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Accepted Manuscript Version

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Publisher: Cogent OA

Journal: Cogent Medicine

DOI: http://dx.doi.org/10.1080/2331205X.2019.1619896
The association of serum markers of fibrosis and development of liver cirrhosis in chronic hepatitis B patients: a systematic review and meta-analysis

Yongdi Chen, MPH 1, Gaofeng Cai, MSc 1, Chu Zhang 2, Jun Yao 1, Zhengting Wang, MSc 1, Zhifang Wang, Ph.D 1, Chonggao Hu, MSc 1,*, Huakun Lv, MSc 1,3,*, Li Li, MPA 1,*, and Biao Zhou, Ph.D 1,*

1 Zhejiang Provincial Center for Disease Control and Prevention, 3399 Binsheng Road, Hangzhou 310051, China; ydchen@cdc.zj.cn (Y.C); gfcai@cdc.zj.cn (G.C.); jyao@cdc.zj.cn (J.Y.); ztwang@cdc.zj.cn (Zhe.W.); zfwang@cdc.zj.cn (Zhi.W.)
2 College of Humanities and Management, Zhejiang Chinese Medical University, Hangzhou 310051, China; ZCC352520978@163.com (C.Z.)
3 Zhejiang provincial key laboratory of infectious disease vaccine and prevention and control, 3399 Binsheng Road, Hangzhou 310051, China
*Corresponding authors: chghu@cdc.zj.cn (C.H.), phone:+86-571-8711-5104; hklv@cdc.zj.cn (H.L.), phone:+86-571-8711-5133; lli@cdc.zj.cn (L.L.), phone: +86-571-8711-5121; bzhou@cdc.zj.cn (B.Z.), phone:+86-571-8711-5099.

**Subheadings:** The correlation between fibrosis and liver cirrhosis: a meta-analysis.
Abstract

Liver fibrosis is reversible by immune treatments in the early stages of cirrhosis development, but not in later stages. At present, the value of the markers for indicating an increased risk of cirrhosis is controversial, and thus we executed this meta-analysis.

Retrospective and longitudinal studies of chronic hepatitis B patients were retrieved from PubMed, Elsevier, Springer, Wiley, OVID, and EBSCO. Mean differences with 95% confidence intervals of four fibrosis markers were calculated using Review Manager 5.1.

Twenty-one studies that included 732 cases and 1025 controls were analyzed. The pooled mean differences of the serum markers with 95% confidence interval were hyaluronic acid 229.95 (173.94–285.96) ng/mL, laminin 78.73 (45.86–111.60) ng/mL, type III precollagen 69.10 (49.55–88.65) ng/mL, and type IV collagen 97.12 (62.32–131.92) ng/mL.

Elevated serum hyaluronic acid, laminin, type III precollagen and type IV collagen increased the risk of liver cirrhosis development in chronic hepatitis B patients.

Keywords: hepatitis B; liver cirrhosis; fibrosis; risk factor; meta-analysis
Introduction
Hepatitis B virus (HBV) infection is a public health challenge. About 360 million people are chronically infected with HBV worldwide, including up to 30 million living in China \[1, 2\]. The long-term consequences of HBV infection include the evolution of liver fibrosis (LF) and liver cirrhosis (LC). The 1-year cumulative incidence of LC in chronic HBV infection is estimated to be 2.1%–6% \[3\]. LC is a serious condition. Five-year survival with compensated LC is 80%–86%, but it is only 14%–30% with decompensated LC. The 1-year cumulative incidence of decompensation has been estimated as 10% \[4-6\]. The previous research has revealed that fibrosis is reversible in the early stages of cirrhosis development, but not in later stages \[7\].

In general, fibrosis can be improved by cytokine regulating and controlling immune responses, and this improvement can be performed by changing the serum cytokine levels, for instance, TGF-β, IL-6 and IL-17 \[8, 9\]. At present, treatments are available for changing serum cytokine levels. Moreover, Cai’s study also showed that, in CHB patients, changed of serum levels for TGF-β, IL-6, IL-10 and IL-17 could change degree of liver fibrosis and risk of LC development \[10\].

In a general way, serum hyaluronic acid (HA), laminin (LN), type III precollagen (PC III) and type IV collagen (C IV) are taked as revaluating the value of serum fibrotic markers in clinical practice and reflecting the presence and extent of fibrosis \[11,12\]. As these four serological indicators can be assayed at local hospitals, studies that evaluated their use were evaluated for inclusion in this meta-analysis. Many previous studies have evaluated the effectiveness of these indicators as markers of the development of LF and LC, for instance, the studies for HA, LN, PC III and C IV \[13-24\], the studies for HA, PC III and C IV \[25-28\], the studies for HA, LN and C IV \[29, 30\], and the studies for HA, LN and PC III \[31-33\]. However, conclusions of their usefulness in identifying patients at increased risk of LC are not consistent. As the influence of random errors can be
reduced by conducting a meta-analysis, mean difference (MD) in the serum values and the 95% confidence interval (CI) for these four indicators were calculated to determine if they are effective as markers of the development of LC in patients with chronic HBV infection.

**Materials & Methods**

*Search strategy*

Articles were retrieved from the Chinese Medical Journal Database, PubMed, Elsevier, Springer, Wiley, OVID, and EBSCO by searching the titles and abstracts of articles published between 2006 and 2016 for the key words “fibrosis”, “liver cirrhosis”, and “hepatitis B”. The analysis was conducted following the PRISMA meta-analysis guidelines [34].

*Data extraction*

two independent reviewers assessed the retrieved articles using a standard data extraction form designed by the study investigators, being total number of cases, mean and standard deviation in case group, and total number, mean and standard deviation in control group. The unit of measurement for the studied variables is "ng/mL" or can be converted to "ng/mL". The normal critical value of four serum fibrosis markers for healthy people are HA<84 ng/mL, LN<133 ng/mL, PC III<120 ng/mL and C IV<84 ng/mL.

Discrepancies in reviewer decisions on which articles should be included were resolved by discussion. The standards for final evaluation should be following inclusion and exclusion criteria: retrospective or longitudinal studies of consecutive patient series published in English or Chinese were eligible for inclusion. Studies were excluded if they reported outcomes of patients with hepatitis viruses other than HBV as the etiological agent, or did not report usable values of serum markers of fibrosis. Duplicate published reports of the same study were excluded.
Sensitivity Analysis
We omitted the studies with wide interval of 95%CI for MD values in subgroup analysis, and pooled and gained the pooled MD\textsubscript{CI} with 95%CI for LN, PC III, C IV and HA, and compared the pooled MD\textsubscript{CI} with the pooled MD, respectively. And then, we omitted the studies with maximum value of weight in subgroup analysis, and pooled and gained the pooled MD\textsubscript{weight} with 95%CI for LN, PC III, C IV and HA, and compared the pooled MD\textsubscript{weight} with the pooled MD, respectively.

Statistical analysis
MD and 95% CI were the primary outcomes of efficacy. Fixed- or random-effect models were used to perform the meta-analysis. Q and I\textsuperscript{2} statistics were used to assess study heterogeneity. If P was > 0.1, then a fixed effects model was used, and if it was ≤ 0.1 a random-effects model was used. Statistical analysis was performed using Review Manager 5.0 software (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes.htm). The MDs were not pooled if there were fewer than five evaluable differences in the values of a serum fibrosis marker.

Results

Literature search
A flow chart of the study selection process is shown in Fig. 1. A total of 21 study reports were included in the meta-analysis.

Study characteristics
The 21 studies included 732 cases and 1025 controls. The MD and their 95% CI for serum fibrosis markers are shown in Figs 2 and 3. The study characteristics, region, study type, numbers of case and control participants, serum fibrosis markers, sample size, male/female ratio, and mean participant age (years) are
shown in Table 1.

Fig. 1 A flow chart of the study selection process

Fig. 2 The pooled MD results for serum HA and LN
Fig. 3 The pooled MD results for serum PC III and C IV

Table 1. Characteristics of the studies.

<table>
<thead>
<tr>
<th>Study region</th>
<th>Study type</th>
<th>Participants category(case/control)</th>
<th>Serum fibrosis markers</th>
<th>Sample size (n)</th>
<th>Male/female</th>
<th>Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gansu, Lanzhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>25, 28</td>
<td>36/17</td>
<td>42±12</td>
</tr>
<tr>
<td>Zhejiang, Hangzhou</td>
<td>Retrospective study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>43, 29</td>
<td>33/10, 23/6</td>
<td>48.0±6.9, 44.5±7.8</td>
</tr>
<tr>
<td>Xinjiang, Wulumuqi</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>90, 60</td>
<td>63/27, 38/22</td>
<td>47.3±9.2, 30.9±9.5</td>
</tr>
<tr>
<td>Zhejiang, Linhai</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>56, 65</td>
<td>50/6, 50/15</td>
<td>30-77, 18-68</td>
</tr>
<tr>
<td>Jiangxi, Nanchang</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>61, 115</td>
<td>53/8, 102/1</td>
<td>17-62</td>
</tr>
<tr>
<td>Shandong, Weifang</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>134, 143</td>
<td>187/9, 0</td>
<td>48.21±15.2</td>
</tr>
<tr>
<td>No.</td>
<td>Region</td>
<td>Study Type</td>
<td>Disease Description</td>
<td>HA, LN, PC III, C IV</td>
<td>Count</td>
<td>Range (min, max)</td>
</tr>
<tr>
<td>-----</td>
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</tr>
<tr>
<td>19</td>
<td>Guangdong, Longchuan</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>17, 48</td>
<td>38/27, 48.3±6.8</td>
</tr>
<tr>
<td>20</td>
<td>China, Shanghai</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>30, 40</td>
<td>18/12, 23/17, 34±12.22</td>
</tr>
<tr>
<td>21</td>
<td>China, Guangzhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>42, 112</td>
<td>106/4, 21-68</td>
</tr>
<tr>
<td>22</td>
<td>Fujian, Nanping</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>17, 54</td>
<td>51/20, 45±12</td>
</tr>
<tr>
<td>23</td>
<td>Hubei, Xianning</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>38, 144</td>
<td>102/8, 26.4±7.2</td>
</tr>
<tr>
<td>24</td>
<td>Ningxia, Yinchuan</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III, C IV</td>
<td>24, 49</td>
<td>55/18, 36.96±12.2</td>
</tr>
<tr>
<td>25</td>
<td>Fujian, Fuzhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, PC III, C IV</td>
<td>19, 35</td>
<td>57/17, 45.1±11.2</td>
</tr>
<tr>
<td>26</td>
<td>Jilin, Changchun</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, PC III, C IV</td>
<td>25, 93</td>
<td>22/3, 78/15, 51±10, 39±11</td>
</tr>
<tr>
<td>27</td>
<td>Shandong, Jinan</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, PC III, C IV</td>
<td>20, 55</td>
<td>14/6, 41/14, 45.8±15.0, 39.8±13.4</td>
</tr>
<tr>
<td>28</td>
<td>Guangdong, Yangjiang</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, PC III, C IV</td>
<td>31, 91</td>
<td>83/39, 15-61</td>
</tr>
<tr>
<td>29</td>
<td>Zhejiang, Huzhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, C IV</td>
<td>41, 75</td>
<td>66/50, 39.8±12.5</td>
</tr>
<tr>
<td>30</td>
<td>China, Beijing</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, C IV</td>
<td>49, 108</td>
<td>37/12, 79/29, 42.1±16.2, 41.7±18.5</td>
</tr>
<tr>
<td>31</td>
<td>Hubei, Shiyan</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III</td>
<td>42, 63</td>
<td>27/15, 33/30, 39±3, 36±5</td>
</tr>
<tr>
<td>32</td>
<td>Henan, Zhengzhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III</td>
<td>38, 71</td>
<td>61/48, 18-69</td>
</tr>
<tr>
<td>33</td>
<td>Guangdong, Huizhou</td>
<td>Longitudinal study</td>
<td>LC with chronic HBV infection/CHB</td>
<td>HA, LN, PC III</td>
<td>50,100</td>
<td>37/13, 70/30, 43.1±17.2, 42.7±19.5</td>
</tr>
</tbody>
</table>
Effectiveness of serum fibrosis markers for predicting the development of LC

The four serum fibrosis markers that were evaluated included HA (21 studies, 1757 research objects), LN (18 studies, 1489 research objects), PC III (18 studies, 1499 research objects) and C IV (17 studies, 1397 research objects). The pooled MDs and 95% CI were HA 229.95 (173.94–285.96) ng/mL, LN 78.73 (45.86–111.60) ng/mL, PC III 69.10 (49.55–88.65) ng/mL, and C IV 97.12 (62.32–131.92) ng/mL.

The study heterogeneity evaluation found significant variation of the study-specific MDs for all four serum markers (all p < 0.10). Consequently, the MDs of the four markers were pooled with random-effect models. The pooled MD results for serum HA and LN and the development of LC in HBV patients are shown in Fig. 2, and the results for serum PC III and C IV are shown in Fig. 3.

Publication bias

A funnel plot of the articles included in the meta-analysis (Fig. 4) is symmetrical, with the axis of symmetry (MD = 0) to the right of center.

Sensitivity Analysis

Considering the reliability of pooled MD for LN, PC III, C IV and HA, we
omitted the studies with wide interval of 95%CI for MD values, the pooled MD_{CI} with 95%CI was as follows: the pooled MD_{CI} with 95%CI was 69.67[37.38,101.96] for LN after omitting Liu’s studies\textsuperscript{[15]}, and the pooled MD_{CI} with 95%CI was 64.84[45.16, 84.52] for PC III after omitted Zhang’s studies\textsuperscript{[24]}, and the pooled MD_{CI} with 95%CI was 97.20[62.11,132.30] for C IV after omitted Jiang’s studies\textsuperscript{[22]}, and the pooled MD_{CI} with 95%CI was 228.69[172.38, 285.00] for HA after omitted Jiang’s studies\textsuperscript{[22]}. These pooled MD_{CI} with 95%CI were very close to respective pooled MD with 95%CI. The subgroup characteristics of serum markers of fibrosis associated with LC in CHB patients after omitting the studies with wide interval of 95%CI for MD values in subgroup analysis were shown in Table 2.

We omitted the studies with maximum value of weight in subgroup analysis, the pooled MD_{weight} with 95%CI was 78.57[52.24,104.89] for LN after omitted 4 studies\textsuperscript{[16,17,19,28]}, and the pooled MD_{weight} with 95%CI was 86.62[43.56, 129.67] for 3 after omitted PC III studies\textsuperscript{[17,21,27]}, and the pooled MD_{weight} with 95%CI was 99.37[73.52, 125.22] for C IV after omitted 2 studies\textsuperscript{[17,27]}, and the pooled MD_{weight} with 95%CI was 272.02[166.59,377.45] for HA after omitted 7 studies\textsuperscript{[18,22,30,32]}. These pooled MD_{weight} with 95%CI were close to respective pooled MD with 95%CI. The subgroup characteristics of serum markers of fibrosis associated with LC in CHB patients after omitting the studies with maximum value of weight in subgroup analysis were shown in Table 2.
Table 2. The subgroup characteristics of serum markers of fibrosis associated with LC in CHB patients after omitting the studies with maximum value of weight and wide interval of 95%CI for MD values in subgroup analysis

<table>
<thead>
<tr>
<th>fibrosis markers</th>
<th>MD (95%CI)</th>
<th>MD(95%CI) after omitted reference</th>
<th>Omitted reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>omitting the studies with wide interval of 95%CI for MD values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subgroup analyses by LN</td>
<td>78.73 (45.86–111.60)</td>
<td>69.67(37.38-101.96)</td>
<td>15</td>
</tr>
<tr>
<td>subgroup analyses by PC III</td>
<td>69.10 (49.55–88.65)</td>
<td>64.84(45.16-84.52)</td>
<td>24</td>
</tr>
<tr>
<td>subgroup analyses by C IV</td>
<td>97.12 (62.32–131.92)</td>
<td>97.20(62.11-132.30)</td>
<td>22</td>
</tr>
<tr>
<td>subgroup analyses by HA</td>
<td>229.95 (173.94–285.96)</td>
<td>228.69(172.38-285.00)</td>
<td>22</td>
</tr>
<tr>
<td>omitting the studies with maximum value of weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>subgroup analyses by LN</td>
<td>78.73 (45.86–111.60)</td>
<td>78.57(52.24-104.89)</td>
<td>16,17,19,28</td>
</tr>
<tr>
<td>subgroup analyses by PC III</td>
<td>69.10 (49.55–88.65)</td>
<td>86.62(43.56-129.67)</td>
<td>17,21,27</td>
</tr>
<tr>
<td>subgroup analyses by C IV</td>
<td>97.12 (62.32–131.92)</td>
<td>99.37(73.52-125.22)</td>
<td>17,27</td>
</tr>
<tr>
<td>subgroup analyses by HA</td>
<td>229.95 (173.94–285.96)</td>
<td>272.02(166.59-377.45)</td>
<td>18-22,30,32</td>
</tr>
</tbody>
</table>
Discussion

The meta-analysis found that elevated serum HA, LN, PC III and C IV indicated an increased risk of developing LC. The result is consistent with the findings of a previous study by Liu et al\cite{15}, who reported increases group by group for serum HA, LN, PC III, and C IV in healthy controls group, mild hepatitis group, moderate hepatitis group, and LC groups. All four markers were significantly higher in LC than in the other groups \cite{15}. Therefore, in patients with chronic HBV infection, once serum value of any marker of HA, LN, PC III, and C IV are higher than cut off value of normal critical value of corresponding marker in healthy people, being HA>84 ng/mL, LN>133 ng/mL, PC III>120 ng/mL and C IV>84 ng/mL, these high-risk patients should be closely monitored to prevent the development of LC.

Fibrosis and inflammation of liver tissue are both involved in the pathogenesis of LC, and the findings of this meta-analysis are consistent with Du et al\cite{27}, who found that the serum levels of HA, LN, PC III and C IV were positively correlated with both fibrosis stage and liver inflammation grade. The demonstration by Zhou et al. that showed serum HA, LN, PC III and C IV were positively correlated with hepatic histopathological stage\cite{35}, adds to the evidence that elevations of serum levels might accompany disease progression, and that early treatment is indicated for chronic HBV infection with elevated serum HA, LN, PC III and C IV.

This meta-analysis also found by Sensitivity Analysis that, the studies with wide interval of 95%CI for MD values and the studies with maximum value of weight in subgroup analysis were omitted, the numerical size of pooled MD for LN, PC III, C IV and HA were similar to the numerical size of pooled MD before omitted in subgroup analysis respectively, and these showed that the pooled MD for LN, PC III, C IV and HA were reliable and stable.
The study limitations included the eligibility of only articles published in English or Chinese, and the heterogeneity of the included studies. Even though the MDs of the four markers were pooled using a random-effects method, study heterogeneity may have influenced the findings.

**Conclusions**

Elevated serum HA, LN, PC III and C IV in patients with chronic HBV infection increased the risk of developing LC. High-risk patients should be closely monitored and receive early treatment to prevent the development of LC.

**Authors’ contributions**


**Acknowledgments**

We thanked Yanhong Yu, Mengxin Xu and Qiaolu Hon for checking the data in Hangzhou Normal University.

**Funding**

This work was supported by National Natural Science Foundation of China (grant numbers No. 31500751, 2015) and Ministry of Science and Technology supporting the National Scientific and Technological Major Project of China (grant numbers No. 2017ZX10105001–002, 2017).

**List of abbreviations**

The following abbreviations are used in this manuscript:

- HA  hyaluronic acid
- LC  liver cirrhosis
- LN  laminin
- LF  liver fibrosis
PC III type precollagen
C IV type collagen
CI confidence intervals
CHB chronic hepatitis B
HBV hepatitis B virus
MD mean difference
CMJD Chinese Medical Journal Database

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Public Interest Statement

The study focused on 30 million of chronic hepatitis B patients, and our study demonstrated that, in chronic hepatitis B (CHB) patients, elevated serum hyaluronic acid (HA), laminin (LN), type III precollagen (PCⅢ) and type IV collagen (CⅣ) increased the risk of liver cirrhosis development. At present, these serum indicators can be tested routinely by grassroots health institutions and can be reduced by therapy. In fact, fibrosis is reversible in the early stages of cirrhosis development, thus timely therapy can control the progress of liver cirrhosis. The clinical medicine and potential public health significance is great.

Author Statement

We are engaged in the research on the prevention and control of infectious diseases, especially the research on the prevention and control of viral hepatitis. This study will be the basis of the research on the prevention and control of viral hepatitis in the next stage.