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Research Article

Analysis of Risk Factors for Development of Hepatocellular Carcinoma in Chronic HBV - Infected Liver Cirrhosis Patients: A Meta-Analysis

Abstract

The 5-year cumulative incidence rate of hepatocellular carcinoma (HCC) in chronic HBV -infected liver cirrhosis (LC) patients was up to 5%-30%. However, existing medical interventions can't cure chronic HBV -infected LC patient. At present, the association between risk factors and development of chronic HBV -infected HCC have been explored by previous studies, but the results remains inconsistent. We took the chronic HBV -infected LC patients as the research object. We systematically searched for studies evaluating whether those proposed factors changed HCC risk from Chinese Medical Journal Database, Chinese National Knowledge Infrastructure, Pubmed, Elsevier, Springer, Wiley, OVID, EBSCO in BoKu data service platform. Odds ratios (OR) with 95% confidence intervals (CI) were calculated by Review Manager 5.0. In this meta-analysis, 1088 cases and 602 controls from 6 studies were included. Our results showed that pooled OR with 95% CI for the factors analyzed were: non-antiviral treatment 3.59(2.73, 4.72), high HBV DNA levels 3.12(2.29, 4.25), drinking alcohol 1.86(1.41, 2.26), a family history of HCC 10.12(4.23, 24.25), male gender 1.48(1.13, 1.95), smoking 2.93(1.99, 4.40), a history of diabetes mellitus 5.87(3.06, 11.27), a family history of HBV 1.20(0.92,1.57), a history of fatty liver 2.29(1.22,4.32) and HBeAg positive 2.05(1.15, 3.68), respectively. Non-antiviral treatment, high HBV DNA levels, drinking alcohol, smoking, a family history of HCC, male gender, a history of diabetes mellitus, a history of fatty liver and HBeAg positive can increase the development risk of HCC in chronic HBV -infected LC patients from currently available evidence.

Abbreviations

HCC: Hepatocellular Carcinoma; LC: Liver Cirrhosis; CI: Confidence Intervals; HBV: Hepatitis B Virus; Hbsag: Hepatitis B Virus Surface Antigen; Hbeag: Hepatitis B E Antigen; CNKI: National Knowledge Infrastructure; CMJD: Chinese Medical Journal Database; M: Model; F: Fixed-Effect Model; R: Rrandom-Effect Model

Introduction

Liver cancer is the fifth most common carcinoma and the third most common cause of cancer-related deaths worldwide, resultting in about 500,000 deaths every year [1–3]. Liver cancer consists predominantly of HCC, in China, and the number of HCC accounts for 55% of all HCC cases in the world and the incidence of HCC is increasing now [4,5].

In view of a large of scale of the public health problem triggered by HCC, over the past few decades, some measures, reducing the lyngbya toxins in drinking water and reducing the aflatoxin content in food and inoculating Hepatitis B vaccine in all newborns to effectively block mother-to-infant HBV transmission, have been implemented in China [6–8]. However, the HBV infection rate of the adult still is high, and there are 9.3 million chronic HBV -infected people [9,10]. Moreover, the incidence of HCC still is increasing, in which HCC with chronic HBV -infected account for approximately 80% [11].

Whereas chronic HBV -infected LC patients will be the major source of HCC over the next 50 years, with LC rate of 70% -90% in HBV -infected HCC patients, and the 5-year cumulative incidence rate of HCC in chronic HBV -infected LC patients was up to 5% -30% [12]. However, existing medical interventions can't cure chronic HBV -infected LC patients and the development of HCC goes through a long history.

At present, some behavior intervention measures have already prevented.

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Chronic HBV -infected LC patient's condition deterioration. Hence, our study focused on the chronic HBV -infected LC patients.

Previous studies have indicated the risk factors included a family history of HCC, smoking, high level of HBV replication and the use of alcohol, however the effects of these factors were controversial [13-19]. In view of a large of scale of the public health problem accompanied with chronic HBV -infected LC patients, the major risk factors for HCC development in chronic HBV -infected LC patients were analyzed to control the development of HCC.

Meta-analysis can implement statistical analysis for combining and contrasting results from different studies, and meta-analysis can reduce random error and identify associations or patterns in the context of a variety of evidence. In this study, we performed this meta-analysis to identify the associations between possible factors and the development of HCC with chronic HBV infection.

Materials and Methods

Literature and Search Strategy

All articles were retrieved from the following databases in BoKu data service platform: Chinese Medical Journal Database (CMJD), Chinese National Knowledge Infrastructure (CNKI), Pubmed, Elsevier, Springer, Wiley, OVID and EBSCO

Searches were performed via using the search field "Title/Abstract" and using the search terms ("cirrhosis") and ("hepatitis b") and ("risk factor") from PubMed, Elsevier, Springer, Wiley, OVID , EBSCO in BoKu data service platform. Searches were performed via using the search field "Abstract" and using the search terms ("cirrhosis") and ("hepatitis b") and ("risk factor") from CNKI and CMJD data journals published between January 2011 and September 2016.

The present study was carried out following Meta-analysis in PRISMA guidelines [20].

Inclusion and exclusion criteria

In our search, only primary studies were included. All eligible articles were case-control or cohort studies between January 2011 and September 2016 and the articles were published in Chinese or English.

Studies were included in the meta-analysis provided that: (1) the article was a cohort study or a case-control and the article had been publicated with full text available; (2) all cases and controls were diagnosed by national diagnostic criteria existing at that time, and possible risk factors were reported; and (3) the data was reported and can be used to calculate OR with 95% CI.

Studies were excluded from the meta-analysis when: (1) The article reported other forms of viral hepatitis (hepatitis A or C or D or E or G) as the etiological agent. (2) The article did not provide a workable value for the main variable.

Data extraction

Two independent reviewers finished an assessment using a standardized data extraction form designed by our group so as to decide whether an article should be included or excluded. Data were extracted from each study by two separate investigators.

Discrepancies between the decisions of the two reviewers were discussed. If a consensus was not achieved, a third reviewer made the last decision. Articles were examined to eliminate duplicate reports of the same research.

The following information was extracted from all of the acquired studies: the study type, the numbers of patients in each group, and the characteristics of each group at baseline (including female/male ratio, average and median ages). Definition of main outcomes: liver cirrhosis and HCC were diagnosed by the guidelines at that time [21,22].

Statistical analysis

The OR with 95% CI was used as the main outcomes to measure efficacy. Analyses were performed using Review Manager 5.0 (Cochrane Collaboration, Rigshospitalet, Denmark). The OR was not pooled when the number of OR of the risk factor were less than 4. All of the P-values were two-sided. Meta-analysis was performed using either the fixed-effect or random-effect model, depending on the statistical heterogeneity among studies as evaluated by Cochran's chi-square test [23]. Statistical heterogeneity among studies was assessed using the Q and I2 statistics. In this meta-analysis, when $p \leq 0.1$ the random-effect model was employed, and when $p > 0.1$ the fixed effects model was employed. In this meta-analysis, subgroup analyses were used to analyze the associations between different risk factors and HCC, and funnel plot were used to examine publication bias.

Results

Literature search

The selection of included studies in this meta-analysis was shown in figure 1.

According to the inclusive and exclusive criteria, all articles were retrieved and carefully reviewed to assess the eligibility. Six eligible studies were identified after screening of 348.

Characteristics of the studies

A total of 6 studies, including 1088 cases and 602 controls were included in our research. Among the six studies, following categories were studied: drinking alcohol (1690 cases), smoking (1690 cases), non-antiviral treatment (1450 cases), high HBV DNA levels (1543 cases), HBeAg positive (983cases), family histories of HCC (1356 cases), a history of diabetes mellitus (1690 cases), a family history of HBV (1225 cases), a history of fatty liver (1395 cases) and male gender (1690 cases). The details of all of the studies evaluated in this meta-analysis are shown in table 1 [14–19]. Six studies fulfilled the requirements and these included 1690 objects (Table 1).

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The available sample size of each study was ranging from 120 to 715 objects. The mean age and the percentage of females also changed greatly (Table 1).

Effects of Related Factors on the Development of HCC

The effects of non-antiviral treatment (four studies, 1450 research objects), drinking alcohol (six studies, 1690 research objects), smoking (six studies, 1690 research objects), high HBV DNA levels (five studies, 1543 research objects), HBeAg positive (three studies, 983 research objects), family histories of HCC (five studies, 1356 research objects) a history of diabetes mellitus (six studies, 1690 research objects), a family history of HBV (four studies, 1225 research objects), a history of fatty liver (four studies, 1395 research objects) and gender (male) (six studies, 4984 research objects) on the development of HCC were investigated in this analysis and the results are displayed there (Figures 2–6), respectively.

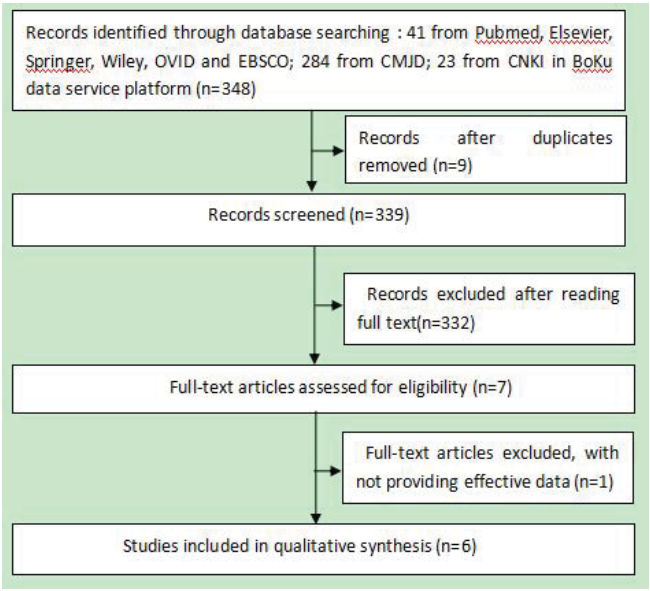

Figure 1: Flow chart of selecting studies inclused in this meta-analysis. Abbreviations: CNKI: Chinese National Knowledge Infrastructure; and CMJD: Chinese Medical Journal Database.

The pooled OR with 95% CI for the ten factors investigated were: non-antiviral treatment 3.59 (2.73, 4.72), high HBV DNA levels 3.12 (2.29, 4.25), drinking alcohol 1.86 (1.41, 2.26), a family history of HCC 10.12 (4.23, 24.25), male 1.48 (1.13, 1.95), smoking 2.93 (1.99, 4.40), a history of diabetes mellitus 5.87 (3.06, 11.27), a family history of HBV 1.20 (0.92,1.57), a history of fatty liver 2.29 (1.22,4.32) and HBeAg positive 2.05 (1.15, 3.68), respectively.

The heterogeneity test showed that the variation of study-specific OR for high HBV DNA levels, non-antiviral treatment, drinking alcohol, smoking, a family history of HCC, a history of diabetes, HBeAg positive and male were statistically($p < 0.10$), therefore, the results for these factors were pooled via using the random effect method. The heterogeneity test indicated that the variation of study-specific OR were not statistically significant ($p > 0.10$), therefore, the results for the other factors were pooled via using the fixed effect method. The results of statistical analysis and calculation are shown in table 2.

Sensitivity Analysis and Publication Bias

In some subgroups, in view of the enormous heterogeneity,

Table 1: Characteristics of the studies.

Study	Region	Study Type	Participants Category(Case/ Control)	Sample Size (n)	Male/ Female	Age (Years)	Risk Factors
Chen, 2012	Jiangsu, Qidong	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	330, 110	285/45, 85/25	52.4 ± 10.6, 51.4 ± 10.6	drinking alcohol, smoking, non-antiviral treatment, HBV DNA levels, family histories of HCC, family histories of hepatitis B, a history of fatty liver, a history of diabetes mellitus, male gender
Shi, 2013	China,Shanghai	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	80, 40	61/19, 29/11	48.7 ± 4.1, 50.1 ±16.3	drinking alcohol, smoking, HBV DNA levels, family histories of HCC, family histories of hepatitis B, a history of fatty liver, a history of diabetes mellitus, HBeAg positive, male gender
Wang, 2015	Henan, Luohe	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	60,60	38/22,48/12	44.6 ± 6.5	drinking alcohol, smoking, family histories of HCC, family histories of hepatitis B, a history of fatty liver, a history of diabetes mellitus, male gender
Zhang, 2015	China,Shanghai	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	434281	365/69,220/61	50.5 ± 11.1, 52.6 ± 10.9	drinking alcohol, smoking, non-antiviral treatment, HBV DNA levels, family histories of HCC, family histories of hepatitis B, a history of fatty liver, a history of diabetes mellitus, HBeAg positive, male gender
Sun, 2015	Henan,Pingdinsan	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	110,37	95/15, 29/8	52.0 ± 10.6, 51.0 ± 10.5	drinking alcohol, smoking, HBV DNA levels, family histories of HCC, a history of diabetes mellitus, non-antiviral treatment, male gender
Li, 2015	Guizhou,Guiyang	case-control study	chronic HBV -infected HCC/ chronic HBV -infected LC	74,74	65/9, 66/8	65.7±10.7,65.7 ± 10.7	drinking alcohol, smoking, non-antiviral treatment, HBV DNA levels, a history of diabetes mellitus, HBeAg positive, male gender

Abbreviations: HCC, hepatocellular carcinoma; LC, liver cirrhosis.

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we used sensitivity analysis to identify possible heterogeneous records from eligible studies. After omitting the selected studies, the study-specific OR results with lower degree of heterogeneity are shown in Table 3, and the effects of seven factors on the development of HCC are displayed in figure 3–6, respectively. A funnel plot for publication bias is displayed in figure 7.

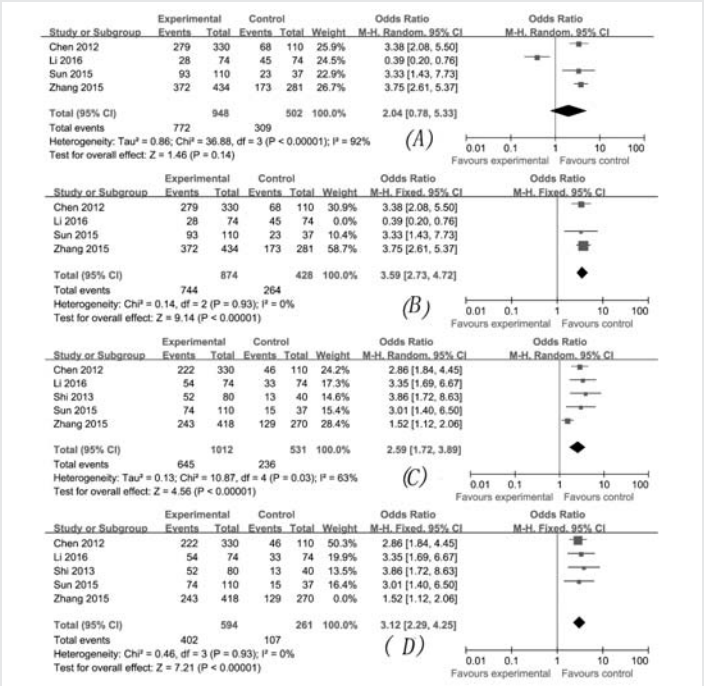

Figure 2: Effects of statistical analysis for possible risk factors of HCC development in chronic HBV -infected LC patients: (A) non-antiviral treatment; (B) non-antiviral treatment adjusted; (C) high HBV DNA levels, and (D) high HBV DNA levels adjusted.

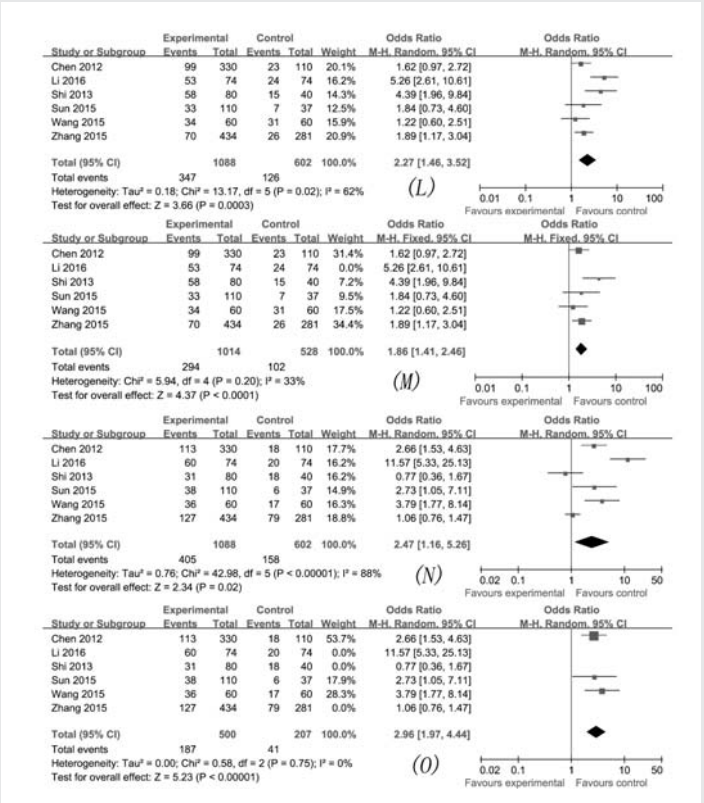

Figure 3: Effects of statistical analysis for possible risk factors of HCC development in chronic HBV -infected LC patients: (L) drinking alcohol; (M) drinking alcohol adjusted; (N) Smokig, and (O) Smokig adjusted.

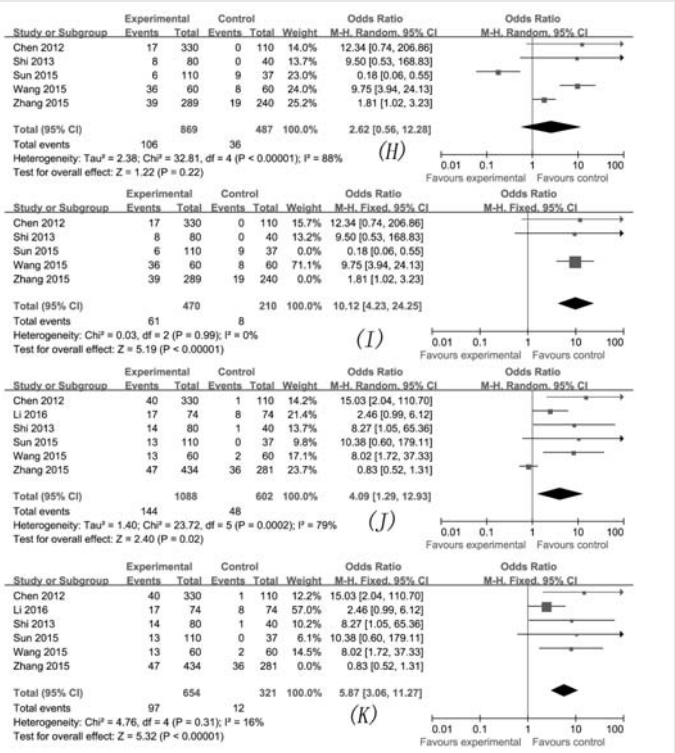

Figure 4: Effects of statistical analysis for possible risk factors of HCC development in chronic HBV -infected LC patients: (H) a family history of HCC; (I) a family history of HCC adjusted; (J) a history of diabetes mellitus, and (K) a history of diabetes mellitus adjusted.

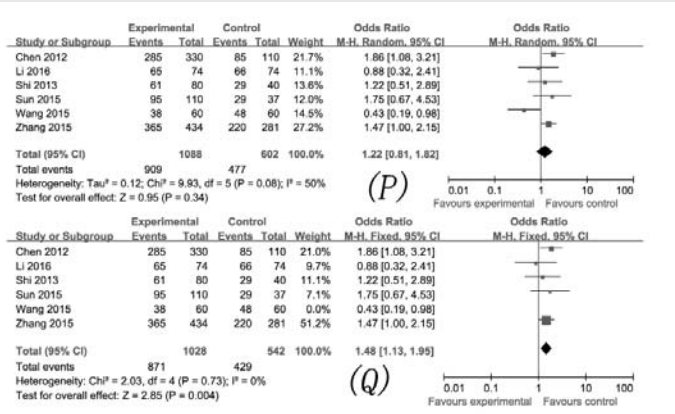

Figure 5: Effects of statistical analysis for possible risk factors of HCC development in chronic HBV -infected LC patients: (P) male gender; (Q) male gender adjusted.

Discussion

The development of HCC goes from liver damage to liver fibrosis to liver cell transformation, and multiple risk factors can affect progression of the development of HCC. In this study, we finished a comprehensive analysis of risk factors for the development of HCC with chronic HBV infection. In this meta-analysis, we collated literature to definite the association between possible factors and the development of HCC in chronic HBV -infected LC patients.

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Our meta-analysis result indicated that, compared with not having the Corresponding factor, the chronic HBV -infected LC patients with high HBV DNA levels have more than threefold the risk of HCC development. Other studies also confirmed this findings [24,25]. This indicated that antiviral treatment could greatly decrease the number of HCC development in chronic HBV -infected LC patients.

Our meta-analysis result also indicated that, compared with not having the corresponding factor, drinking alcohol can increase the risk of HCC development. Drinking alcohol can result in chronic oxidative stress and cytokines production and can result in the development of HCC under chronic inflammation condition [26]. These findings also were confirmed by other studies [27,28]. In addition, this study showed that smoking can increase the risk of HCC development, and the results were confirmed by other study [29]. Furthermore, this study also showed that a history of liver fatty and a history of diabetes can increase the risk of HCC development, and the results were confirmed by other studies [30,31]. Since the proportion of the population with these risk factors is high in menfolk, professional health education should be enhanced to changes bad behavioral to control the development of HCC.

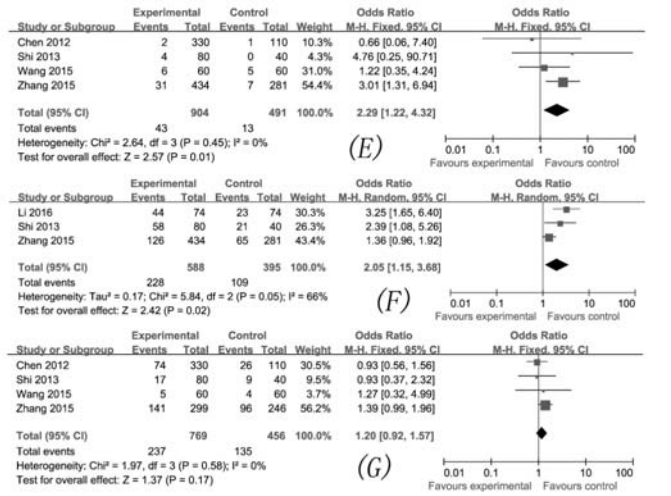

Figure 6: Effects of statistical analysis for possible risk factors of HCC development in chronic HBV -infected LC patients: (E) a history of fatty liver; (F) HBeAg positive; (G)a family history of HBV infection.

This study showed that a family history of HCC, non-antiviral treatment and male gender did not affect HCC development, After omitting those studies resulting in the development of heterogeneity, the above-mentioned three factors were associated with an increase risk in the development of HCC with chronic HBV infection [16,17,19]. A family history of HCC can increase the risk of HCC, and that may be connected with the genetic susceptibility to HCC and with the same carcinogenic factors exposed. In addition, this study also showed that a family history of hepatitis B did not affect HCC development, and the results were also different from that observed in previously reported research [27]. A possible reason for this was that the amount of information was not big enough. Confirmatory research should be done to confirm the real association between these factors and the risk of HCC development.

Heterogeneity in the variation of study-specific OR for high HBV DNA levels was determined. One possible reason was that unequal proportion of participants had received antiviral treatment in included study, and after omitting the study, the heterogeneity disappeared [17].

In addition, in the variation of study-specific OR for drinking alcohol and smoking, heterogeneity was found. One possible reason is that there was information bias in one retrospective study and three retrospective studies, respectively [15,17,19]. These studies were excluded, in the variation of study-specific OR for these two factors, and heterogeneity was not found.

In this study, in the variation of study-specific OR for a history of diabetes and a history of fatty liver, heterogeneity was found. One possible reason is that the patient's age and patient's illness vary slightly from study to study anyhow [15-17,19]. These studies were excluded, in the variation of study-specific OR for these two factors, and heterogeneity was not found.

This study has several limitations: (1) In our analysis, six eligible studies were included, and the sample size was limited in subgroup analysis which could have small affected the results. (2) Some non-randomized designs and retrospective studies are susceptible to various biases, for example, selecting inappropriate subjects. These biases could have decreased

Table 2: The test results of possible risk factors associated with HCC in chronic HBV-infected LC patients.

Risk Factors	No. of Studies (Cases/Controls)	OR			M	Heterogeneity		
		Z	P_{OR}	OR (95% CI)		X^2	P_H	I^2 (%)
non-antiviral treatment	4 (948/502)	1.46	>0.05	2.04 (0.78, 5.33)	R	36.88	<0.1	92
drinking alcohol	6(1088/602)	3.66	<0.05	2.27 (1.46, 3.52)	R	13.17	<0.1	62
smoking	6 (1088/602)	2.34	<0.05	2.47(1.16, 5.26)	R	42.98	<0.1	88
high HBV DNA levels	5 (1012/531)	4.56	<0.05	2.59 (1.72, 3.89)	R	10.87	<0.1	63
HBeAg positive	3(588/395)	2.42	<0.05	2.05 (1.15, 3.68)	R	5.84	<0.1	66
family histories of HCC	5 (869/487)	1.22	>0.05	2.62 (0.56, 12.28)	R	32.81	<0.1	88
family histories of HBV infection	4 (769/456)	1.37	>0.05	1.20 (0.92,1.57)	F	1.97	>0.1	0
a history of diabetes mellitus	6(1088/602)	2.4	<0.05	4.09 (1.29,12.93)	R	23.72	<0.1	79
a history of fatty liver	5 (904/491)	2.57	<0.05	2.29 (1.22,4.32)	F	2.64	>0.1	0
male gender	6(1088/602)	0.95	>0.05	1.22 (0.81, 1.82)	R	9.93	<0.1	50

Abbreviations: HCC = hepatocellular carcinoma; OR = Odds ratio; CI = confidence intervals; M =model; F = fixed-effect Model; R = random-effect model

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Table 3: The adjusted test results of risk factors associated with HCC in chronic HBV -infected LC patients.

Risk Factors	No. of Studies (Cases/Controls)	OR			M	Heterogeneity			Omitted study
		Z	P_{OR}	OR (95% CI)		X^2	P_H	I^2 (%)	
high HBV DNA levels	4 (594/261)	7.21	<0.05	3.12 (2.29, 4.25)	F	0.46	>0.1	0	[17]
drinking alcohol	5 (1014/528)	4.37	<0.05	1.86 (1.41, 2.26)	F	5.94	>0.1	33	[19]
non-antiviral treatment	3 (874/428)	9.14	<0.05	3.59 (2.73, 4.72)	F	0.14	>0.1	0	[19]
smoking	3 (500/207)	5.16	<0.05	2.93(1.99, 4.40)	F	0.58	>0.1	0	[15,17,19]
family histories of HCC	3 (470/210)	5.19	<0.05	10.12 (4.23, 24.25)	F	0.03	>0.1	0	[17,19]
a history of diabetes mellitus	5 (654/321)	5.32	<0.05	5.87(3.06, 11.27)	F	4.76	>0.1	16	[17]
male gender	5 (1028/542)	2.85	<0.05	1.48(1.13, 1.95)	F	2.03	>0.1	0	[16]

Abbreviations: HCC = hepatocellular carcinoma; OR = Odds ratio; CI = confidence intervals; M = model; F = fixed-effect model

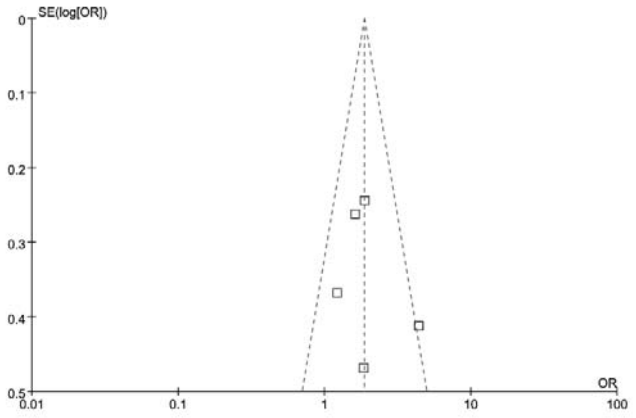

Figure 7: A funnel plot for publication bias.

slightly the internal and external validity of this study. (3) Publication bias could exist in some subgroup analyses, in view of the low possible publication rate for negative studies.

Conclusions

This meta-analysis draw a conclusion that non-antiviral treatment, high HBV DNA levels, drinking alcohol, smoking, a family history of HCC, male gender, a history of diabetes mellitus, a history of fatty liver and HBeAg positive can increase the development risk of HCC in chronic HBV - infected LC patients from currently available evidence.

Authors' contributions

Jianmin Jiang, Xiang Lyu, Zhifang Wang, Huakun Lv, and Yongdi Chen designed the study. Xiang Lyu and Kui Liu did the statistical analysis. Xiang Lyu, Sichao Huang, Zhengting Wang, Gaofeng Cai, Jun Yao, Zhenggang Jiang and Zhengting Wang prepared the manuscript. Jianmin Jiang, Huakun Lv, and Yongdi Chen did the critical review of the manuscript. All authors read and approved the final manuscript.

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