

# Supplementary Content

**Low level of hepatitis B viremia is associated with increased risk of hepatocellular carcinoma in compensated cirrhotic patients**

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This supplementary material has been provided by the authors to give readers additional information about their work.

## Supplementary Table 1 Studies excluded (n=8) with reasons

Studies excluded	Reasons
Lok,2016[1]	This is a review.
Kim,2020[2]	This is an editorial
Min,2018[3]	This is an editorial.
Choi2022[4]	This is an abstract, and its full article has been included in this meta.
Kim,2017[5]	Not the target population: patients with an unclear type of cirrhosis.
Wang,2021[6]	Not the target contrast: the antiviral vs non-antiviral.
Mak,2021[7]	Not the target population: There is no LLV grouping.
Sun,2021[8]	Not the target population: patients with fibrosis instead of cirrhosis.

1. Lok, A.S.F., et al., *Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis*. Hepatology, 2016. **63**(1): p. 284-306.
2. Kim, J.H. and D.H. Sinn, *Low-level viremia in patients undergoing antiviral therapy: Does it indicate time for a change?* Clin Mol Hepatol, 2020. **26**(3): p. 315-317.
3. Min, A.D., *Low-level viremia in hepatitis b patients on antiviral treatment: Can we ignore it?* Hepatology, 2017. **66**(2): p. 312-314.
4. Choi, J., et al., *LOW LEVEL OF HEPATITIS B VIREMIA INCREASES THE RISK OF HEPATOCELLULAR CARCINOMA IN PATIENTS WITH UNTREATED COMPENSATED CIRRHOSIS*. Gut, 2022. **71**: p. A11.
5. Kim, J.H., et al., *Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment*. Hepatology, 2017. **66**(2): p. 335-343.
6. Wang, X., et al., *Antiviral Therapy Reduces Mortality in Hepatocellular Carcinoma Patients with Low-Level Hepatitis B Viremia*. J Hepatocell Carcinoma, 2021. **8**: p. 1253-1267.
7. Mak, L.Y., et al., *Residual HBV DNA and pgRNA viraemia is associated with hepatocellular carcinoma in chronic hepatitis B patients on antiviral therapy*. Journal of Gastroenterology, 2021. **56**(5): p. 479-488.
8. Sun, Y., et al., *Persistent Low Level of Hepatitis B Virus Promotes Fibrosis Progression During Therapy*. Clin Gastroenterol Hepatol, 2020. **18**(11): p. 2582-2591.e6.

**Supplementary Table 2 Quality assessment of the included observational studies by Newcastle-Ottawa scale.**

Author (Publication Year)	Newcastle-Ottawa Scale									Total
	Selection			Comparability			Outcome			
	a	b	c	d	e	f	g	h	i	
Huang, 2023	1	1	1	1	1	1	1	1	1	9
Lee, 2020	1	1	1	1	0	0	1	1	1	7
Lee, 2022	1	1	1	1	1	1	1	1	1	9
Sinn, 2015	1	1	1	1	0	0	1	1	1	7
Yang, 2023	1	1	1	1	1	1	1	1	1	9
Zhang, 2021	1	1	1	1	0	0	1	1	1	7

- a. Representativeness of the exposed cohort.
- b. Selection of the non-exposed cohort.
- c. Ascertainment of exposure.
- d. Demonstration that outcome of interest was not present at start of study.
- e. Comparability of cohorts on the basis of the design or analysis (adjusted for hepatitis B e antigen).
- f. Comparability of cohorts on the basis of the design or analysis (adjusted for any other factor).
- g. Assessment of outcome.
- h. Was follow-up long enough for outcomes to occur. (At least 1 year to eliminate seasonal effects of influenza).
- i. Adequacy of follow-up of cohorts.

## Supplementary Table 3 GRADE assessment

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LLV	MVR	Relative (95% CI)	Absolute		
<b>HCC</b>												
6	observational studies	no serious risk of bias	serious <sup>1</sup>	no indirectness	serious imprecision	strong association <sup>2</sup> increased effect for RR ~1 <sup>3</sup>	-/1864	-/1291	HR 2.06 (1.36 to 3.13)	-	MODERATE	CRITICAL
<b>decompensation of cirrhosis</b>												
3	observational studies	no serious risk of bias	serious <sup>4</sup>	no indirectness	serious <sup>5</sup>	strong association <sup>2</sup>	-/912	-/803	HR 2.06 (0.89 to 4.76)	-	VERY LOW	IMPORTANT
<b>liver-related events</b>												
3	observational studies	no serious risk of bias	very serious <sup>6</sup>	no indirectness	serious <sup>5</sup>	strong association <sup>2</sup>	-/837	-/557	HR 1.84 (0.92 to 3.67)	-	VERY LOW	IMPORTANT

<sup>1</sup> I<sup>2</sup>=51%

<sup>2</sup> The number of patients is greater than 1000.

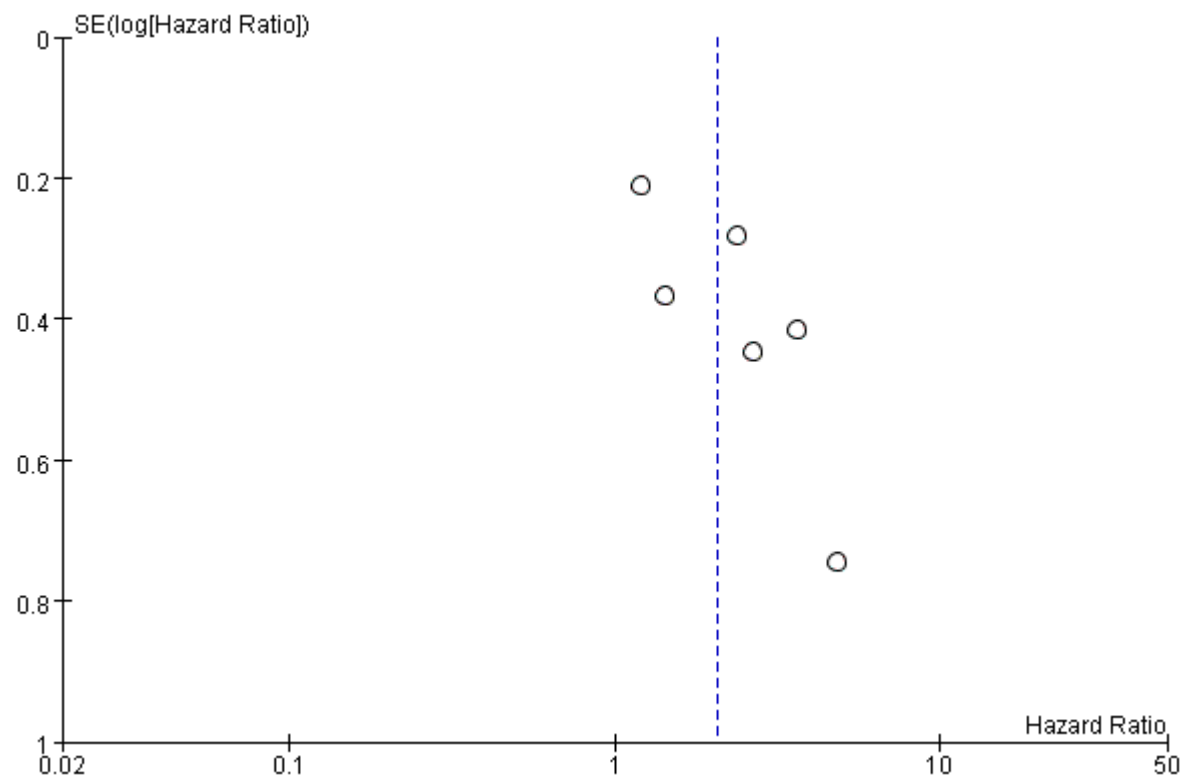
<sup>3</sup> HR: 2.06, 95% CI: 1.36, 3.13; p = 0.0006

<sup>4</sup> I<sup>2</sup>=69%

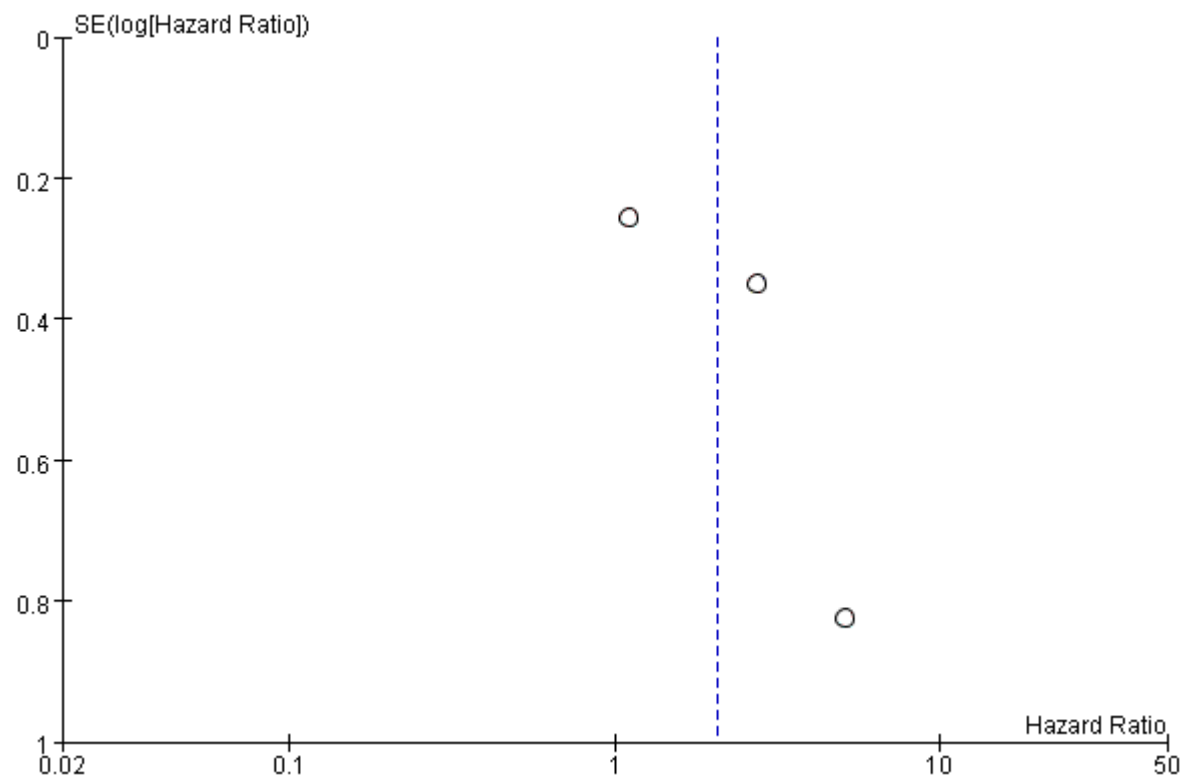
<sup>5</sup> The lower 95% CI (0.868) include 1.00

<sup>6</sup> I<sup>2</sup>=72%; The definition of ending is not exactly the same.

Supplementary Figure 1. Funnel plot for the association between LLV and HCC.



Supplementary Figure 2. Funnel plot for the association between LLV and decompensated cirrhosis.



Supplementary Figure 3. Funnel plot for the association between LLV and liver-related events.

