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Research Article

Meta-Analysis of Risk Factors for Development of Liver Cirrhosis in Chronic Hepatitis B Patients

Abstract

Chronic hepatitis B virus (HBV) infection and chronic hepatitis C virus (HCV) are main reasons for the development of liver cirrhosis (LC) on a worldwide scale. Chronic HBV infection is a main reason for the development of LC in high-risk areas, for example, China and Africa, whereas chronic HCV infection is a main reason in developed countries. In China, the harm of LC is serious, and 30 million of chronic hepatitis B (CHB) patients is the major source of LC and the one-year cumulative incidence rate of LC in CHB patients was 2.1% - 6%. The risk factors of the development of LC in CHB patients reported were controversial.

Therefore, we took CHB as participants, and we searched for studies in Chinese Medical Journal Database, Pubmed, Elsevier, Springer, Wiley, OVID, and EBSCO via BoKu data service platform, and did a meta-analysis and evaluated whether those published risk factors changed the development risk of LC. Both odds ratio (OR) and mean difference (MD) with 95% confidence intervals (CI) were calculated by Review Manager 5.0.

In this meta-analysis, 2928cases and 6530controls from 29 studies were analyzed. The pooled OR with 95% CI for 5 factors analyzed were: drinking alcohol 1.32 (1.11, 1.59), cigarette smoking 1.26 (1.04, 1.52), hepatitis B e antigen (HBeAg) seropositivity 0.42 (0.19, 0.94), a family history of hepatitis B 1.95 (1.05, 3.62), and male gender 1.33 (1.08, 1.65), respectively. And the pooled MD with 95% CI for 6 factors analyzed were: serum aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio 0.29(0.18,0.39), serum total bilirubin (TBil) levels 8.25(5.58,10.92)umol/L, duration of hepatitis B 2.68(2.21,3.15) years, age 7.37(4.60,10.14)years, serum alpha fetoprotein (AFP) levels -0.91(-16.04,14.22) ug/L, and serum HBV DNA levels 0.37 (-0.28, 1.02)copies/ml, respectively.

In CHB patients, habits of drinking alcohol and cigarette smoking, elevated serum levels of TBil and serum AST/ALT ratio, increased duration of hepatitis B, a family of hepatitis B, male gender and older age can increase the risk of LC development.

Abbreviations

HBV: Hepatitis B Virus; HBeAg: Hepatitis B e Antigen; HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; LC: Liver Cirrhosis; CHB: Chronic Hepatitis B; TBil: Total Bilirubin; AFP: Alpha Fetoprotein; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; CI: Confidence Intervals; MD: Mean Difference; CMJD: Chinese Medical Journal Database

Introduction

Chronic HBV infection and chronic HCV infection are main reasons for the development of LC and hepatocellular carcinoma (HCC) on a worldwide scale. Chronic HBV infection is a main reason for the development of LC and HCC in high-risk areas, for example, China and Africa, whereas chronic HCV infection is a main reason for the development of LC and HCC in developed countries, for example, the United States.

At present, chronic HBV infection is a serious threat to public health. According to the statistics, there were 2 billion people infected, and 360 million of these people are chronically infected [1]. In China, there are 120 million people infected, and 30 million of these people are CHB patients [2]. In long-term disease development of these chronic hepatitis B from one thing to another, chronic persistent infection of hepatitis B virus and recurrent inflammatory necrosis of the liver result in regeneration and repair, hepatic stellate cells activation, intrahepatic connective tissue dysplasia and a massive diffuse Extracellular matrix anomaly deposition, and result in Hepatic fibrosis and even LC.

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In China, CHB patients are the major source of LC and the rate of chronic HBV infection in LC patients was 66% [3]. The one-year cumulative incidence rate of LC in CHB patients was 2.1% - 6% [4]. Fibrosis is the main intermediate link in the development of LC. At present, it is generally believed that liver fibrosis is reversible and reversal of fibrosis can prevent the progression of most chronic liver diseases, whereas LC is irreversible. Once LC occurs, the one-year cumulative incidence rate of decompensated LC was 10%, and the one-year cumulative incidence rate of HCC was 2%-7% [5]. Moreover, the risk of LC is enormous. The 5 - year survival rate of compensated LC was 80% - 86%, and the 5 - year survival rate of decompensated LC was low to 14% - 30% [6,7]. Therefore, we research risk factors of the development of LC in CHB patients to eliminate the risk factors for high-risk groups and to decrease or prevent the development of LC.

In CHB patients, hepatic inflammation, poor healthy behavior, and replication state of HBV were the major cause of the deterioration such as drinking alcohol, cigarette smoking, serum TBil levels, serum AST/ALT ratio, serum HBV DNA levels and so on. These indicators have been indicated the risk factors of LC development by previous studies, and these indicators also can be detected routinely by grassroots health institutions, however, the effects of these factors were controversial [8-36].

Meta-analysis can reduce random error and increase test power. In this study, we pooled both OR and MD with 95% CI for these factors to identify the associations between possible factors and the development of LC in CHB patients.

Materials and Methods

Literature and search strategy

All articles were retrieved from the following databases via BoKu data service platform: Chinese Medical Journal Database (CMJD), Pubmed, Elsevier, Springer, Wiley, OVID, EBSCO.

In search field, "MeSH Terms" were used to search, and the search terms ("hepatitis B"), ("liver cirrhosis") and ("risk factor") were used, and articles were published between January 2007 and January 2017.The present study was carried out following Meta-analysis in PRISMA guidelines [37].

Inclusion and exclusion criteria

Studies were included in this meta-analysis provided that: all eligible articles were retrospective study continuously or longitudinal study, and only primary studies published in English or in Chinese were included.

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

Data extraction

To decide whether an article should be included or excluded, two independent reviewers carried out an assessment using a standardized data extraction form designed by our group. 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, the decision was made by a third reviewer. Articles were examined to eliminate duplicate reports of the same research.

Statistical analysis

The OR or MD with 95% CI was used as the main outcomes to measure efficacy. 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 [38]. Statistical heterogeneity among studies was assessed using the Q and I^2 statistics. The random-effect model was employed provided that P≤ 0.1, and the fixed effects model was employed provided that P>0.1. Analyses were performed using the software Review Manager 5.0 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes.htm). The OR or MD wasn't pooled when the number of OR of the risk factor were less than 5.

Results

Literature search

The selection of included studies in this meta-analysis was shown in figure 1. Twenty-seven eligible studies were identified after screening of 872 based on the inclusive and exclusive criteria.

Characteristics of the studies

In this meta-analysis, 29 studies were included, and 2928 cases and 6530 controls from these studies were analyzed, including the OR or MD and their 95% CIs for risk factors, shown in figures 2-6. The characteristics of the studies, including number of reference, study region, study type, participants category for case/control, risk factors, sample size , male/ female and age (years), are shown in table 1.

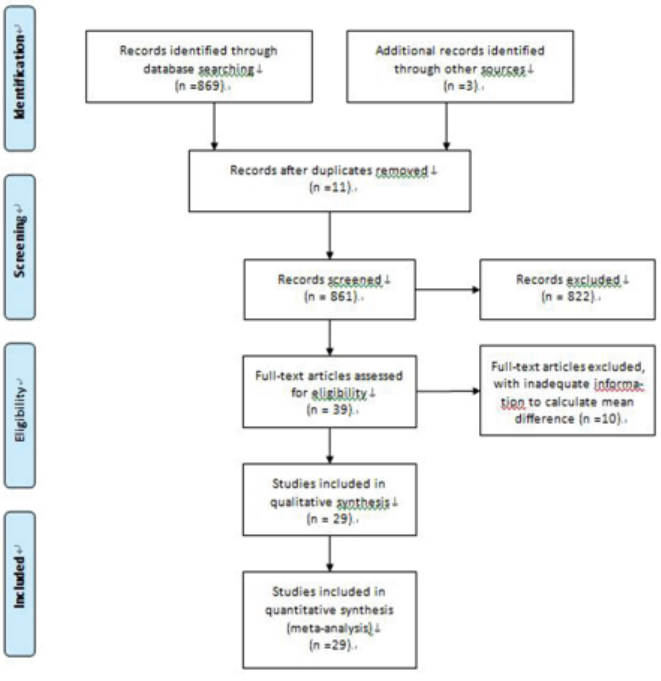

Figure 1: Flowchart of the selection of studies for inclusion in this meta-analysis.

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Table 1: The characteristics of the studies.

Study	Region	Study Type	Participants Category (Case/Control)	Study Factors
15	SiChun, Luzhou	retrospective study	LC/CHB	HBV DNA,AST/ALT, male, age
21	China, Tianjin	retrospective study	LC/CHB	TBil, HBeAg, age,
17	Taiwan, Taipei	Longitudinal study	LC/CHB	HBeAg, male, cigarette smoking, drinking alcohol
18	China, Shanghai	Longitudinal study	LC/CHB	AST/ALT, AFP, age, duration of hepatitis B, HBeAg, HBV DNA, male, cigarette smoking, TBil, a family history of hepatitis B, drinking alcohol
27	Shanxi, Xian	retrospective study	LC/CHB	Age, HBeAg
31	Shandong, Lunan	retrospective study	LC/CHB	age, HBeAg, HBV DNA, male
19	China, Guangxi	retrospective study	LC/CHB	AFP, age, male, cigarette smoking, TBil, drinking alcohol
24	Hebei, Baoding	retrospective study	LC/CHB	AST/ALT, age, HBeAg, HBV DNA, male, TBil
35	Fujian, Nanping	retrospective study	LC/CHB	AFP,HBV DNA,
20	China, Beijing	retrospective study	LC/CHB	age, HBeAg, HBV DNA, male, TBil, drinking alcohol
25	China, Guangxi	retrospective study	LC/CHB	AFP, age, male, cigarette smoking, TBil, drinking alcohol
28	China, Xinjiang	retrospective study	LC/CHB	AFP, age, male, cigarette smoking, TBil, drinking alcohol
32	China, Chongqing	retrospective study	LC/CHB	age, duration of hepatitis B, HBeAg, HBV DNA, male, a family history of hepatitis B, drinking alcohol
34	China, Guangxi	Longitudinal study	LC/CHB	duration of hepatitis B, HBeAg, HBV DNA, male, a family history of hepatitis B
26	China, Chongqing	retrospective study	LC/CHB	AST/ALT, age, HBeAg, HBV DNA, male,
9	Jiangxi, Nanchang	retrospective study	LC/CHB	AST/ALT, age, HBV DNA,
14	China, Beijing	retrospective study	LC/CHB	AST/ALT, age, HBeAg, HBV DNA, male
29	Hubei, Wuhan	retrospective study	LC/CHB	age, HBV DNA, male, TBil
23	Guangxi, Guilin	retrospective study	LC/CHB	age, HBV DNA, male, TBil,
13	China, Shanghai	retrospective study	LC/CHB	age, HBV DNA, male, TBil
22	China, Beijing	retrospective study	LC/CHB	age, HBV DNA, male, TBil
33	Guangdong, Meizhou	retrospective study	LC/CHB	AFP,HBV DNA
30	Jiangxi, jiujiang	retrospective study	LC/CHB	age, HBV DNA, male, TBil
11	Hubei, shiyan	retrospective study	LC/CHB	age, HBV DNA, male, duration of hepatitis B, HBeAg
8	China, shanghai	retrospective study	LC/CHB	age, AFP, male, HBeAg, TBil
12	Guangtong, yangjiang	retrospective study	LC/CHB	age, HBV DNA, male, duration of hepatitis B, HBeAg
36	Guangxi, nanning	retrospective study	LC/CHB	cigarette smoking, drinking alcohol
16	China, shanghai	Longitudinal study	LC/CHB	HBV DNA, male,
10	Hebei, Shijiazhuang	retrospective study	LC/CHB	age, HBV DNA, ssmale

Effects of related factors on the development of LC

In this analysis, the effects of the following 11 factors were analyzed: drinking alcohol (7 studies, 4985 research objects), cigarette smoking (5 studies, 4217research objects), serum TBil levels (12 studies, 2336 research objects), serum AST/ALT ratio (5 studies, 917 research objects), serum HBV DNA levels (23 studies, 8187 research objects), HBeAg seropositivity (14 studies, 5827 research objects), serum AFP levels (4 studies, 861 research objects), a family history of hepatitis B (5 studies, 980 research objects), duration of hepatitis B (7 studies, 1359 research objects), age (24 studies, 5257 research objects), and gender (male) (24 studies, 8403 research objects), and the results are displayed in figures 2-6.

The pooled OR with 95% CI for 5 factors analyzed were: drinking alcohol 1.32 (1.11, 1.59), cigarette smoking 1.26 (1.04, 1.52), HBeAg seropositivity 0.42 (0.19, 0.94), a family history of hepatitis B 1.95 (1.05, 3.62), and male gender 1.33 (1.08, 1.65), respectively. The pooled MD with 95% CI for 6 factors analyzed were: serum AST/ALT ratio 0.29(0.18, 0.39), serum total bilirubin (TBil) levels 8.25(5.58,10.92)umol/L, duration of hepatitis B 2.68(2.21,3.15) years, age 7.37(4.60,10.14)years, serum alpha fetoprotein (AFP) levels -0.91(-16.04,14.22) ug/L, and serum HBV DNA levels 0.37 (-0.28, 1.02)copies/ml, respectively.

The heterogeneity test showed that the variation of study-specific OR or MD for serum HBV DNA levels, serum TBil levels, serum AST/ALT ratio, age, duration of hepatitis B, HBeAg seropositivity, a family history of hepatitis B and gender were statistically significant ($p < 0.10$), therefore, the effects for these factors were pooled via using the random effect method.

The heterogeneity test showed that the variation of study-specific OR or MD for the other factors were not statistically

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significant ($p > 0.10$), therefore, the effects for these factors were pooled via using the fixed effect method.

The analysis results of enumeration data shown in figures 2,3, and the analysis results of measurement data were shown in figures 4-6.

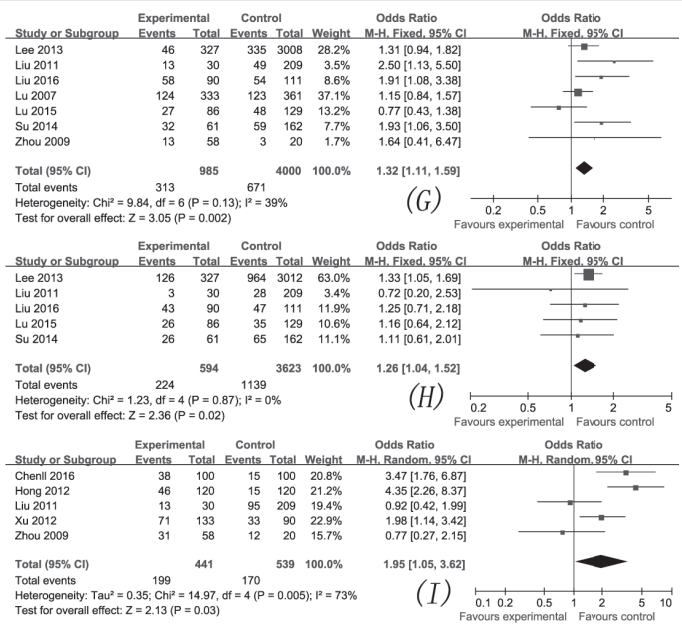

Figure 2: Effects of Related Factors on the Development of LC in CHB patients (enumeration data G: drinking alcohol; H: cigarette smoking; I: a family history of hepatitis B).

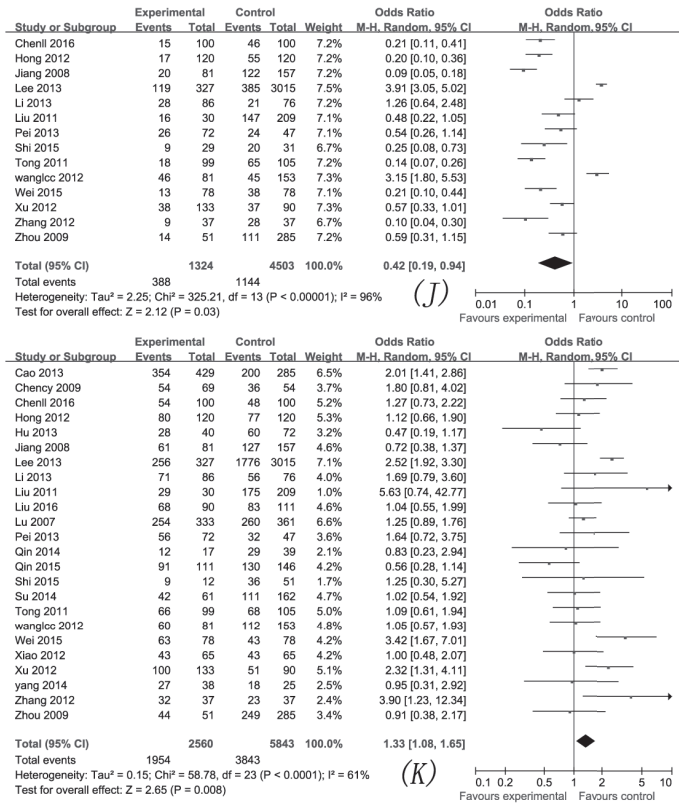

Figure 3: Effects of Related Factors on the Development of LC in CHB patients (enumeration data J: HBeAg seropositivity; K: gender (male)).

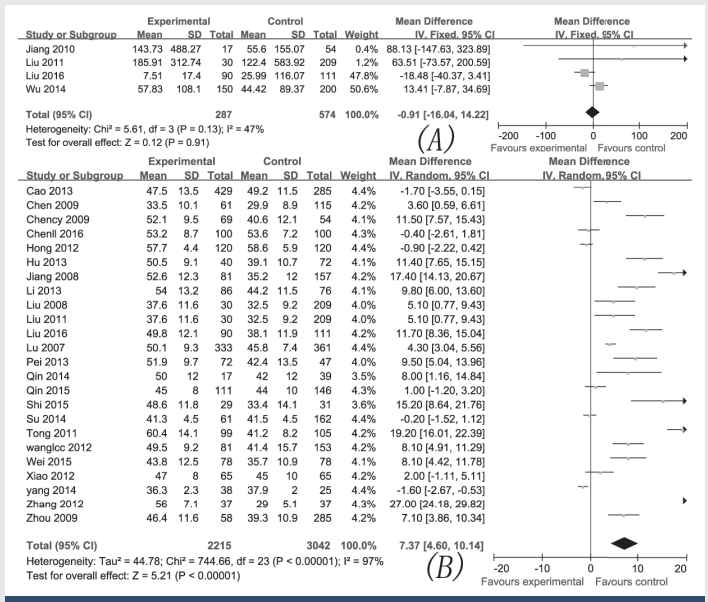

Figure 4: Effects of Related Factors on the Development of LC in CHB patients (measurement data A: serum AFP levels; B: age).

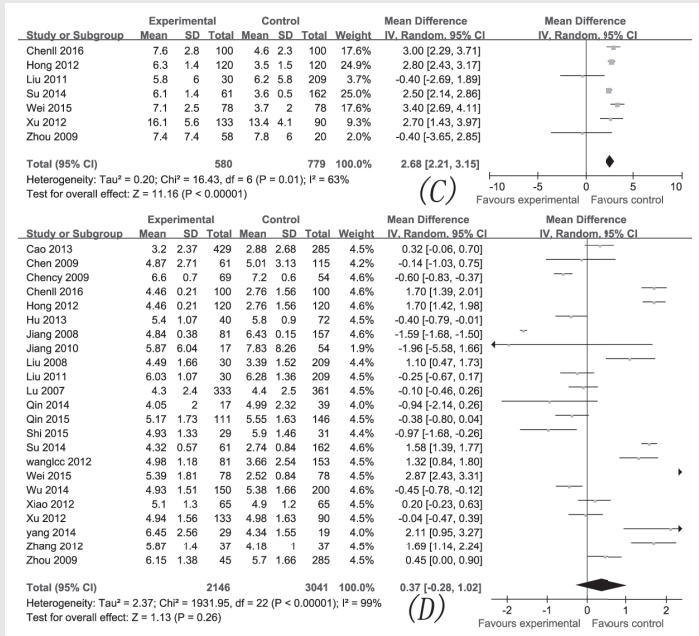

Figure 5: Effects of Related Factors on the Development of LC in CHB patients (measurement data C: duration of hepatitis B; D: serum HBV DNA levels).

Publication bias

Articles published in the distribution is symmetrical and majority of the articles are in the funnel plot, and symmetrical axis is off center axis (OR=1) and is at the right side of the center axis. A funnel plot for publication bias is displayed in figure 7.

Discussion

Our meta-analysis demonstrated that, for CHB patients, elevated serum AST/ALT ratio and serum TBil levels, and increased duration of hepatitis B could significantly increase the risk of LC development. These findings also were confirmed by original studies [12,14,25,28]. In general, ALT is distributed

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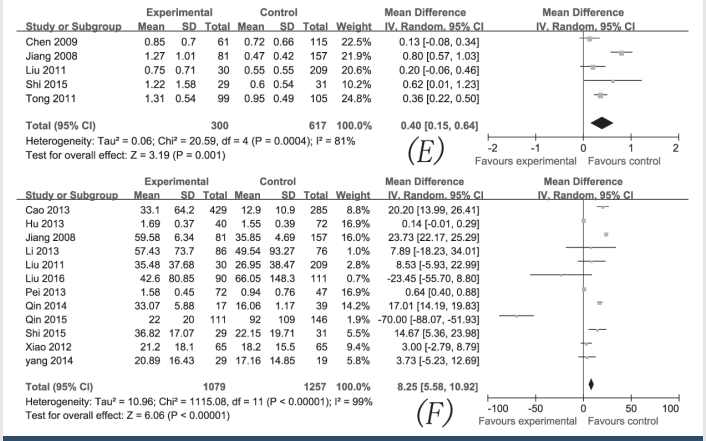

Figure 6: Effects of Related Factors on the Development of LC in CHB patients (measurement data E: serum AST/ALT ratio; F: serum TBil levels).

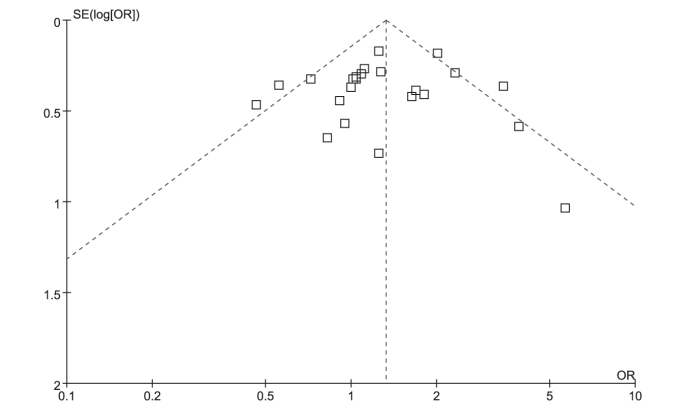

Figure 7: A funnel plot for publication distribution.

in liver cell plasma, and AST is distributed in liver cells and mitochondria. In the early stages in CHB, serum ALT levels rise more than serum AST levels, but, in LC stage, liver cell damage is serious and mitochondria have also been severe damage, therefore, serum AST levels rise more than the ALT. Serum TBil levels is an important index to judge the damage degree of liver cell. All of above-mentioned hinted that decreasing liver damage could significantly decrease clinical course of CHB and decrease the number of LC development in CHB patients.

Our meta-analysis also demonstrated that, for CHB patients, drinking alcohol and cigarette smoking could significantly increase the risk of LC development. These findings also were confirmed by a meta-analysis of risk factors for development of HCC in similar subjects [39]. This result hinted that banning drink alcohol and cigarette smoking could decrease the number of LC development. The study's result also showed a family history of hepatitis B, older age and male gender also could significantly increase the risk of LC development, and these results were existing facts.

Our meta-analysis result indicated that, HBeAg seropositivity can significantly decrease the risk of LC development, and this result was not easily understood or accepted, thus this will be an observation point for the future. Our meta-analysis result also indicated that, serum HBV DNA levels cannot significantly change the risk of LC development, and the result was different from the result in prospective cohort study [17], however, it was unknown that whether these were connected with that some patients had received antiviral treatment [40-42]. In future study, participants should be classified by antiviral treatment, but the study should meet the requirements of ethics.

This study has several limitations: (1) in subgroup analysis, the sample size for AFP was small. (2) There may be present some information recall bias in retrospective studies. (3) And only primary studies published in English or in Chinese were included. All of the points above may be a slight impact on this meta-analysis result.

Conclusion

In CHB patients, habits of drinking alcohol and cigarette smoking, elevated serum levels of TBil and serum AST/ALT ratio, increased duration of hepatitis B, a family of hepatitis B, male gender and older age can increase the risk of LC development.

Acknowledgment

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Authors' Contribution

Study design: G.C., B.Z., L.L.Y.C., C.H. Statistical analysis and interpretation: L.L., Y.C. Manuscript preparation: L.L., Zhi. W, J.Y., G.C., Z.J., Zhe.W, Y.Y, X.M., H.Q. Critical review of manuscript: B.Z., Y.C., C.H. All authors read and approved the final manuscript.

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