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Significant histologic alterations in untreated chronic hepatitis B children: a meta-analysis

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Abstract

Background Chronic hepatitis B (CHB) in children poses a significant public health challenge, yet data on the prevalence of significant liver lesions in this group are limited.

Methods A comprehensive meta-analysis pooled data on the proportion of significant liver lesions among CHB children. Using the double arcsine transformation and a random-effects model, we combined data on moderate to severe liver inflammation, fibrosis, and cirrhosis. Subgroup analysis and meta-regression were conducted to explore heterogeneity.

Results Twenty-two studies with 3,037 participants were included. The proportion of moderate to severe inflammation was 41.54% [95% Confidence Interval (CI): 29.14–54.47%], notable fibrosis was 31.71% [95% CI: 23.85–40.11%], and cirrhosis was 2.27% [95% CI: 1.06–3.82%]. Inflammation varied significantly by age group: < 6 years, 36.21%; 6–12 years, 53.72%; 12–18 years, 31.40% ($p < 0.01$). ALT ≥ 80 U/L was associated with higher inflammation (57.78%) compared to ALT < 80 U/L (29.73%) ($p < 0.01$). Cirrhosis also varied significantly by age group.

Conclusions A substantial proportion of CHB children have significant liver lesions, underscoring the need for enhanced screening and monitoring.

Keywords CHB, Children, Inflammation, Fibrosis, Cirrhosis, Proportion, Liver, ALT, HBV, Region

Introduction

Chronic hepatitis B (CHB) remains a major global public health concern, with approximately 1.5 million new cases of hepatitis B virus (HBV) infection reported annually [1]. Although the infection rate among children has declined over recent decades, it continues to pose significant challenges. According to data from the Polaris Observatory Collaborators [2], the global prevalence of hepatitis B surface antigen (HBsAg) among children under five years old was estimated at 0.7% in 2022. Despite efforts to prevent maternal-to-infant transmission, these measures often fall short due to uneven regional development and significant individual variability. Pediatric HBV infections are characterized by a high rate of chronicity, with 90% of perinatal infections and 25%–30% of infant

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infections progressing to chronic infection [3]. Our previous research [4] highlighted the global, regional, and national burdens of HBV-related cirrhosis in children and adolescents, estimating that approximately 46.5 million children are affected by HBV-related chronic liver disease. The average annual percent change (AAPC) in incidence has increased in low-middle sociodemographic index (SDI) areas (AAPC: 0.12 [95% CI: 0.04–0.20]).

Several consensus and guidelines [5–8] have indicated that liver damage in most children with chronic HBV infection is relatively mild. However, some children may still develop significant histological changes, potentially leading to cirrhosis, liver cancer, and other severe conditions. A recent retrospective study revealed that a significant proportion of untreated children with chronic hepatitis B exhibited moderate to severe liver inflammation or fibrosis, with some even developing cirrhosis. Notably, when liver biopsies were performed at age ≤ 3 years and ALT levels exceeded 80 U/L, the proportion of moderate fibrosis and cirrhosis exceeded 80% [9]. Understanding the pathological progression of liver disease is essential for determining the timing of antiviral therapy. To date, no comprehensive study has summarized the significant histological changes in children with CHB who have not received antiviral treatment. Therefore, conducting a meta-analysis to assess the prevalence of moderate to severe inflammation, notable fibrosis, and cirrhosis in children with CHB is crucial. This analysis will provide valuable scientific evidence to inform the development of early intervention and treatment strategies for these children.

Methods

Our systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [10] (Supplementary Table 1). The current systematic review has been officially registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42024559936.

Search strategy

The meta-analysis was strictly conducted following the recommendations and standards by PRISMA [11]. We systematically searched PubMed, Web of Science, EMBASE, Scopus, and Cochrane Library from inception until June 20, 2024. The search strategy was developed with the assistance of a librarian, incorporating a comprehensive set of search terms (Supplementary Table 2). References from relevant systematic reviews were also manually searched to identify additional qualifying studies. Two independent authors (XG and JL) performed the literature search without language restrictions.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Children with a definitive diagnosis of treatment-naïve CHB, defined as children who have not received any antiviral treatment for chronic hepatitis B [8, 12]. "Treatment-naïve" refers to children who have not undergone any antiviral therapy for CHB prior to the study; (2) The studies reporting the proportion of inflammation grade or fibrosis or cirrhosis in untreated CHB children with available liver biopsy data.

Exclusion criteria: (1) Children suffering from alternative forms of chronic viral hepatitis, including hepatitis C virus, hepatitis D virus, or co-infection with human immunodeficiency virus, as well as other chronic liver disorders stemming from autoimmune processes, genetic factors, drug-induced causes, and the like; (2) No definitive method for liver tissue examination; (3) No valid data or complete data that can be extracted; (4) The patient does not have data for calculating the proportion of significant histological changes; (5) Studies which publication type was comment, review article, or randomized controlled trial were also excluded. Detailed inclusion and exclusion criteria are presented in Supplementary Table 3.

Screening and data extraction

Three researchers (CYH, XG, and YFP) independently screened the titles and abstracts of all documents, creating a preliminary screening database in Endnote (version X.9). Based on the prespecified eligibility criteria, two reviewers (CYH and ZWW) assessed the full texts to determine study inclusion. The extracted data were subsequently reviewed and verified by another author (PYF) before proceeding to data cleaning and analysis.

The extracted data encompassed details such as the author, publication year, title, country, sample size, study type, demographic information, and the status of inflammation, fibrosis, and cirrhosis, along with the pathological scoring system used. In the Scheuer scoring system [13], a score exceeding 2 for inflammation or fibrosis indicates moderate to severe inflammation ($G \geq 2$) or notable fibrosis ($S \geq 2$). Using Zachary's method for converting liver biopsy pathology scores, moderate to severe inflammation is also defined as a histological activity index (HAI) of 5 or higher when using the Ishak [14] or Knodell [15] scoring systems, or as an A score of 2 points or higher when applying the Metavir [16] scoring system. For fibrosis, a score above 2 is considered significant. Specifically, a fibrosis score of 4 (G4 or F4) in the Scheuer or Metavir systems, and a score of 5 to 6 (F5–6) in the Ishak system, are indicative of liver cirrhosis. Any uncertainties regarding eligibility were resolved through consensus and expert discussion.

Study quality assessment

Four reviewers (PYF, GX, QYJ and JLF) applied the Agency for Healthcare Research and Quality (AHRQ) [17] to evaluate the quality of cross-sectional studies. The AHRQ scoring system ranges from 1 to 11 points, with scores of 1–3 indicating low quality, 4–7 indicating medium quality, and 8–11 indicating high quality. The Newcastle–Ottawa Scale(NOS) [18], recommended by the Cochrane Collaboration Group, was used by two reviewers (PYF, QYJ) to evaluate the quality of cohort studies. A full score on this scale is 9 points (studies of 0–3 points were low quality, those of 4–6 points were considered as moderate quality, and a score >6 points was indicative of high quality). Discrepancies in the quality assessment stages was resolved through consensus and group discussions. The quality score evaluations by the AHRQ and NOS scoring systems are presented in Supplementary Table 4 and Supplementary Table 5, respectively.

Statistical analysis

The pooled proportion estimations were calculated after applying the Freeman-Tukey double arcsine transformation and returning the 95% confidence intervals (CIs) back to proportions [19]. The I² statistic [20] was used to evaluate the heterogeneity; I² value greater than 75%, between 25 and 75%, and less than 25% were considered to indicated high, moderate, and low heterogeneity, respectively. The data were deemed significantly heterogeneous if the I² value exceeded 50%, and in such cases, the random effects model was employed. Conversely, if the I² value was less than or equal to 50%, the fixed-effects model was utilized. Given the heterogeneity observed across the primary studies [19], a random-effects model

was employed to aggregate the proportions. For subgroup comparisons, we utilized the chi-square test to evaluate disparities among various groups.

The next steps involved identifying publication bias, assessing methodological quality, and determining true heterogeneity through funnel plots in meta-analysis. The Egger test [21] utilizes linear regression, while Begg's test relies on rank correlation statistics, to evaluate publication bias in Meta-analysis. Furthermore, the trim-and-fill method [18] were applied to correct for publication bias. The meta-regression analysis was to investigate the potential sources of heterogeneity among the included studies and to examine the association between the effect sizes and various study-level characteristics. The meta-analyses was conducted using R version 4.3.2 with the “meta” and “metafor” packages. A value of *p* < 0.05 was taken to indicate statistical significance.

Results

Results of the search and characteristics of the included studies

A total of 25,656 records were included, consisting of 3,767 peer-reviewed literature and 21,889 duplicates. After removing duplicates, titles and abstracts were screened based on the inclusion and exclusion criteria, a total of 336 potentially relevant full-text articles were independently reviewed. The procedure of the literature search and study selection was presented in Fig. 1. Finally, 22 studies [9, 22–42] meeting our inclusion criteria were identified, including 15 retrospective cohort studies, 6 prospective cohort studies and 1 cross-sectional study. The characteristics of the included studies are compiled and presented in Table 1. The included studies covered a publication period from 1990 to 2022, including 7

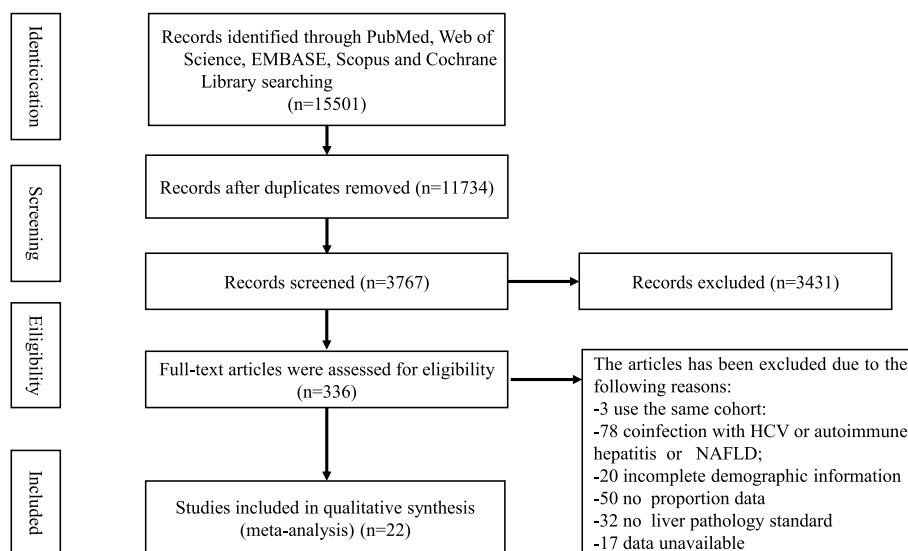


Fig. 1 Flowchart for study selection in the meta-analysis

Table 1 Characteristics of studies included in this meta-analysis

| First Author | Publication Year | Country | Study Type | Age [#] | Total | Male/Female | Moderate to severe inflammation | Sig-nificant fibrosi | Cirrhosis | Histology assessment |
|----------------------|------------------|---------|-----------------|----------------------|-------|-------------|---------------------------------|----------------------|-----------|----------------------|
| Bortolotti [39] | 1998 | Italy | Prospective | 5.5 ± 3.4 | 185 | 107/78 | 18 | NA | 3 | Knodell |
| Moreno [34] | 1999 | Spain | Retrospective | 6.3 (0.6–12.5) | 28 | NA | 8 | NA | 1 | Scheuer |
| Marx [40] | 2002 | Canada | Prospective | 4.7 ± 4.6 | 41 | NA | 8 | 3 | 1 | Ishak |
| Wen [41] | 2004 | China | Prospective | NA | 100 | NA | NA | NA | 2 | Ishak |
| Zhang [37] | 2004 | China | Cross-sectional | NA | 560 | NA | 132 | NA | NA | Ishak |
| Boxal [38] | 2004 | UK | Prospective | NA | 35 | NA | 26 | 7 | 2 | Ishak |
| Lebensztejn [31] | 2005 | Poland | Retrospective | 10 | 63 | 41/22 | NA | 7 | NA | Batts and Ludwig |
| Lebensztejn | 2006 | Poland | Retrospective | 7.46 ± 4.05 | 190 | 138/52 | 62 | 66 | 1 | Knodell |
| Bortolotti [36] | 2006 | Italy | Retrospective | 4.8 ± 3.2 | 8 | 6/2 | 1 | NA | 0 | Ishak |
| Lisewska [21] | 2008 | Poland | Retrospective | 7.49 ± 4.01 | 200 | 145/55 | 58 | 70 | 2 | Knodell |
| Kemnitz [30] | 2009 | Poland | Retrospective | 6.65 ± 3.42 | 105 | 93/12 | 12 | 2 | NA | Knodell |
| Sokucu [24] | 2010 | Turkey | Retrospective | 9 (8–13) | 25 | 19/6 | 4 | 9 | 2 | Scheuer |
| Konstantynowicz [35] | 2011 | Poland | Cross-sectional | 11.9 ± 3.1 | 39 | 25/14 | 18 | 9 | NA | Ishak |
| Spiewak [26] | 2016 | Turkey | Retrospective | 12.8 ± 2.4 | 30 | 19/11 | 5 | 16 | 1 | Knodell |
| Murray [33] | 2016 | USA | Retrospective | 9.05 ± 4.98 | 78 | 39/39 | NA | 4 | 1 | Ishak |
| Wang [23] | 2019 | China | Retrospective | 6.0 (3.0–13.0) | 560 | 494/66 | 362 | 274 | NA | Metavir |
| Emiroglu [29] | 2019 | Turkey | Retrospective | 4.97 ± 3.72 | 12 | NA | 4 | 5 | NA | Scheuer |
| Baez [22] | 2020 | USA | Retrospective | 8 (4–13) | 134 | 68/66 | 90 | 21 | 4 | Ishak |
| Zhang [27] | 2021 | China | Retrospective | 6 (3–10) | 116 | 80/36 | NA | 51 | NA | Scheuer |
| Liang [28] | 2021 | China | Retrospective | 6.4 (3.9–10.4) | 80 | 57/23 | 34 | 29 | NA | Scheuer |
| Hu [9] | 2022 | China | Retrospective | 5.1(0.8–15) | 278 | 177/101 | 208 | 155 | 23 | Metavir |
| Luo [25] | 2022 | China | Retrospective | 3.96 (0.83–14.58) | 148 | 107/44 | NA | 26 | 2 | Scheuer |

[#]Age is expressed by median ± standard deviation or median combined with interquartile range

studies from Asia, 12 studies from Europe, and 3 studies from North America. A total of 3,037 patients were included in the meta-analysis, with the youngest group having an average age of 3.96 (0.83–14.58) years and the oldest group being an average age of 12.8 ± 2.4 years. Four distinct scoring systems were employed in assessing liver pathology, namely, the Scheuer, Ishak, Knodell, and Metavir scoring systems.

The proportion of moderate to severe inflammation ranged from 12.5% (1/8) to 74.8% (208/278), with a median values of 33.3%. The proportion of notable fibrosis ranged from 17.6% (26/148) to 56% (155/278), with a median of 36.1%. Among the 18 studies reporting on cirrhosis, most indicated a cirrhosis prevalence of less than 5%, although one study reported a rate as high as 8.3% (23/278).

Proportion of moderate to severe inflammation, notable fibrosis, and cirrhosis

As depicted in Fig. 2, the pooled proportion of patients with moderate to severe inflammation was 41.54%

(95%CI: 29.14–54.47). This estimate was derived from 16 studies involving a total of 2414 patients. The results were heterogeneous, with an I^2 statistic of 97.4%. In Fig. 3, the pooled proportion of patients with notable fibrosis was 33.89% (95%CI:26.44–41.74), which was calculated from 15 studies involving a total of 1899 patients. The results were heterogeneous, with an I^2 statistic of 90.7%. In Fig. 4, the pooled proportion of patients with cirrhosis was 2.27% (95%CI: 1.06–3.82). This estimate was derived from 16 studies involving a total of 1648 patients. The results in this case were also heterogeneous, with an I^2 statistic of 58.3%.

Subgroup analysis and meta-regression in moderate to severe inflammation, notable fibrosis, and cirrhosis

The proportion of individuals with moderate to severe inflammation, notable fibrosis, and cirrhosis across various subgroups analysis was presented in Fig. 5 and Supplementary Table 6. The proportions of moderate to severe inflammation in younger than 6 years group, 6–12 years group and 12–18 years group showed

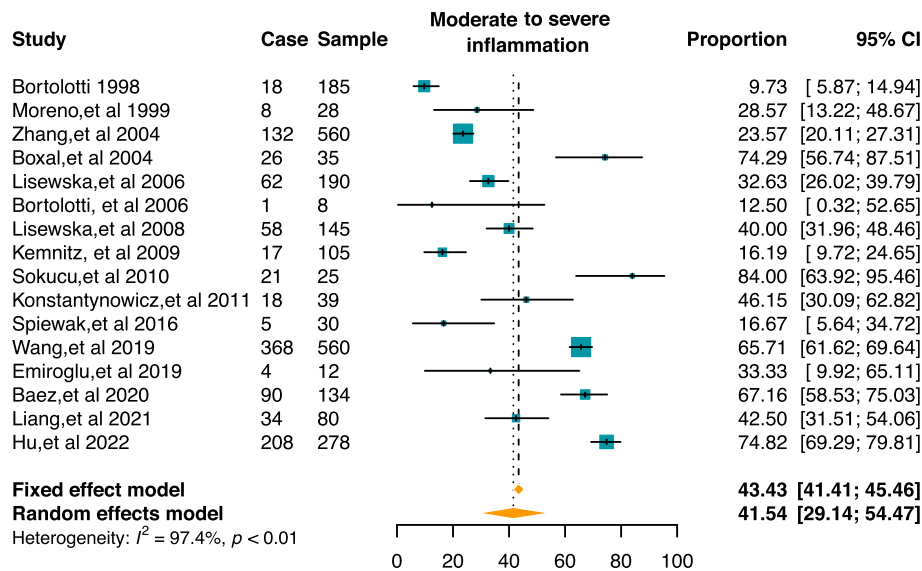


Fig. 2 Proportion of moderate to severe inflammation in CHB children

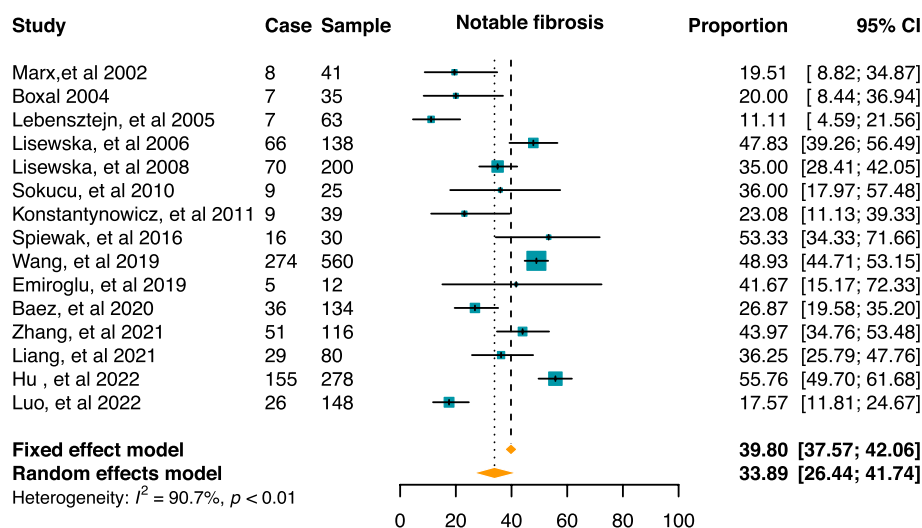


Fig. 3 Proportion of notable fibrosis in CHB children

statistically significant [36.21% (95%CI: 5.29%–85.22%) vs 53.72% (95% CI: 40.75%–66.20%) vs 31.40% (95%CI: 17.52%–49.66%), $p < 0.01$] respectively. While in the sensitivity analysis, age showed no significant difference ($p = 0.51$). At ALT level, ALT ≥ 80 U/L group have a higher proportion than ALT < 80 U/L group [57.78% (95%CI: 42.61%–71.62%) vs 29.73% (95%CI: 15.35%–49.69%), $p < 0.01$]. While in the sensitivity analysis, ALT showed no significant difference ($p = 0.49$). Furthermore, the proportion of moderate to severe inflammation was higher in Asia at 51.68% (95% CI: 30.97–71.83) compared to Europe at 33.43% (95% CI: 20.19–49.91), with a p value than 0.01.

Not completely identical, the proportion of the notable fibrosis in younger than 6 years group, 6–12 years group

and 12–18 years group showed no significant difference [51.66% (95%CI:46.89–56.38) vs 26.56% (95%CI:16.23–39.55) vs 36.72% (95%CI:18.40–59.79), $p = 0.35$]. Also in the sensitivity analysis, age showed no significant difference ($p = 0.40$). ALT ≥ 80 U/L group have a slightly higher proportion than ALT < 80 U/L group [42.10% (95%CI: 31.24%–53.77%) vs 34.97% (95%CI: 15.53%–61.14%), $p = 0.13$].

Regarding the proportion of cirrhosis, there were no statistically significant differences between Asia and Europe. Only in younger than 6 years group, 6–12 years group and 12–18 years group showed significant difference [2.79% (95% CI: 1.17%–6.42%) vs 1.62% (95% CI: 0.86%–3.30%) vs 2.50% (95% CI: 0.62%–9.45%), $p < 0.01$]

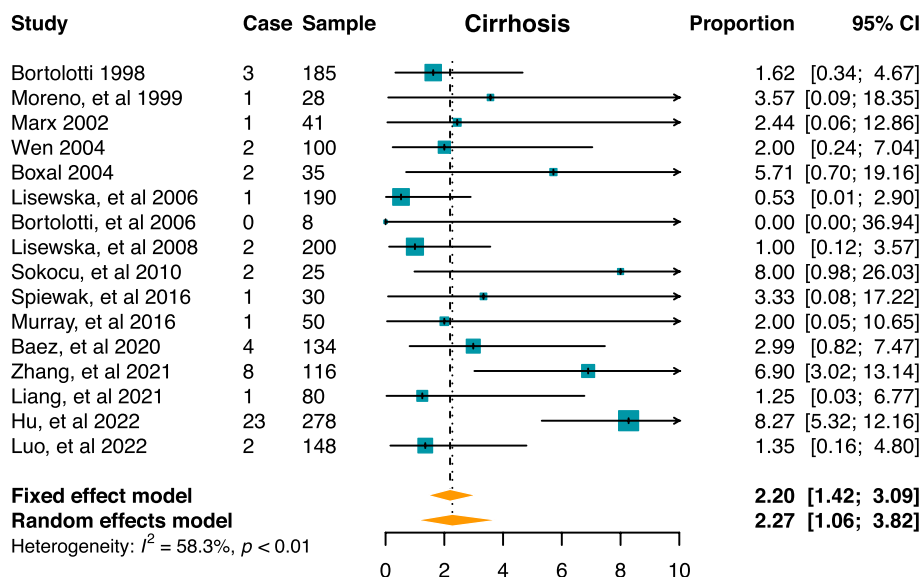


Fig. 4 Proportion of cirrhosis in CHB children

respectively. While in the sensitivity analysis, age showed no significant difference ($p = 0.84$).

Studies quality assessment

Sixteen retrospective cohort studies and four prospective cohort studies were evaluated by using the NOS system, respectively. Two cross-sectional studies were evaluated by using the AHRQ system. The scores assigned to each study using the NOS are detailed in Supplementary Table 3. There were no studies of low quality. Likewise, the scores assigned to each study using the AHRQ are detailed in Supplementary Table 4, and all studies showed high quality.

Publication bias

An assessment of publication bias was conducted to ensure the robustness of our findings. Visual inspection of the funnel plot revealed a slight asymmetry, indicating potential publication bias in the included studies (Supplementary Fig. 1A-C). However, in the aspect of moderate to severe inflammation, this asymmetry was not statistically significant upon further analysis using Egger's regression test ($p = 0.79$) and Begg's rank correlation test ($p = 0.89$). With respect to notable fibrosis, this asymmetry was not statistically significant upon further analysis using Egger's regression test ($p = 0.06$) and Begg's rank correlation test ($p = 0.66$). Finally, for cirrhosis, this asymmetry was not statistically significant upon further analysis using Egger's regression test ($p = 0.66$) and Begg's rank correlation test ($p = 0.05$). The quantitative results of Egger's regression test and Begg's rank correlation test are detailed in Supplementary Table 7. Furthermore, the trim and fill method was also utilized to assess

publication bias, and the results revealed no significant differences (Supplementary 1D-F).

Sensitivity analysis

To further assess the robustness of our findings, a sensitivity analysis was performed for moderate to severe inflammation, notable fibrosis, and cirrhosis. After excluding each study, we reran the meta-analysis and found that the pooled effect estimate remained largely unchanged, suggesting that any individual study did not overly influence our original findings. The specific results were presented by using forest plots (Supplementary Fig. 2A-C).

Discussion

Children's immune systems were not fully developed, making them prone to immune tolerance to HBV, thus complicating the pathogenesis of pediatric hepatitis B. Wang et al. [43], found that over 70% of grey zone CHB patients exhibited significant histological evidence of disease. In another study, Zhang et al. [22] reported that in untreated adults with CHB who have normal ALT levels, the proportion of those with moderate to severe inflammation was 35% (95% CI: 27–43). However, there is no currently evidence-based medicine evidence on the histological changes of the liver in CHB children. Through a comprehensive effort, our study is the first to report a significant proportion of liver lesions in untreated CHB children. The outcomes of our comprehensive meta-analysis reveal that notable histological alterations are not uncommon in CHB children who have not undergone treatment. Specifically, approximately 40% of these children exhibit moderate to severe inflammation or notable fibrosis, while the proportion of cirrhosis stands

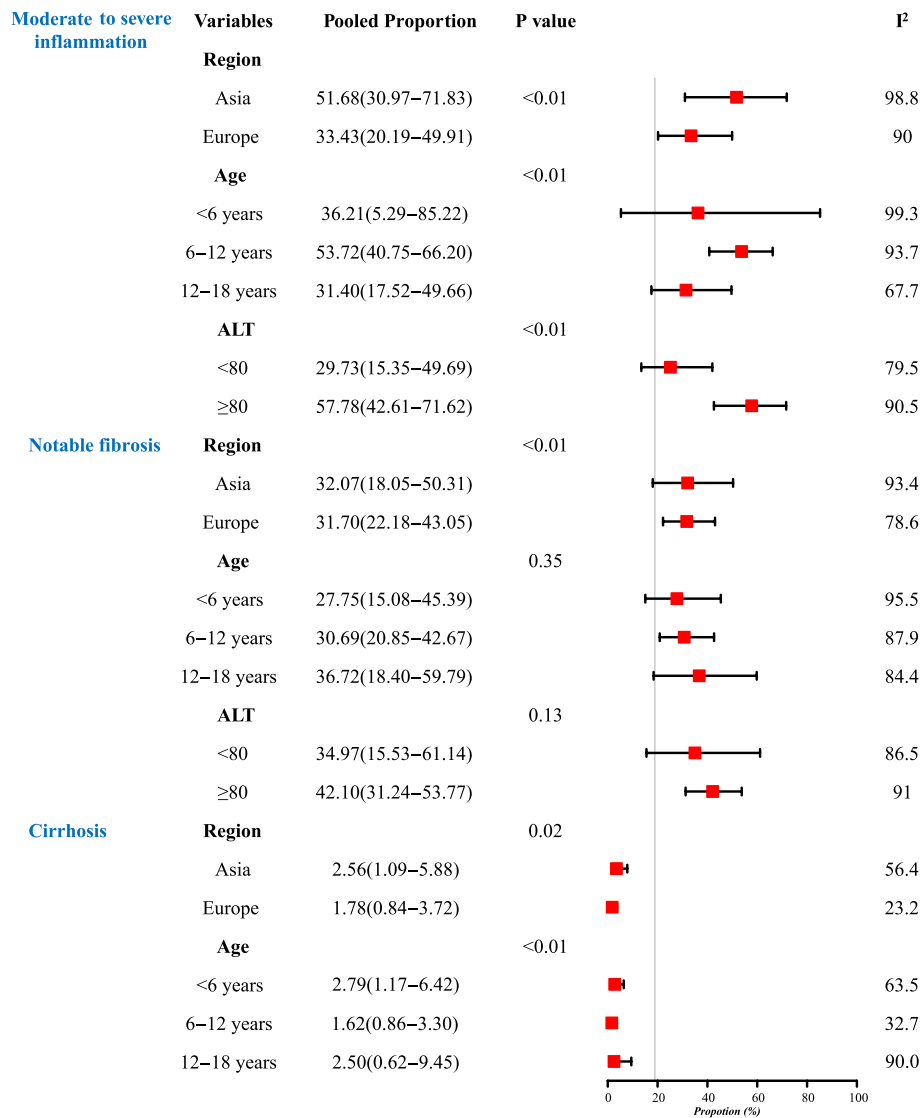


Fig. 5 Summary of the proportion of significant liver lesions different subgroups

at approximately 2%. Previous guidelines and expert [23, 24] have maintained that HBV infection in children is associated with no significant symptoms, causes minimal liver histological damage, and has a low risk of liver disease progression. Our results indicate that a considerable proportion 41.54% (95%CI: 29.14–54.47) of CHB children have significant moderate to severe inflammation. Furthermore, our results show that 33.89% (95%CI: 26.44–41.74) of CHB children have already progressed to notable fibrosis. Our findings indicate a notable prevalence of moderate to severe liver inflammation, notable fibrosis, and cirrhosis in this pediatric population, emphasizing the need for early intervention and continuous monitoring. When comparing our findings with adult CHB populations, several key differences emerge. Adults often develop severe liver disease, including cirrhosis and hepatocellular carcinoma, after decades of

chronic infection. In contrast, our data suggest that significant liver damage can occur much earlier in children, possibly due to their prolonged immune tolerance phase, where the immune system fails to effectively clear the virus, leading to chronic inflammation and fibrosis.

In subgroup analysis, our study revealed that among the cases of moderate to severe inflammation in the proportion of different age groups (6 years group, 6–12 years group and 12–18 years group), the proportion in the 6–12 years group was the highest [53.72% (95%CI: 40.75–66.20)], which suggests the necessity of initiating antiviral treatment at an early age in young children to mitigate the occurrence of significant liver inflammation. Moreover, researches [25, 26] showed that age is a key factor in the cure rate of children with chronic hepatitis B, and the younger the age, the better the antiviral treatment effect may be. Jiang et al. [27] found through the

construction of a nomogram model that ALT is an independent prognostic factor for predicting significant liver inflammation changes in adult patients with CHB. One respective cohort [9] reported that ALT levels exceeding 80 U/l may serve as a robust indicator of the extent of hepatic inflammation. Another large prospective cohort [23] study also revealed a moderate correlation between ALT and hepatic inflammation. Along these lines, our results further preliminarily indicate that the higher the ALT level is, the higher the proportion of significant liver inflammation is, and the proportion was relatively high in ALT \geq 80U/L group [57.78% (95%CI: 42.61–71.62)]. Unfortunately, unlike liver fibrosis, which can be predicted through non-invasive diagnostic methods, such as Aspartate aminotransferase to platelet ratio index (APRI), Fibrosis index based on the 4 factors (FIB-4) index and liver stiffness measurement [44], changes in the degree of liver inflammation can only be confirmed through pathological biopsy. In addition, the Expert Consensus on Hepatitis B Prevention and Treatment for Children in China [5] also proposes, that even for children with chronic HBV infection who have normal ALT levels (\leq ULN), liver histopathological evaluation may be considered, especially in children over seven years old. There is thus an urgent need to develop a non-invasive diagnostic prediction model for moderate to severe inflammation in CHB children.

Similar to the case of moderate to severe inflammation in liver, notable fibrosis exhibits significant differences across different regions. Some experts [45] believe that most CHB children have mild conditions, but a few children may develop fibrosis. Interestingly, the proportion of notable fibrosis in CHB children exceeds 30%. Across different age groups, the proportion of notable fibrosis is also around 30%. While there is an increase in the proportion of fibrosis with age, there is no significant difference among the various age groups. It is possible that the changes in liver fibrosis in CHB children are more gradual compared to the changes in the degree of inflammation. In all cases, the diagnosis and treatment of liver fibrosis require patience, careful observation, and early and effective intervention measures. Chang Meihui [46] et al. found that the HBsAg level in childhood can predict the risk of progressive liver fibrosis in adulthood. If the HBsAg level can be effectively reduced during childhood, the risk of disease progression in adulthood can be significantly lowered. Moreover, Hu et al. [47] recently indicated that lamivudine has the potential to reverse fibrosis in CHB children. Lamivudine has shown good short-term efficacy in the treatment of chronic hepatitis B in children, especially in preschool-aged children. However, its long-term use faces certain challenges, primarily including the risk of resistance mutations. Therefore, when using lamivudine in clinical practice, careful

consideration must be given to balancing its efficacy and potential risks [48]. Although methods such as transient elastography, platelet ratio index, and hyaluronic acid [49] have been used to predict the occurrence of liver fibrosis in children with chronic hepatitis B, their application scenarios are limited to small samples and single centers, and their reliability and practicability remain to be determined. Efforts should also be made to conduct more precise non-invasive screening for liver fibrosis among children, thus enabling early warning and monitoring of the occurrence of end-stage liver diseases, such as cirrhosis and even liver cancer.

Our meta-analysis revealed significant variations in the proportion of cirrhosis across various age subgroups. Specifically, among CHB children under 6 years old, the proportion of cirrhosis reached 2.79% (95%: 1.17–6.43), which is higher than that of CHB children aged 6 to 12 years old 1.62 (95%: 0.86–3.30). Zhu et al. [50] previously reported that the proportion of notable fibrosis and liver cirrhosis reached up to 10.9% among children aged 1–7 years with HBeAg-positive chronic hepatitis B. However, our previous study [51] on the disease burden of hepatitis B-related cirrhosis in children revealed that children under 5 years old have the lowest prevalence of cirrhosis among all children. This may be attributed to the fact that part of CHB children included in our study were hospitalized patients with a high proportion of elevated ALT levels, leading to a relatively higher proportion of cirrhosis. Children with hepatocellular carcinoma mostly have cirrhosis as the basis [52]. In this context, our findings support the early initiation of antiviral therapy in pediatric CHB patients, particularly those with elevated ALT levels and significant liver inflammation or fibrosis. The high prevalence of significant liver pathology observed in our study suggests that delaying treatment until adulthood may increase the risk of irreversible liver damage and reduce the effectiveness of later interventions. Guidelines and consensus [5, 6, 8] recommend that children with cirrhosis should be given antiviral treatment as soon as possible and monitored regularly.

Our study also has certain limitations. Firstly, there may be potential selection bias, as most children with chronic hepatitis B are hospitalized or outpatient patients. The proportion of potentially eligible pediatric patients with liver histological changes is high, but our included studies also comprised CHB children who have normal ALT levels. Secondly, although hepatitis B vaccination, HBV-DNA levels, HBV genotype, sex and other potential factors may be related to histological changes in the liver, due to the possibility of data availability in the literature, we were unable to extract data for subgroup analysis. Thirdly, due to the special nature of children, their willingness to undergo liver biopsy may not be as high as adults, which may result in a certain difference

between the actual proportion of significant liver inflammation and fibrosis and our research results. Fourthly, the age groups for inflammation and fibrosis categorization were based on the age of the children at the time of liver biopsy, rather than the age of HBV infection, while our analysis objectively reflects the relationship between the duration of chronic HBV infection and liver histological changes. Despite these limitations, our study provides valuable insights into the burden of significant histological changes in untreated pediatric CHB patients. The observed high rates of liver inflammation and fibrosis, even in the absence of clinical symptoms, suggest that current monitoring practices may need to be revised to incorporate more frequent and detailed assessments.

Conclusions

In conclusion, our meta-analysis highlights the significant burden of liver disease in children with CHB who have not received antiviral treatment. The findings support the need for early and aggressive monitoring strategies to identify those at risk of disease progression. Future research should focus on overcoming the data limitations identified in this study, enabling more precise and tailored management of pediatric CHB. Multicenter prospective studies with standardized methodologies and comprehensive data collection are crucial to further elucidate the natural history of CHB in children and optimize therapeutic approaches.

Abbreviations

| | |
|----------|--|
| CHB | Chronic Hepatitis B |
| HBV | Hepatitis B Virus |
| ALT | Alanine Aminotransferase |
| HBsAg | Hepatitis B Surface Antigen |
| AHRQ | Agency for Healthcare Research and Quality |
| NOS | Newcastle–Ottawa Scale |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| CI | Confidence Interval |
| TyG | Triglyceride–Glucose Index |
| eGDR | Estimated Glucose Disposal Rate |
| SDI | Socio-Demographic Index |
| I^2 | I-Square Statistic |
| HIA | Histological Activity Index |
| FIB-4 | Fibrosis Index Based on Four Factors |
| APRI | Aspartate Aminotransferase to Platelet Ratio Index |
| PROSPERO | International Prospective Register of Systematic Reviews |
| CI | Confidence Interval |

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-025-11876-5>.

Supplementary Material 1. Publication bias of this meta-analysis.

Supplementary Material 2. Sensitivity analysis of this meta-analysis.

Supplementary Material 3.

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None.

Authors' contributions

CYH was responsible for the conceptualisation, methodology, formal analysis and investigation. CYH, XG, JL, and YFP screened titles, abstracts, and full text. PYF, GX, QYJ and JLF assessed risk of bias. CYH prepared the first draft of the manuscript. MZ was responsible for the coordination of tasks. FSW and MZ accessed and verified all data. All authors had access to the data and accept responsibility to submit for publication.

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Data availability

The complete datasets are available upon request from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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