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Research Article

Risk Assessment of Colorectal Carcinomas in Co-Infected Hepatitis B Patients

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Received: October 17, 2021; **Published:** January 31, 2022

Abstract

Introduction: Colorectal cancers are the third most common cancer with 1.93 million cases and second cause by cancer-related mortality worldwide in 2020 (WHO). The incidence rate follows a slow and steady increasing trend in Eastern Europe in line with the World. Aside from genetic susceptibility, lifestyle, environmental factors and chronic infections and Other lower GI disorders 596 UEG Journal | Abstract Book inflammations are the well-known causes of colorectal cancers. Hepatitis B is the third most common infectious agent that is attributable to cancer risk worldwide by 16.3% [1]. HBS Ag seropositivity is well-linked with hepatocellular carcinomas but the link between HBV and other cancers are not well established.

Aims and Methods: Our aim is to examine the interconnections between HBV infections and colorectal cancers and to assess the degree of the associated risk between them. A selective search strategy was performed to search for relevant original articles using databases in OVID and 7 were selected. The studies selected for analysis varies within etiologies and outcomes and due to dichotomous nature of the events, we used pooled Odds ratio (ORs) in line with confidence intervals using Mantel-Haenszel method. A random-effects model applied for pooled rates to rule out the high heterogeneity according to DerSimion's study. I2 was calculated to measure the degree of heterogeneity. A bias assessment was made and L'abbe plot was used to assess the strength of the results [3].

Results: Pooled analysis after application of random effects, clearly demonstrated a significant association between colorectal cancers and viral hepatitis of all kinds (OR = 1,29; 95% CI: 1,13 - 1,47, I2 = 74,3% and p = 0,0001) Also calculated, Pearson's contingency coefficient confirms (0,53) the correlation between HBV co-infection and colorectal carcinoma. If the coefficient lays between 0,5 to 1,0, it is said to be a high degree of correlation with strong probability [2]. 74,3% of I2 may represent substantial heterogeneity in the pooled analysis, thus a publication bias analysis performed and plotted. Results did not demonstrate a great degree of asymmetry that should lead to high bias and Egger's Bias indicator was consistent with the low bias power of the study [3]. Egger bias = 0,84 (95%CI = 2,7 to 4,4) P = 0,54 Study 1: OR 1,27 95%CI, 1,2 - 1,33 Study 2: OR 1,16 95%CI, 0,71 - 1,89 Study 3: OR 1,60 95%CI, 0,88 - 2,91 Study 4: OR 1,1 95%CI, 1,01 - 1,19 Study 5: OR 1,93 95%CI, 1,46 - 2,55 Study 6: OR 1,96 95%CI, 1,03 - 1,54.

Conclusion: 97,544 co-infected HBV patients out of 910,592 patients were studied. Relative risk analysis and statistics suggested that there may be a strong correlation between HBV and colorectal neoplasia. The risk of developing colorectal neoplasia for HBV patients was 1.7 times higher (RR = 1.70) in comparison with the control groups [4]. There are numerous studies evaluating the association between hepatocellular carcinomas and Hepatitis infections and it is said to increase the risk by 3-fold [7]. However, the number of studies conducted on HBV and colorectal cancers are very limited while Hepatitis is the third most infectious agent that poses an attributable risk to all types of cancers [8]. There are numerous rural areas in Eastern Europe where Hepatitis B infections can be found as high as 6 - 8% [9]. It would be useful to analyze the association with further studies and be able to provide stronger evidence in order to improve the screening rate and standards of colorectal cancers among patients with Hepatitis B infections. Regular fecal immunochemical test (FIT) and colonoscopy may be considered by physicians in co-infected patients. Larger scale studies should be conducted.

Keywords: *Colorectal Cancers; Fecal Immunochemical Test (FIT); Colonoscopy; Hepatitis B Patients*

Introduction

Colorectal cancers are the third most common cancer with 1.93 million cases and second cause by cancer-related mortality worldwide in 2020 (WHO). Incidence rate follows a slow and steady increasing trend in Central and Eastern Europe in line with the World. Aside from genetic susceptibility, lifestyle, environmental factors and chronic infections and inflammations are the well-known causes of colorectal cancers. Hepatitis B is the third most common infectious agent that is attributable to cancer risk worldwide by 16.3% (IARC) [1]. HBS Ag seropositivity is well linked with hepatocellular carcinomas but the link between HBV and other cancers are not well established.

Aims and Methods

Our aim is to examine the interconnections between HBV infections and colorectal cancers and to assess the degree of the associated risk between them.

A selective search strategy was performed to search for relevant original articles using OVID in Medline R, EMBASE and Cochrane library. "Hepatitis", "Hepatitis B", "HBV", "cancer", "colon", "colorectal", "colonoscopy", "diagnosis" were used as the main keywords. A flow chart of search strategy can be seen as a flowchart in figure 1.

We took 7 studies into our study after a limited search strategy. Study selection was made basis on the outcome and etiology of the studies. Articles written in English available with full-text were included into study. The criteria to include the studies are as follows:

- Patients with co-infection of HBV or HCV infection (One exception was made for HIV in one of the studies.
- Control population.
- Study focus on Colorectal cancers, rectal cancers and adenomas.
- Study design; prospective or retrospective, case-control studies, cohort studies, clinical trials.

One exception was made for a conference abstract due to its interesting nature relevant to our study aim which demonstrated results from patients who were receiving long-term oral Nucleoside analogue treatment. The study was analyzed for posing any possible additional risk of development of colorectal cancers.

Statistical analysis

Our main focus was to measure the risk of colorectal neoplasia including adenomas. The studies selected for analysis varies within etiologies and outcomes and the dichotomous nature of the events, we used pooled Odds ratios (ORs) in line with confidence intervals using Mantel-Haenszel calculation. A random-effects model was applied for pooled rates to rule out the high heterogeneity according to DerSimion and Laird's studies. I^2 was calculated to measure the degree of heterogeneity. Bias assessment was made and L'abbe and bias plots were visualized to assess the strength of the results. All statistical analysis were performed using Statsdirect.

Study 1

A population based case-control study in Taiwanese population in 69,478 CRC patients and same number of controls reached a result of 5.09% of new cases among the patients that were identified with HBV infection.

Study 2

A retrospective study in Turkey included 8322 cancer patients with and 96000 controls in their study. The HbsAg positivity rate was 3.65% and 3.3% respectively. The study demonstrated a number of 3.8% of new cases in colon cancers and 5.6% of rectal carcinomas among the patients.

Study 3*

A cohort conducted in Hong-Kong among 45,299 Chronic Hepatitis B patients focused on all malignancies among these patients taking nucleoside analogue treatment showed that risk of developing colorectal carcinomas was 2.17 times higher in CHB patients taking nucleoside analogues as a long-term treatment.

Study 4

A retrospective chart review studied in USA in 555 patients undergoing screening colonoscopy whom 71 one of them are diagnosed with CHB. The results showed a higher incidence rate of colorectal adenomas in CHB group. However, it did not show a statistical significance.

Study 5

A cohort study conducted in South Korea in 155,674 patients, where 3.5% of them were with positive HBsAg serology.

Study 6

A population based cohort in Canada among 658,697 participants identified a higher risk of colorectal cancers among patients whom are co-infected with HBV, HCV and HIV.

Study 7

A small clinical trial conducted on 133 patients undergoing colonoscopy were taken into the study and matched with a healthy uninfected HBV group. The study reached a conclusion that HBV group had a higher rate of colorectal adenoma and advanced adenoma than the HBV-uninfected group and there is significant association between HBV infection and colorectal adenomas.

Study	Country	Study Design	Etiology	No. of patients	Study focus
Fu-Hsiung Su., *et al*.	Taiwan	A population-based Case-control Study	HBV Control	69,478 69,478	Colorectal Cancer versus Non-CRC control
Kocoglu., *et al*.	Turkey	A retrospective case-control study	All HBV HCV	3890 142 48	Colon Cancer Rectal Cancer
*Wong., *et al*.	Hong Kong	Cohort Study	HBV	45,299	Colorectal Cancer
Patel., *et al*.	USA	Retrospective Chart Review	HBV Control	71 484	Colorectal Adenoma
Jung., *et al*.	South Korea	A retrospective cohort study	HBV Control Non-HBV (HCV) Non-HCV Control	5476 150,198 240 154,940	Colorectal Adenoma vs control HVC vs Control CRC HBV vs Control HCV vs Control
Darvishian., *et al*.	Canada	A population-based cohort	HBV only HCV only HIV only HCV+HBV HBV+HIV HCV+HIV HCV+HBV+HIV Control	14,913 34,807 4,846 3,472 679 2,688 1240 596,072	Colorectal Liver Pancreatic Cancers
Kim., *et al*.	South Korea	Retrospective Case-Control Study	HBV Control	133 399	Colorectal Adenoma+HBV vs Control Colorectal Carcinoma+HBV vs Control

Table 1

Study	Odds Ratio	95% CI	P value	HR
Fu-Hsiung Su., *et al.*	1.27	1.20-1.33	<0.001	-
Kocoglu., *et al.*	1.16	0.71-1.89	<0.001	-
Patel., *et al.*	1.60	0.88-2.91	= 0.040	-
Jung., *et al.*	1.10	1.01-1.19	= 0.025	-
Darvishian., *et al.*	1,93	1.46-2.55	<0.001	2.47
Wong., *et al.*	1.236	1.03-1.54	<0.001	-

Table 2: *Odd's Ratio and confidence intervals of substudies.*
**Only HBV related outcomes and adjusted O.R's are taken into final calculation.*
P values lower than < 0.05 are considered statistically significant.

Study	Standardized Effect	Standard Error	% Weights (fixed, random)	
Fu-Hsiung Su., *et al.*	1,27	0,02624	66,173166	30,719323
Kocoglu., *et al.*	1,16	0,249767	0,730345	5,70847
Patel., *et al.*	1,6	0,305104	0,489441	4,062362
Jung., *et al.*	1,1	0,041838	26,028517	28,565109
Darvishian., *et al.*	1,93	0,142262	2,251224	12,862033
Wong., *et al.*	1,26	0,10261	4,327307	18,082704

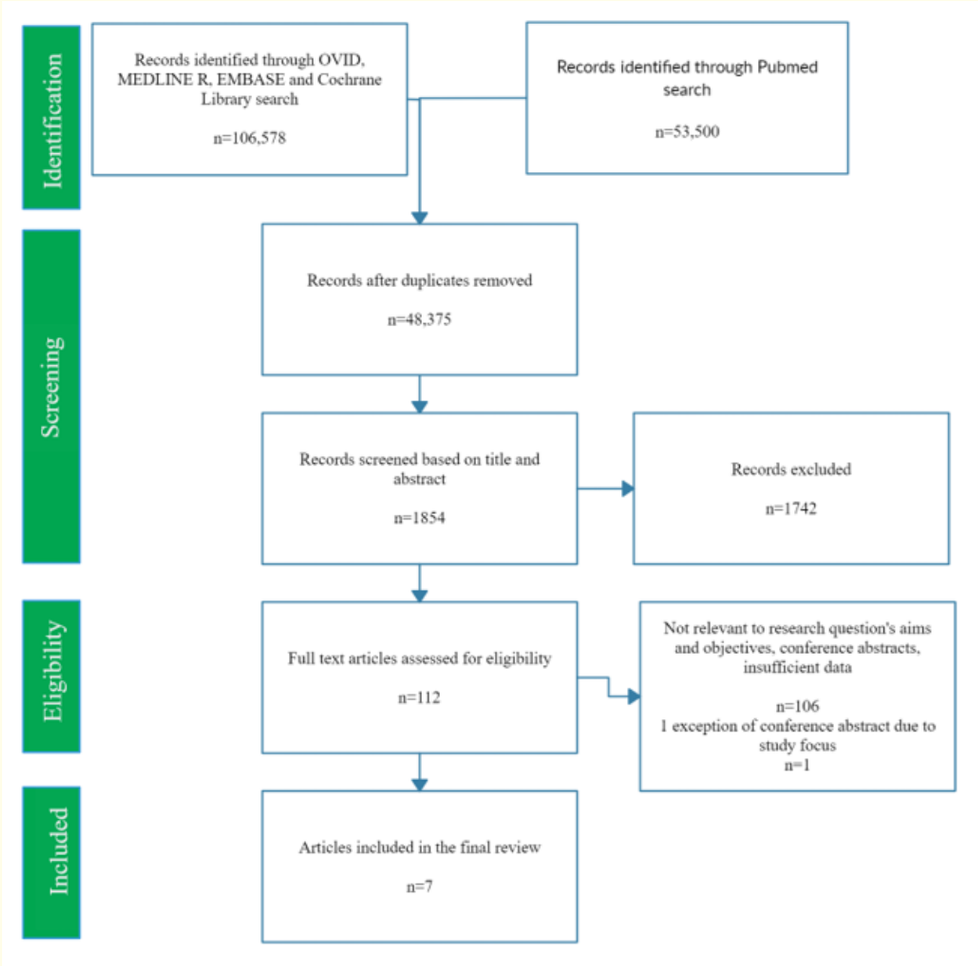
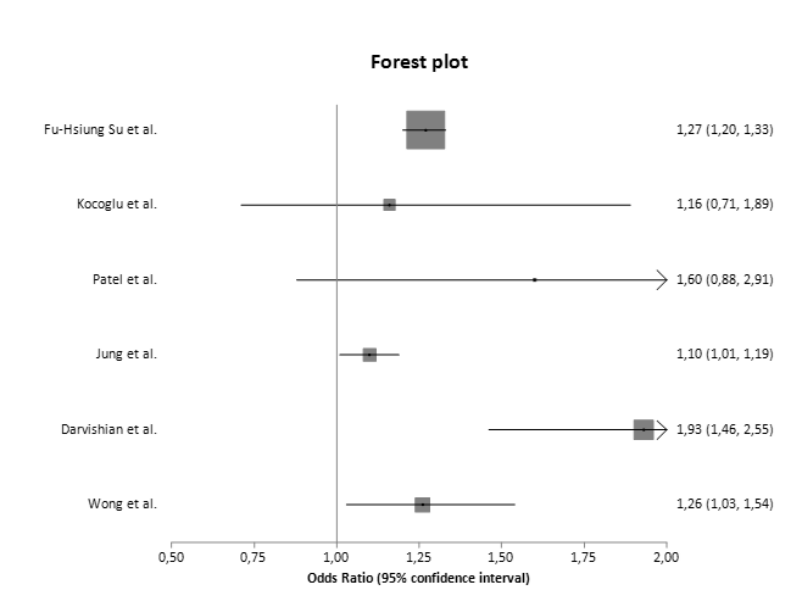


Figure 1: *Prisma flowchart of search strategy.*



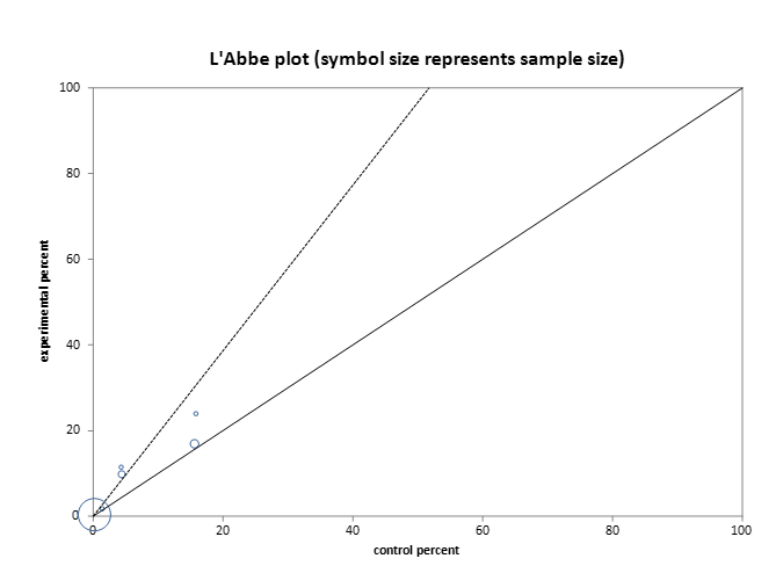


Figure 2: *Random effects (DerSimonian-Laird)*

Pooled odds ratio = 1,289916 (95% CI = 1,133909 to 1,467387)

Z (test Odds Ratio) = 3,870738 P = 0,0001

Pearson's contingency = 0,53638.

Bias indicator

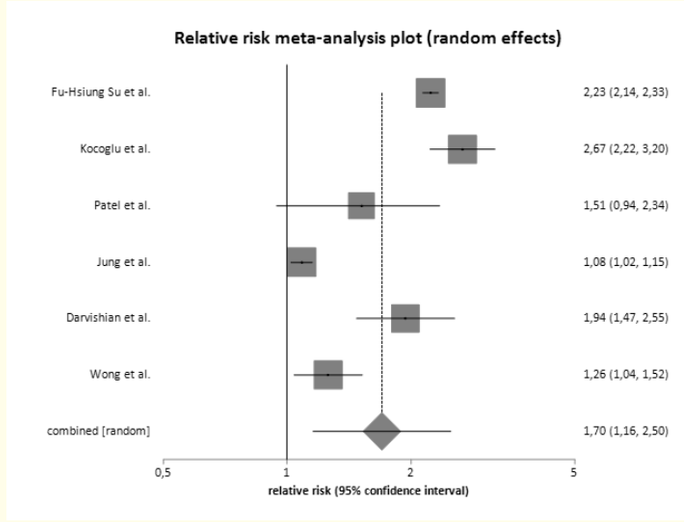
Non-combinability of studies

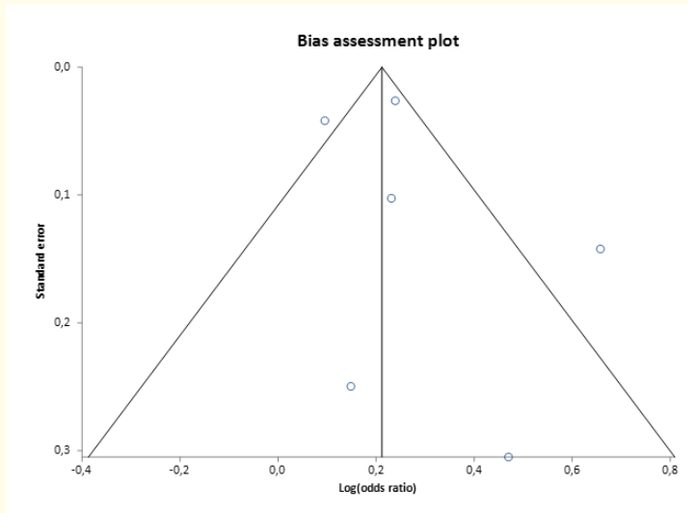
Cochran Q = 19,459513 (df = 5) P = 0,0016

Moment-based estimate of between studies variance = 0,013393

I2 (inconsistency) = 74,3% (95% CI = 20% to 86,9%)

Egger bias = 0,846428 (95% CI = -2,746058 to 4,438915) P = 0,5487.


Relative risk meta-analysis plot (random effects)
Fu-Hsiung Su et al.
Kocoglu et al.
Patel et al.
Jung et al.
Darvishian et al.
Wong et al.
combined [random]
2,23 (2,14, 2,33)
2,67 (2,22, 3,20)
1,51 (0,94, 2,34)
1,08 (1,02, 1,15)
1,94 (1,47, 2,55)
1,26 (1,04, 1,52)
1,70 (1,16, 2,50)
0,5
1
2
5
relative risk (95% confidence interval)


Bias assessment plot
Standard error
0,0
0,1
0,2
0,3
-0,4
-0,2
0,0
0,2
0,4
0,6
0,8
Log(odds ratio)

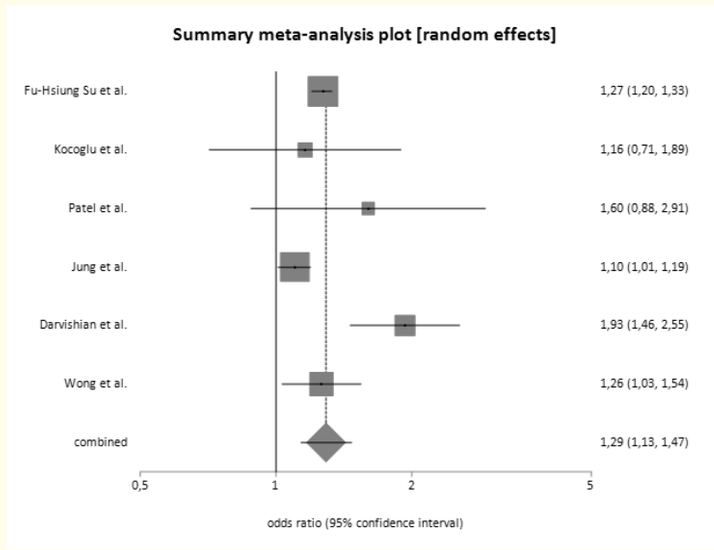

Summary meta-analysis plot [random effects]
Fu-Hsiung Su et al.
Kocoglu et al.
Patel et al.
Jung et al.
Darvishian et al.
Wong et al.
combined
1,27 (1,20, 1,33)
1,16 (0,71, 1,89)
1,60 (0,88, 2,91)
1,10 (1,01, 1,19)
1,93 (1,46, 2,55)
1,26 (1,03, 1,54)
1,29 (1,13, 1,47)
0,5
1
2
5
odds ratio (95% confidence interval)

Figure 3

Results

Pooled analysis after application of random-effects, clearly demonstrated a significant association between colorectal cancers and viral hepatitis of all kinds. (OR = 1,29; 95% CI: 1,13-1,47, I^2 = 74,3% and p = 0,0001) Also calculated, Pearson's contingency coefficient confirms (0,53) the correlation between HBV co-infection and colorectal carcinoma. If the coefficient lays between 0,5 to 1,0, it is said to be high degree of correlation with strong probability [2]. 74,3% of Higgins number may represent substantial heterogeneity in pooled analysis, thus a publication bias analysis performed and plotted. Results did not demonstrated great degree of asymmetry that should lead to high bias and Egger's Bias indicator was consistent with low bias power of the study [3].

Clarification of heterogeneity was limited because only a few number of studies included with different main focus in the study.

Kim's paper was excluded from statistical analysis because it was a clinical trial but will be taken into account for extended analysis of the results and association.

Discussion and Conclusion

In this paper, 97,544 co-infected HBV patients out total of 910,592 patients were studied. Relative risk analysis and statistical calculations suggested that there may be a strong correlation between HBV and colorectal neoplasia. The risk of developing colorectal neoplasia for HBV patients was 1.7 times higher (RR = 1.70) in comparison with the control groups [4]. There was one exception made by taking conference abstract into study, as the paper's main focus was detection of cancers among the chronic hepatitis b patients receiving long term nucleoside analogue treatment. The main reason for investigating this paper was to elucidate the risk difference and exclusion of confounding. The treatment itself might be a sole or an additional risk factor in developing colorectal cancers, therefore the relative risk of the paper was assessed and found lower than combined average of all pooled studies (RR = 1,26 95% CI 1,04 - 1,52). "However, the incidence rates of colorectal cancer and cervical cancer were higher in NA-treated CHB patients" [5].

Kim's paper which was not taken into statistical analysis was assessed for the sequence of colorectal adenoma and carcinoma. However, the nature of the clinical trial impose a selection bias for the small sized study and the incidence rate of all cancers were higher than average incidence in both adenoma versus control and carcinoma group [6].

There are numerous of studies evaluating the association between hepatocellular carcinomas and Hepatitis infections and it is said to increase the risk by 2.5 to 4 fold [7]. However, the number of studies conducted on HBV and colorectal cancers are very limited while Hepatitis is the third most infectious agent that pose attributable risk to all types of cancers [8]. There are numerous rural areas in Eastern Europe where Hepatitis B infections can be found as high as 6 - 8% [9]. It would be useful to analyze the association with further studies and be able to provide stronger evidence in order to improve the screening rate and standards of colorectal cancers among patients with Hepatitis B infections. Regular fecal immunochemical test (FIT) and colonoscopy may be considered by physicians in co-infected patients [10-14].

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Volume 9 Issue 2 February 2022