# Supplementary Table 8. MOOSE checklist

|  |  |
| --- | --- |
| **Criteria** | **Brief description of how the criteria were handled in the meta-analysis** |
| **Reporting of background should include** |
|  | Problem definition | In the treatment-naive CHB patients with normal ALT, there were still some patients with significant histological changes. The proportion of significant histological changes remains controversial. We aimed to analyze the proportion of significant inflammation or fibrosis and cirrhosis among these patients. |
|  | Hypothesis statement | Significant histologic changes are not rare in the treatment-naive CHB patients with persistent normal ALT. |
|  | Description of study outcomes | Proportion of significant histological changes |
|  | Type of exposure or intervention used | Treatment-naive CHB patients |
|  | Type of study designs used | Case-control studies, prospective cohort studies, and cross-sectional studies were included. Studies of reverse association were excluded. |
|  | Study population | Unrestricted |
| **Reporting of search strategy should include** |
|  | Qualifications of searchers | Credentials of the two investigators (CZ, ZW) are indicated in the author list. |
|  | Search strategy, including time period included in the synthesis and keywords | Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched from inception to January 10th, 2020.Keywords: “chronic hepatitis B”, “liver biopsy”, “alanine aminotransferase” |
|  | Databases and registries searched | Medline, Embase, and the Cochrane Central Registry of Controlled Trials |
|  | Search software used, name and version, including special features | We did not employ search software. EndNote was used to merge retrieved citations and eliminate duplications. |
|  | Use of hand searching | We hand-searched bibliographies of related papers. |
|  | List of citations located and those excluded, includingjustifications | Details of the literature search process are outlined in the flow chart. The citation list is available in Supplementary Table 2. |
|  | Method of addressing articles published in languages other than English | Language was limited to English. |
|  | Method of handling abstracts and unpublished studies | Not included in abstracts and unpublished studies |
|  | Description of any contact with authors | There is no contact with these authors |
| **Reporting of methods should include** |
|  | Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested | Detailed inclusion and exclusion criteria were described in the Methods section. |
|  | Rationale for the selection and coding of data | Extract demographic features, clinical data, pathological data, etc., from each study |
|  | Assessment of confounding | The included study must specify the liver pathology scoring system used. 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.) were excluded. In addition, the sensitivity of the included study was analyzed. |
|  | Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results | Funnel plot (and trim-and-fill analysis, which yields an effect adjusted for funnel plot asymmetry), and Begg’s test and Egger’s test to examine the potential publication bias. In addition, if two or more studies were published based on the same data, the article with the highest quality was included. |
|  | Assessment of heterogeneity | Considering the low incidence of interest events, double arcsine transformation was used to calculate the proportion of significant histological changes and cirrhosis. Q-statistics and Cochrane Q-test were used to assess heterogeneity between studies, where *p*<0.10 was regarded to be statistically significant. 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.Heterogeneity was expected, so all analyses were performed with a random-effects model. |
|  | Description of statistical methods in sufficient detail to be replicated | Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods. |
|  | Provision of appropriate tables and graphics | Fig. 1. Flowchart for study selection in the meta- analysis.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.Fig. 4. Summary of the proportion of significant fibrosis in different subgroups.Fig. 5. Summary of the proportion of cirrhosis in different subgroups.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). |
| **Reporting of results should include** |
|  | Graph summarizing individual study estimates and overall estimate | Fig. 2 |
|  | Table giving descriptive information for each studyincluded | Table 1 |
|  | Results of sensitivity testing | Supplementary Table 6 |
|  | Indication of statistical uncertainty of findings | 95% CIs were presented with all summary estimates, *I*2 values, and results of sensitivity analyses |
| **Reporting of discussion should include** |
|  | Quantitative assessment of bias | In the sixth paragraph of the discussion, this paper describes in detail the causes of heterogeneity. |
|  | Justification for exclusion | We excluded patients with other chronic liver diseases, because other chronic liver diseases usually make the liver disease worse. In addition, the combined tumor cases represent a special group of patients that need to be treated differently. In order to avoid misjudgment in clinical decision-making. |
|  | Assessment of quality of included studies | We discussed the results of the sensitivity analyses and potential reasons for the observed heterogeneity. |
| **Reporting of conclusions should include** |
|  | Consideration of alternative explanations for observed results | We discussed potential unmeasured confounding factors, such as patient selection bias and invasive liver biopsies. We also boldly speculate that the real significant histological changes of the liver may be higher than our statistics indicate. |
|  | Generalization of the conclusions | In summary, significant histologic changes are present in approximately one-third of treatment-naive CHB patients with normal ALT levels, and about 3% of the patients even progressed to cirrhosis. It is worth noting that the proportion of significant fibrosis and cirrhosis in patients over 40 years-old were more than twice as high as those in the younger patients. 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. |
|  | Guidelines for future research | The liver histological changes of treatment-naive CHB patients with normal ALT are not as optimistic as we thought. Special care needs to be taken when making decisions regarding these patients not needing anti-HBV treatment. |