Unsatisfying antiviral therapeutic effect in patients with mother-to-child transmissed chronic hepatitis B virus infection: a prospective multi-center clinical study

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Abstract

Background: Few data are available regarding the progression of liver disease and therapeutic efficacy in chronic hepatitis B virus (HBV) carriers infected by mother-to-child transmission (MTCT). This study aimed to investigate these two aspects by comparing the adult chronic HBV carriers in MTCT group with those in horizontal transmission group.

Methods: The 683 adult chronic HBV patients qualified for liver biopsy including 191 with MTCT and 492 with horizontal transmission entered the multi-center prospective study from October 2013 to May 2016. Biopsy results from 217 patients at baseline and 78 weeks post antiviral therapy were collected.

Results: Patients infected by MTCT were more likely to have e antigen positive (68.6% *vs.* 58.2%, $\chi^2 = -2.491$, $P = 0.012$) than those with horizontal transmission. However, in patients with MTCT, levels of alkaline phosphatase (ALP) ($P = 0.031$), Fibroscan ($P = 0.013$), N-terminal propeptide of Type III procollagen (PIIINP) ($P = 0.014$), and Laminin (LN) ($P = 0.006$) were high, in contrast to the patients with horizontal transmission for whom the levels of albumin (ALB) ($P = 0.041$), matrix metalloproteinase-3 (MMP-3) ($P = 0.001$) were high. The 47.2% of patients with MTCT and 36.8% of those with horizontal transmission had significant liver fibrosis ($P = 0.013$). Following antiviral therapy for 78 weeks, 21.2% and 38.0% patients with MTCT and horizontal transmission acquired hepatitis B e antigen (HBeAg) clearance, respectively ($P = 0.043$), and the virological response rates were 54.7% and 74.1% in the MTCT and horizontal groups, respectively ($P = 0.005$). MTCT was a risk factor for HBeAg clearance and virological response.

Conclusion: Adult patients with MTCT were more prone to severe liver diseases, and the therapeutic efficacy was relatively poor, which underlined the importance of earlier, long-term treatment and interrupting perinatal transmission.

Trial Registration: NCT01962155; https://clinicaltrials.gov.

Keywords: Chronic Hepatitis B virus infection; Horizontal transmission; Mother-to-child transmission; Progression of disease; Therapeutic efficacy

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Introduction

Hepatitis B virus (HBV) is a hepatotropic virus that can cause both acute and chronic disease. Some chronic carriers even develop fatal diseases, including cirrhosis and hepatocellular carcinoma (HCC). An estimated 257 million people in the world are suffering from chronic HBV infection, leading to nearly one million deaths annually.[1,2]

The likelihood that an HBV infection will become chronic infection depends on the age when infection happens. Less than 5% of healthy people who are infected with HBV in their adulthood will develop chronic infection. In contrast, children who infected HBV before the age of six tend to have 30% to 50% chance to become chronic carriers, and in infants the chance increases to 90%.[1] Thus, mother-to-child transmission (MTCT) is the most crucial mode of transmission that leads to chronic HBV infection. Previous studies on Chinese patients suggested that despite 94% of children received postnatal active immunization, MTCT is the major route of new HBV infections, which accounts for 36% to 45% of chronic HBV infection.[3,4] Moreover, perinatal or early childhood transmission has been reported to cause up to one third of chronic HBV infections even in hypoendemic areas.[5]

According to the mechanisms of host immune responses to HBV replication, the nature phases of chronic HBV infection has been divided into multiple phases, including immune tolerance (IT), immune clearance, low replicative, reactivation, and occult HBV infection.[6] Recently, the natural history was renovated due to the increasing challenges to presumed host immune responses, including hepatitis B e antigen (HBeAg)-positive/negative chronic HBV infection, HBeAg-positive/negative chronic hepatitis B (CHB) and hepatitis B surface antigen (HBsAg)-negative phase[7].

Whether IT phase is disease-free is currently still under arguments. Historically, an impaired Th1-associated immune response was the main characteristic of neonate immune system, which induced an "immuno-tolerant state" and established a persistent infection with minimal or no liver fibrosis in the host.[6,8-12] However, Kennedy *et al*[13] revealed that HBV infection found in adolescents was not related to tolerogenic T-cell pattern. In addition, the efficacy of combined nucleos(t)ide analogue/interferon-alpha treatment or interferon-alpha monotherapy in IT children was superior to that in adults.[14,15] These findings therefore have challenged the conception of "IT"[16].

Almost all chronic HBV carriers infected by MTCT has a relatively long "IT phase" (2–3 decades of persistent infection),[17] however, whether this phase is really asymptomatic requires further study. We collected data from a nationwide multi-center, longitudinal study in the mainland of China and aimed to investigate the progression of liver disease and therapeutic efficacy by comparing the adult chronic HBV carriers in MTCT group with those in horizontal transmission group.

Methods

Ethical approval

This study was approved by the Ethics Committee of Peking University First Hospital and other 23 teaching hospitals. All study subjects gave written informed consents prior to the study. This study has been registrated at ClinicalTrials.gov (NCT01962155).

Patients

This study was a multi-center, prospective, longitudinal study including 24 teaching hospitals in the mainland of China and carried out between the period of October 2013 and May 2016. A total of 770 treatment-naïve adult chronic HBV infective patients with HBsAg positive for at least 6 months were recruited in the study. The exclusion criteria included: (i) other forms of chronic liver disease (CLD); (ii) heavy alcohol consumption (>20 g per day); (iii) receiving previous treatment with either bicyclol or antiviral drugs within 26 weeks; (iv) decompensate liver cirrhosis and HCC; (v) incomplete data; (vi) unqualified liver biopsy. Details of the inclusion and exclusion criteria had been reported previously.[18] The transmission routes of HBV infection were recorded when patients were recruited. Clinical data were collected within two weeks before liver biopsy.

Liver histological assessment

Liver biopsies were performed at baseline (before the patients started antiviral therapy) and week 78 (after the patients accomplished 78-week antiviral therapy) to assess the stages of liver fibrosis and grades of necro-inflammation. A biopsied specimen with length ≥2.0 cm and at least 11 portal tracts was considered adequate. All liver tissue samples were blindly and independently evaluated by two pathologists. When discrepancies occurred, the third experienced pathologists made the final decision. Liver fibrosis and necro-inflammation were assessed with the Ishak scoring system.[19] Ishak fibrosis score (F) ≥3 was considered significant fibrosis (SF), and histology activity index (HAI) ≥5 was considered moderate to severe inflammation. Histological improvement was defined as ≥2-point decrease in the HAI score and with no progressing in the fibrosis score at 78 weeks after baseline.[20] Fibrosis improvement was defined as at least 1-point decrease in Ishak fibrosis score, whereas at least 1-point increase was considered as fibrosis progression.

Laboratory examination

Patient's blood samples were collected at each time of liver biopsy and the serums were used to detect the non-invasive markers of liver fibrosis or inflammation, including laminin (LN), hyaluronic acid (HA), N-terminal propeptide of Type III procollagen (PIIINP), Collagen IV alpha 1 (COL4A1), matrix metalloproteinase-3 (MMP-3), platelet derived growth factor-BB (PDGF-BB), von Willebrand factor A2 (vWF-A2), Galectin-3, monocyte chemoattractant protein 1 (MCP1), soluble CD163 (sCD163), α2-macroglobulin (α2-MG), haptoglobin (Hp), YKL-40,

Angiopoietin-like 2 (ANGPTL2). LN, HA, and PIIINP were assessed using a chemiluminescence immunoassay kit (Yuande Bio-Medical Engineering Co., Ltd, Beijing, China). MMP-3, PDGF-BB, vWF-A2, Galectin-3, MCP1, sCD163, and COL4A1 were measured by Luminex screening system (R&D, Minneapolis, MN, USA). α2-MG and Hp were detected by Human cytokines/ Chemokine panel I (Millipore, Billerica, MA, USA). HBV DNA and HBV serological markers were detected using Roche COBAS TaqMan platform and relevant Roche Elecsys® assays (Roche, USA).

Liver stiffness measurement

Liver stiffness measurement (LSM), via 1-dimensional ultrasound TE (FibroScan®, Echosens, Paris, France), was evaluated in fasting patients at baseline and week 78. All operators who were blinded to the patients' clinical data were trained according to the manufacturer's recommendations. Liver stiffness values are expressed in kilopascals (kPa) (range: 2–75 kPa). Only a procedure with at least ten valid measurements, an interquartile range (IQR)/median value (M) <30% and a success rate >60% was considered reliable.[21]

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). Patients' characteristics were expressed as median (IQR), or numbers of cases and percentages, as appropriate. Continuous variables were compared using Student *t* test or Mann-Whitney tests, whereas categorical variables were using Chi-square test or Fisher exact test. Univariate and logistic regression analysis was conducted to identify independent predictors associated with HBeAg clearance and virological response. All statistical tests were two-sided, and $P < 0.05$ was considered statistical significance.

Results

Baseline characteristics

A total of 770 treatment-naïve adult patients with chronic HBV infection were enrolled in this study, and 52 patients with drinking history, 29 patients with medications history, and 6 patients with unqualified liver biopsy were excluded. The remaining 683 patients including 191 patients with MTCT and 492 patients with horizontal transmission were analyzed at baseline [Figure 1]. The median age of the treatment-naive patients (514 men and 169 women) was 37.0 (30.0–46.0) years, median body mass index was 23.0 (21.2–24.9) kg/m^2. Baseline median HBV DNA and alanine transaminase (ALT)/ upper limit of normal (ULN) were 6.3 $\log_{10}$IU/mL and 1.3, respectively. Out of all these patients, 271 (39.7%) patients had Ishak fibrosis score ≥3, 398 (58.3%) patients had HAI ≥5, and 461 (67.5%) patients needed antiviral treatment [Table 1].

We compared the characteristics between the MTCT and horizontal transmission groups. Patients with MTCT were more likely to be e antigen positive (68.6% *vs.* 58.2%, $\chi^2 = -2.491$, $P = 0.012$) than those in horizontal transmission group. Although without statistically significance, the surface antigen quantification (3.7 [3.2–4.3] $\log_{10}$IU/mL *vs.* 3.6 [3.1–4.1] $\log_{10}$IU/mL) and HBV DNA quantification (6.6 [5.0–8.0] $\log_{10}$IU/mL *vs.* 6.2 [4.6–7.8] $\log_{10}$IU/mL) were slightly higher in MTCT group than those in horizontal transmission group. In patients with MTCT, alkaline phosphatase (ALP)/ULN ($Z = 2.162$, $P = 0.031$) was high, in contrast to the patients with horizontal transmission for whom the levels of albumin (ALB) (44.0 [40.0–46.6] g/L *vs.* 44.2 [41.8–47.0] g/L, $Z = -2.045$, $P = 0.041$) and serum creatinine (66.4 [56.4–76.0] μmol/L *vs.* 70.0 [61.0–80.3] μmol/L, $Z = -2.528$, $P = 0.011$) were high. More patients with MTCT had LSM value ≥9 kPa than those with horizontal transmission (51.5% *vs.* 40.2%, $P = 0.013$). The median LSM values in MTCT and horizontal transmission patients were 9.1 (6.3–14.0) kPa and 8.0 (5.7–12.1) kPa, respectively [Table 1].

Performance of non-invasive markers associated with liver disease in adult patients infected by MTCT and horizontal transmission

Numerous non-invasive markers are currently used to diagnose different stages of liver fibrosis for the inevitable limitations of liver biopsy. Several classical non-invasive markers, such as PIIINP, HA, LN, COL4A1, MMP, and PDGF-BB, were analyzed in our study. Furthermore, some emerging non-invasive markers including ANGPTL2, YKL-40 and sCD163 were also detected. In patients with MTCT, the level of PIIINP ($P = 0.014$) and LN ($P = 0.006$) were high, in contrast to the patients with horizontal transmission for whom the level of MMP-3 ($P = 0.001$) was high. In patients without SF, the MTCT group was with higher level of vWF-A2, Galectin-3, Hp and MCP1 than the horizontal transmission group; in patients with SF, the level of PDGF-BB was higher in MTCT group than in horizontal transmission group. The level of MMP-3 was always low in MTCT group irrespective of the stages of liver fibrosis [Table 2].

Histological presentation in MTCT and horizontal transmission group

All 683 adult patients with chronic HBV infection had qualified liver biopsy results. At baseline, 52.9%, 41.4%, and 5.8% patients had histologically proved no/mild/ moderate fibrosis (F0–2), significant/advanced fibrosis (F3–4), and cirrhosis (F5–6) in MTCT group, respectively. The corresponding proportions in horizontal transmission group were 63.2%, 32.1%, and 4.7%, respectively. The 47.2% patients in MTCT group were with Ishak fibrosis score ≥3, while this proportion in horizontal transmission group was 36.8% ($P = 0.013$). The proportions of patients with HAI ≥5 were 60.7% in MTCT group and 57.3% in horizontal transmission group [Table 1]. Overall, patients who were necessary to receive antiviral treatment (with Ishak fibrosis score ≥3 or HAI ≥5) were 137 (71.7%) and 324 (65.9%) in MTCT and horizontal transmission groups respectively [Figure 2].

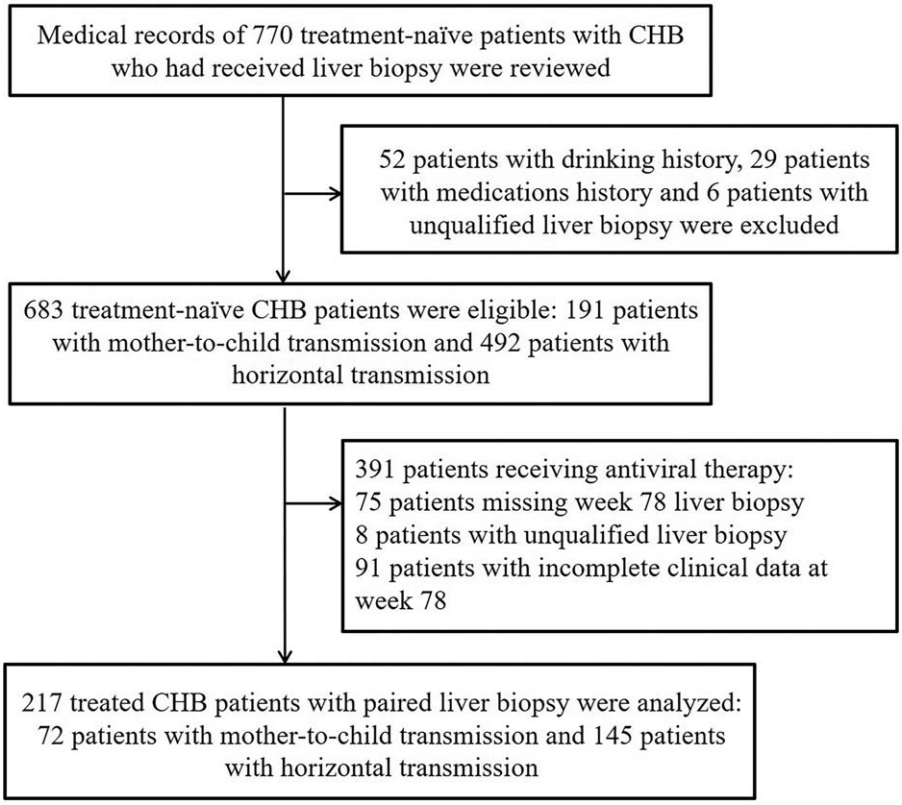

Figure 1: The flow chart of study design. CHB: Chronic hepatitis B.

Antiviral treatment response in MTCT and horizontal transmission group

Of 683 adult chronic HBV patients who were analyzed at baseline, 391 patients received antiviral therapy and were prospectively followed up to 78 weeks for a second liver biopsy. Ishak fibrosis scores were available at baseline and the week 78 from 217 patients including 72 patients with MTCT and 145 patients with horizontal transmission [Figure 1]. After 78 weeks of treatment, the proportion of patients with HBeAg clearance among MTCT group and horizontal transmission group was 21.6% and 38.5% ($P = 0.044$), respectively. The incidence of virological response (HBV DNA<20 IU/mL) in MTCT group was significant lower than those in horizontal transmission group (56.9% *vs.* 75.2%, $P = 0.006$). The HBeAg seroconversion rate at week 78 was 13.5% in MTCT group and 26.6% in the horizontal transmission group. There were no significant difference in the incidence of histological response and fibrosis stabilization or reversion between adult patients with MTCT and those with horizontal transmission [Table 3].

Independent variables associated with HBeAg clearance and virological response

Variables associated with the HBeAg clearance after 78-week antiviral treatment were first assessed by univariate analysis and MTCT mode, Ishak fibrosis score, anti-HBc and COL4A1 were significantly related to HBeAg clearance [Tables 4 and 5]. Subsequent multivariate analysis showed that the MTCT mode of HBV infection ($P = 0.028$) and Ishak fibrosis score ($P = 0.013$) at baseline were the independent predictors of HBeAg clearance [Table 4]. Similarly, age, MTCT mode, HBsAg, the positive rate of HBeAg, HBV DNA, and Galectin-3 were significantly associated with virological response, and MTCT mode of HBV infection ($P = 0.038$), the positive rate of HBeAg ($P = 0.022$) and HBV DNA ($P = 0.023$) at baseline were the independent predictors of virological response [Table 5].

Discussion

Although several studies on the natural history of childhood-onset HBV infection have been reported, few of them had focused on the difference in the natural history of the liver disease between the adult patients infected by MTCT and those by horizontal transmission.[17] In the present study, we investigated the progression of liver disease and therapeutic efficacy of adult patients with chronic HBV infection by comparing chronic carriers in MTCT group with those in horizontal transmission group.

More adult chronic HBV patients by MTCT were HBeAg positive, with high quantification of HBsAg and high viral load than those with horizontal transmission, which suggested that those patients were seemed to be in the immune tolerant phase. However, compared to patients with horizontal transmission, the level of ALP was higher

Table 1: Baseline characteristics of CHB patients infected via mother-to-child transmission or horizontal transmission.

Variables	Total ($n = 683$)	Mother-to-child transmission ($n = 191$)	Horizontal transmission ($n = 492$)	Statistics	P
Age (years)	37.0 (30.0–46.0)	38.0 (29.0–46.0)	37.0 (30.0–46.0)	−0.076*	0.939
Male gender, *n* (%)	514 (75.3)	130 (68.1)	384 (78.0)	2.712†	0.007
BMI (kg/m^2)	23.0 (21.2–24.9)	22.9 (20.9–24.6)	23.0 (21.2–25.0)	−0.855*	0.392
PLT ($\times 10^9$/L)	167.5 (133.8–206.0)	160.5 (129.3–196.5)	171.0 (134.3–209.0)	−1.795*	0.073
ALT/ULN	1.3 (0.8–2.3)	1.2 (0.8–2.5)	1.3 (0.8–2.2)	−0.053*	0.958
AST/ULN	1.0 (0.7–1.6)	1.0 (0.7–1.9)	1.0 (0.7–1.5)	1.143*	0.253
ALP/ULN	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.6 (0.5–0.7)	2.162*	0.031
GGT/ULN	0.6 (0.4–1.2)	0.7 (0.4–1.3)	0.6 (0.4–1.1)	1.091*	0.275
Albumin (g/L)	44.1 (41.3–47.0)	44.0 (40.0–46.6)	44.2 (41.8–47.0)	−2.045*	0.041
TBIL (μmol/L)	14.0 (11.0–18.4)	14.0 (11.1–18.5)	14.0 (10.8–18.4)	0.483*	0.629
AFP (ng/mL)	3.6 (2.4–6.3)	4.0 (2.6–8.3)	3.5 (2.4–6.1)	1.642*	0.101
INR	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	0.429*	0.668
Creatinine (μmol/L)	69.5 (59.7–79.6)	66.4 (56.4–76.0)	70.0 (61.0–80.3)	−2.528*	0.011
HBV DNA ($\log_{10}$IU/mL)	6.3 (4.8–7.8)	6.6 (5.0–8.0)	6.2 (4.6–7.8)	1.510*	0.131
HBsAg ($\log_{10}$IU/mL)	3.6 (3.2–4.2)	3.7 (3.2–4.3)	3.6 (3.1–4.1)	1.647*	0.100
HBeAg, positive, *n* (%)	416 (60.9)	131 (68.6)	285 (58.2)	−2.491†	0.012
Anti-HBc ($\log_{10}$IU/mL)	4.5 (4.0–4.9)	4.5 (4.0–4.8)	4.5 (4.1–4.9)	−0.029*	0.977
LSM	8.3 (5.9–12.6)	9.1 (6.3–14.0)	8.0 (5.7–12.1)	2.486*	0.013
<9 kPa, *n* (%)	328 (56.4)	83 (48.5)	245 (59.8)		
9–11 kPa, *n* (%)	95 (16.4)	35 (20.5)	60 (14.6)		
≥12 kPa, *n* (%)	158 (27.2)	53 (31.0)	105 (25.6)		
HAI	5 (3–7)	5 (3–7)	5 (3–7)	0.956*	0.339
<5, *n* (%)	285 (41.7)	75 (39.3)	210 (42.7)		
≥5, *n* (%)	398 (58.3)	116 (60.7)	282 (57.3)		
Fibrosis stages	2 (1–3)	2 (1–4)	2 (1–3)	1.974*	0.048
F0, *n* (%)	25 (3.7)	9 (4.7)	16 (3.3)		
F1, *n* (%)	179 (26.2)	43 (22.5)	136 (27.6)		
F2, *n* (%)	208 (30.5)	49 (25.7)	159 (32.3)		
F3, *n* (%)	131 (19.2)	41 (21.5)	90 (18.3)		
F4, *n* (%)	106 (15.5)	38 (19.9)	68 (13.8)		
F5–6, *n* (%)	34 (5.0)	11 (5.8)	23 (4.7)		
Patients with significant liver fibrosis, *n* (%)	271 (39.7)	90 (47.1)	181 (36.8)	2.475†	0.013
Patients who need antiviral therapy, *n* (%)	461 (67.5)	137 (71.7)	324 (65.9)	1.470†	0.141

Parameters are expressed as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. AFP: Alpha fetoprotein; ALP: Alkaline phosphatase; ALT: Alanine transaminase; Anti-HBc: Hepatitis B core antibody; AST: Aspartate transaminase; BMI: Body mass index; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transpeptidase; HAI: Histology activity index; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; LSM: Liver stiffness measurement; PLT: Platelet counts; TBil: Total bilirubin; ULN: Upper limit of normal. *Z value, †χ^2 value.

and ALB was lower in patients with MTCT, which implied a more severe liver damage. What is more, the serum level of some non-invasive markers reflecting liver damage including PIIINP, LN, and COL4A1 also increased in MTCT group. MMPs inevitably participated in extracellular matrix (ECM) turnover during fibrogenesis, especially during fibrolysis.[22] The level of MMP-3 in MTCT group was observably lower than that in horizontal transmission group. Transient elastography (TE), a novel, noninvasive, and reproducible tool, has been widely used in evaluating liver fibrosis by LSM recently[21] and the diagnostic accuracy has been adequately validated in various CLD.[23,24] In MTCT group, the median LSM value was 9.1 kPa, which was 1.1 kPa higher than the horizontal transmission group. Perinatal acquired chronic HBV infection was generally considered to have a long "immune tolerant phase"–a phase with a lack of disease activity,[17,25] but this chronic infection did not seem to be disease-free in our study.

Mason *et al*[26] reported that HBV-DNA integration and clonal hepatocyte expansion, two potential initiating events for HCC, were detected in patients considered IT, indicating hepatocarcinogenesis could be underway. Kennedy *et al*[13] found that children and young patients with CHB have an HBV-specific immune profile which could trigger a far stronger immune response than that observed in older CHB patients. Vanwolleghem *et al*[27] performed a systems biology study and pointed toward a highly active role for innate interferon (IFN) and B-cell

Table 2: Characteristics of non-invasive markers related to liver disease in CHB patients in two groups.

Study population non-invasive markers	Total	Mother-to-child transmission	Horizontal transmission	*Z*	*P*
All (*n*)	683	191	492		
PIIINP (ng/mL)	2.9 (1.6–4.7)	3.2 (1.9–5.2)	2.7 (1.5–4.5)	2.455	0.014
HA (ng/mL)	99.1 (79.8–135.3)	102.6 (83.2–141.6)	97.8 (79.0–134.6)	1.190	0.234
LN (ng/mL)	37.1 (13.2–87.7)	44.1 (16.9–121.8)	34.0 (11.2–75.5)	2.729	0.006
COL4A1 (ng/mL)	0.8 (0.6–1.1)	0.9 (0.6–1.2)	0.8 (0.6–1.1)	1.956	0.050
MMP-3 (ng/mL)	15.0 (9.8–21.8)	13.4 (7.8–19.5)	15.7 (10.5–22.2)	−3.247	0.001
PDGF-BB (ng/mL)	59.8 (35.5–87.2)	57.6 (35.3–89.4)	61.3 (35.9–87.2)	−0.145	0.884
Haptoglobin (mg/dL)	22.4 (7.3–67.6)	24.0 (7.4–92.8)	21.0 (7.2–57.2)	1.203	0.229
vWF-A2 (ng/dL)	20.6 (12.7–31.3)	22.3 (14.2–32.1)	19.8 (12.4–30.5)	1.793	0.073
Galectin-3 (ng/mL)	2.3 (2.0–2.7)	2.4 (2.1–2.8)	2.3 (2.0–2.7)	1.867	0.062
MCP1 (ng/dL)	28.6 (20.0–42.8)	30.8 (21.6–46.3)	28.2 (19.3–42.5)	1.673	0.094
sCD163 (mg/L)	1.3 (0.7–2.2)	1.3 (0.7–2.2)	1.4 (0.8–2.2)	1.845	0.065
α2-MG (g/L)	1.2 (0.9–1.9)	1.2 (0.8–1.8)	1.2 (0.9–1.9)	−0.610	0.542
YKL-40 (ng/mL)	26.9 (16.0–50.4)	27.1 (18.1–56.3)	26.9 (15.5–48.1)	1.707	0.088
ANGPTL2 (ng/mL)	4.3 (3.3–5.9)	4.5 (3.5–6.3)	4.3 (3.2–5.7)	1.697	0.090
Patients without significant fibrosis (*n*)	412	101	311		
MMP-3 (ng/mL)	15.2 (9.6–22.1)	13.7 (7.5–20.8)	15.5 (10.1–22.5)	−2.013	0.044
vWF-A2 (ng/dL)	19.8 (12.1–30.0)	22.3 (14.3–31.8)	18.2 (11.7–28.4)	2.072	0.038
Galectin-3 (ng/mL)	2.4 (2.0–2.8)	2.5 (2.1–2.9)	2.3 (2.0–2.8)	2.421	0.015
Haptoglobin (mg/dL)	24.9 (8.0–78.0)	36.5 (11.2–129.0)	23.9 (8.5–65.8)	2.215	0.027
MCP1 (ng/dL)	28.7 (19.8–45.0)	33.3 (21.8–51.8)	27.6 (19.3–42.6)	2.538	0.011
Patients with significant fibrosis (*n*)	271	90	181		
MMP-3 (ng/mL)	15.0 (9.8–21.8)	13.5 (8.2–17.4)	15.9 (11.0–21.8)	−2.704	0.007
PDGF-BB (ng/mL)	26.9 (16.0–50.4)	57.6 (37.3–86.1)	49.2 (30.1–72.8)	2.281	0.023

Parameters are expressed as median (interquartile range). Units are in parentheses. α2-MG: α2-macroglobulin; ANGPTL2: Angiopoietin-like 2; CHB: Chronic hepatitis B; COL4A1: Collagen IV alpha 1; HA: Hyaluronic acid; LN: Laminin; MCP-1: Monocyte chemoattractant protein 1; MMP-3: Matrix metalloproteinase-3; PDGF-BB: Platelet derived growth factor-BB; PIIINP: N-terminal propeptide of Type III procollagen; sCD163: Soluble CD163; vWF-A2: von Willebrand factor A2 von Willebrand factor A2.

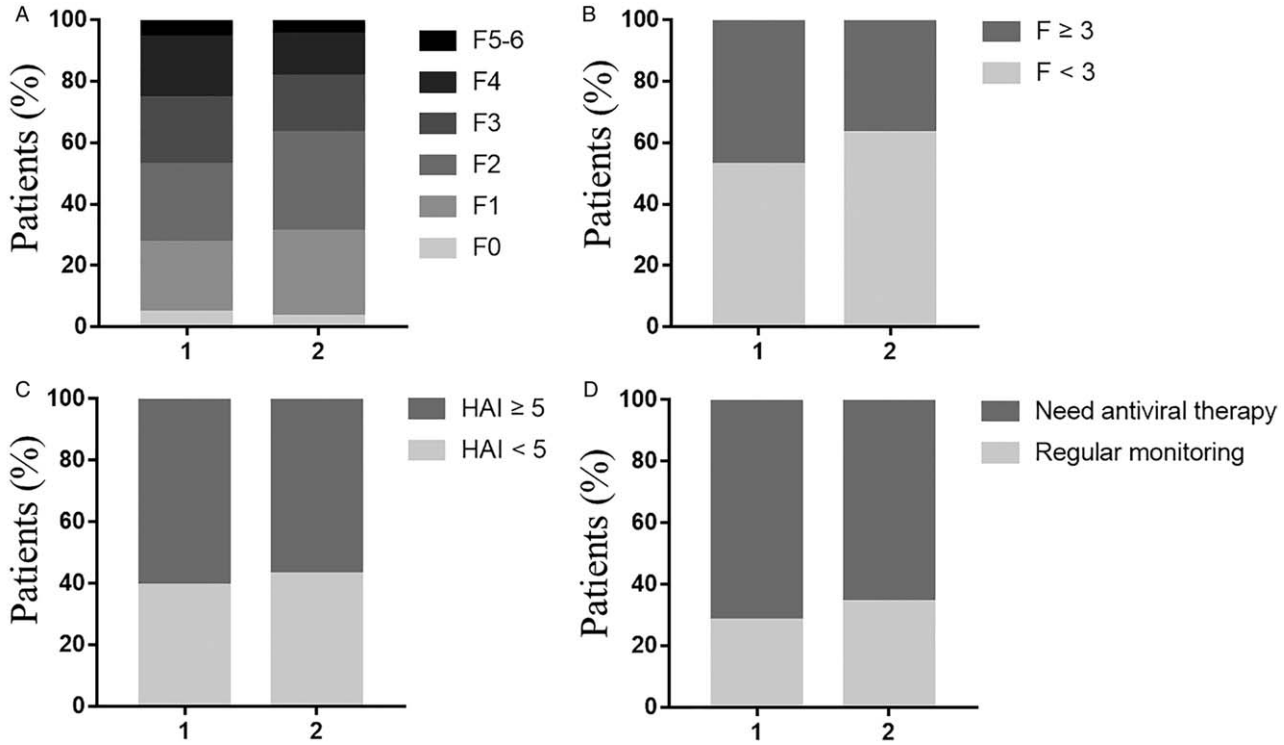

Figure 2: Distributions of (A) different stages of liver fibrosis, (B) the significant fibrosis (F ≥ 3), (C) the moderate to severe inflammation (HAI ≥ 5) and (D) the patients who needed antiviral therapy (F ≥ 3 or HAI ≥ 5) at baseline. 1: Patients with mother-to-child transmission; 2: Patients with horizontal transmission; F: Ishak fibrosis score; HAI: Histology activity index.

Table 3: Virological and histological responses in 217 CHB patients after 78 weeks of antiviral therapy.

Variables	Mother-to-child transmission ($n=72$)	Horizontal transmission ($n=145$)	χ^2 value	*P*
HBeAg clearance	11/51 (21.6)	30/78 (38.5)	4.059	0.044
HBeAg seroconversion	7/51 (13.5)	21/78 (26.6)	3.161	0.075
Virological response (HBV DNA<20 IU/ml)	41/72 (56.9)	109/145 (75.2)	7.490	0.006
Histological response	38/72 (52.8)	74/145 (51.0)	0.059	0.809
Fibrosis stabilization + reversion	57/72 (78.7)	110/145 (74.8)	0.296	0.586

Parameters are expressed as *n*/*N* (%) for categorical variables. CHB: Chronic hepatitis B; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus.

Table 4: Factors associated with HBeAg clearance (129 CHB patients with HBeAg positive at baseline).

	Univariate analysis				Multivariate analysis	
Parameters	HBeAg not clearance ($n=88$)	HBeAg clearance ($n=41$)	Statistics	*P*	OR (95% CI)	*P*
Age (years)	35.0 (27.3–41.8)	36.0 (29.0–41.5)	0.256*	0.798		
Male gender, *n* (%)	65 (73.9)	35 (85.4)	−1.425†	0.147		
BMI (kg/m^2)	22.9 (21.0–25.0)	23.0 (21.2–24.3)	0.028*	0.978		
ALT/ULN	1.6 (1.0–2.6)	2.5 (0.9–6.9)	1.659*	0.097		
AST/ULN	1.2 (0.9–1.9)	1.7 (0.8–3.1)	1.404*	0.160		
ALP/ULN	0.7 (0.5–0.8)	0.6 (0.5–0.8)	−0.308*	0.758		
GGT/ULN	0.9 (0.6–1.6)	0.9 (0.7–1.7)	0.610*	0.542		
Albumin (g/L)	43.1 (39.8–45.7)	41.6 (38.0–45.3)	−1.439*	0.150		
INR	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.779*	0.463		
PLT	160.5 (125.0–196.0)	173.0 (145.0–211.5)	1.796*	0.073		
Creatinine (μmol/L)	69.7 (57.0–79.7)	69.0 (63.0–78.6)	0.352*	0.725		
Mother-to-child transmission, *n* (%)	41 (45.6)	11 (26.8)	−2.007†	0.044	0.336 (0.127–0.890)	0.028
Ishak fibrosis score	3 (2–4)	2 (2–4)	−2.512*	0.012	0.590 (0.390–0.893)	0.013
HAI	6 (5–7)	6 (5–8)	0.447*	0.655		
LSM (kPa)	11.2 (8.2–16.6)	11.1 (8.4–16.0)	0.382*	0.703		
HBV DNA ($\log_{10}$IU/mL)	7.1 (5.9–8.0)	6.5 (5.4–7.5)	−1.929*	0.054		
HBsAg ($\log_{10}$IU/mL)	3.6 (3.2–4.2)	3.6 (3.2–3.9)	0.094*	0.925		
Anti-HBc ($\log_{10}$IU/mL)	4.6 (4.1–5.0)	4.9 (4.6–5.1)	2.614*	0.009		
PIIINP (ng/mL)	3.8 (2.3–5.6)	3.7 (2.1–7.3)	0.647*	0.518		
LN (ng/mL)	90.1 (29.7–219.7)	72.1 (38.8–142.9)	−0.234*	0.815		
COL4A1 (ng/mL)	1.1 (0.8–1.5)	0.9 (0.8–1.2)	−2.079*	0.038		
MMP-3 (ng/mL)	14.8 (9.8–20.4)	13.5 (9.3–19.8)	−0.137*	0.891		
vWF-A2 (ng/dL)	21.0 (12.2–30.1)	17.4 (11.1–27.6)	−0.821*	0.412		
Galectin-3 (ng/mL)	2.4 (2.1–2.7)	2.5 (2.0–2.9)	0.562*	0.574		
Haptoglobin (mg/dL)	23.7 (7.0–41.5)	21.0 (4.3–54.5)	−0.353*	0.724		
MCP1 (ng/dL)	27.7 (18.9–45.4)	27.2 (17.4–40.0)	−0.232*	0.817		
PDGF-BB (ng/ml)	59.1 (31.9–79.6)	67.8 (42.4–85.9)	1.001*	0.317		

Parameters are expressed as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. ALP: Alkaline phosphatase; ALT: Alanine transaminase; Anti-HBc: Hepatitis B core antibody; AST: Aspartate transaminase; BMI: Body mass index; COL4A1: Collagen IV alpha 1; GGT: Gamma-glutamyl transpeptidase; HAI: Histology activity index; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; LN: Laminin; LSM: Liver stiffness measurement; MCP-1: Monocyte chemoattractant protein 1; MMP-3: Matrix metalloproteinase-3; PDGF-BB: Platelet derived growth factor-BB; PIIINP: N-terminal propeptide of Type III procollagen; PLT: Platelet counts; ULN: Upper limit of normal; vWF-A2: von Willebrand factor A2. *Z value, †χ^2 value.

responses during IT phase. Previous research studied the virologic and histologic features of CHB patients without symptom and discovered that a fair proportion of patients have significant histologic fibrosis.[28] And on this basis, our data provided some conclusive proof that the adult patients with MTCT were more likely to suffer severe liver disease than those with horizontal transmission, which may be induced by active innate immune and HBV-specific T cells.

Classically, patients in IT phase are excluded from antiviral therapy based on European Association for the Study of the Liver (EASL) & American Association for the Study of Liver Diseases (AASLD) guidelines,[29] and the arguments against treatment have focused on drug cost, potential drug resistance, and drug toxicity related to long-term therapy.[30] A stronger argument objects to treatment has been the perceived disease-free and impaired HBV-specific T and B cells in IT phase. Recently, the validity of these

Table 5: Factors associated with virological response ($n = 217$).

Parameters	Univariate analysis				Multivariate analysis	
	HBV DNA not clearance ($n = 67$)	HBV DNA clearance ($n = 150$)	Statistics	*P*	OR (95% CI)	*P*
Age (years)	34.0 (27.0–41.0)	39.0 (32.8–49.0)	3.047	0.002		
Male gender, *n* (%)	50 (74.6)	114 (76.0)	−0.217†	0.828		
BMI (kg/m^2)	23.0 (21.0–25.3)	23.1 (21.2–24.5)	−0.201*	0.841		
ALT/ULN	1.7 (0.9–3.3)	1.4 (0.9–2.6)	−0.518*	0.605		
AST/ULN	1.3 (0.8–2.3)	1.1 (0.8–1.9)	−0.481*	0.630		
ALP/ULN	0.6 (0.5–0.8)	0.6 (0.5–0.8)	0.555*	0.579		
GGT/ULN	0.8 (0.6–2.0)	0.9 (0.5–1.6)	−0.856*	0.392		
Albumin (g/L)	43.7 (39.7–46.0)	43.0 (40.2–45.7)	−0.295*	0.768		
INR	1.1 (1.0–1.1)	1.1 (1.0–1.1)	0.799*	0.424		
PLT	156.0 (125.0–197.0)	158.0 (122.0–194.0)	−0.026*	0.979		
Creatinine (μmol/L)	72.0 (57.0–82.0)	66.2 (59.7–78.3)	−1.087*	0.277		
Mother-to-child transmission, *n* (%)	31 (46.3)	41 (27.3)	−2.730†	0.006	0.489 (0.250–0.960)	0.038
Ishak fibrosis score	3 (2–4)	3 (2–4)	−0.167*	0.867		
HAI	6 (4–8)	6 (5–7)	0.443*	0.658		
LSM (kPa)	11.3 (8.6–16.6)	10.5 (7.5–15.4)	−1.093*	0.275		
HBsAg ($\log_{10}$IU/mL)	3.7 (3.2–4.2)	3.4 (3.0–3.6)	−3.145*	0.002		
HBeAg, positive, *n* (%)	53 (79.1)	76 (50.7)	3.933*	0.000	2.545 (1.147–5.647)	0.022
HBV DNA ($\log_{10}$IU/mL)	7.1 (5.7–8.1)	5.9 (4.5–7.0)	−4.334*	0.000	0.751 (0.587–0.961)	0.023
Anti-HBc ($\log_{10}$IU/mL)	4.6 (4.3–5.0)	4.8 (4.3–5.0)	1.009*	0.313		
PIIINP (ng/mL)	3.6 (1.9–5.7)	3.9 (2.3–6.0)	0.959*	0.338		
LN (ng/mL)	69.7 (33.8–165.9)	63.4 (23.5–189.0)	−0.225*	0.822		
COL4A1 (ng/mL)	1.1 (0.8–1.5)	1.0 (0.7–1.2)	−1.936*	0.053		
MMP-3 (ng/mL)	13.4 (9.7–18.8)	15.1 (10.1–20.9)	1.327*	0.185		
vWF-A2 (ng/dL)	23.0 (12.2–31.1)	20.6 (12.6–28.2)	−0.457*	0.648		
Galectin 3 (ng/mL)	2.5 (2.2–2.9)	2.3 (1.9–2.7)	−2.292*	0.022		
Haptoglobin (mg/dL)	21.2 (5.2–42.2)	23.9 (7.7–54.5)	0.881*	0.378		
MCP1 (ng/dL)	25.3 (16.8–42.1)	27.9 (18.6–40.4)	0.774*	0.439		
PDGF-BB (ng/mL)	58.3 (26.1–84.0)	64.1 (35.6–88.2)	1.057*	0.291		

Parameters are expressed as median (interquartile range) for continuous variables, or *n* (%) for categorical variables. ALP: Alkaline phosphatase; ALT: Alanine transaminase; Anti-HBc: Hepatitis B core antibody; AST: Aspartate transaminase; BMI: Body mass index; COL4A1: Collagen IV alpha 1; GGT: Gamma-glutamyl transpeptidase; HAI: Histology activity index; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; LN: Laminin; LSM: Liver stiffness measurement; MCP-1: Monocyte chemoattractant protein 1; MMP-3: Matrix metalloproteinase-3; PDGF-BB: Platelet derived growth factor-BB; PIIINP: N-terminal propeptide of Type III procollagen; PLT: Platelet counts; ULN: Upper limit of normal; vWF-A2: von Willebrand factor A2. *Z value, †χ^2 value.

arguments, which were acquired from animal models or relied on serologic assays in a clinical setting and lacked liver histological evidence, were challenged.[16]

Up to now, liver biopsy has been the gold standard in evaluating liver histology.[31] In our study, 47.2% of chronic HBV infective patients with MTCT had significant liver fibrosis while the proportion in those with horizontal transmission was 36.8%, which coincided with Kumar study.[28] More than half of the patients in two group with moderate to severe liver inflammation, and more than two-thirds of the patients in MTCT group (71.7%) needed antiviral therapy. Our data suggested that patients with MTCT had more significant liver damage than patients with horizontal transmission.[29]

Furthermore, we evaluated the therapeutic efficacy of adult CHB patients with different modes of transmission based on HBeAg clearance, HBeAg seroconversion, and virological response. After 78-week antiviral therapy, the proportions of HBeAg clearance that occurred in patients with MTCT and in those with horizontal transmission were 21.2% and 38.0%, respectively. The 13.5% patients with MTCT acquired HBeAg seroconversion and 26.6% patients with horizontal transmission got HBeAg seroconversion, although there was no statistical difference in the ratio. There was significant difference found in the incidence of virological response between the two group, 56.9% patient in MTCT group obtained virological response while this proportion was as high as 75.2% in horizontal transmission group. Furthermore, multivariate analysis showed that MTCT was a risk factor for HBeAg clearance and virological response. In light of these findings, we concluded that the therapeutic efficacy of adult CHB patients with MTCT was relatively poor and the antiviral treatment time of MTCT group should be extended in the future clinical practice.

Several limitations should be noted in our study. The mode of transmission was recorded at the time of enrollment on the basis of patient's description of his/her family history of HBV infection and his/her HBV infection history, only

patients whose mother with chronic HBV infection or chronic hepatitis B during and after childbirth will be included in MTCT group. Even so, it was hardly to distinguish the adult patients infected with HBV by vertical transmission mode and those horizontally infected from their mother immediately after birth. In addition, only 217 patients with paired liver biopsies were included in the antiviral efficacy analysis, including 72 patients with MTCT. In future researches, we will expand the sample size to verify the point of view of our study.

In conclusion, compared with horizontal transmission group, the patients in MTCT group is characterized by a longer duration of viraemia, severe liver disease and poor therapeutic efficacy, which emphasizes the significance of earlier and longer treatment in patients infected by MTCT. Meanwhile, it is more meaningful to actively interrupt the perinatal transmission as we lived in an area of high chronic HBV prevalence.

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Conflicts of interest

None.

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