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Original Article

Significant Histologic Changes Are Not Rare in Treatment-naive Hepatitis B Patients with Normal Alanine Aminotransferase Level: A Meta-analysis

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Abstract

Background and Aims: Chronic hepatitis B is the main cause of liver cancer. However, the most neglected group has been treatment-naive chronic hepatitis B patients with normal alanine aminotransferase (ALT). People have tended to subjectively assume that the liver lesions of these patients are not serious and do not need antiviral treatment. However, the truth is not as optimistic as we thought. We aimed in this study to analyze the proportion of significant inflammation or fibrosis in aforementioned patients. ***Methods:*** Medline, Embase, and Cochrane Library were searched up to January 10th 2020, to identify studies of these patients with liver biopsy. The double arcsine method was used with a random-effect model to combine the proportion of significant inflammation or fibrosis. Potential heterogeneity was explored by subgroup analysis and meta-regression. Outcome of interests included the proportion of significant inflammation or fibrosis and cirrhosis. The secondary outcome was to find the risk factors of significant histological changes. ***Results:*** Nineteen eligible studies, with 2,771 participants, were included. The pooled proportion of significant inflammation or fibrosis was 35% [95% confidence interval (CI): 27 to 43] and 30% (95% CI: 25 to 36), respectively. The pooled proportion of cirrhosis was 3% [95% CI: 1 to 5, (12 studies; 1,755 participants)]. In subgroup analysis, old age [vs. young (<40 years-old), 44% vs. 26%, p=0.012] was significantly associated with higher fibrosis stage as well as cirrhosis [vs. young (<40 years-old), 4.8% vs. 1.8%, p<0.001]. ***Conclusions:*** About 1/3 of the treatment-naive chronic hepatitis B patients with normal ALT show significant histological changes, and some even have cirrhosis.

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Introduction

Chronic hepatitis B CHB) infection remains an important global public health problem. Hepatitis B surface antigen (HBsAg) seroprevalence is about 3.61% all over the world, of which about 240 million people are chronically infected.[1]

Current CHB practice guidelines from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (commonly known as the APASL) stratify patients using serum tests for alanine aminotransferase (ALT), HBV DNA and hepatitis B e antigen (HBeAg) to evaluate the need for liver biopsy or antiviral therapy.[2–4] According to the current recommendations of the aforementioned guidelines,[2–4] treatment and liver biopsy are not recommended in CHB patients with normal ALT (except for special cases, such as liver cirrhosis, hepatitis C or human immunodeficiency virus infection, tumor chemotherapy, etc.), regardless of HBeAg status and HBV DNA level. However, recently, numerous studies have shown that there are varying degrees of moderate and severe inflammation or significant fibrosis, and even liver cirrhosis in patients with CHB whose ALT remains normal. The proportion of severe inflammation ranges from 4% (6/140)[5] to 63% (60/95),[6] while the proportion of significant fibrosis ranges from 9% (10/113)[7] to 56% (63/113)[8] and the proportion of liver cirrhosis ranges from 0% (0/140)[5] to 19% (22/113).[8]

All aforementioned guidelines suggest the need for antiviral treatment for moderate and severe inflammation or fibrosis. Therefore, it is necessary to summarize the proportion of significant histological changes in CHB patients with normal ALT, so as to adjust the indications for antiviral therapy and liver biopsy. In addition, an American population-based study (including 39,206 people)[9] found that

Keywords: Significant histologic changes; Chronic hepatitis B; Normal ALT; Meta-analysis.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CI, confidence interval; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NOS, Newcastle–Ottawa scale; PLT, platelet; Tbil, total bilirubin; ULN, upper limit of normal.

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the mortality of adults with CHB was still higher than that of uninfected patients, despite improved treatment. Those with chronic infection had 1.9-fold [95% confidence interval (CI): 1.1 to 3.3] and 13.3-fold (95% CI: 3.9 to 45.5) increased hazard of all-cause mortality and liver-related mortality compared to uninfected patients. In order to improve the survival rate of patients with CHB, it is necessary to start antiviral therapy in eligible patients.

The primary goal of this study was to identify the proportion of significant hepatic inflammation or fibrosis and cirrhosis in CHB patients with normal serum ALT levels. The secondary goal was to identify possible indications of significant histological changes.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10] and MOOSE check list (Supplementary Tables 7, 8), and was registered at International Prospective Register of Systematic Reviews (PROSPERO number: CRD42020164923).

Search strategy and selection criteria

Medline, Embase, and the Cochrane Central Register of Controlled Trials databases were searched from inception to January 10th, 2020 using the following keywords: "chronic hepatitis B", "liver biopsy", and "alanine aminotransferase". Two reviewers independently screened the potential publication titles and abstracts, and reviewed the full-text of the eligible articles. In addition, if two or more studies were published based on the same data, the article with the highest quality was included.

The selected studies met the following inclusion and exclusion criteria:

Inclusion criteria were definite diagnosis of treatment-naive chronic hepatitis B. CHB patients with normal ALT, and available liver biopsy data (inflammation grade or fibrosis stage).

Exclusion criteria were sample size less than 50 CHB patients, patients with other forms of chronic viral hepatitis (hepatitis C virus, hepatitis D virus, or human immunodeficiency virus co-infection) and other chronic liver diseases (autoimmune, genetic, drug-induced etc.), patients with liver cancer or liver transplantation, reviews, editorials, letters, guidelines, and protocol type publications, or language other than English (Supplementary Table 1).

Data extraction

Two authors (CZ and ZW) independently reviewed each included paper using a standardized form for extraction of data including basic patient information [e.g., author's name, publication year, study design, country, age, sex, sample size, body mass index (BMI)], clinical data [e.g., HBV DNA, HBeAg status, ALT, aspartate aminotransferase (AST), γ-glutamyl transpeptidase, albumin, total bilirubin (Tbil), platelet (PLT)], and pathological data (e.g., inflammation grade, fibrosis stage, pathological scoring system). Any discrepancies were resolved by discussion by the senior investigators (HZ, GQW).

Quantitative variables were expressed as the mean±standard deviation and categorical variables were demonstrated with number and percentage. If the quantitative variables in the original study were expressed as median and interquartile range or median with maximum and minimum, they were converted to mean±standard deviation by means of mathematical statistics.[11–13] Furthermore, singularities were handled by adding one to all cell frequencies of studies with a zero cell count.

According to the standards of the EASL2017 guidelines,[3,4] we defined 40 U/L as the normal ALT upper limit of normal (commonly referred to as ULN). The pathological scoring system was converted to Scheuer's scoring system.[14] In the Scheuer's score system, the inflammation or fibrosis score was more than 2 points, which was considered as moderate to severe inflammation (G ≥2) or significant fibrosis (S ≥2). According to Zachary D. Goodman's liver puncture pathology score conversion method, if using the other scoring system of inflammation, histological activity index (HAI) ≥5 (Ishak[15] or Knodell[16] scoring system) or A ≥2 (Metavir scoring system)[17] were also defined as moderate to severe inflammation.[18] The fibrosis scoring system used >2 points to indicate significant fibrosis. Scheuer's or Metavir fibrosis scoring system score of 4 (G4 or F4) and Ishak fibrosis scoring system score of 5 to 6 (F5–6) were considered to indicate liver cirrhosis.

Quality assessment

Two independent investigators (CZ, ZW) assessed study quality using the Newcastle-Ottawa scale (commonly referred to as NOS)[19] for all the prospective and retrospective studies, including eight items (Supplementary Table 3). Studies with a score of ≤4, 5–6, and >6 were considered as having high, moderate, and low risk of bias, respectively.

Outcome measure

The primary outcome of interests were the proportion of significant histological changes (moderate to server inflammation or significant fibrosis) and the proportion of cirrhosis in CHB patients with normal ALT. The secondary outcome of interest was to find the risk factors of significant histological changes.

Statistical analysis

Considering the low incidence of interest events, the double arcsine transformation was used to calculate the proportion of significant histological changes and cirrhosis.[20] Q-statistics and Cochrane Q-test were used to assess heterogeneity between studies, where $p<0.10$ was regarded as statistically significant.[21,22] The I^2 statistic was calculated to describe the percent of observed variation across studies caused by heterogeneity, with an I^2 statistic of >75%, 25–75%, and <25% considered as high, moderate, and low heterogeneity, respectively.[21] Heterogeneity was expected, so all analyses were performed with a random-effects model. Subgroup analysis and meta-regression analysis were performed to explore potential sources of heterogeneity. Factors examined included study design (prospective vs. retrospective), region (Asian vs. Europe vs. Middle East vs. North America), age (<40 years vs. ≥40 years), BMI (<24 kg/m^2 vs. ≥24 kg/m^2), HBV DNA (<6 log10 IU/mL vs. ≥6 log10 IU/mL), Tbil (<17.1 μmol/L vs. ≥17.1 μmol/L), PLT (<200 ×10^9/L vs. ≥200 ×10^9/L), ALT (<25 U/L vs. ≥25 U/L), and AST (<25 U/L vs. ≥25 U/L). In subgroup analyses, we examined differences between groups with the chi-square test. In addition, to examine the impact of a single study on total effect, sensitivity analysis was carried out by leaving out one study each time.

Funnel plot (and trim-and-fill analysis,[23] which yields an effect adjusted for funnel plot asymmetry), Begg's test and

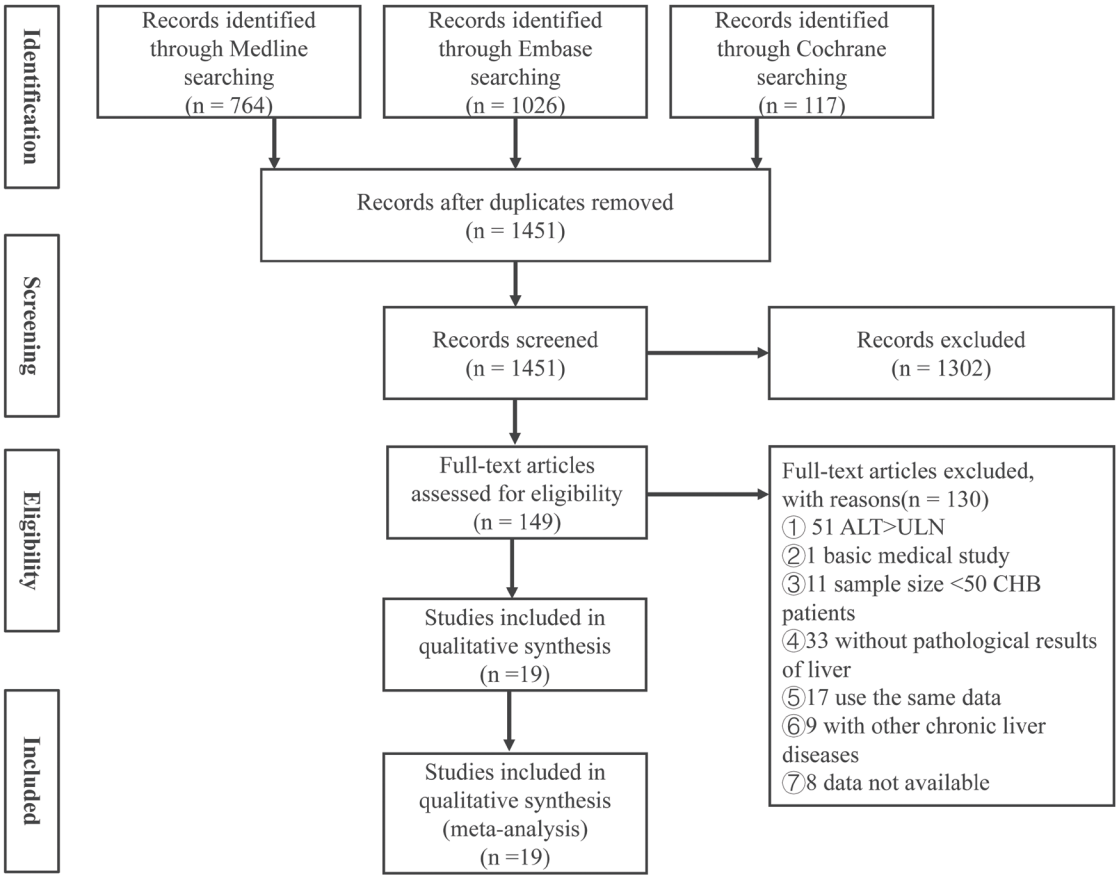

Fig. 1. Flowchart for study selection in the meta-analysis.

Egger's test were used to examine potential publication bias. A *p*-value of <0.05 was considered to be statistically significant. Analyses were done with Stata 15.0 (StataCorp LLC, College Station, TX, USA) and R version 3.6.2 using the meta and metafor packages.

Results

Search results and study characteristics

A total of 1,907 citations were retrieved from the Medline, Embase, and Cochrane Library database search. After screening of titles and abstracts for relevant publications and removal of duplicates, 149 potential articles were eligible for full-text screening, of which 19 studies[5–8,24–38] (including 2,771 participants; Supplementary Table 2) met our inclusion criteria and were included in the meta-analysis (Fig. 1).

The characteristics of the included studies are summarized in Table 1,[5–8,24–38] Supplementary Tables 4 and 5. Among the 19 studies published from 2007 to 2018, there were 7 prospective studies and 13 studies from the Asian region. The total number of people included in each study was quite different, with a median of 120 (ranging from 59 to 455). The youngest mean age was 23.8±6.7 years-old and the oldest was 50.0±15.0 years-old. The median male-to-female ratio was 1.9. Only one study did not report HBV DNA data, and 72.2% (13/18) of the remaining 18 studies had HBV DNA average of >6 log10 IU/mL. For other clinical data (such as ALT, AST, HBeAg status, etc.), please see Supplementary Table 4.

Four different scoring systems were used in the evaluation of liver pathology, including Scheuer's, Ishak, Knodell and Metavir scoring systems. The proportion of moderate to severe inflammation ranged from 4% (6/140) to 63% (60/95), with a median of 36%. The proportion of significant fibrosis ranged from 9% (10/113) to 56% (63/113), with a median of 30%. Twelve studies reported on cirrhosis; in most (11/12), the proportion of cirrhosis was <5%, but in one study, the proportion of liver cirrhosis was as high as 19% (22/113).

Methodological quality assessment

All of the selected studies were assessed for methodological quality by NOS. The NOS score of each study is presented in Supplementary Table 3. Ten studies[5,6,8,24,30,31,33,34,38] were of high quality and 9 studies[7,25–29,32,35–37] were of moderate quality. There were no studies with low quality.

Proportion of moderate to severe inflammation, significant fibrosis and liver cirrhosis

As shown in Figure 2A, the pooled proportion of moderate to severe inflammation was 35% (95% CI: 27 to 43). In the HBeAg-positive patients and the HBeAg-negative patients (Supplementary Fig. 2A) the rate of severe inflammation

Table 1. Characteristics of studies included in the meta-analysis

First author (Year)	Study design	Country	Age	Total	Male/ Female	Moderate to severe inflammation	Significant fibrosis	Cirrhosis	Histology assessment
Lai M[32] (2007)	Retrospective	USA	36.7±5.3	59	24/35	20	11	2	Scheuer's
Papatheodoridis G[8] (2008)	Prospective	Greece	50.0±15.0	113	74/39	61	63	21	Ishak
Kumar M[33] (2008)	Prospective	India	27.7±15.3* /34.6±14.5#	131	102/29	69	37	2	Knodell and Metavir
Nguyen MH[30] (2009)	Retrospective	USA	44.8±11.4	101	52/49	22	30	0	Scheuer's
Chen EQ[36] (2010)	Retrospective	China	33.0±10.1	141	82/59	67	47	NA	Scheuer's
Gui HL[34] (2010)	Retrospective	China	33.6±10.4	252	176/76	55	40	NA	Ishak
Montazeri G[38] (2010)	Prospective	Iran	36.7±12.0	132	80/52	53	40	NA	Knodell and metavir
Sanai FM[28] (2011)	Prospective	KSA	35.0±11.5	108	69/39	37	32	1	Metavir
Lesmana CR[31] (2011)	Prospective	Indonesia	41.5±10.7	103	58/45	57	56	NA	Metavir
Alam S[37] (2011)	Retrospective	Bangladesh	26.8±7.9	181	151/30	95	36	2	Knodell and metavir
Liao B[5] (2013)	Retrospective	China	23.8±6.7* /35.4±7.2#	140	73/67	6	59	0	Metavir
Wan R[27] (2015)	Retrospective	China	33.8±8.9	125	82/43	46	38	3	Scheuer's
Gong X[35] (2015)	Retrospective	China	32.0±12.2* /41.8±9.6	100	70/30	13	37	NA	Scheuer's
Tan Y[7] (2015)	Retrospective	China	32.4±13.2	113	77/36	66	10	0	Knodell
Ormeci A[29] (2016)	Retrospective	Turkey	42.8±11.32	120	58/62	18	43	0	Ishak
Zhou J[24] (2017)	Prospective	China	37.6±10.1* /42.3±10.6#	193	134/59	70	63	NA	Ishak
Tan YW[6] (2017)	Retrospective	China	34.5±11.2	95	70/25	60	23	NA	Knodell
Xing YF[26] (2018)	Prospective	China	34.9±6.4	455	287/168	137	182	6	Ishak
Xu Z[25] (2018)	Retrospective	China	33.3±8.3	109	91/18	13	23	3	Scheuer's

*HBeAg-positive; #HBeAg-negative. Based on the Ishak scoring system, the definition of moderate to severe inflammation by Gui HL (2010) was HAI ≥4, by Papatheodoridis G (2008), Zhou J (2017), and Xing YF (2018) was HAI ≥5, and by Ormeci A (2016) was HAI ≥6. Based on the Knodell scoring system, Kumar M (2008), Montazeri G (2010), Alam S (2011), Tan Y (2015) and Tan YW (2017) defined moderate to severe inflammation as HAI ≥4.

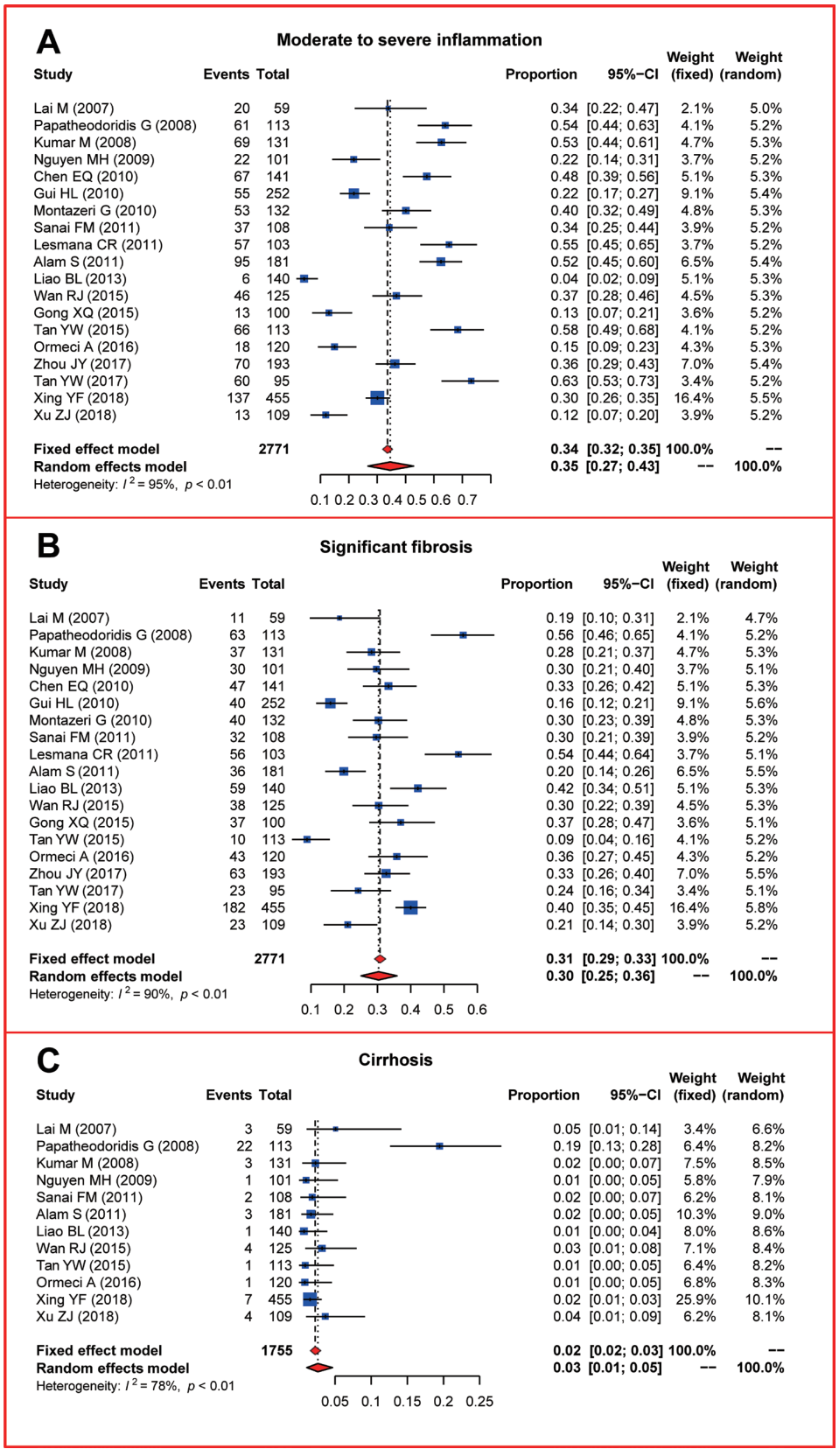

Fig. 2. Proportion of significant pathological changes in patients with CHB and normal ALT. (A) Inflammation grade ≥2. (B) Fibrosis stage ≥2. (C) Cirrhosis.

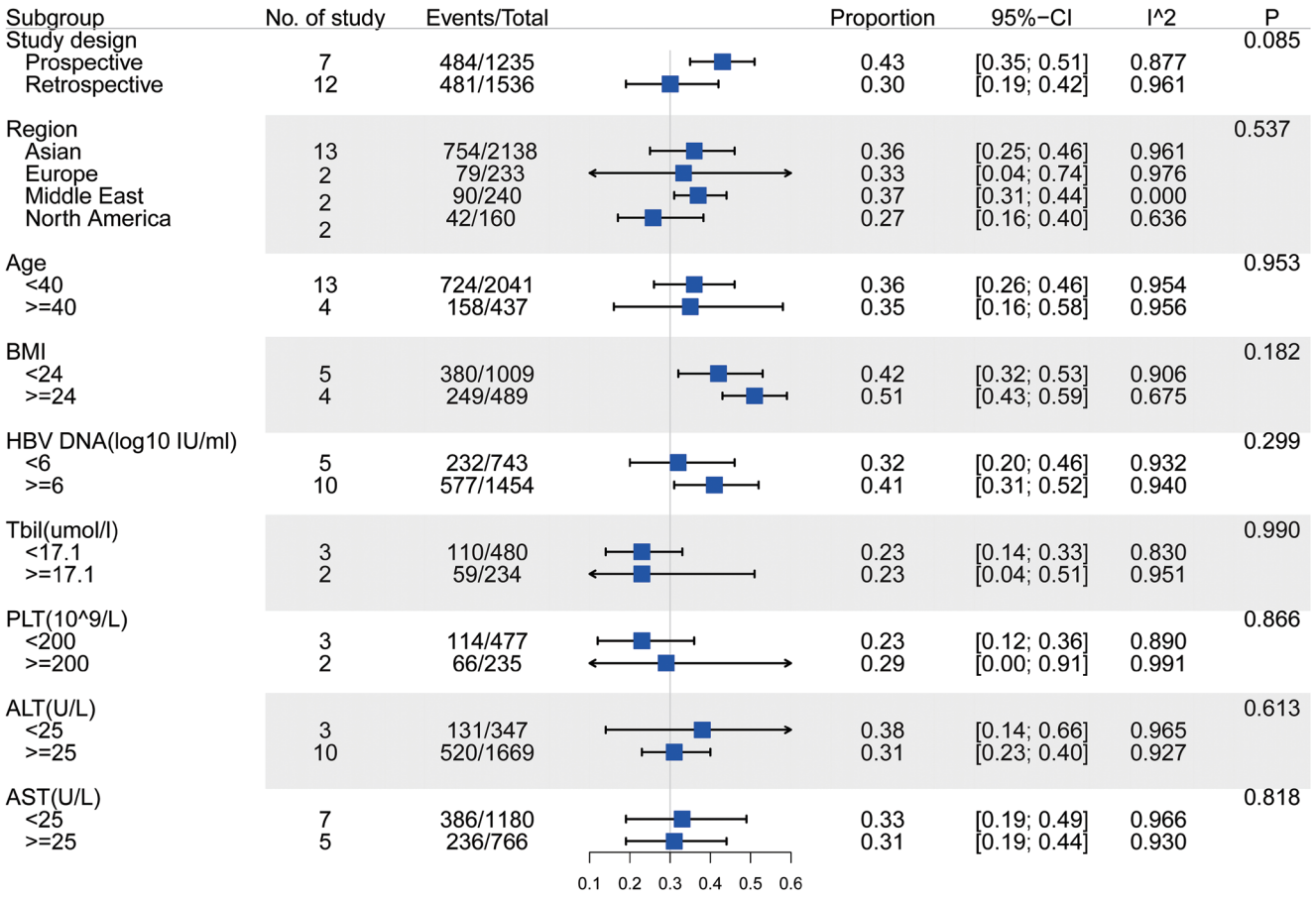

Fig. 3. Summary of the proportion of moderate to severe inflammation in different subgroups.

was 34% (95% CI: 19 to 50) and 32% (95% CI: 21 to 43), respectively, but the difference between the two was not statistically significant (p=0.806). The pooled proportion of significant fibrosis (Fig. 2B) was 30% (95% CI: 25 to 36), 27% (95% CI: 18 to 36) in the HBeAg-positive patients and 34% (95% CI: 26 to 42) in the HBeAg-negative patients; again, the between-group difference was not statistically significant (p=0.255; Supplementary Fig. 2B). The proportion of liver cirrhosis (Fig. 2C) accounted for 3% (95% CI: 1 to 5), and there was no significant difference between the HBeAg-positive and HBeAg-negative patients [2% (95% CI: 1 to 4) vs. 3% (95% CI: 0 to 8), p=0.571; Supplementary Fig. 2C].

Subgroup analysis and meta-regression

Proportion of moderate to severe inflammation: Figure 3 and Supplementary Table 6 shows the proportion of moderate to severe inflammation in different subgroups and meta-regression results. Prospective studies (n=7) seemed to have a higher proportion of moderate to severe inflammation than retrospective studies (n=12), but the difference was not statistically significant [43% (95% CI: 35 to 51) vs. 30% (95% CI: 19 to 42), p=0.087] nor by meta-regression (p=0.126). There was no statistical difference in age (<40 years vs. ≥40 years), BMI (<24 kg/m^2 vs. ≥24 kg/m^2), HBV DNA (<6 log10 IU/mL vs. ≥6 log10 IU/mL), Tbil (<17.1 μmol/L vs. ≥17.1 μmol/L), PLT (<200×10^9/L vs. ≥200×10^9/L), ALT (<25 U/L vs. ≥25 U/L) and AST (<25 U/L vs. ≥25 U/L). Similarly, there was no statistical difference by meta-regression.

Proportion of significant fibrosis: The results of subgroup analysis and meta-regression of significant fibrosis ratio are shown in Figure 4 and Supplementary Table 6. Similar to the proportion of moderate to severe inflammation, the proportion of significant fibrosis in prospective studies was higher than that in retrospective studies, and the difference was statistically significant [38% (95% CI: 31 to 46) vs. 26% (95% CI: 20 to 32), p=0.011]. The result by meta-regression was also significant (p=0.013). The proportion of significant fibrosis in people >40 years-old [44% (95% CI: 31 to 57)] was almost twice as high as that in people <40 years-old [26% (95% CI: 20 to 32)]. There were significant differences in subgroup analysis (p=0.012) and meta regression (p=0.009). The remaining seven subgroups (region, BMI, HBV DNA, Tbil, PLT, ALT, and AST) were also analyzed, and no statistical difference was found in either subgroup analysis or meta-regression.

Proportion of liver cirrhosis: Figure 5 and Supplementary Table 6 show the proportion of liver cirrhosis. In the subgroup analysis, only the factor of age (<40 years or ≥40 years) showed statistically significant difference [1.8% (95% CI: 1.1 to 2.6) vs. 4.8% (95% CI: 0 to 19.2), p<0.001]. No statistical difference was found in the other nine subgroups (study design, region, BMI, HBV DNA, Tbil, PLT, ALT, and AST). However, there was statistical significance in AST and region by meta-regression, probably because the range of 95% CI in subgroups with AST was so large that there was no statistical difference in subgroup

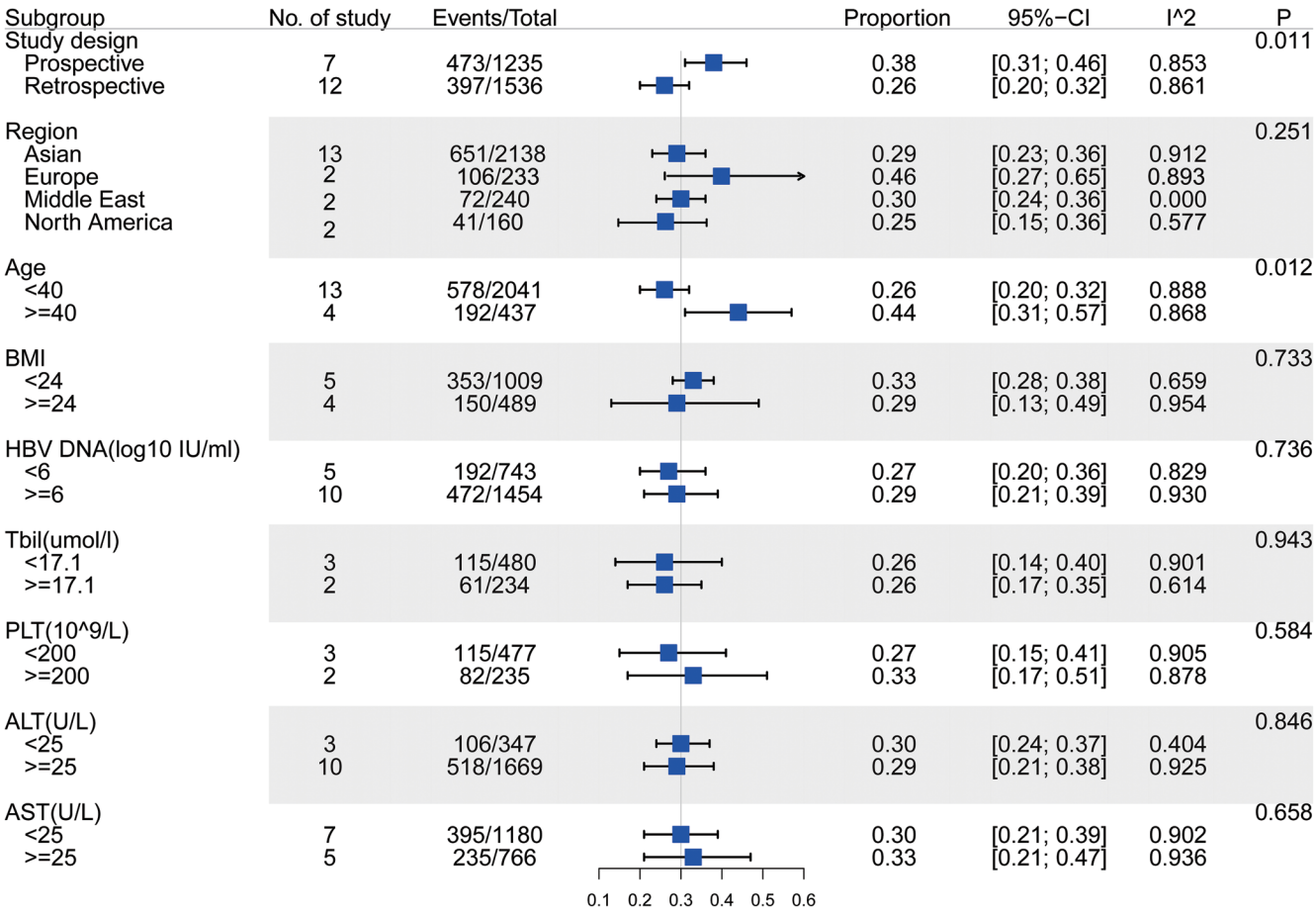

Fig. 4. Summary of the proportion of significant fibrosis in different subgroups.

analysis. For region subgroup analysis, only one study was included in two subgroups, so it was necessary to be cautious in explaining the proportion of liver cirrhosis in different subgroups.

Publication bias and sensitivity analysis

We drew a funnel plot and conducted a trim-and-fill analysis (Fig. 6). For moderate to severe inflammation, funnel plot (Fig. 6A) showed a slight asymmetry. However, both Begg's test (p=0.834) and Egger's test (p=0.573) did not indicate publication bias. Two studies were added to the trim-and-fill analysis (Fig. 6D) but there was no significant change in the proportion of moderate to severe inflammation [adjusted value: 32% (95% CI: 24 to 40)].

In the aspect of significant fibrosis, funnel plot (Fig. 6B), Begg's test (p=0.779) and Egger's test (p=0.672) were also applied, and the findings indicated that there was no publication bias. Trim-and-fill analysis (Fig. 6E) added six studies but did not significantly change the proportion of significant fibrosis [adjusted value: 37% (95% CI: 31 to 43)].

For proportion of cirrhosis, the aforementioned analysis was also carried out. The funnel plot (Fig. 6C) was symmetrical, without any study added or deleted in the trim-and-fill analysis (Fig. 6F). The Begg's test (p=0.063) and Egger's test (p=0.298) also showed no publication bias.

Sensitivity analysis was carried out on moderate to severe inflammation, significant fibrosis and cirrhosis, and the results were robust. We excluded each study in turn, and the results did not change much (see Supplementary Fig. 1 for details).

Discussion

The findings of our systematic review and meta-analysis show that significant histologic changes are not rare among the treatment-naive CHB patients with normal ALT. Among them, the proportion of moderate to severe inflammation or significant fibrosis was about one-third, and the proportion of cirrhosis was about 3%.

A previous study[39] has reported the proportion of significant fibrosis. On the basis of this, we have added several new research results in recent years to supplement the data of significant fibrosis. What is more important, we have improved the data of the proportion of moderate to severe inflammation and cirrhosis, which are as important as fibrosis evaluation in histological evaluation. Moreover, AASLD2018, EASL2017 and APASL2016 guidelines have recognized noninvasive alternatives for the evaluation of liver fibrosis, such as liver stiffness measurement (transient elastography).[2–4,40] However, there was no recognized evaluation method for liver histological inflammation, except liver biopsy. To some extent, the progression of inflammation was more hidden than fibrosis, and our data show that the proportion of moderate and severe inflammation [35% (95% CI: 27 to 43)] was higher than that of sig-

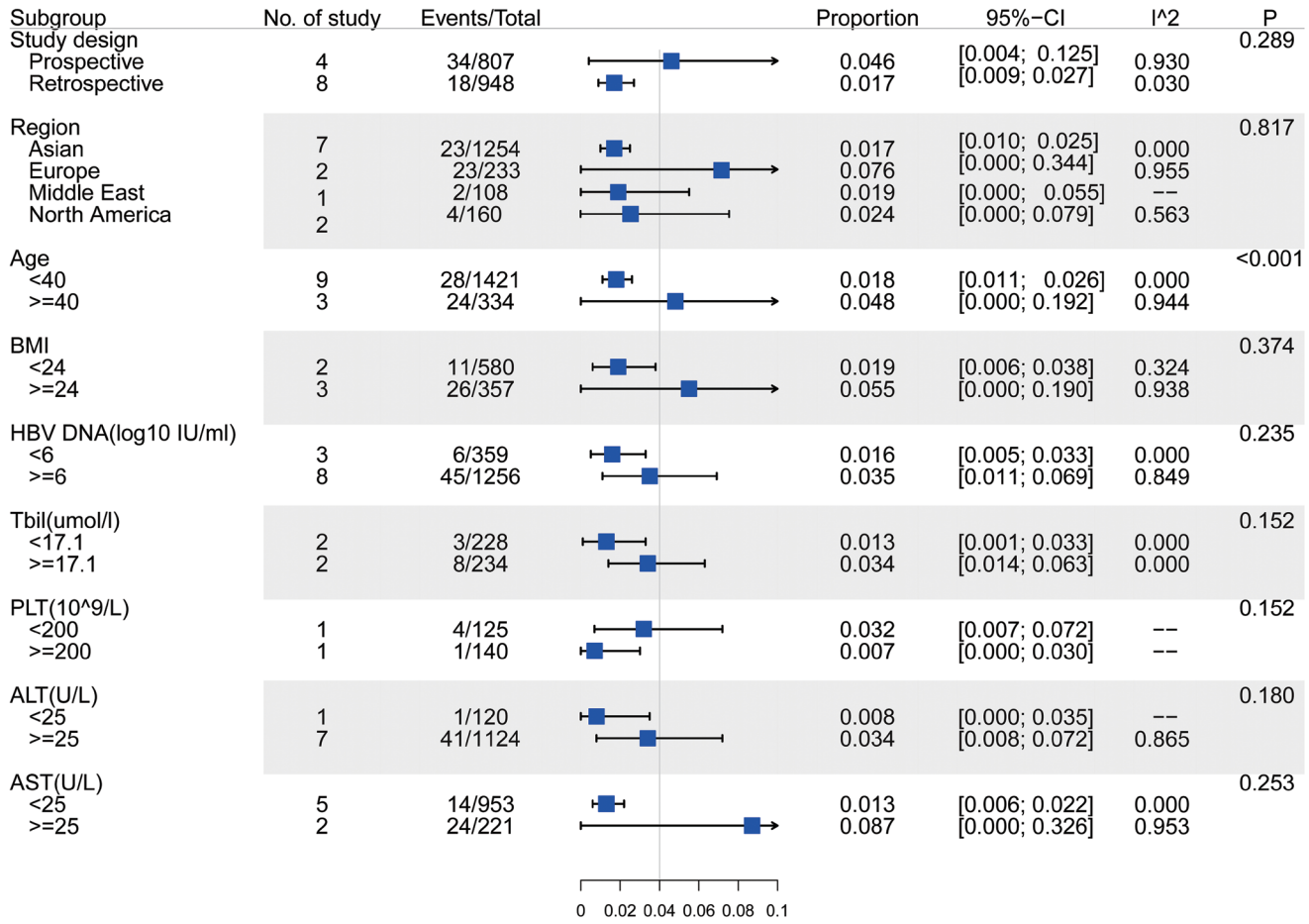

Fig. 5. Summary of the proportion of cirrhosis in different subgroups.

nificant fibrosis [30% (95% CI: 25 to 36)]. Previously, it has been believed that CHB patients with normal ALT did not need special treatment, mainly observation, and only a clear family history of liver cancer or other special circumstances need to be paid attention to. But our study gives a different answer. Although ALT has its simple and rapid advantages in the evaluation of chronic liver disease, there are too many factors that affect the concentration of ALT in serum, so the specificity of reflecting liver inflammation is not high. Especially, when other liver diseases or systemic diseases were involved in the liver, the limitations of ALT became more obvious.

If CHB patients do not start antiviral therapy in time, the disease can progress to liver cirrhosis or even liver cancer. At present, first-line antiviral drugs (i.e. entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide) have a good effect on inhibiting virus and improving liver histological inflammation and fibrosis.[41] Therefore, it is necessary to make clear the proportion of significant histological changes (including inflammation and fibrosis) in CHB patients with normal ALT. Meanwhile, identifying possible signs in people with significant histological changes is also momentous.

Our study found that there were obvious differences in significant fibrosis among different age subgroups (>40 years-old or not), suggesting that age was as an important sign of significant fibrosis. Similarly, age also showed value in cirrhosis. Previously, there have been some small sample studies, ranging from 10s to 100s, that support our conclusions. Research findings by Xing *et al*.[26] and Tan *et al*.[7] also support this view, but authors of the former believed that the age of 50 needed special attention. Sanai *et al*.[28] held that serum HBV DNA levels are predictive of liver fibrosis in CHB but found it to be in the mildly elevated ALT population. However, our results did not suggest the role of HBV DNA in the differential diagnosis of significant fibrosis. We also used HBV DNA level of 7 log10 IU/mL and 8 log 10 IU/mL as cutoff values, and found no statistical difference (data not shown). There are other indicators (collagen 4, laminin, procollagen III N-terminal peptide, hyaluronic acid, etc.) and models (APRI, FIB-4, etc.) that suggest significant fibrosis which need further study.

Unfortunately, no distinguishing indication of moderate and severe inflammation can be found. Considering the studies by Park *et al*.[42] and Kumar *et al*.,[33] persistent high ALT (0.5–1 of ULN) may be an indicator of liver histological inflammation. However, our research showed a lack of statistical significance for ALT differences among groups (<25 U/L vs. ≥25 U/L, p=0.613) and the possible reason was that some of the included studies did not provide the original ALT mean in the original text; thus, we could only use mathematical statistics to estimate the possible mean, and this approach may have caused some errors. Therefore, it may patients with high normal of ALT for a long time may still be worthy of our attention. In addition, our team[24,43] and Xia *et al*.[44] have shown that quantitative anti-hepatitis B core antibody measures have good application value in reflecting liver inflammation and natural history of hepatitis B. The quantitative anti-hepatitis B core antibody measure in the

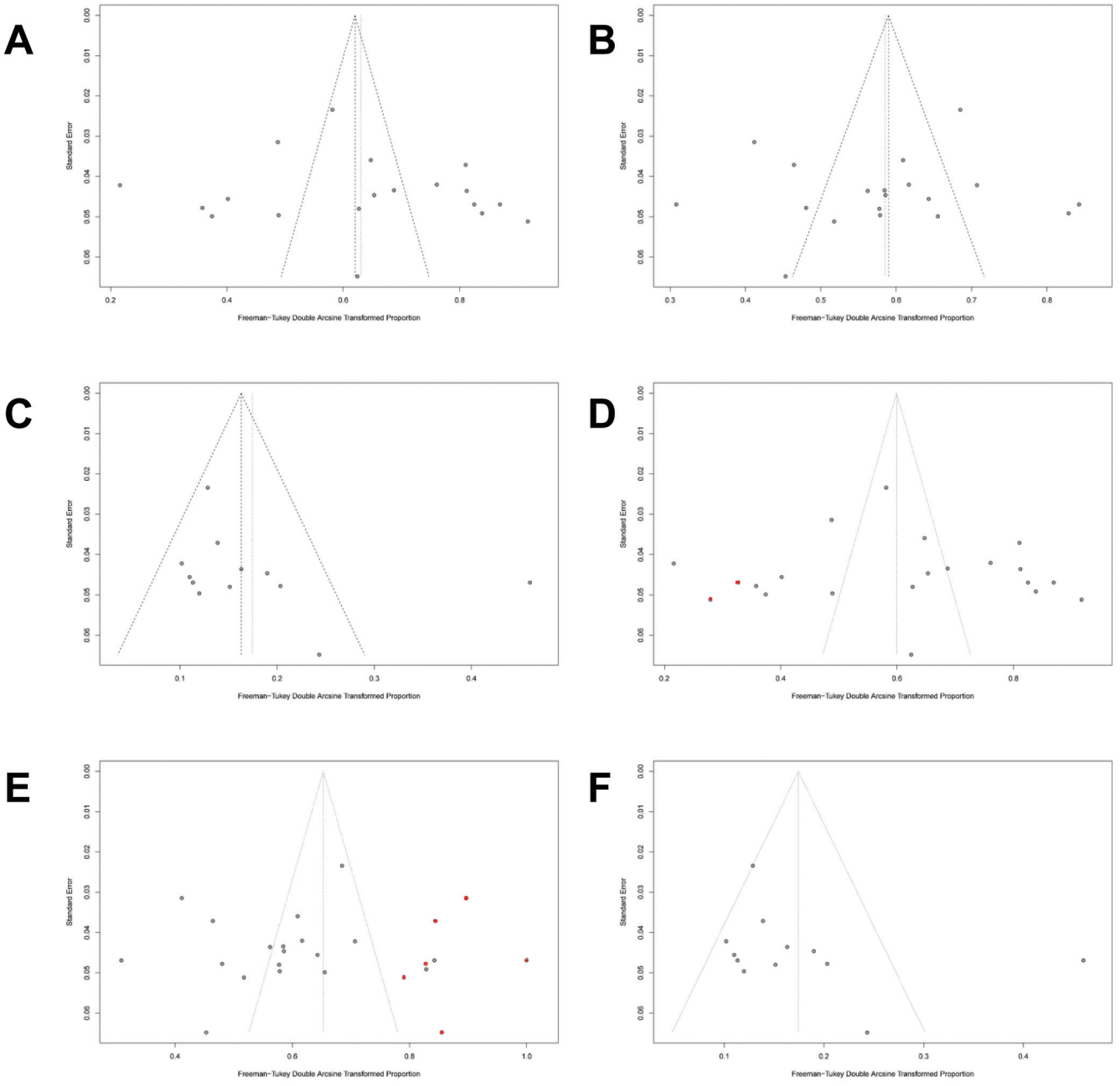

Fig. 6. Funnel plot and trim-and-fill analysis plot. (A) Funnel plot of the proportion of moderate to severe inflammation. (B) Funnel plot of the proportion of significant fibrosis. (C) Funnel plot of the proportion of cirrhosis. (D) Trim-and-fill plot of the proportion of moderate to severe inflammation (two studies were added, as shown by the red points in the figure). (E) Trim-and-fill plot of the proportion of significant fibrosis (six studies were added, as shown by the red points in the figure). (F) Trim-and-fill plot of the proportion of cirrhosis (no studies were added).

immune tolerance stage was significantly lower than that in the immune clearance stage.

Although subgroup analysis and meta-regression were carried out as far as possible, there was still some heterogeneity implication for outcomes. According to the results of proportion of significant fibrosis subgroup analysis, different ALT levels may represent the main source of heterogeneity (I^2: 40.4% vs. 92.5% in ALT <25 U/L and ≥25 U/L, respectively). Several factors can explain the source of heterogeneity in proportion of cirrhosis. Among them, prospective studies had greater heterogeneity than regression studies (I^2: 93.0% vs. 3.0%), and older age had greater heterogeneity than younger age (I^2: 94.4% vs. 0.0%). Unfortunately, the source of moderate and severe inflammatory heterogeneity has not been found. We speculate that the first reason may be that there was no recognized value for the normal upper limit of ALT, which was considered by the APASL and EASL guidelines as 40 U/L but by the AASLD guidelines as 35 U/L for male and 25 U/L for female. Second, compared with the pathological evaluation of fibrosis, the evaluation of inflammation was more easily affected by the scoring system and pathologists, especially upon the

application of Ishak and Knodell scoring systems, as the items were too detailed to form a unified consensus.

Our study has several limitations. First, there may be a patient selection bias in this study. For the CHB patients with normal ALT, both the patients and doctors were reluctant to carry out invasive liver biopsy due to its inherent risks, which reduced the implementation of liver biopsy to a certain extent. Therefore, the proportion of significant histological changes may be higher in actuality than this study found. Second, there were non-randomized controlled trials among the included studies. Although the results of publication bias were negative, their inclusion inevitably reduced the overall quality of the study.

Conclusions

In summary, significant histologic changes present in approximately one-third of treatment-naive CHB patients with normal ALT levels, and about 3% of patients even progressed to cirrhosis. It is worth noting that the proportion of significant fibrosis and cirrhosis in people >40 years-old are more than twice as high as those in younger people. The management of treatment-naive CHB patients with normal ALT remains a challenge and requires an individualized approach, in addition to the standardized paradigms recommended by current guidelines.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Search of the literature and data extraction (CZ, ZW), drafted the manuscript (CZ), creation of figures and table (CZ, ZW, JWL), methodological guidance (HZ), and provision of the overall principle and oversight of the direction of the study (HZ, GQW).

Data sharing statement

All data are available upon request.

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