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Keywords: Hepatitis B; Liver cirrhosis; Cytokines; Meta-analysis

Research Article

The correlation between serum cytokine levels and liver cirrhosis in chronic hepatitis B patients: A meta-analysis

Abstract

Background: The harm of liver cirrhosis (LC) is serious, and the development of LC is primarily resulted from chronic hepatitis B virus (HBV) in high-risk such as China and Africa and chronic hepatitis C virus (HCV) in developed areas such as United States. Currently, there were 360 million chronic HBV-infected people on a global scale, and 30 million chronic hepatitis B (CHB) patients in China. In general, cytokines can regulate immune responses or contribute to deleterious tissue injury. However, the effects of these cytokines reported were controversial. Therefore, we executed a meta-analysis evaluating whether these cytokines can change the development risk of LC.

Methods: CHB patients were taken as participants, and studies were searched from Springer, Wiley, Chinese Medical Journal Database, PubMed, Elsevier, OVID, EBSCO, Mean difference (MD) with 95% confidence intervals (CI) were calculated by Review Manager 5.1.

Results: In this meta-analysis, 731 cases and 1012 controls from 30 studies were analyzed. The pooled MD of the serum cytokines were transforming growth factor-β1 (TGF-β1): 25.86 (95% CI : 184.73-286.99) pg/ml, interleukin(IL)-6: 56.35 (95% CI : 19.00-93.70) pg/ml, IL-17:22.07(95% CI : 11.77-32.37) pg/ml, IL-10:-3.24 (95% CI : -4.11, -2.36) pg/ml, and interferon-γ (IFN-γ): 1.50(95% CI : -4.34-7.35) pg/ml, respectively.

Discussion: In CHB patients, elevated of serum levels for TGF-β, IL-6, and IL-17 can increase the risk of LC development, whereas elevated of serum levels for IL-10 decreased the risk. We suggest high-risk subjects with elevated of serum levels for these cytokines should be closely monitored and receive treatment timely for reducing the development of LC.

Abbreviations

HBV: Hepatitis B Virus; HBeAg: Hepatitis B e Antigen; HCV: Hepatitis C Virus; HCC: Hepatocellular Carcinoma; LC: Liver Cirrhosis; CHB: Chronic Hepatitis B; TGF-β: Transforming Growth Factor-β; IL: Interleukin; IFN-γ: Interferon-γ; CI: Confidence Intervals; MD: Mean Difference; CMJD: Chinese Medical Journal Database

Introduction

The harm of LC is serious. The 5 - year survival rate for compensated LC patients was 80% - 86%, and 14% - 30% for decompensated LC patients [1,2]. The development of LC is primarily resulted from chronic HBV in high-risk areas such as China and Africa and chronic HCV in developed areas such as the United States.

Currently, chronic HBV infection still is a serious threat to people. On a global scale, there were 360 million chronic infected population [3], and there were 30 million CHB patients in China [4]. The immune dysfunction and imbalance of immune regulation resulted in condition recurrent and worse of these CHB patients from one thing to another, and then resulted in hepatic fibrosis and even LC.

The basic reasons for the formation of liver fibrosis and LC is imbalance between synthesis and degradation of hepatic extracellular matrix.

In general, cytokines can regulate immune responses, and cytokines can mediate or contribute to deleterious tissue injury only under certain conditions.

Therefore, we research serum cytokines such as TGF-β, IL and so on.

TGF-β has regulatory functions in many biological processes, Such as extracellular matrix protein expression, cell proliferation, protein decomposition and expression of

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cell adhesion receptor. TGF-β also has regulatory functions in a variety of pathogenic process, such as inflammatory tissue repair, fibrosis and tumor. TGF-β in human body exist three isomers TGF-β1, TGF-β2, and TGF-β3 [5,6]. At present, only TGF-β1 function was recognized, in this study, only TGF-β1 was used as the research variables.

IL are small molecules active peptides produced by a set of many kinds of cells, regulating the body's normal immune response, such as IL – 6, as inflammatory cytokines, have a strong chemotaxis and activated neutrophils role [7].

At present, there are effective treatments to improve these serum cytokine levels. In addition, these serum cytokines have been investigated as the possible risk factors for the development of LC by previous studies, and these serum cytokines also can be detected routinely in basic level hospitals, such as the studies for IL-6 [8-13], the studies for IL-17 [14-18], the studies for IL-10 [18-21], the studies for the studies for IFN-γ [22-26], and the studies for TGF-β [27-37]. However, the effects of these serum cytokines were controversial.

Random error can be reduced and test power can be increased by meta analyzing. In this study, we pooled MD with 95% CI for these serum cytokines in order to identify whether these cytokines changed the risk of LC development. And then to control the risk factors for high-risk groups and to decrease the development of LC.

Materials and Methods

Literature and search strategy

All articles were retrieved from Springer, OVID, PubMed, Elsevier, Chinese Medical Journal Database (CMJD), Wiley, EBSCO. Searches were done in search field "MeSH Terms", and the search terms ("hepatitis B") and ("liver cirrhosis") and ("cytokines") were used.

The present study was carried out following Meta-analysis in PRISMA guidelines [38].

Inclusion and exclusion criteria

Studies were included in this study when: [1], retrospective continuously or longitudinal study [2], original research published in English or in Chinese [3], Eligible research articles not captured by the research strategies detailed above were included by bibliography searches.

Studies were excluded from this study provided that: [1] the article reported simultaneously two or more kinds of hepatitis virus as the etiological agent [2], the article did not provide a workable value for the serum cytokines.

Data extraction

An assessment was executed by two independent reviewers based on a standardized data extraction form designed by our group so as to decide that an article was included or excluded. Data was extracted from each study by two separate reviewers.

Discrepancies between the decisions of the two reviewers were discussed for a settlement of all these discrepancies. Duplicate reports of the same articles were eliminated by checking.

Statistical analysis

The MD with 95% CI was used as the main outcomes to measure efficacy. The fixed-effect or random-effect model was used for executing Meta-analysis to pool the MD with 95% CI.

The statistical heterogeneity among studies was evaluated by Q test and I2 test. When P≤ 0.1 the random-effects model was operated, and when P>0.1 the fixed effects model was operated. Analyses were executed by the software Review Manager 5.1 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes. htm). The MD wasn't pooled when the number of MD of the serum cytokine marker were less than 5.

Results

Literature search

In this meta-analysis, thirty studies were eligible, and the flowchart of studies selected for inclusion in this meta-analysis was shown in figure 1.

Thirty eligible studies were identified and included in this meta-analysis.

Characteristics of the studies

In this meta-analysis, 30 studies, and 731cases and 1012 controls from 30 included studies were analyzed, including the MD and their 95% CIs for serum cytokine markers, shown in figures 2,3. The characteristics of the studies, including number of reference, study region, study type, participants category for case/control, serum cytokine markers, sample size, male/female and age (years), are shown in table 1.

Effects of related factors on the development of LC

In this analysis, the 5 serum cytokine markers analyzed were listed as follows: TGF-β1 (13 studies, 671 research objects), IFN-γ (6studies, 439 research objects), serum IL-6 (7studies, 484 research objects), serum IL-17 levels (7 studies, 485 research objects), and serum IL-10 levels (5 studies, 470 research objects), and the results are displayed in figures 2,3.

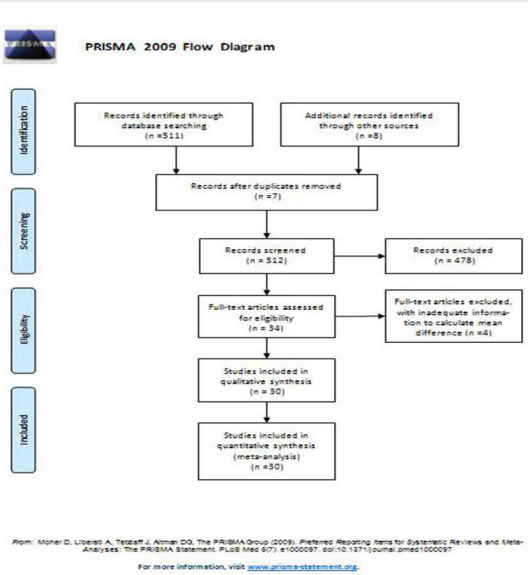

Figure 1: Flowchart of studies selected for inclusion in this meta-analysis.

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Table 1: The characteristics of the studies.

No. of reference	Region	Study type	Participants category(case/ control)	Sample size (n)	Male/ female	Age (years)	Cytokines
8	Fujian, Zhangzhou	longitudinal study	chronic HBV -infected LC/CHB	38, 56	89/45	18-77	IL-6
9	Shandong,Dongyin	longitudinal study	chronic HBV -infected LC/CHB	15,43	11/4, 30/13	47.8,36.5	IL-6
10	China, shanghai	longitudinal study	chronic HBV -infected LC/CHB	32,36	-	-	IL-6, IL-10
11	Shanxi, xian	longitudinal study	chronic HBV -infected LC/CHB	15,20	-	-	IL-6,TNF-α
12	Jiangsu, Nantong	longitudinal study	chronic HBV -infected LC/CHB	40, 37	63/24	47.47±13.50	IL-6,TNF-α
13	China, shanghai	longitudinal study	chronic HBV -infected LC/CHB	14,18	12/2, 15/3	38-56,23-49	IL-6,TNF-α
14	Guangxi, Nanning	longitudinal study	chronic HBV -infected LC/CHB	36, 21	28/8, 14/7	27-71, 18-71	IL-17
15	Jiangsu, Changzhou	longitudinal study	chronic HBV -infected LC/CHB	16, 56	10/6, 34/22	53.4±8.0, 49.4±8.7	IL-17
16	Shandong, Jinan	longitudinal study	chronic HBV -infected LC/CHB	42, 36	29/13, 23/13	51.86±11.11, 31.03±14.06	IL-17
17	China, chongqing	longitudinal study	chronic HBV -infected LC/CHB	27,40	15/12,26/14	40.04±16.37,34.61±11.89	IL-17, TGF-β1
18	Fujian, quanzhou	longitudinal study	chronic HBV -infected LC/CHB	28,70	21/7, 55/15	43.5±14.4, 33.1±10.3	IL-10,IL-17, TGF-β1
19	Guangdong, Dongguan	longitudinal study	chronic HBV -infected LC/CHB	86, 68	52/46, 39/29	45.2±7.3, 37.1±6.2	IL-10
20	Guangxi, nannin	longitudinal study	chronic HBV -infected LC/CHB	12,18	40,2	39.5+11.4	IL-10,IFN-γ
21	China, Shanghai	longitudinal study	chronic HBV -infected LC/CHB	60, 60	35/25, 30/30	50.50±8.58, 50.15±8.84	IL-10, IL-6
22	Jiangsu, changzhou	longitudinal study	chronic HBV -infected LC/CHB	33,71	101/28	47±13.7	IFN-γ
23	Jiangsu, Nantong	longitudinal study	chronic HBV -infected LC/CHB	41, 36	54/23	41.47±14.80	IFN-γ
24	Shandong, Jinan	longitudinal study	chronic HBV -infected LC/CHB	32,34	23/9, 21/13	52.06±11.39, 30.65±14.26	IFN-γ, IL-17
25	Xinjiang, Shihezi	longitudinal study	chronic HBV -infected LC/CHB	36, 54	30/6, 42/12	44.9±8.7, 38.5±8.6	IFN-γ
26	Hunan, Changsha	longitudinal study	chronic HBV -infected LC/CHB	35, 37	-	-	IFN-γ, IL-17
27	Shandong,Dongyin	longitudinal study	chronic HBV -infected LC/CHB	19,13	-	22-50	TGF-β1
28	gansu, lanzhou	longitudinal study	chronic HBV -infected LC/CHB	25, 28	36/17	42±12,	TGF-β1
29	Liaoning, Dalian	longitudinal study	chronic HBV -infected LC/CHB	14, 13	-	-	TGF-β1
30	Gansu, Qinghai	longitudinal study	chronic HBV -infected LC/CHB	50, 30	32/18, 17/13	-	TGF-β1
31	Zhejiang, Wenzhou	longitudinal study	chronic HBV -infected LC/CHB	15,15	10/5, 9/6	46.00±10.97 44.40±11.90	TGF-β1
32	Fujian, fuzhou	longitudinal study	chronic HBV -infected LC/CHB	17,35	50/13	20-54	TGF-β1
33	Zhejiang, wenzhou	longitudinal study	chronic HBV -infected LC/CHB	28,20	19/9, 13/7	26-72, 21-65	TGF-β1
34	Jiangsu, nantong	longitudinal study	chronic HBV -infected LC/CHB	24,39	89/35	25-61	TGF-β1
35	Ninxia, yinchuan	longitudinal study	chronic HBV -infected LC/CHB	24,18	-	17-66	TGF-β1
36	Guangdong, longchuan	longitudinal study	chronic HBV -infected LC/CHB	17,29	38,27	26-65	TGF-β1
37	Fujian, fuzhou	longitudinal study	chronic HBV -infected LC/CHB	19,14	57,17	20-54	TGF-β1

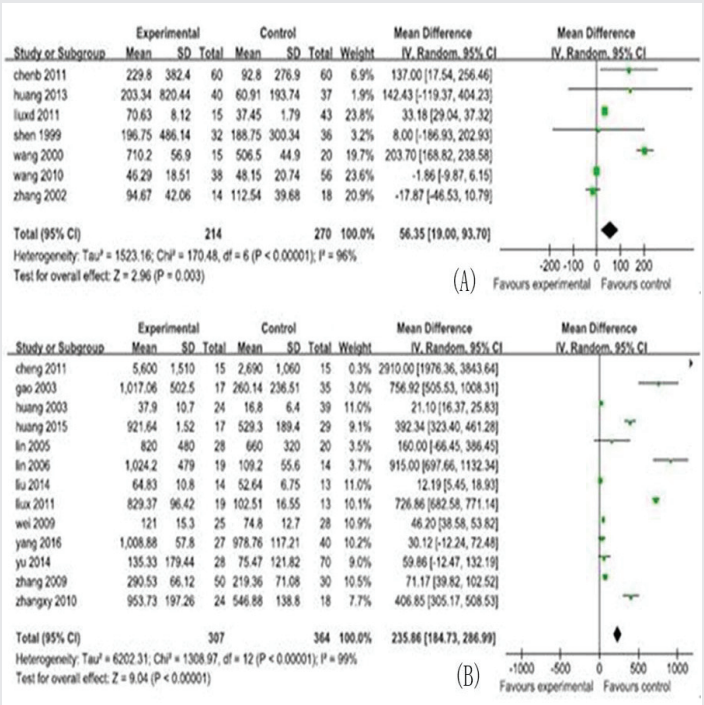

Figure 2: Effects of Related serum cytokine levels on the Development of LC in CHB patients (enumeration data: A: IL-6; B: TGF-β1;)

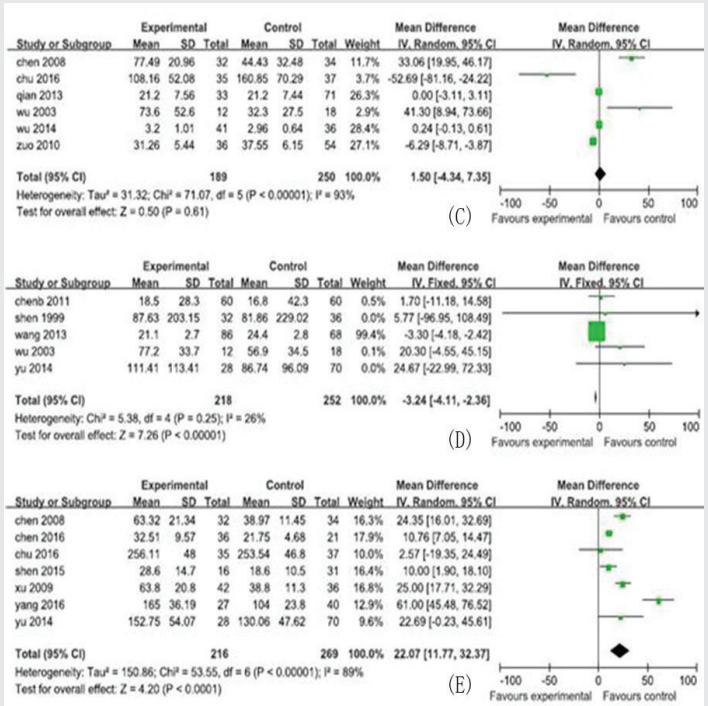

Figure 3: Effects of Related serum cytokine levels on the Development of LC in CHB patients (enumeration data: C: IFN-γ; D: IL-10; E: IL-17;)

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The MD with 95% CI test showed that the variation of study-specific MD for serum levels for TGF-β, IFN-γ, IL-6, and IL-17 were statistically significant ($p < 0.10$), and then, the effects for these were pooled via operating the random-effect method, whereas the IL-10 for the fixed-effect method ($p>0.10$). The analysis results of serum cytokine levels were shown in figures 2,3.

Publication bias

Articles published in the distribution is symmetrical and majority of the articles are in triangle of the funnel plot, and symmetrical axis is off center axis (MD=0) and is at the right side of the center axis. A funnel plot for published bias is shown in figure 4.

Discussion

Our meta-analysis demonstrated that, for CHB patients, elevated of serum levels for TGF-β, and IL-17 can significantly increase the risk of LC development. These finding was supported by the previous studies listed as follows: the studies for TGF-β [36,37,39], and the study for IL-17 [15], and these previous studies found that along with progressing of disease in liver, elevated of serum levels for these cytokines can goes up step by step. IL-6 can increase the risk of LC development. This finding was not consistent with the result of study by Zhou taking primary biliary cirrhosis as the research object [40].

Our meta-analysis demonstrated that, for CHB patients, elevated serum levels IL-10 can decrease the risk of LC development. These finding was confirmed by original studies [41]. In addition, IL-22, a member of the IL-10 family, that elevated of IL-22 levels can decrease the risk of LC development also was confirmed in animal and cytological experiments [42]. Whether IL-10 play a role in anti-fibrosis in CHB patients, and that needs further study and must meet the requirements of ethics at the same time.

Our meta-analysis also demonstrated that, for CHB patients, elevated serum levels IFN-γ didn't change the risk of LC development. However, the study by Zhou found serum levels of IFN-γ in primary biliary cirrhosis patients was lower than that in CHB patients [40]. And that whether IFN-γ was connected with the risk of LC development remains to be further studied.

This study has two limitations: [1] in subgroup analysis, the sample size for IFN-γ and IL-10 was small [2], and only primary studies published in English or in Chinese were included. Two points above may be a slight impact on this study results.

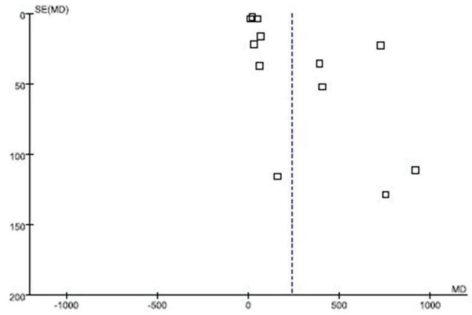

Figure 4: A funnel plot for published distribution.

Conclusion

In CHB patients, elevated of serum levels for TGF-β, IL-6, and IL-17 can increase the risk of LC development, whereas elevated of serum levels for IL-10 decreased the risk. We suggest high-risk subjects with elevated of serum levels for these cytokines should be closely monitored and receive treatment timely for reducing the development of LC.

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Authors' contributions

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

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