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Effect of coffee consumption on liver fibrosis and cirrhosis among hepatitis B patients: A meta-analysis

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Abstract

Background and Aims: Coffee consumption has preventive effect on liver fibrosis and cirrhosis among patients with hepatitis C and nonalcoholic fatty liver disease (NAFLD). Existing evidence on its effect on hepatitis B virus (HBV) patients are limited and contradicting.

Methodology: Literature search was done through PubMed, MEDLINE and google scholar. Four studies including HBV patients were reviewed which correlated coffee consumption on advanced fibrosis and cirrhosis using risk ratio (RR) via RevMan 5.4. The cut-off for high coffee consumption was > 2 cups of coffee per day in three studies and consumption of coffee, 4 to 7 days per week in one study.

Results: The summary estimate for any coffee consumption vs no consumption on cirrhosis was RR 1.03 (95% confidence interval [CI], 0.65-1.63). Summary estimate for advanced fibrosis for any coffee consumption vs no consumption was RR 0.90 (95% CI, 0.25-3.21). Comparison of low coffee consumption vs no consumption on cirrhosis showed RR 1.10 (95% CI, 0.82-1.49) and on advanced fibrosis showed RR 1.02 (95% CI, 0.33-3.16). In terms of high coffee consumption on cirrhosis RR 0.99 (95% CI, 0.33-2.96) while on advanced fibrosis was RR 0.79 (95% CI, 0.24-2.63). Results showed that the presumed effect of coffee on prevention of liver fibrosis and cirrhosis was not observed.

Conclusion: Among HBV patients, coffee consumption has no significant effect on cirrhosis. There is a possible protective association for advanced fibrosis at higher coffee intake, but certainty is limited by heterogeneity, measurement variability, and confounding.

Keywords: *Meta-analysis, Coffee, Liver fibrosis, Cirrhosis, Hepatitis B*

Introduction

Coffee consumption has been one of the well-studied beverages worldwide in terms of its health benefits.[1] Several observational studies, meta-analysis and systemic reviews published indicate the preventive effect of coffee on liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) among patients with chronic liver disease.[1,2] While this effect is well-established among hepatitis C and nonalcoholic fatty liver disease (NAFLD) patients, there is limited evidence on the effect of coffee on liver fibrosis among HBV patients.

The antioxidant effect of coffee and its protective effects have been proposed in a variety of

conditions ranging from cardiovascular disease, stroke, type 2 diabetes and Parkinson disease.[2] Prevention of progression of liver fibrosis and cirrhosis is gaining spotlight with increasing evidence in favor of increased coffee consumption. Proposed mechanisms on anti-fibrotic effect of coffee include its action on hepatic stellate cells (HSC) through caffeine which inhibit focal adhesion kinase (FAK) and actin synthesis. It also increases HSC apoptosis and intracellular F-actin and cAMP expression as well as through inhibition of procollagen type 1C and alpha-smooth muscle actin (α-SMA) expression. On the other hand, the action of caffeine on hepatocytes include decrease in transforming growth factor beta (TGF-B) and stimulation of adenylate-rich elements (ARE)-regulated signaling.[2,3]

In terms of the antioxidant effects on hepatocytes, the chemicals involved are hydrophilic (caffeine and polyphenols like chlorogenic acids) and hydrophobic (cafestol, kahweol and trigenolline), including Mailard, reaction products. The proposed mechanisms of these chemicals include prevention and downregulation of immune and inflammatory markers such as interferon gamma (IFN-Y), chemokine coded CX33CL1 or fractakine, chemokine ligand4 or CCL4 also called macrophage inhibitory protein (MIP-1b), fibroblast growth factor-2 (FGF-2) and tumor necrosis factor receptors (sTNFRII).[3]

Based on the study by Bravi et al. in 2013, the prevalence of HBsAg positivity locally remains in the hyperendemic range at 16.7%, which is estimated as 7.3 million adult Filipinos infected with HBV.[4] HBV is still a major cause of chronic liver disease in the Philippines and the risk of chronicity and development of complications like fibrosis, cirrhosis and hepatocellular carcinoma remains.[4]

With the promising benefits of coffee consumption, it is valuable to document evidence to help provide recommendations for prevention of HBV-related fibrosis and cirrhosis progression. Barre et al. in 2022 concluded that elevated coffee consumption is consistently associated with lower risk of significant liver fibrosis, similar to the results of Chen et al. in 2018 citing inverse association. [6,7] On the other hand, the study of Brahmania et al. (2020) and Ong et al. (2011) showed that coffee consumption has no association with liver fibrosis.[5,6,7,8] Conflicting results of existing articles warrant analysis of the effects of coffee on HBV patients through meta-analysis.

Methodology

Search Strategy

Pubmed, MEDLINE and google scholar databases were searched for all articles using the following search terms: “coffee”, “hepatitis B”, “liver fibrosis” and “cirrhosis”. We limited the search to studies performed on human beings and articles published in English literature. Published articles which included observational studies, cross-sectional and cohort studies were analyzed. Relevant studies cited on references of relevant articles were reviewed. The following criteria were used in including studies in the meta-analysis: 1) provided information on the association between coffee and liver fibrosis and/or cirrhosis using risk ratio (RR), with the corresponding 95% confidence interval (CI); 2) included chronic hepatitis B patients in the study population; 3) original cohort or cross-sectional studies; 4) published in English language as a full-length article.

The following details were determined from each article: study design, year of publication, number of subjects included, country, age, body mass index (BMI), measure of outcome, quantity of coffee consumption, and findings. Similarly, we retrieved the measure of association risk ratio (RR) and the corresponding 95% CI. When the number of events in the population was not mentioned, the data was derived from the tabular data using odds ratio. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the individual studies (Appendix A). Two independent reviewers performed the assessment of articles using NOS. In case of disagreement, a third independent reviewer served as an arbiter to settle the decision.

Statistical Analysis

We derived summary estimates of RR using random-effects model. The heterogeneity among studies was evaluated using chi-square test. Heterogeneity was quantified using I^2 statistic representing that the degree of variation among included studies is secondary to heterogeneity rather than chance. Sensitivity analysis was also done to determine which study contributed mainly to heterogeneity.

The quantity of coffee consumption was categorized into low vs high and was compared to no consumption, including occasional consumption. It was acknowledged that different cut-off points were used by different studies on high coffee consumption: more than 2 cups of coffee per day in three studies and consumption of coffee 4 to 7 days per week in one study.

The RR of coffee consumption was computed. Subgroup analysis was done regarding studies which quantified coffee consumption into no/occasional vs low vs high as defined in the article. Forrest plots were used to show study effects and summary estimates for each included article based on the quantity of coffee consumption.

Results

The literature search yielded 28 articles (Figure 1). Publications that did not fulfill the inclusion criteria were excluded and five studies were considered. However, one retrospective cross-sectional study did not provide the odds ratio based on quantity of coffee consumption, hence was also excluded. In this meta-analysis, three cohort studies (two prospective, one retrospective) and one cross-sectional study were reviewed.

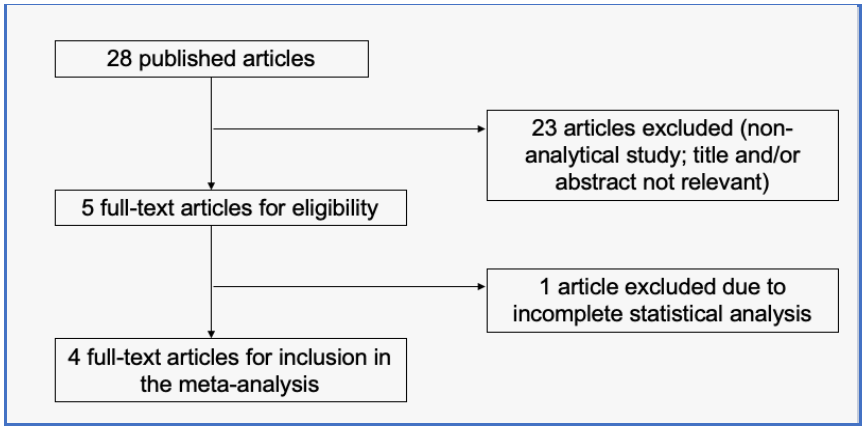

Figure 1. Flowchart of the selection of studies on coffee consumption and liver fibrosis/cirrhosis among chronic hepatitis B patients.

Table 1 shows the summary of the four included studies. Two of which came from Asia (Taiwan and Hongkong), the other two were from France and United States of America. In terms of age, majority were < 65 years old and based on their BMI, majority belong to the normal to overweight category, based on World Health Organization classification. Different outcomes were measured in these studies including non-invasive markers: AST to platelet ratio (APRI), Fibrosis-4 (FIB-4), gamma-glutamyltransferase to platelet ratio (GPR), Hui's index and transient elastography.

Coffee drinkers were subdivided into those who have low vs high consumption of coffee. Outcomes measured included presence of advanced fibrosis and cirrhosis which were defined as: Barre 2022 and Brahmania 2020 on cirrhosis (FIB-4 >3.25), Chen 2018 and Ong 2011 on advanced fibrosis (liver elastography >9kPa for normal ALT, >12kPa for elevated ALT; FIB-4 >1.45). Noninvasive test of liver cirrhosis and/or advanced fibrosis had been advocated short of doing liver biopsy. Several studies documented the relevance and accuracy of these measures and correlated it with the HBV status. The cut-off for high coffee consumption was more than 2 cups of coffee per day in three studies and consumption of coffee 4 to 7 days per week in one study.

Figure 2 shows the summary RR of cirrhosis on any coffee consumption vs no consumption including the study of Barre in 2022 and Brahmania in 2020. The summary estimate was 1.03 (95% confidence interval [CI], 0.65-1.63). Heterogeneity was found between the two studies with Chi^2 of 1.86 and I^2 of 46%. The effect of coffee consumption on advanced fibrosis was done by analyzing the studies of Chen in 2018 and Ong in 2011. In terms of summary, RR of advanced fibrosis on any consumption vs no coffee consumption, figure 3 showed that the summary estimate was 0.90 (95% CI, 0.25-3.21). Its heterogeneity was significant as measured by Chi^2 of 4.86 (I^2 = 79%).

Table 1. Studies assessing impact of coffee consumption on prevention of liver fibrosis and cirrhosis

Study	Year	Design	Population	Age, years	BMI	Country	Coffee consumption	Measure of Outcome	Findings	Quality score*
Barre et al	2022	Cross-sectional	3720	--	--	France	None Low: </= 2 cups/day High: >3 cups/day	Non-invasive markers: APRI, FIB-4, and GPR	Elevated coffee consumption was consistently associated with lower risk of significant liver fibrosis.	6
Brahmania et al	2020	Prospective cohort	1320	<65yo: 1253 ≥65yo: 67	<18.5: 47 18.5-24.99: 658 25-29.9: 397 ≥30: 155	United States of America	None/Occasional Low: 1-2 cups/day High: >/= 3 cups/day	Non-invasive index of liver fibrosis: FIB-4	Coffee consumption has no association with FIB-4 levels.	5
Chen et al	2018	Retrospective cohort	328	<65yo: 314 ≥65yo: 14	<24: 167 24-27: 95 >27: 66	Taiwan	None Low: 1-3 days/week High: 4-7 days/week	Non-invasive predicting indices of liver fibrosis: APRI, FIB-4, Hui's index	Coffee consumption was inversely associated with liver fibrosis	4
Ong et al	2011	Prospective cohort	1045	≤45yo: 483 >45yo: 562	Normal: 515 Overweight: 253 Obese: 277	Hongkong SAR	None Low: <2 cups/day High: >2 cups/day	Liver stiffness measurement by transient elastography Prediction of significant fibrosis by Hui's Index	Coffee intake does not affect liver stiffness in chronic HBV-infected patients.	7

*based on Newcastle-Ottawa scale

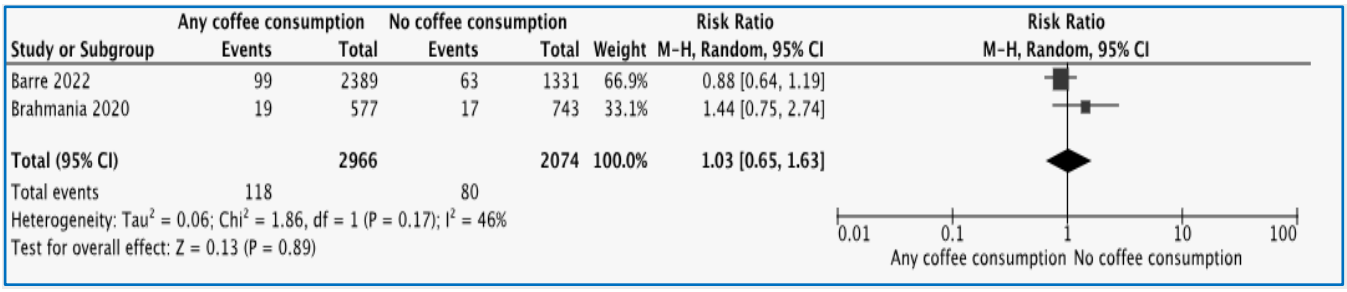

Figure 2. Summary of RR of cirrhosis on any coffee consumption vs no consumption

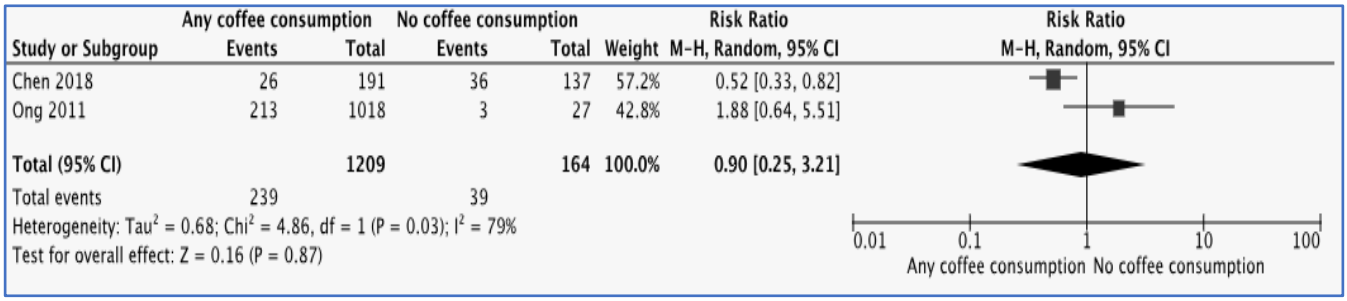

Figure 3. Summary of RR of advanced fibrosis on any coffee consumption vs no consumption

Comparison of low coffee consumption vs no consumption on cirrhosis showed RR 1.10 (95% CI, 0.82-1.49) and on advanced fibrosis showed RR 1.02 (95% CI, 0.33-3.16). Heterogeneity was likewise assessed with $Chi^2 = 0.40$ ($I^2 = 0\%$) and $Chi^2 = 3.35$ ($I^2 = 70\%$) for low consumption vs no consumption of coffee among patients with cirrhosis and advanced fibrosis, based on figures 4 and 5, respectively.

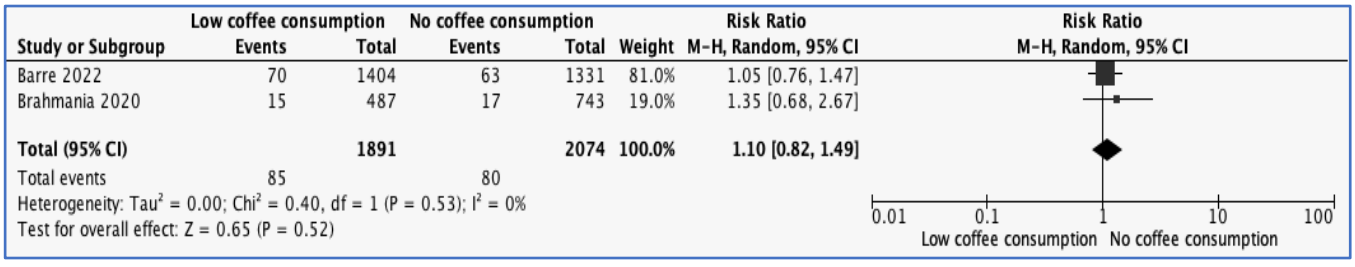

Figure 4. Summary of RR of cirrhosis on low coffee consumption vs no consumption

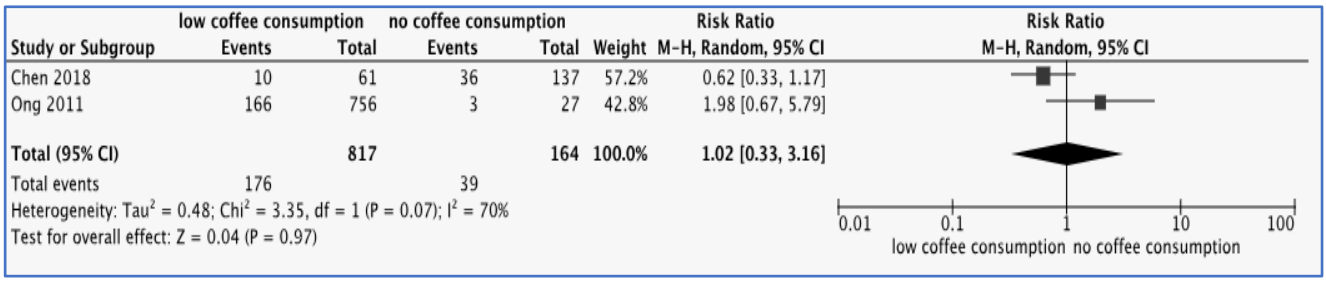

Figure 5. Summary of RR of advanced fibrosis on low coffee consumption vs no consumption

In terms of high coffee consumption on cirrhosis, RR was 0.99 (95% CI, 0.33-2.96) while on advanced fibrosis, RR was 0.79 (95% CI, 0.24-2.63). Heterogeneity was measured with $Chi^2 = 3.78$ ($I^2 = 74\%$) and $Chi^2 = 3.97$ ($I^2 = 75\%$) for high consumption vs no consumption of coffee among patients with cirrhosis and advanced fibrosis, based on figures 6 and 7, respectively.

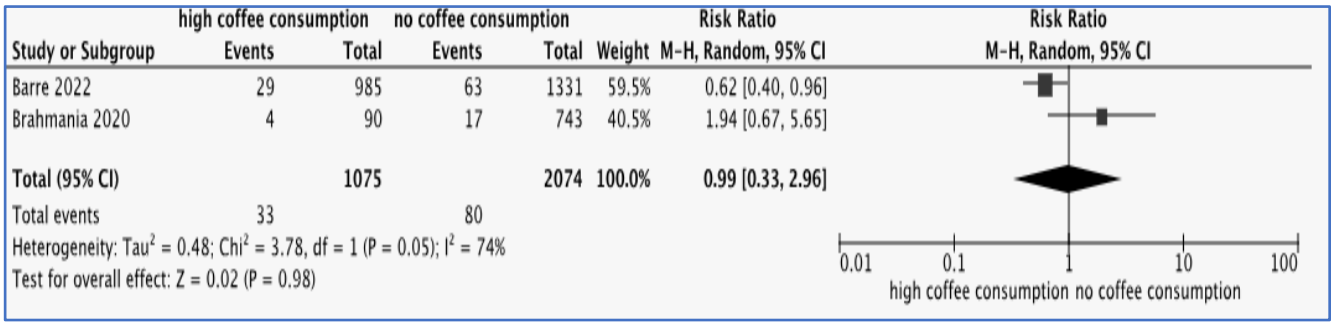

Figure 6. Summary of RR of cirrhosis on high coffee consumption vs no consumption

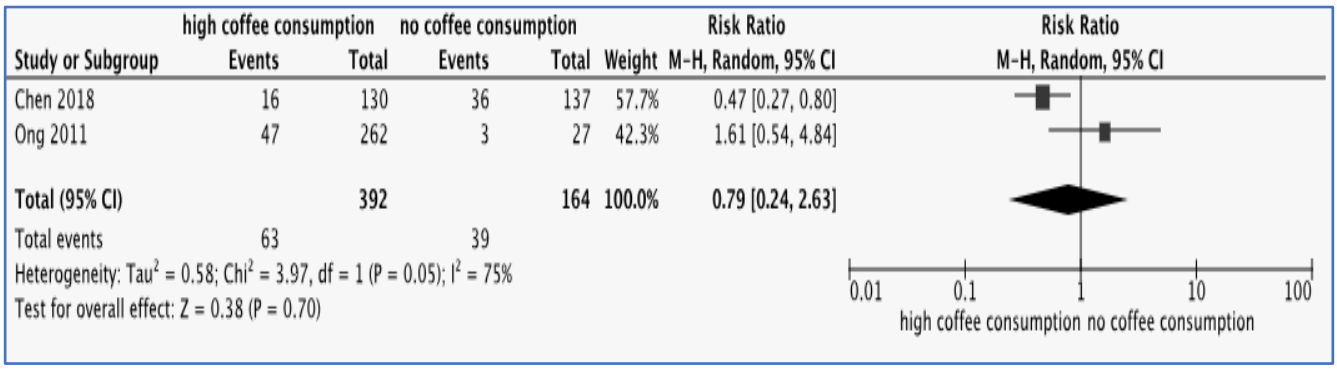

Figure 7. Summary of RR of advanced fibrosis on high coffee consumption vs no consumption

Results showed that the presumed effect of coffee consumption on the prevention of progression of liver fibrosis and cirrhosis was not observed in this study. However, studies which assessed the effect of coffee on advanced liver fibrosis, Chen (2018) and Ong (2011), showed a trend towards protective effect with high coffee consumption. Studies that assessed the effect of coffee intake on liver cirrhosis, consistent results of no statistical significance were shown. The high heterogeneity in the analysis indicated that the results of individual studies were widely different.

Discussion

In this study, we found that any coffee consumption, whether low or high intake, had no effect of liver cirrhosis among HBV patients. However, there was a trend towards a protective effect of high coffee consumption in the prevention of advanced liver fibrosis. Stratification of patients based on the level of coffee consumption and the outcomes measured gave good avenue for analysis. Our results on the prevention of cirrhosis consistently coincided with previous studies of Ong (2011) and Brahmania (2020).[5,6] The seemingly inverse relationship of coffee consumption and advanced fibrosis coincided with the results of Barre (2022) and Chen (2018).[6,7]

Despite therapeutic advances, patients who are chronically infected with HBV are at high risk of liver fibrosis, cirrhosis and even hepatocellular carcinoma.[2,4] It may be difficult to establish a significant non-pharmaceutical therapy for prevention of liver fibrosis and cirrhosis. Available data on relationship of coffee consumption with possible preventive effect on progression or development of cirrhosis or advanced fibrosis are limited.

Studies on coffee consumption point towards potential favorable effects on health, including antioxidants such as phenolic compounds, melanoidins and diterpenes. It has also been inversely related to hepatic enzymatic activity including glutamyltransferase and serum alanine aminotransferase. In addition, some studies associate coffee consumption inversely with cirrhosis.[5,6]

Cirrhosis regression may be possible after HBV treatment if cirrhosis is recent which highlights the importance of managing liver fibrosis in HBV infected patients, and to identify risk factors for its progression.[6] There are studies that did not indicate the treatment status of HBV patients which may have contributed to the heterogeneity of the studies. Doing subgroup analysis of patients based on HBV treatment status and quantity of coffee consumption may better represent the treatment effects measured in this study.[4,5,7]

The presumed protective effect of coffee consumption on liver fibrosis was previously cited in patients with non-alcoholic fatty liver disease, alcoholic liver disease and hepatitis C virus (HCV) infection.[6,8] In the study of Barre et al. in 2022, elevated coffee consumption was consistently associated with lower risk of significant liver fibrosis.[6] However, using FIB-4 as a surrogate marker, it showed that there were 29 out of 985 patients who had high consumption of coffee had cirrhosis while 63 out of 1331 patients who did not drink coffee had cirrhosis (p = 0.62; 95% CI, 0.40-0.96). Brahmania et al. in 2020 showed that 4 out of 90 patients who had high consumption of coffee had cirrhosis while 17 out of 743 patients who did not drink coffee had cirrhosis with (p = 1.94; 95% CI, 0.67-5.65).[8] The summary estimate indicated that there were more HBV patients with cirrhosis who consumed more coffee.

Moreover, the summary RR of advanced fibrosis on any coffee consumption or high coffee consumption vs no consumption was 0.90 (CI 0.25-3.21) and 0.79 (CI 0.24-2.63), respectively, which showed a trend towards a protective role of coffee for advanced fibrosis. This apparently dose-dependent effect on HBV patients taking more than 2 cups of coffee per day or who drank coffee 4 to 7 days a week might be due to caffeine content and/or antioxidant and antifibrotic properties of coffee such as polyphenols, caffeine, cafestol, kahweol and trigenolline. Anti-inflammatory effects of coffee in this regard might be due to down regulation of immune and inflammatory markers[1,3,7].

Advanced liver fibrosis was assessed by two studies included in this meta-analysis. Chen et al. in

2018 mentioned that coffee consumption was inversely associated with liver fibrosis.[7] Among patients who consumed increased amount of coffee, 16 out of 130 had advanced fibrosis while 36 out of 137 non-coffee drinkers developed advanced liver fibrosis. Ong et al. in 2011 cited that coffee intake did not affect liver stiffness in chronic HBV infected patients.[5] In this study, 47 out of 262 high coffee drinkers and 3 out of 27 non-coffee drinkers developed advanced fibrosis. Overall, with a p-value 0.90 (95% CI, 0.53, 1.54), the summary estimate indicated that even with coffee consumption there was still increased risk of advanced fibrosis. These results coincided with this study's findings such that the risk ratio of cirrhosis on any coffee consumption or high coffee consumption vs no consumption was 1.03 (CI 0.65-1.63) and 0.99 (CI 0.33-2.96), respectively, showing no significant effect of prevention of cirrhosis despite coffee intake. The lack of effect of coffee consumption among HBV patients with cirrhosis may be linked to the virological and genetic factors in fibrogenesis which are less affected by caffeine intake.[5,8,9]

Limitations of this study include the variation in measure of outcomes. Surrogate non-invasive markers, such as APRI, FIB-4 and GPR, used in this study do not always direct histology or long-term clinical outcomes especially in HBV studies. Chen et al. (2018) used too low FIB-4 cut-off of >1.45 to measure significant fibrosis in comparison to cut off of >3.25 among the three other studies. Only one study used liver elastography as measure of advanced fibrosis. Likewise, observational data could not prove causality. Moreover, residual confounding factors such as alcohol intake, smoking, presence of comorbidities like diabetes mellitus and other possible chronic liver diseases remain possible. Risk factors for metabolic dysfunction-associated steatotic liver disease (MASLD) are important to be accounted for as potential confounding factor in this study.

According to the study of Ong et al. in 2011, patients who drink coffee regularly tend to drink alcohol, hence the importance of taking this into consideration.[5] However, other studies did not include this factor among the HBV patients. ALT measurements were not specified in each study which may affect the interpretation of results[5,7]. Differences in consumption habits should also be taken into consideration. The type of coffee and addition of sucrose, a source of profibrotic fructose, may affect the outcomes. Liver fibrosis, naturally, is dynamic. Depending on the circumstances, it may progress or regress, hence indicating the limitation of cross-sectional studies.[2,6,7]

Conclusion

Our study demonstrates that coffee consumption, regardless of intake level, does not confer a significant protective effect against liver cirrhosis among patients with chronic hepatitis B infection. These findings are consistent with prior studies, suggesting that the progression to cirrhosis in HBV patients may be largely driven by virological, genetic, and disease-specific factors that are less influenced by coffee intake.

Nevertheless, there is a consistent trend toward a protective association between higher levels of coffee consumption and reduced risk of advanced liver fibrosis, indicating a potential dose-dependent benefit. This observed trend may be attributable to the anti-inflammatory, antioxidant, and antifibrotic properties of coffee constituents such as caffeine and polyphenols. Despite this, the evidence remains insufficient to establish coffee consumption as an effective non-pharmacologic intervention for preventing fibrosis progression or cirrhosis in HBV-infected individuals. Variability in outcome measures, reliance on surrogate fibrosis markers, limited adjustment for confounding factors, and the observational nature of available studies limit the strength of conclusions. Future well-designed prospective studies, incorporating standardized fibrosis assessment tools, detailed quantification of coffee intake, HBV treatment status, and key metabolic and lifestyle confounders, are warranted to better clarify the role of coffee consumption in liver disease progression among HBV patients.

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Appendix

Appendix A. Supplementary Table 1. Newcastle-Ottawa Scale

Criteria	Barre 2022	Brahmania 2020	Chen 2018	Ong 2011
Selection				
Representativeness of the exposed cohort	*	*	*	*
Selection of the non-exposed cohort	*	*		*
Ascertainment of exposure	*		*	*
Demonstration that outcome of interest was not present at start of study		*		*
Comparability	*		*	*
Comparability of cohorts on the basis of the design or analysis		*		
Outcome				
Assessment of outcome	*		*	*
Follow-up long enough for outcomes to occur	*			*
Adequacy of follow-up of cohorts		*		