495; 0.535001] 2.3% 3.7%
Solay AH 2018 0 1 0.000000 [0.000000; 0.975000] 0.1% 0.6%
Ting SW 2018 2 10 0.200000 [0.025211; 0.556095] 1.0% 2.6%
Liu R 2023 0 14 0.000000 [0.000000; 0.231636] 1.3% 3.0%
Sanz-Bueno J 2015 0 6 0.000000 [0.000000; 0.459258] 0.6% 1.9%
Chiu HY 2013 2 11 0.181818 [0.022831; 0.517756] 1.0% 2.7%
Al Mutairi N 2018 0 1 0.000000 [0.000000; 0.975000] 0.1% 0.6%
Snast I 2017 0 1 0.000000 [0.000000; 0.975000] 0.1% 0.6%
Chen YM 2017 2 6 0.333333 [0.043272; 0.777222] 0.6% 1.9%
Wang ST 2021 2 8 0.250000 [0.031854; 0.650856] 0.8% 2.3%
Cases collection (IL-23) 2019-23 0 5 0.000000 [0.000000; 0.521824] 0.5% 1.7%
Cases collection (IL-12/IL-23) 2013-22 0 4 0.000000 [0.000000; 0.602365] 0.4% 1.5%
Cases collection (IL-17) 2018-22 0 8 0.000000 [0.000000; 0.369417] 0.8% 2.3%
Cases collection (Jak inhibitors) 2020-21 0 1 0.000000 [0.000000; 0.975000] 0.1% 0.6%
Common effect model 334 0.153537 [0.102544; 0.210027] 31.3% .
Random effects model 0.042505 [0.000000; 0.135055] . 39.6%
Heterogeneity: I^2 = 59%, τ^2 = 0.0245, p < 0.01
Common effect model 1077 0.027424 [0.013341; 0.044959] 100.0% .
Random effects model 0.010355 [0.000000; 0.045116] . 100.0%
0 0.2 0.4 0.6 0.8
Heterogeneity: I^2 = 78%, τ^2 = 0.0217, p < 0.01
Test for subgroup differences (common effect): χ^2_1 = 64.44, df = 1 (p < 0.01)
Test for subgroup differences (random effects): χ^2_1 = 4.80, df = 1 (p = 0.03)

5


Study
Events
Total
Proportion
95%-CI
Weight (common)
Weight (random)
Treatment type = IL-17
Qin Hui 2022 0 20 0.000000 [0.000000; 0.168433] 2.8% 4.2%
Megna M 2022 1 32 0.031250 [0.000791; 0.162171] 4.4% 6.0%
Galluzzo M 2019 0 5 0.000000 [0.000000; 0.521824] 0.8% 1.3%
Chiu HY 2018 8 49 0.163265 [0.073223; 0.296571] 6.8% 8.2%
Cases collection (IL-17) 2018-22 0 18 0.000000 [0.000000; 0.149296] 2.5% 3.8%
Common effect model 124 0.041591 [0.006994; 0.093605] 17.3% .
Random effects model 0.026366 [0.000000; 0.108160] . 23.5%
Heterogeneity: I^2 = 56%, τ^2 = 0.0134, p = 0.06
Treatment type = IL-12/IL-23
Kłujszo EH 2021 0 5 0.000000 [0.003413; 0.520914] 0.8% 1.3%
Solay AH 2018 1 7 0.142857 [0.035948; 0.570712] 1.0% 1.7%
Ting SW 2018 3 54 0.055556 [0.001578; 0.141112] 7.5% 8.8%
Liu R 2023 0 17 0.000000 [0.000000; 0.168420] 2.4% 3.6%
Sanz-Bueno J 2015 0 6 0.000000 [0.000000; 0.458253] 0.9% 1.5%
Sanz-Bueno J 2015 0 5 0.000000 [0.017527; 0.519718] 0.8% 1.3%
Chiu HY 2013 2 14 0.142857 [0.008515; 0.425679] 2.0% 3.1%
Al Mutairi N 2018 0 9 0.000000 [0.010805; 0.346243] 1.3% 2.1%
Snast I 2017 0 26 0.000000 [0.000000; 0.086546] 3.6% 5.1%
Hayashi M 2014 0 5 0.000000 [0.041887; 0.518513] 0.8% 1.3%
Cases collection (IL-12/IL-23) 2013-22 1 10 0.100000 [0.026244; 0.449189] 1.4% 2.3%
Common effect model 158 0.014348 [0.000000; 0.052088] 22.4% .
Random effects model 0.014348 [0.000000; 0.052088] . 32.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.69
Treatment type = Jak inhibitors
Harigai M 2020 8 269 0.029740 [0.008730; 0.053448] 36.8% 18.7%
Chen YM 2017 2 81 0.024691 [0.000000; 0.038093] 11.1% 11.3%
Wang ST 2021 4 72 0.055556 [0.000000; 0.108582] 9.9% 10.5%
Cases collection (Jak inhibitors) 2020-21 0 11 0.000000 [0.003161; 0.291366] 1.6% 2.5%
Common effect model 433 0.022701 [0.008199; 0.042076] 59.5% .
Random effects model 0.022701 [0.008199; 0.042076] . 43.0%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.71
Treatment type = IL-23
Cases collection (IL-23) 2019-23 0 6 0.000000 [0.007434; 0.461641] 0.9% 1.5%
Common effect model 721 0.012601 [0.002799; 0.027126] 100.0% .
Random effects model 0.015583 [0.002166; 0.036866] . 100.0%
Heterogeneity: I^2 = 2%, τ^2 = 0.0023, p = 0.43
Test for subgroup differences (common effect): χ^2_3 = 2.63, df = 3 (p = 0.45)
Test for subgroup differences (random effects): χ^2_3 = 1.10, df = 3 (p = 0.78)
0
0.1
0.2
0.3
0.4
0.5

Evidence-Based Medicine: Trust, But Verify



RESULTS

What are the true results?

- effect size, CIs, τ^2, I, Q, sensitivity, Doi + LFK

APPLICABILITY

Are they applicable to my patient?

Good science requires more than headlines—it requires critical appraisal.

Bias and Heterogenity in Meta-Analysis

1 Heterogeneity

I² statistic

Percentage of

Tau² (τ^2)

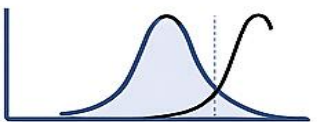
Estimates between-

Heterogeneity: $I^2 = 78\%$, $\tau^2 = 0.0217$, $p < 0.01$

Test for subgroup differences (common effect): $\chi^2_1 = 64.44$, df = 1 ($p < 0.01$)

Test for subgroup differences (random effects): $\chi^2_1 = 4.80$, df = 1 ($p = 0.03$)

4 P value



P value for Q

Assesses

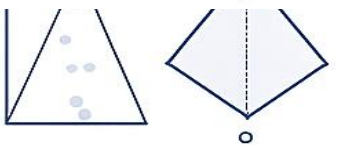
5

ROBINS-I

Risk of bias in non-tandomized studies (low/moderate/serious)

Newcastle–Ottawa Scale (NOS)

Assesses study quality (selection. comparability, outcomes)



Egger Test & Funnel Plot

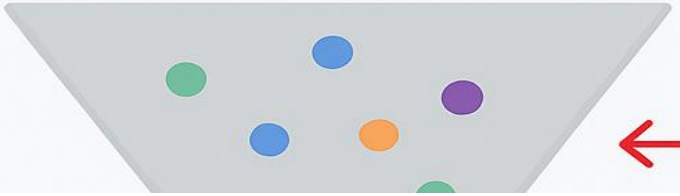
Quantifies bias using DOI plot
LFK | = no bias

DOI Plot & LFK Index

Quantifies bias using Doi plot (LFK |<1 = no bias| >2 = major bias)

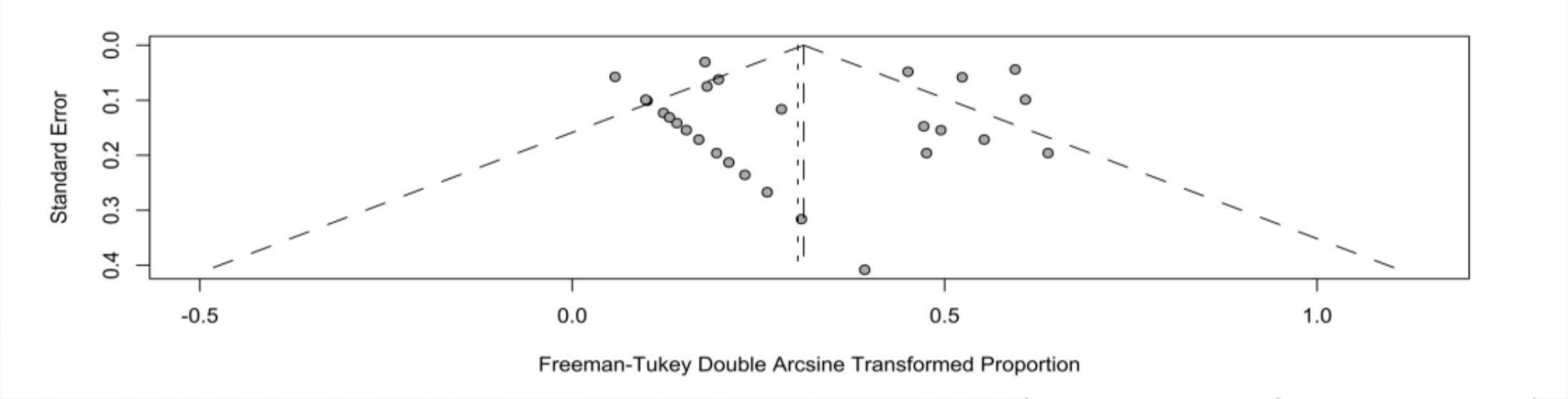
Heterogeneity and bias evaluation ensure the robustness and validity of meta-analysis findings.

FUNNEL PLOT ASYMMETRY ≠ PUBLICATION



Not always publication

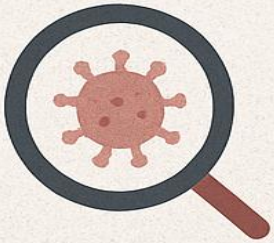
LIMITATIONS OF FUNNEL PLOTS



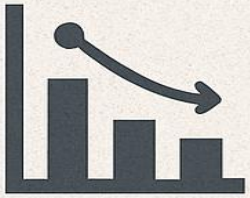
Use funnel plots as exploratory tools only.
Always complement with sensitivity analyse & bias assessments

Low diagnostic accuracy

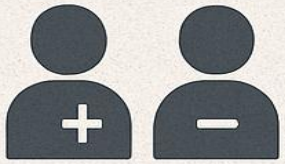
ERRORS IN META-ANALYSIS



First error in search strategy: missing disease to include in search strategy



Using wrong statistics



Including patients with mixing patients on HBV treatment with non-HBV treatment

Mixing HBsAg patients with negative HBsAg and positive HBc

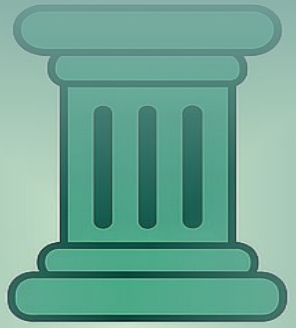
Mixing different drug class

Evidence-Based Medicine: Trust, But Verify

VALIDITY

Is this study valid?

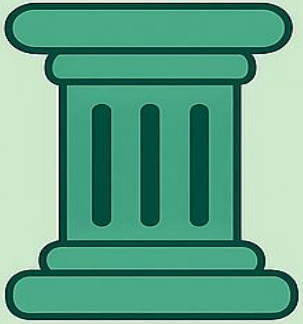
- methods
- search
- analysis



RESULTS

What are the true results?

- effect size, CIs, τ^2, I, Q, sensitivity, Doi + LFK



APPLICABILITY

Are they applicable to my patient?

Good science requires more than headlines—it requires critical appraisal.

Identifying and Correcting Methodological Gaps in Meta-Analysis

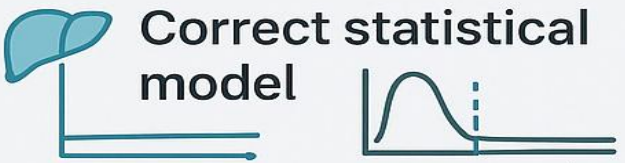
Previous meta-analysis

- Statistical wrong methods
- Poor data extraction
- Unclear inclusion criteria
- Weak search strategy

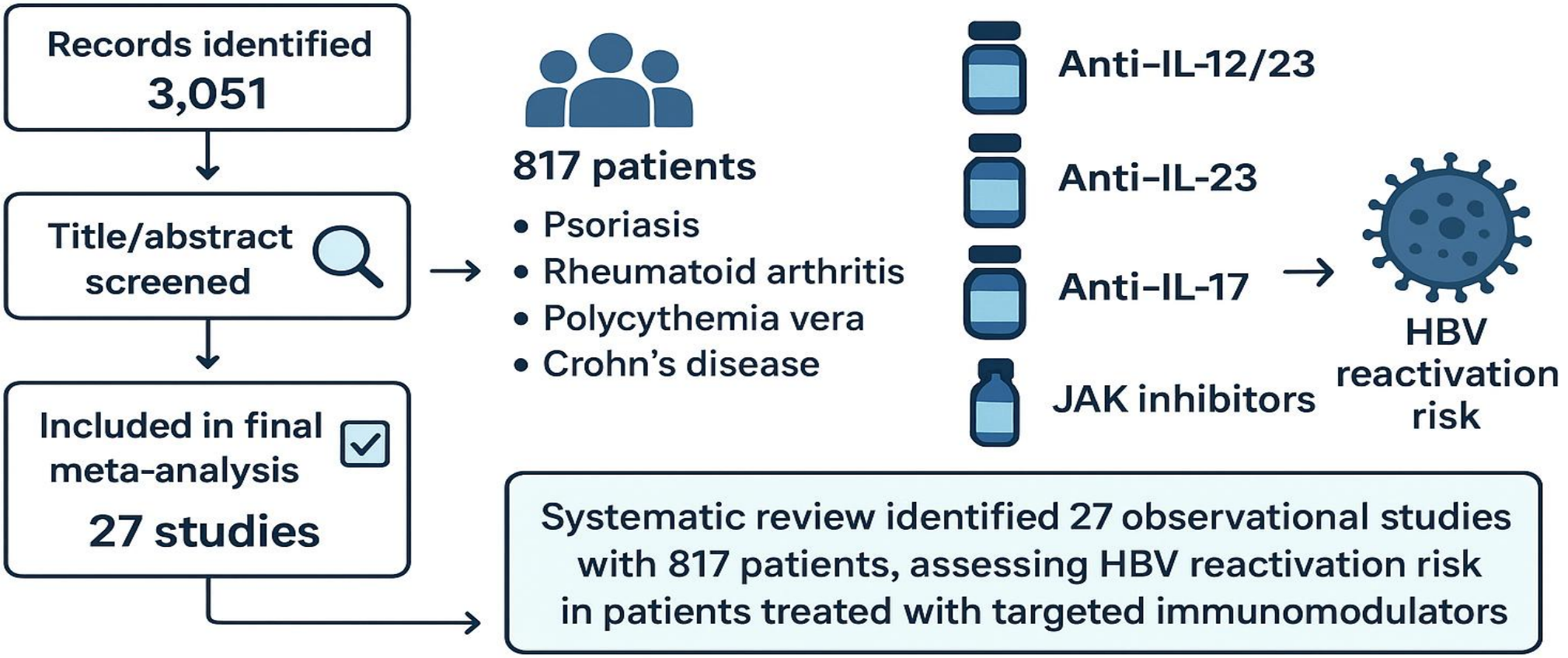
Reconstructed the workflow using evidence-based statistical and methodological standards

Our corrected meta-analysis

- Search strategy
- Inclusion/exclusion criteria
- Data extraction
- Correct statistical model

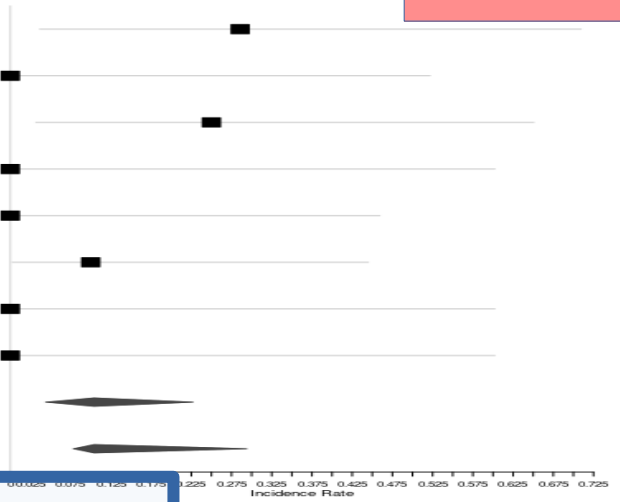


Systematic Review & Meta-Analysis: HBV Reactiivation with Anti-IL12/23, Anti-IL-23, Anti-IL-17, Inhibitors



HBsAg(+)

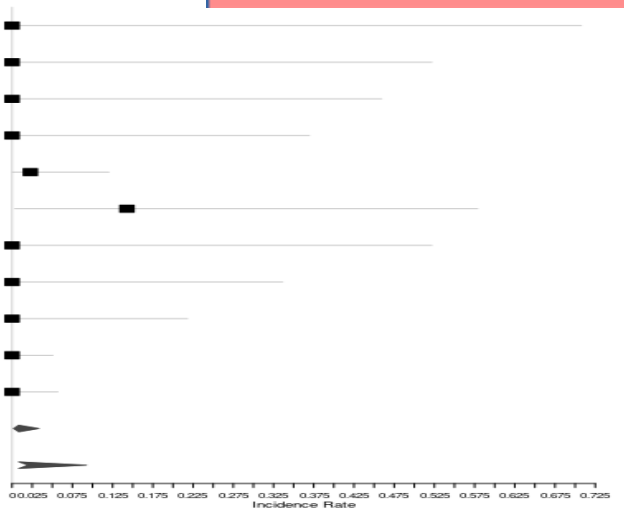
Study	Events/Total	Incidence [95% CI]	Weight (Random, %)
Chiu/UST/2013	2 / 7	0.29 [0.04-0.71]	23.41%
Hayashi/2014	0 / 5	0.00 [0.00-0.52]	7.51%
Ting/UST/2018	2 / 8	0.25 [0.03-0.65]	24.59%
Siegel/UST/2019	0 / 4	0.00 [0.00-0.60]	7.38%
Liu-Rongbei/UST/2023	0 / 6	0.00 [0.00-0.46]	7.61%
Huang-Yu-Huei/GUS/ 2023	1 / 10	0.10 [0.00-0.45]	14.75%
Wen-sheng Lu /GUS/2025	0 / 4	0.00 [0.00-0.60]	7.38%
Wen-sheng Lu /UST/2025	0 / 4	0.00 [0.00-0.60]	7.38%
Pooled		**0.10 [0.04-0.23]**	
Prediction Interval		**Prediction: 0.08–0.29**	



Heterogeneity: I^2 = 0.00%, τ^2 = 0.00; Q = 2.54 (p = 0.92); 95% PI: 0.08–0.29

HBsAg(-)/Anti-HBc(+)

Study	Events/Total	Incidence [95% CI]	Weight (Random, %)
Chiu/UST/2013	0 / 3	0.00 [0.00-0.71]	7.2%
Hayashi/2014	0 / 5	0.00 [0.00-0.52]	7.54%
Sanz-Bueno/UST/2015	0 / 6	0.00 [0.00-0.46]	7.64%
AlMutairi/UST/2018	0 / 8	0.00 [0.00-0.37]	7.77%
Ting/UST/ 2018	1 / 44	0.02 [0.00-0.12]	16.08%
Solay/UST/2018	1 / 7	0.14 [0.00-0.58]	14.1%
Kłujszo/UST/2022	0 / 5	0.00 [0.00-0.52]	7.54%
Gargiulo,/RZB/2022	0 / 9	0.00 [0.00-0.34]	7.82%
Ciolfi/RZB/2024	0 / 15	0.00 [0.00-0.22]	7.97%
Huang-Yu-Huei/GUS/2024	0 / 71	0.00 [0.00-0.05]	8.17%
Mortato/GUS/2025	0 / 63	0.00 [0.00-0.06]	8.16%
Pooled		**0.01 [0.00-0.03]**	
Prediction Interval		**Prediction: 0.02–0.09**	



Heterogeneity: I^2 = 0.00%, τ^2 = 0.00; Q = 6.39 (p = 0.78); 95% PI: 0.02–0.09

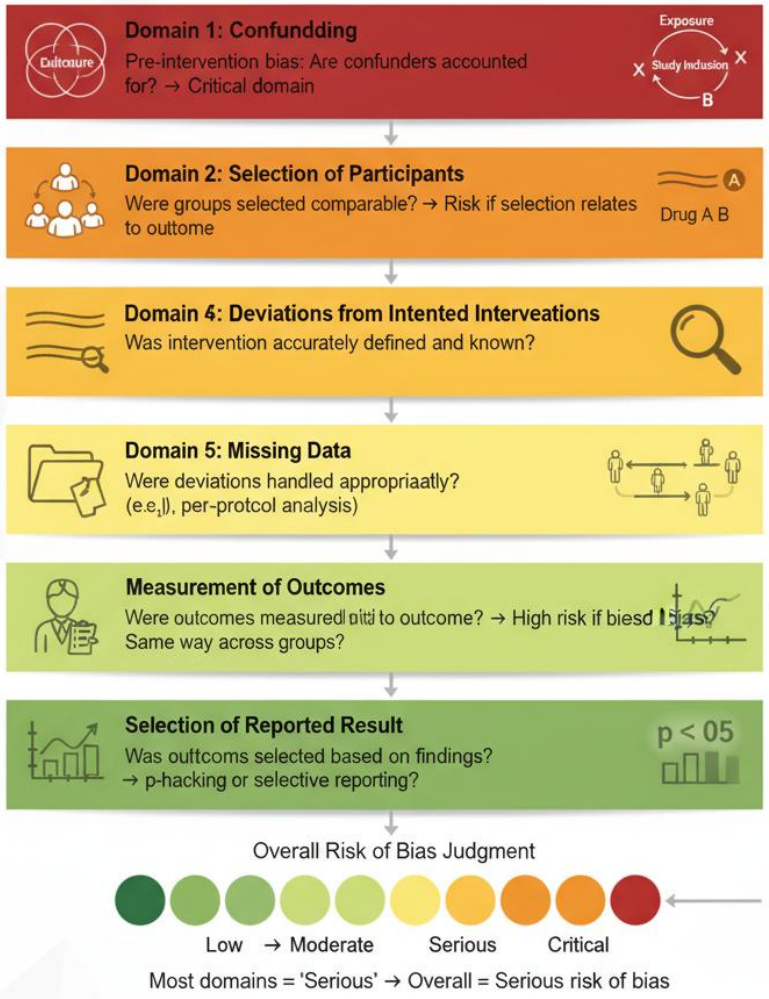
ROBINS-I tool

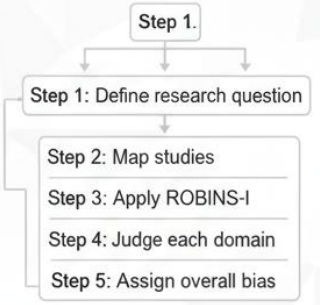
Non-randomised studies of the effects of interventions (NRSI) are critical to many areas of healthcare evaluation. Designs of NRSI that can be used to evaluate the effects of interventions include observational studies such as cohort studies and case-control studies in which intervention groups are allocated during the course of usual treatment decisions, and quasi-randomised studies in which the method of allocation falls short of full randomisation. The ROBINS-I tool ("Risk Of Bias In Non-randomised Studies - of Interventions") is concerned with evaluating risk of bias in estimates of the effectiveness or safety (benefit or harm) of an intervention from studies that did not use randomisation to allocate interventions.

Cochrane Scientific Committee recommendation (Full statement, July 2017):

ROBINS-I is the preferred tool to be used in Cochrane Reviews for non-randomized studies of interventions, although it is not mandatory, and will require author teams to have sufficient knowledge and experience to apply the tool. An alternative option is the Newcastle-Ottawa Scale. Please await further announcements on guidance and support to implement this tool.

Undertanding ROBINS-I: Assesing Risk of Bias in Non-Randomized Studies





Cochrane
Developed by Cochrane & collaborators

Risk of bias domains

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Chiu et al .	-	+	+	+	-	+	+	-
SW Ting et al	-	+	+	+	-	+	+	-
Liu et al	-	+	+	+	-	+	+	-
Huang et al	-	+	+	+	+	+	+	-
Ciolfi et al	-	+	+	+	+	+	+	-
Snast et al	-	+	+	+	-	+	+	-
Gargiulo et al	X	+	+	+	+	+	X	X
Qin et al	X	-	-	-	+	+	+	X
Mortato et al	-	+	+	+	+	+	+	-
Liu et al .	X	-	+	-	-	+	+	X
Galluzzo et al	X	+	+	+	-	+	+	X
Chiu et al	X	+	+	+	+	+	-	X
Ozçelik et al	X	+	+	+	+	+	X	X
Wang et al	X	-	+	-	-	+	+	X
Chen et al	X	-	+	-	+	+	+	X
Harigai et al	-	-	+	-	-	+	+	X
Garcia-Horton et al	-	-	-	-	-	+	+	X
Duan et al	X	-	-	-	-	+	+	X
Gill et al	X	-	-	-	+	+	+	X

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
+ Low

Leave-One-Out Sensitivity Analysis in Meta-Analysis

What Is It?

Meta-analysis → remove ne study → re-run

Purpose

Check if results are driven by a single study

See if pooled effect or heterogeneity changes

Test stability & reliability of findings

Does any single study change the conclusion?
Leave-one-out helps test & strengthen confiden.

How to Interpret

Consistent → robust

When outliers or low-quality studies exist

In systematic reviews to support guidelines

Limitations

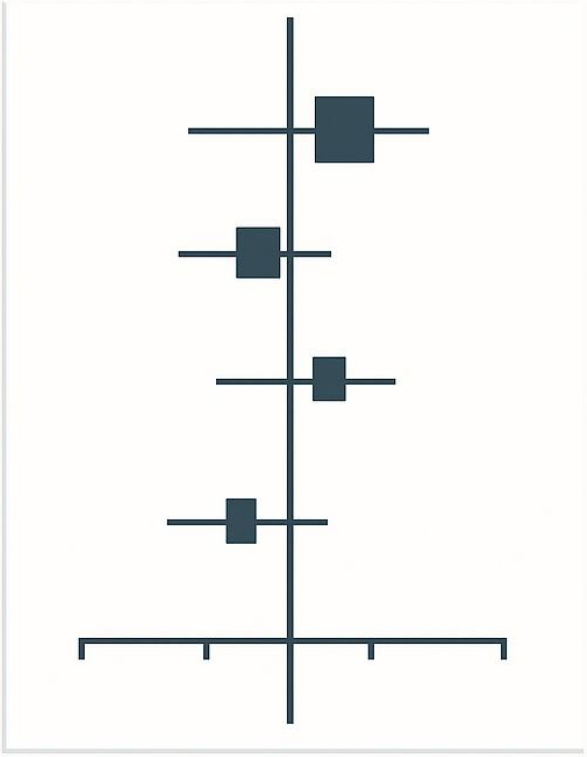
Doesn't fix bias (e.g. publication bias)

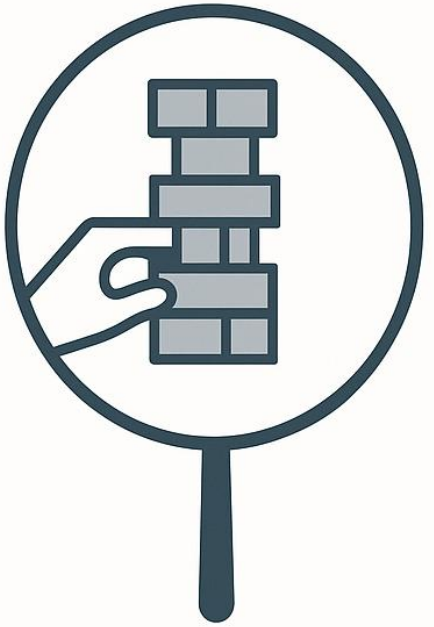
Less useful with very few studies (<5)

Should be paired with subgroup / meta-regression

Two Ways to Look at a Meta-Analysis

Weight





Influence

Study Weight

Definition:
Contribution of each study to pooled effect

Determined by:
- Sample size (larger n–higher weight)
- Within-study variance (lower variance – higher weight)
- Model choice (fixed vs. random effects)

Interpretation:
- High weight = • stronger pull on pooled result
- Not automatically "influential"

LOO Sensitivity

Definition:
Re-run meta-analysis exludes one study each time

Purpose:
- Detect if one study drives results or heterogeneity
- Identify outliers/influentiial studies

Interpretat ion:
- Change when removed → influential
- Stable across removals → robust

Key Difference
- Weight = built-in, reflects precision & size LOO = external stress-test of robustness

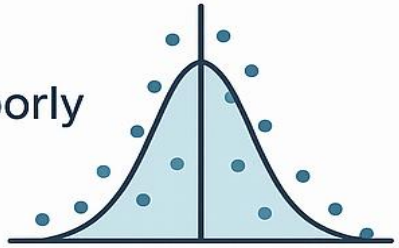
DOI Plot (Luis Furuya-Kanamori) & LFK Index

DOI Plot

What it is An alternative to funnel plot for proportional meta-analysis

Why

Funnel plots perform poorly with proportions (esp. near 0 or 1)



How it looks

DOI plot grapphs effect size (proportion) on the x-axis against a measure of precision on the y-axis

LFK Index

What it is A quantitative measure of DOI plot asymmetry

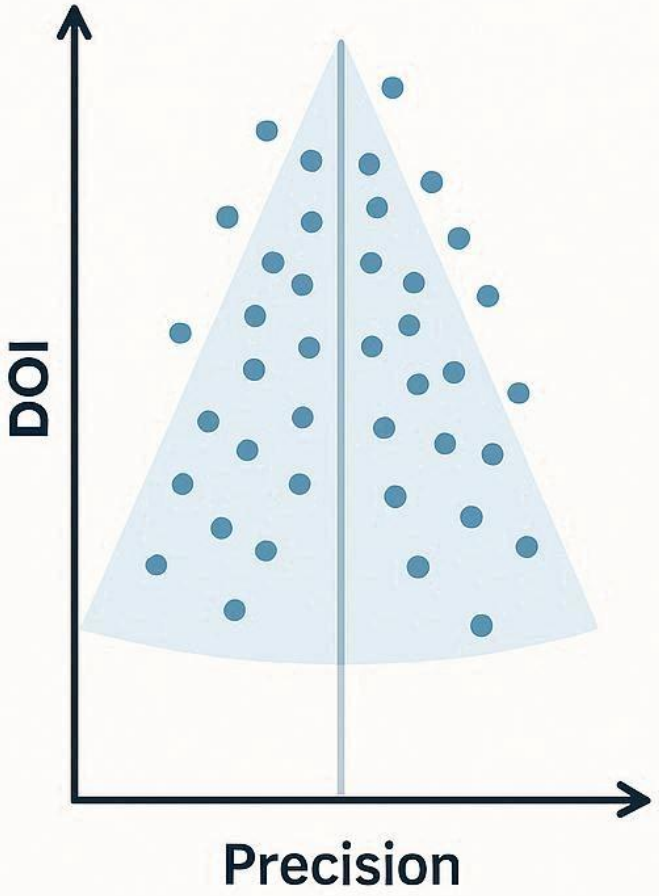
Interpretation

- $|LFK| \leq 1$ → No asymmetry
- $1 < |LFK| \leq 2$ Minor asymmetry
- $|LFK| > 2$ → Major asymmetry

Why useful Objective cutoff (vs. subjective funnel-plot interpretation ')

Bottom line **DOI + LFK index = better tools than funnel plot + Egger's test in proportion meta-analysis**

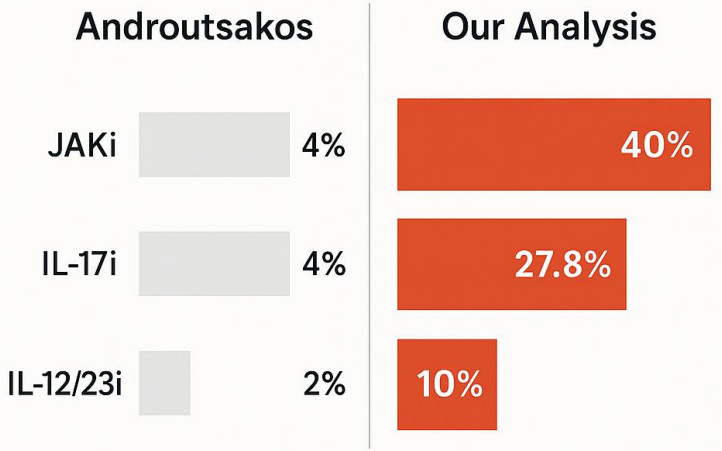
PUBLICATION BIAS CHECK



LFK = -0,8

The Reveal: True Risk Exposed

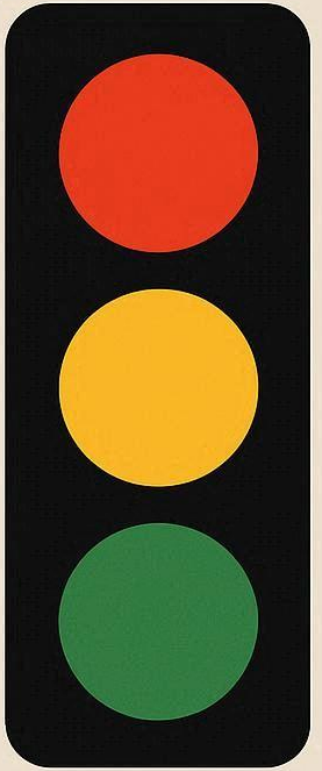
When Methods Change, The Story Changes



An order of magnitude higher risk — this changes everything

From Evidence to Action

Clinical Implications of Rigorous Evidence



HBsAg+ on JAKi/IL-17i
→ Prophylaxis mandatory

HBsAg+ on IL-12/23i
→ Prophylaxis or very tight monitoring

Occult/resolved HBV
→ Standard monitoring

Universal HBV screening before immunosuppression

RHEUMATOLOGY

British Society for Rheumatology

Volume 64, Issue 3
March 2025

JOURNAL ARTICLE

Hepatitis B reactivation in PsA patients: an SLR and meta-analysis for IL-17, IL-23 and JAK inhibitors

FREE

Theodoros Androutsakos , Konstantinos Dimitriadis , Maria-Loukia Koutsompina , Konstantinos D Vassilakis , Avraam Pouliakis , George E Fragoulis

Rheumatology, Volume 64, Issue 3, March 2025, Pages 935–942,
https://doi.org/10.1093/rheumatology/keae445

Article Contents

Table 14. Risk of HBV reactivation in individuals undergoing immunosuppressive therapies.

Risk of reactivation	HBsAg-positive or HBsAg-negative/anti-HBc-positive but HBV DNA-positive	HBsAg-negative/anti-HBc-positive (HBV DNA-negative)*
High >10%	• Immunosuppression in the context of stem cell transplantation[604] • High-dose combination chemotherapy (*e.g.* R–CHOP)[605] • B cell-depleting therapies[606] • CAR-T cell immunotherapy targeting B cells (BCMA, CD19)[577] • HCC therapies (TACE, radiotherapy, resection, ablation, systemic therapies)[598] • Anthracyclines[607] • Anti-TNF therapies[586] • Corticosteroids (>4 weeks, >20 mg/day)[608] • Cyclophosphamide[609] • JAK inhibitors[610] • IL-6 receptor antagonists[594] • Anti-IL-17[610–612] • Tyrosine kinase inhibitors[593,613]	• Immunosuppression in the context of stem cell transplantation[614] • High-dose combination chemotherapy (*e.g.* R–CHOP)[605] • B cell-depleting therapies[595,596] • HCC therapies (TACE)[599,600] • Anthracyclines[588] • T cell-depleting therapy belatacept – 17% in the setting of transplantation[615]
Moderate intermediate (1-10%)	• Anti-IL-12/23 (*e.g.* ustekinumab)[586] • T cell activation blocking therapies (ex. abatacept, belatacept)[616] • mTOR inhibitors[617]	• T cell-depleting therapies (*e.g.* abatacept[577]) • CAR-T cell immunotherapy • Corticosteroids (>40 mg)[585] • Anti-TNF therapies[586] • Anti-IL-12/23[586,610] • Anti-IL-17[610] • JAK inhibitors[590,610] • Tyrosine kinase inhibitors (*e.g.* ibrutinib) • Cyclophosphamide[524]
Low (<1%)	• Azathioprine[588] • Methotrexate[588] • Mycophenolate mofetil[588] • Corticosteroids (low-dose <10 mg/day)[608] • Immune checkpoint inhibitors[588]	• Azathioprine[588] • Methotrexate[588] • Mycophenolate mofetil[588] • mTOR inhibitors[617] • Corticosteroids (<40 mg/day) for ≤1 week)[585]

HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolisation.
*The classification of moderate/high risk in HBsAg-negative/anti-HBc-positive patients in some cases is based on low-certainty evidence, with safety and prophylaxis decisions balanced against risk assessment.

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*The classification of moderate/high risk in HBsAg-negative/anti-HBc-positive patients in some cases is based on low-certainty evidence, with safety and prophylaxis decisions balanced against risk assessment.

The incidence of hepatitis B reactivation in patients receiving ustekinumab: a systematic review and proportional meta-analysis

Marouf M. Alhalabi and Rasha Almokdad

Background: This meta-analysis will evaluate the risk of hepatitis B reactivation in patients treated with ustekinumab for inflammatory bowel disease and psoriasis. We aim to determine the true incidence of this adverse event, reconcile discrepancies in reported reactivation rates, and elucidate the associated risk.

Methods: We conducted a rigorous systematic review adhering to established guidelines. Major databases like MEDLINE, Google Scholar, CENTRAL, and ClinicalTrials.gov were searched. Studies involving patients with documented hepatitis B infection undergoing ustekinumab therapy were included. Patients receiving concurrent antiviral medications were excluded. To account for potential underreporting, studies without reactivation events or with sample sizes ≥3 were also considered by using generalized linear mixed models and Clopper–Pearson confidence intervals. This review was prospectively registered in PROSPERO (CRD42023418130).

Results: We analyzed data from nine studies involving 104 hepatitis B virus (HBV)-infected patients. The pooled HBV reactivation (HBVr) incidence among hepatitis B surface antigen-positive patients was 10% [95% confidence interval (CI): 0–31%], with low heterogeneity ($I^2 = 7.13\%$, $\tau^2 = 0.4$) and a nonsignificant Q-statistic ($Q = 5.38$, $P = 0.37$). For the occult HBV-infected patients, the pooled HBVr incidence was 3% (95% CI: 0–11%), with no heterogeneity ($I^2 = 0\%$, $\tau^2 = 0.0$) and a nonsignificant Q-statistic ($Q = 2.7$, $P = 0.61$). The reactivation rates showed high consistency across studies, with no significant difference between the two groups.

Conclusions: While our data suggest lower HBVr risk with ustekinumab, confirmation is needed due to limited sample size and retrospective design. Eur J Gastroenterol Hepatol 37: 1–9

Graphical Abstract: *http://links.lww.com/EJGH/B67*

BMJ Open

Risk of hepatitis B virus reactivation associated with interleukin inhibitor therapies: protocol for a systematic review and meta-analysis

Marouf Mouhammad Alhalabi ,[1] Hussam Aldeen Alshiekh [2]

To cite: Alhalabi MM, Alshiekh HA. Risk of hepatitis B virus reactivation associated with interleukin inhibitor therapies: protocol for a systematic review and meta-analysis. *BMJ Open* 2025;**0**:e098671. doi:10.1136/bmjopen-2024-098671

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ABSTRACT

Introduction The widespread application of interleukin (IL) inhibitors for various conditions, including gastrointestinal, rheumatologic, dermatologic and pulmonary diseases, has raised concerns regarding the potential for hepatitis B virus reactivation (HBVr). However, the precise risk of HBVr remains unclear due to inconsistencies in existing research. This systematic review aims to quantify the risk of HBVr in patients receiving IL inhibitor therapies.

Methods and analysis This systematic review will follow Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive search will be conducted in MEDLINE, PubMed, Google Scholar, CENTRAL, Scopus, Embase, Web of Science and ClinicalTrials.gov up to October 2025. Two reviewers will independently screen studies and extract data, resolving discrepancies by consensus. Eligible studies will include

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Advanced statistical modelling, including a generalised linear mixed model, will be applied to account for proportional data and study heterogeneity.
⇒ A rigorous and comprehensive search will be conducted across multiple databases, supplemented by citation tracking.
⇒ The predominance of observational studies may introduce selection bias and residual confounding.
⇒ Differences in hepatitis B virus reactivation definitions and diagnostic criteria may limit the comparability of results.
⇒ Subgroup analyses by individual interleukin inhibitors may be restricted by limited study numbers and sample sizes.

Risk of Hepatitis B Reactivation by Biologic Therapy and HBV Serostatus

HBsAg-Negative, Anti-HBc-Positive, Anti-HBs-Negative

Resolved or occult HBV nfection – Higher risk of reactivation

Anti-IL-12/23 inhibitors
(e.g. ustekinumab)

Anti-IL-23 inhibitors
(e.g., guselkumab, risankizmab)

Anti-IL-17 inhibitors
(e.g., secukunumab, ixekizunab)

JAK inhibitors
(e.g., tofacitinib, upadacitinib)

HBsAg-Negative, anti-HBc-Positive, Pnti-HBs-positive

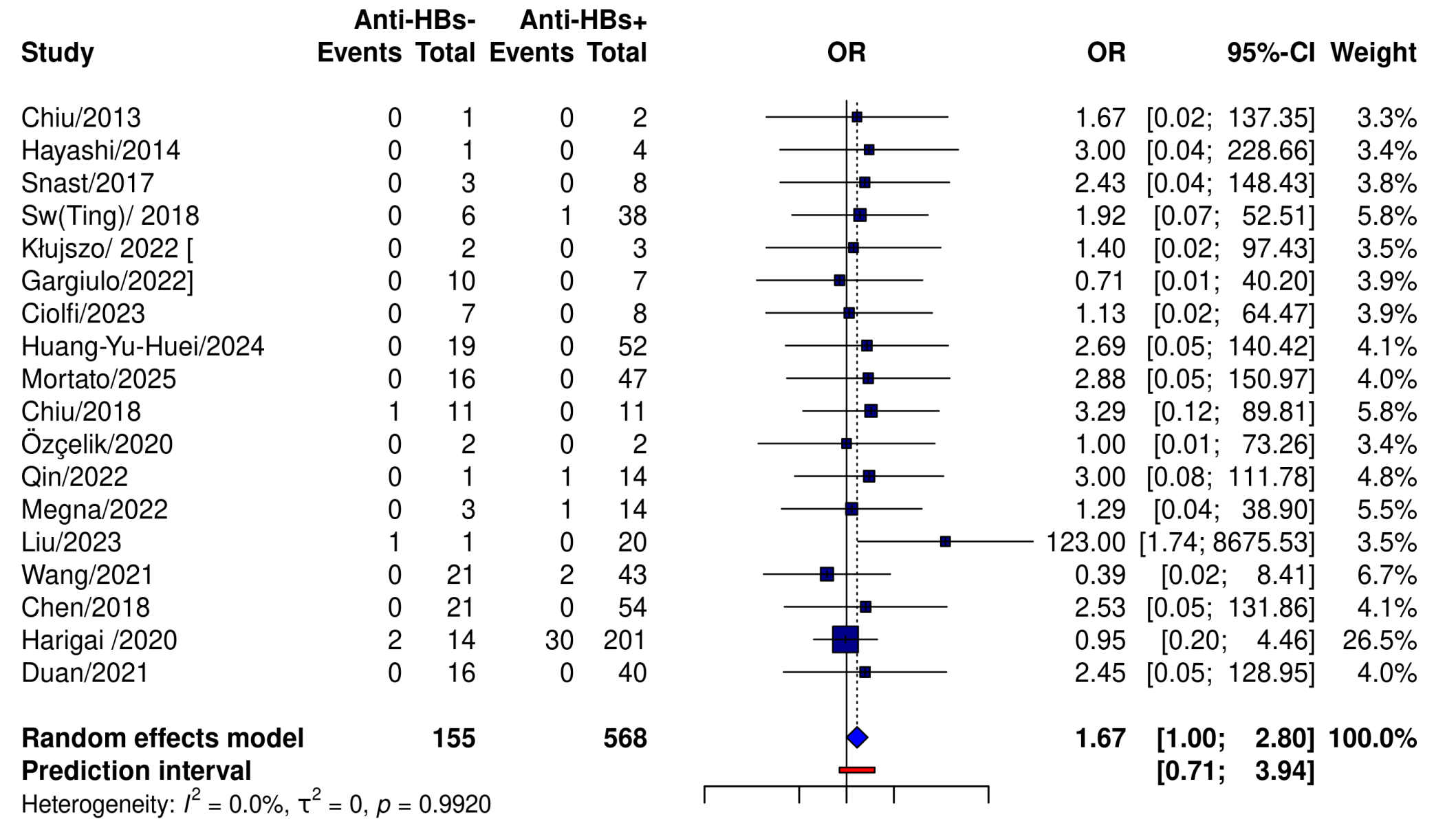
Immune control with prior exposure – Lower risk

Anti-IL-12/23 inhibitors
(e.g., ustekinumab)

Anti-IL-23 inhibitors
(e.g., guseikumab, risankizmab)

Anti-IL-17 inhibitors
(e.g., secukinumab, ixekizumab)

JAK inhibitors
(e.g., tofacitinib, upadacitinib)


Study
Anti-HBs- Events Total
Anti-HBs+ Events Total
OR
OR 95%-CI Weight
Chiu/2013 0 1 0 2 1.67 [0.02; 137.35] 3.3%
Hayashi/2014 0 1 0 4 3.00 [0.04; 228.66] 3.4%
Snast/2017 0 3 0 8 2.43 [0.04; 148.43] 3.8%
Sw(Ting)/ 2018 0 6 1 38 1.92 [0.07; 52.51] 5.8%
Kłujszo/ 2022 [0 2 0 3 1.40 [0.02; 97.43] 3.5%
Gargiulo/2022] 0 10 0 7 0.71 [0.01; 40.20] 3.9%
Ciolfi/2023 0 7 0 8 1.13 [0.02; 64.47] 3.9%
Huang-Yu-Huei/2024 0 19 0 52 2.69 [0.05; 140.42] 4.1%
Mortato/2025 0 16 0 47 2.88 [0.05; 150.97] 4.0%
Chiu/2018 1 11 0 11 3.29 [0.12; 89.81] 5.8%
Özçelik/2020 0 2 0 2 1.00 [0.01; 73.26] 3.4%
Qin/2022 0 1 1 14 3.00 [0.08; 111.78] 4.8%
Megna/2022 0 3 1 14 1.29 [0.04; 38.90] 5.5%
Liu/2023 1 1 0 20 123.00 [1.74; 8675.53] 3.5%
Wang/2021 0 21 2 43 0.39 [0.02; 8.41] 6.7%
Chen/2018 0 21 0 54 2.53 [0.05; 131.86] 4.1%
Harigai /2020 2 14 30 201 0.95 [0.20; 4.46] 26.5%
Duan/2021 0 16 0 40 2.45 [0.05; 128.95] 4.0%
Random effects model 155 568 1.67 [1.00; 2.80] 100.0%
Prediction interval [0.71; 3.94]
Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 0.9920

How Critical Appraisal Transforms Clinical Decisions

The Case of Hepatitis B Reactivation with Novel Immunosuppresives

Flawed evidence

Flawed meta-analyses, wrong models, pooled risk unreliaible

Critical appraisal

Systematic review, correct stratification by HBsAg status

Clinical decision impact

Accurate HBVr risk → Informs antiviral use & safe biologic therapy

Critical appraisal is not academic nitpicking — it transforms patient care

Liver
INTERNATIONAL

Liver International
Original Article

Hepatitis B virus reactivation risk with IL-17, IL-23/IL-12, or JAK inhibitors: a systematic review and meta-analysis

Submission Status	In Screening
Submitted On	5 November 2025 by Marouf Alhalabi
Submission Started	25 August 2025 by Marouf Alhalabi

This submission is under consideration and cannot be edited. Further information will be emailed to you by the journal editorial office.

Submission overview →

Hepatitis B Virus Reactvation Risk with IL-17, IL-23/IL- or or JAK Inhibitors A Systematic review and Meta-analysis

(27 studies, 817 patients)

Assess HBV reactivation (HBV↾) in patients with chronic or occult HBV treated with IL-17, IL-23/IL-12, or JAK inhibitors — no antiviral prophylaxis

Systematic Review + Meta-Analysis
(**PRISMA/MOOSE, PROSPERO:** CRD420241/79)

Results

Anti-HBs
I HBs

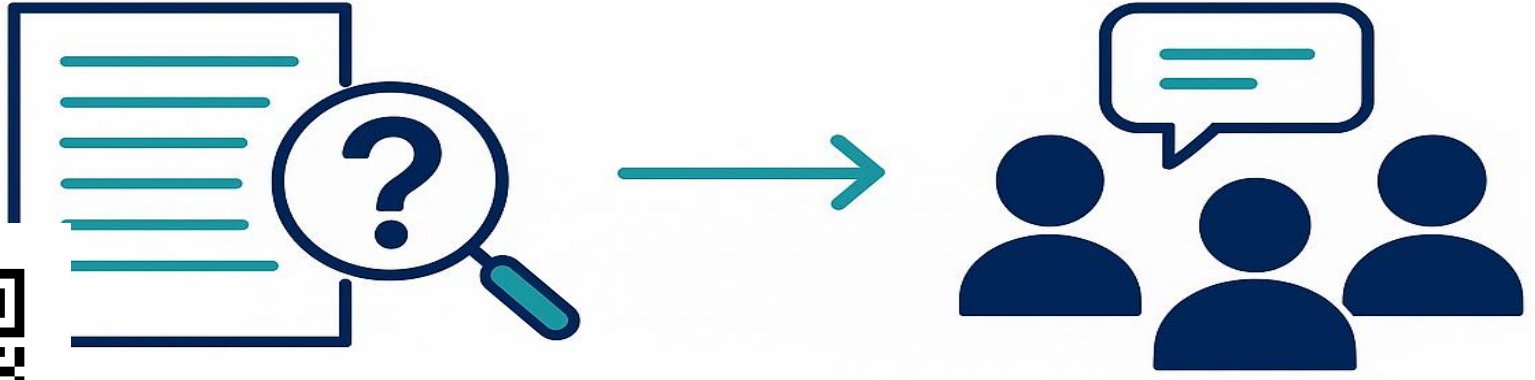
Conclusion

High HBVr risk
JAK, IL-17
(HBsAg* untreated)

Low risk
Anti-HBc*/
Anti-HBs*

Serostatus-based risk stratification and individualized antiviral prophylaxis recommended

Let’s not just read medical articles— let’s challenge them.



Thank you & Questions