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Original Article

Correlations of IFN- γ -inducible protein-10 with the risk of chronic hepatitis B and the efficacy of interferon therapy in Asians

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Abstract: Purpose: The aim of this study was to identify the correlations of IFN- γ -inducible protein-10 (IP-10) with the risk of chronic hepatitis B (CHB) and the efficacy of interferon therapy in Asians. Method: Serum IP-10 levels were assayed using enzyme linked immunosorbent assay (ELISA) in both CHB and control group. CHB group received interferon- α 2b treatment to compare the pre-treatment and post-treatment serum IP-10 levels. Relevant studies met predefined inclusion and exclusion criteria were enrolled into further meta-analysis. Stata 12.0 software was applied for data analysis. Result: Our case-control study demonstrated that CHB group had evaluated serum IP-10 levels compared with control group (285.7 ± 41.6 pg/mL vs. 79.1 ± 33.8 pg/mL, $t = 21.85$, $P < 0.001$). After treatment for 12 weeks, CHB group had remarkably decreased post-treatment serum IP-10 levels than pre-treatment (78.5 ± 20.4 pg/mL vs. 285.7 ± 41.6 pg/mL, $t = 33.76$, $P < 0.001$). No significance was observed on post-treatment serum IP-10 levels between CHB and control group (78.5 ± 20.4 pg/mL vs. 78.1 ± 33.8 pg/mL, $t = 0.07$, $P = 0.947$). Meta-analysis results demonstrated that serum IP-10 levels in CHB group were obviously higher than healthy controls (SMD = 2.21, 95% CI = 1.55~2.87, $P < 0.001$). A subgroup based on the HBeAg states revealed that serum IP-10 levels in both HBeAg-positive and HBeAg-negative CHB patients were notably higher than healthy controls (HBeAg-positive: SMD = 2.00, 95% CI = 1.13-2.87, $P < 0.001$; HBeAg-negative: SMD = 1.34, 95% CI = 0.97-1.72, $P < 0.001$). Conclusion: Serum IP-10 may be correlated with the risk of CHB and the efficiency of interferon therapy, thus IP-10 may be a good biomarker for the diagnosis and treatment of CHB.

Keywords: Chronic hepatitis B, hepatitis B virus, interferon inducible protein 10, interferon- α 2b

Introduction

Chronic hepatitis B (CHB) is one of the leading causes of liver-related morbidity and mortality worldwide, affecting 350 to 400 million people globally with 75% infectors in the Asia-Pacific region [1]. CHB is an immune-mediated infectious disease resulted from complicated interplay among hepatitis B virus (HBV), hepatocytes and the host immune system [2]. The CHB patients were characterized by the infiltration of inflammatory cells including neutrophils, monocytes, natural killer cells and lymphocytes [3]. There are four stages of this disease, namely the immune-tolerant, the immune-active, inactive hepatitis B surface antigen (HBsAg)

positive, and the hepatitis B e antigen (HBeAg)-negative CHB carrier phase [4]. Evidence has been suggested that the active HBV replication is the key factor involved in liver injury and CHB progression, thus the primary aim of CHB treatment is to permanently suppress HBV replication [5]. However, the exact mechanism of HBV activity was not known while evidence demonstrated that the interplay between viral factors and host genetic factors was involved [6]. Currently, indications for CHB treatment initiation were serum aminotransferase levels including Alanine aminotransferase (ALT) levels, serum HBV DNA levels and histological grade [7]. It has been recognized that effective anti-HBV therapy arrests or slows the progression of

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CHB, especially in patients who achieve HBeAg (or further HBsAg) clearance or seroconversion [8]. Many chemokines may implicate in immune reactions in response to HBV infection while chemokine expression and its correlation with virological response in patients with CHB were still unclear [9].

The interferon-gamma inducible protein 10 (IP-10), also known as CXCL10, is a chemokine involved in both innate and acquired immune responses that direct T cells to sites of inflammation [10]. IP-10 was secreted by microglia, macrophages and astrocytes in response to stimulus, such as interferon (IFN)- α , IFN- β , IFN- γ or viruses [11]. A higher pre-treatment serum IP-10 level, which was correlated with a higher HBV DNA loader and greater HBeAg and HBsAg decline, might predict HBeAg loss in HBeAg-positive CHB patients [8]. Increasing evidence showed that serum IP-10 levels were notably correlated with CHB patients [12, 13]. Nevertheless, whether IP-10 expression level is related with the progression of disease caused by HBV infection and with the biochemical and virological factors in patients with CHB remains unclear [8, 13].

To address the correlation of serum IP-10 levels with CHB and to further investigate the efficiency of interferon therapy, this study was performed by investigating the pre-treatment and post-treatment serum ALT levels, one of the widely used biomarker for HBV-related liver cell injury [14], and serum IP-10 levels in a case-control study and a meta-analysis.

Materials and methods

Subjects

From Jan 2012 to Dec 2014, 57 patients (41 male and 16 female) with CHB hospitalized in the Zhongnan Hospital Wuhan University were selected as CHB group. The mean age of CHB group ranged from 25~51 year (mean, 35.8 \pm 10.5 years). All patients were diagnosed with CHB based on criteria from the guideline of prevention and treatment for chronic hepatitis. All patients in CHB group were presented with increased serum ALT levels and were arranged for antiviral therapy. Based on the HBeAg states, 23 patients in case group were HBeAg-positive CHB and 25 patients had HBeAg-negative CHB. Furthermore, 25 healthy con-

trols (21 male and 4 female) were included in current case and control study with mean age of 31.2 \pm 8.5 years (ranging from 25~50 years). This study was approved by the Ethics committee of Zhongnan Hospital Wuhan University and written informed consents were obtained from each patient prior to study.

Sample collection

After an overnight fast, venous blood (3 mL) were collected and maintained in room temperature for 30 min. After centrifugation at 1500 r/min for 15 min, the sample were removed the supernatant and stored at -20°C for further usage.

Detection for ALT and IP-10

The serum ALT level was measured using Beckman LX20 automated analyzer (Beckman Corp., Brea, CA, USA) and Backman kit. The normal serum ALT level was 0~40 U/L. Moreover, the serum IP-10 level was assayed using enzyme linked immunosorbent assay (ELISA) kit (R & D system) and KHB ST-360 ELISA analyzer. All procedures were conducted based on the manufacturer's instructions. Real-time Fluorescence Quantitative PCR (RTFQ-PCR) was conducted to detect the HBV DNA with detection limit of 500 IU/mL by reagent (Da An Gene Co., Ltd. of Sun Yat-Sen University) and PE-5700 thermal cycler. The primers for PCR were as follows: the upstream primer HBxF: 5'-CACTTCGCTTCACCTCTGCA-3', downstream primer HBxR: TGCCTCAAGGTC-GGTCGT-3'; Tap-man probe HBxP: 5'-FAM-ACCACCGTGAACGCCACC-TAMRA-3'. The amplified fragments: 121 bp.

Interferon- α 2b therapy

CHB group (n = 57) were arranged for interferon- α 2b therapy once every other day through subcutaneous injection (6000, 000 IU). The pre-treatment and 12 weeks post-treatment serum samples were respectively obtained for further comparison. According to the virological response in 12 weeks, 48 CHB patients were grouped into responding group with post-treatment serum HBV DNA decreased $\geq 2\log_{10}$ IU/mL compared with pre-treatment [15] and the remaining 9 patients were included in nonresponse group with post-treatment serum HBV

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Table 1. The comparisons conducted on the baseline characteristic in subjects included in both chronic hepatitis B (CHB) group and control group

Group	CHB group (n = 57)	Control group (n = 25)	P
Sex (M/F)	41/16	21/4	0.241
Age (year)	35.8 ± 10.5	31.2 ± 8.5	0.057
BMI (kg/cm ²)	24.9 ± 2.5	25.3 ± 2.8	0.522
Drink history [case (%)]	31 (54.4%)	14 (56%)	0.892
ALT (U/L)	40.6 ± 5.2	32.8 ± 3.5	< 0.001
IP-10 (pg/mL)	285.7 ± 41.6	79.1 ± 33.8	< 0.001

M, male; F, female; BMI, body mass index; ALT, Alanine aminotransferase; IP-10, interferon-gamma inducible protein 10; CHB, Chronic hepatitis B.

DNA decreased < 2log₁₀ IU/mL compared with pre-treatment.

Statistical analysis

Data analysis in current case-control study was conducted utilizing Stata statistical software (Version 12.0, Stata Corporation, College Station, TX, USA). Categorical data were presented with percentages and frequency counts and a χ^2 test was employed to compare the percentages and frequencies, while continuous data were expressed as mean ± standard deviation (mean ± SD) and were tested using student *t* test. Computerized bibliographic databases and manual search were combined to identify relevant articles published prior to Sept. 2014 with language restricted to English and Chinese. Keywords applied in our initial literature search include (“Hepatitis B” or “Hepatitis B, Chronic” or “Hepatitis B virus” or “Chronic Hepatitis B”) and (“Chemokine CXCL10” or “CXCL10 protein, human” or “CXCL10” or “Chemokine CXCL10” or “IP 10” or “IP-10” or “gammaIP-10” or “gammaIP 10” or “Interferon-Inducible Protein 10” or “Interferon Inducible Protein 10” or “Small Inducible Cytokine B10” or “CXC Chemokine IP-10” or “CXC Chemokine IP 10” or “IFN-gamma-Inducible Protein” or “interferon-gamma induced protein 10” or “interferon-gamma-inducible protein 10”). The inclusions for current meta-analysis were: (1) Only those studies conducted to clarify the correlation between serum IP-10 levels and CHB were incorporated; (2) The CHB patients from included studies were diagnosed with CHB based on clear and specific diagnostic criteria; (3) The articles provided with sufficient information on serum

IP-10 levels; (4) Studies with overlapped publication were only enrolled for once with the largest sample size. Ineligibles papers were excluded based on the following exclusion criteria: (1) insufficient data information; (2) significant differences in baseline characteristics between cases and controls; (3) duplicated publications or studies with overlapped data; (4) no clear diagnostic criteria. Two independent investigators were employed for data collection and following descriptive information were recorded: authors, country, years, ethnicity, language, HBeAg status, diagnostic criteria, sex, age, detection method and serum IP-10 levels. The disagreements during data collection were dissolved by discussion with a third investigator. The data analysis in meta-analysis was conducted by STATA 12.0 (Stata Corporation, College Station, TX, USA). The difference on the serum IP-10 levels was calculated by standardized mean difference (SMD) with 95% confidence intervals (95% CI) with Z test to evaluate the combined effect size. Cochran Q-statistic ($P < 0.05$ was considered significant) and I^2 tests to quantify heterogeneity among studies with $P < 0.05$ or I^2 test exhibited > 50% considered as indicator of presence of heterogeneity. Random effects model was applied for the evidence of significant heterogeneity, whereas fixed-effects model was employed based on absence of heterogeneity.

Results

Basic characteristics

The comparisons on the basic characteristics between two groups were presented in **Table 1**. No significances on sex, year, body mass index (BMI) and drink history were found between case and control group (all $P > 0.05$). Prior to treatment, CHB group presented with a remarkable increased serum ALT and IP-10 levels compared with control group (both $P < 0.05$).

Serum ALT and IP-10 levels before and after interferon- α 2b treatment

The post-treatment serum ALT and IP-10 levels of CHB patients was notably decreased compared to pre-treatment ($t = 8.71$, $P < 0.001$; $t = 33.76$, $P < 0.001$), despite no statistical signifi-

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Table 2. The comparisons between pre-treatment and post-treatment serum Alanine aminotransferase (ALT) and IFN- γ -inducible protein-10 (IP-10) levels were conducted in chronic hepatitis B (CHB) patients

Group	Case	ALT (U/L)		IP-10 (pg/mL)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control group	25	32.8 \pm 3.5		78.1 \pm 33.8	
CHB group	57	40.6 \pm 5.2	33.1 \pm 3.9*	285.7 \pm 41.6	78.5 \pm 20.4*
HBeAg-negative	32	36.1 \pm 4.9	32.6 \pm 5.1*	208.6 \pm 35.2	77.5 \pm 19.6*
HBeAg-positive	25	46.4 \pm 5.6	35.0 \pm 2.4*	384.4 \pm 49.8	89.1 \pm 21.4*
Responding group	48	39.6 \pm 5.4	32.9 \pm 4.2*	278.5 \pm 43.1	76.1 \pm 19.7*
Nonresponse group	9	42.1 \pm 5.9	36.2 \pm 4.4*	324.1 \pm 33.7	91.2 \pm 24.1*

ALT, Alanine aminotransferase; IP-10, interferon-gamma inducible protein 10; CHB, Chronic hepatitis B; *: Compared with pre-treatment serum ALT and IP-10 levels.

cance was found between CHB group and control group on post-treatment serum ALT and IP-10 levels ($t = 0.33$, $P = 0.742$; $t = 0.07$, $P = 0.947$). The post-treatment serum ALT and IP-10 levels in both HBeAg-positive and HBeAg-negative CHB patients were reduced compared to pre-treatment (all $P < 0.05$). Based on virological response, CHB patients in both responding group and nonresponse group had a lower post-treatment serum ALT and IP-10 levels than pre-treatment (both $P < 0.05$). After treatment for 12 weeks, the serum ALT and IP-10 levels in HBeAg-negative CHB patients were evidently decreased compared with HBeAg-positive CHB patients (32.6 \pm 5.1 U/L vs. 33.7 \pm 2.4 U/L, $t = 2.17$, $P = 0.034$; 77.5 \pm 19.6 pg/mL vs. 80.1 \pm 21.4 pg/mL, $t = 2.13$, $P = 0.038$). In addition, responding group had declined post-treatment serum ALT and IP-10 levels compared with nonresponse group (32.9 \pm 4.2 U/L vs. 36.2 \pm 4.4 U/L, $t = 2.15$, $P = 0.036$; 76.1 \pm 19.7 pg/mL vs. 91.2 \pm 24.1 pg/mL, $t = 2.04$, $P = 0.046$) (Table 2).

Meta-analysis

Based on our predefined search strategy, 68 studies were identified and after applying our eligibility criteria, 11 studies were fulfilled the inclusion criteria for our meta-analysis with publication year ranging from 2001 and 2014 [3, 8, 16-24]. A total of 482 CHB patients and 205 healthy controls were incorporated in current meta-analysis (Table 3). Random effect model was applied with the presence of heterogeneity ($I^2 = 90.3\%$, $P_h < 0.001$). Our meta-analysis demonstrated that CHB patients presented with a remarkably increased IP-10 serum levels compared with healthy controls (SMD =

2.21, 95% CI = 1.55~2.87, $P < 0.001$) (Figure 1). A subgroup based on HBeAg status revealed that both HBeAg-positive and HBeAg-negative patients had higher serum IP-10 levels than healthy controls (HBeAg-positive: SMD = 2.00, 95% CI = 1.13~2.87, $P < 0.001$; HBeAg-negative: SMD = 1.34, 95% CI = 0.97~1.72, $P < 0.001$) (Figure 2).

Discussion

To clarify the correlation between serum IP-10 levels and CHB, a case-control study and a meta-analysis was conducted. The main results of case-control study and meta-analysis demonstrated that serum IP-10 levels in CHB patients were evidently higher than that in healthy controls, implying that IP-10 may be an important indicator for CHB. Recent reports have also verified that IP-10 was expressed in liver with CHB patients, and this expression varied among patients with different liver diseases [9, 13]. Furthermore, we also found that CHB patients had declined serum IP-10 and ALT levels after treatment and responding group presented with reduced serum IP-10 and ALT levels compared with nonresponse group. Those results suggested the positive correlation between serum IP-10 and ALT levels and serum HBV DNA. Chronic HBV infection reflected a complex interplay between humoral immune response and host immune activities [25]. Serum ALT levels should reflect the degree of liver damage, whereas IP-10 levels may reflect immune activity [26, 27].

It has been recognized that higher ALT levels was a risk predictor for more active immune response against HBV and more extensive

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Table 3. Basic Characteristics for the eleven eligible studies included in current met-analysis

First author	Year	Country	HBeAg status	Diagnostic Criteria	Detecting Method	Number		Gender (M/F)		Age (years)	
						CHB	Control	CHB	Control	CHB	Control
Nishioji K [16]	2001	Japan	Positive	NR	ELISA	20	20	13/7	10/10	41.9 ± 11.5	46.4 ± 14.4
Shi LY [17]	2003	China	Mixed	I	ELISA	58	20	41/17	12/8	32.7 (17-51)	37.1
Wang J [3]	2008	China	Positive	II	ELISA	45	24	25/20	14/10	30 ± 9 (18-50)	25 ± 5 (20-48)
Ding HH [18]	2009	China	Mixed	II	ELISA	19	5	17/2	5/0	36.7 ± 9.0	24.4 ± 3.4
Liu SC-a [19]	2011	China	Positive	III	ELISA	16	28	27/13	24/4	44.2 ± 12.6 (21-72)	36.5 ± 10.9 (17-58)
Liu SC-b [19]	2011	China	Negative	III	ELISA	24	28				
Zhu XJ-a [20]	2011	China	Positive	III	ELISA	33	20	46/20	11/9	38 ± 11(21-61)	39 ± 13 (21-56)
Zhu XJ-b [20]	2011	China	Negative	III	ELISA	33	20				
Li WL [21]	2012	China	Positive	IV	ELISA	50	30	35/15	21/9	27.8 (20-38)	27.1 (20-40)
Jiao YQ [22]	2013	China	Mixed	II	ELISA	40	23	41/22		34.4 ± 9.1 (19-47)	
Okuhara S [23]	2013	Japan	Positive	NR	ELISA	48	10	33/15	NR	55 (24-81)	NR
Lian JQ [24]	2014	China	Mixed	NR	Luminex200	36	10	29/7	7/3	31.3 ± 8.7	28.4 ± 7.3
Wang Y-a [8]	2014	China	Positive	V	ELISA	38	15	22/16	8/7	35.5 ± 10	38 ± 12
Wang Y-b [8]	2014	China	Negative	V	ELISA	22	15	14/8	8/7	40 ± 15	38 ± 12

Liu SC-a: HBeAg positive on subgroup; Liu SC-b: HBeAg negative on subgroup; Zhu XJ-a: HBeAg positive on subgroup; Zhu XJ-b: HBeAg negative on subgroup; Wang Y-a: HBeAg positive on subgroup; Wang Y-b: HBeAg negative on subgroup; NR, Not Reported; I: GB 15990-1995; II: Prevention Guideline for Viral Hepatitis (2000); III: Prevention Guideline for Chronic Hepatitis B (2005); IV: Prevention Guideline for Chronic Hepatitis B (2010); V: APASL, Asian Pacific Association for the Study of the Liver; ELISA, enzyme-linked immunosorbent assay; CHB, Chronic hepatitis B.

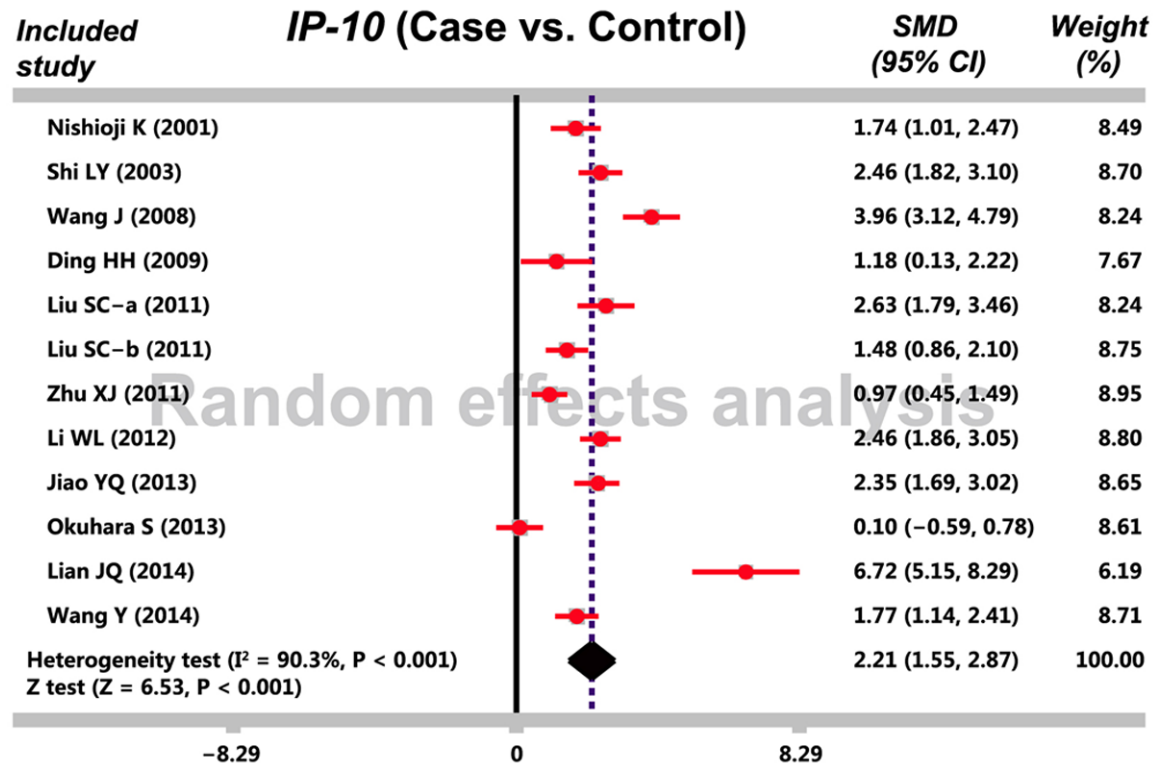


Figure 1. The forest plot in meta-analysis investigates the correlation between serum IFN- γ -inducible protein-10 (IP-10) levels and chronic hepatitis B (CHB).

hepatocyte damage [5, 28]. Given the strong association of IP-10 with ALT, high levels of IP-10 may predict active host immune response, consequently lead to a more active liver inflammation [13]. Generally, IP-10 activated T-lymphocytes and natural killer cells, and then recruited Th cells and monocytes cells to take part in inflammation and immune response through interaction with its CXCR3 receptor, thus facilitating the hepatic necroinflammatory damage in chronic HBV infection [24, 29]. Increasing evidence elucidated that serum IP-10 level may be an important factor in regulation of antiviral immunity and may affect disease progression [8], which was consistent with our results that post-treatment serum IP-10 levels were reduced compared with pre-treatment. A study by Lagging M confirmed that the serum IP-10 and ALT levels are significantly associated with the severity of hepatic inflammation [30]. With respect to this, the serum IP-10 levels were correlated with the CHB and may relate to the disease progression.

In consideration of other related factors may influence the correlation between the serum IP-10 levels and CHB, a further subgroup analy-

sis based on the HBeAg states was performed. The HBeAg-stratified found that CHB patients with HBeAg positive or HBeAg negative both had higher serum IP-10 levels than healthy controls, which was in agreement with previous studies [31, 32]. Moreover, the case and control study also elucidated that after treatment for 12 weeks, the HBeAg-negative CHB patients had decreased serum IP-10 and ALT levels compared with HBeAg-positive CHB patients, which suggested that serum IP-10 and ALT expression levels responds to antiviral therapy.

In summary, our case-control study and meta-analysis revealed that serum IP-10 levels were correlated with the risk of CHB and the efficacy of interferon therapy in Asians, which suggesting that serum IP-10 level may be an important biomarker for the diagnose and treatment of CHB. However, due to the limited sample size of this study, this conclusion needs to be double investigated and validated with a large sample size.

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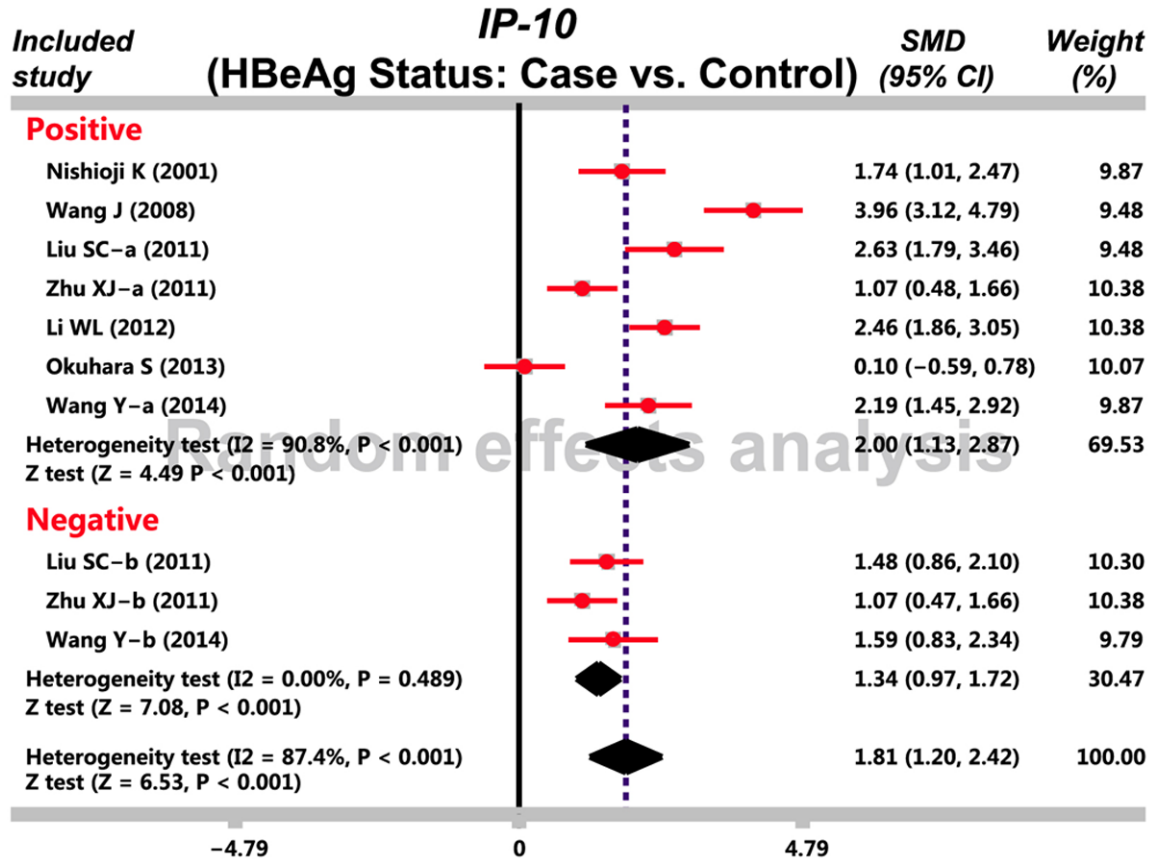


Figure 2. Subgroup analysis based on HBeAg investigates the correlation between serum IFN- γ -inducible protein-10 (IP-10) levels and chronic hepatitis B (CHB).

Disclosure of conflict of interest

None.

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