Use of serum Golgi protein 73 for screening chronic hepatitis B virus infection patients needing antiviral therapy in the community

Jinwei Duan[1], Xiajie Wen[2], Huai Wang[3], Weixin Chen[3], Pei Gao[3], Qianli Yuan[3], Han Zheng[2], Yanna Liu[2], Jiang Wu[3], Jie Wang[2], Mingjie Yao[4], Fengmin Lu[1,2]

[1]Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan 450001, China;
[2]Department of Microbiology and Infectious Disease Center, School of Basic Medical Science, Peking University Health Science Center, Beijing 100191, China;
[3]Department of Immunization, Beijing Centers for Disease Prevention and Control, Beijing Centers for Disease Preventive Medical Research, Beijing 100013, China;
[4]Department of Anatomy and Embryology, School of Basic Medical Sciences, Peking University Health Science Center, Beijing 100191, China.

Chronic hepatitis B virus (HBV) infection is a major global public health problem. Approximately 887,000 people die of HBV infection-related diseases annually, with cirrhosis and hepatocellular carcinoma (HCC) being the principal causes of mortality.[1] Timely antiviral therapy greatly reduces the risks of cirrhosis and HCC. However, unfortunately, of those patients who are eligible for antiviral treatment, only 25% of patients in clinic settings and 12% of those in community settings obtain timely antiviral therapy.[2] Therefore, reliable means of identifying patients with chronic HBV infection that require antiviral therapy are necessary, particularly for use in the community.

Liver biopsy has long been considered the gold-standard method for evaluating liver inflammation and fibrosis, but its routine use for diagnosis and community surveillance is limited because of its invasiveness. Golgi protein 73 (GP73) is a type II transmembrane protein that is located in the Golgi membrane and is recognized and cleaved by proprotein convertases, releasing it into the circulation.[3] Previous clinical studies had shown that serum GP73 concentration is high in patients with obvious liver lesions, including inflammation, fibrosis, and cirrhosis, which suggests that serum GP73 may represent a useful biomarker for the assessment of liver injury.[4] However, it is unclear whether the measurement of serum GP73 concentration would be an effective means of identifying patients with chronic HBV infection in the community who require antiviral therapy. Therefore, in the present study, we aimed to evaluate the use of serum GP73 for the identification of chronic HBV infection requiring antiviral therapy in a community setting.

We performed a cross-sectional study of serum Hepatitis B surface antigen (HBsAg) positive community-dwelling patients who had accepted the health examination from July 2017 to September 2019 in the Beijing Center for Disease Prevention and Control (Beijing, China). The inclusion criteria were as follows: (1) age ≥18 years; (2) HBsAg-positivity (HBsAg ≥0.05 IU/mL) for ≥6 months; (3) availability of blood samples. The exclusion criteria were as follows: (1) history of hepatitis virus infection other than HBV; (2) history of antiviral treatment during the preceding 6 months; (3) pregnancy or other non-viral liver diseases, such as alcohol-related, autoimmune, or drug-induced liver disease. The study was conducted in accordance with the *Declaration of Helsinki* and its amendments and was approved by the Biomedical Ethics Committee of Peking University (No. IRB00001052-19081). Written informed consent was obtained from all the participants.

At present, the latest Chinese guidelines for the prevention and treatment of chronic hepatitis B (CHB) state that the decision to start antiviral therapy should depend on a comprehensive analysis of serum HBV deoxyribonucleic acid (DNA) levels, alanine aminotransferase (ALT) levels, the severity of liver disease, as well as their age, family history, and concomitant diseases.[5] Therefore, the indications for antiviral therapy in this study include the following: (1) serum HBV DNA is positive, ALT levels are persistently abnormal (>upper limit of normal [ULN]), and other causes have been excluded; (2) HBV-related compensated cirrhosis patients with positive serum HBV DNA and HBV-related decompensated cirrhosis patients with positive HBsAg; (3) noninvasive tests or liver

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002051

Jinwei Duan and Xiajie Wen contributed equally to the work.

Correspondence to: Prof. Fengmin Lu, Department of Microbiology and Infectious Disease Center, School of Basic Medical Sciences, Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing 100191, China
E-Mail: lu.fengmin@hsc.pku.edu.cn

Chinese Medical Journal 2022;135(22)

Received: 04-01-2022; **Online:** 27-12-2022 **Edited by:** Peng Lyu and Peifang Wei

biopsy revealing obvious liver inflammation or fibrosis in those with persistently normal ALT levels and age >30 years old.[5] Liver fibrosis and cirrhosis were evaluated by liver stiffness measurement (LSM) using transient elastography. And the participants were allocated to three groups according to the expert consensus[6]: no/mild fibrosis, significant/advanced fibrosis, and cirrhosis [Supplementary Figure 1, http://links.lww.com/CM9/A979].

A total of 1529 patients with a mean age of 48.1 ± 13.13 years were included in this study, of whom 782 (51.1%) were men. The fibrosis/cirrhosis status of each patient was evaluated following the recommended diagnosis workflow,[6] which showed that 1246 patients had no/mild fibrosis, 205 patients had significant/advanced fibrosis, and 68 patients had cirrhosis. The remaining 10 individuals were not assessed for liver fibrosis due to ALT ≥200 U/L or total bilirubin (TBil) ≥51 μmol/L, but still required antiviral therapy. A total of 422 (27.6%) patients met the recommended criteria for antiviral therapy, with abnormal ALT (>ULN) and/or significant or severe fibrosis/cirrhosis.

To determine whether serum GP73 could reflect the severity of liver fibrosis, the concentrations in patients at different stages of fibrosis were compared. This showed that the serum GP73 levels of the non/mild fibrosis group were significantly lower than those of the significant/advanced fibrosis and cirrhosis groups (54.57 ng/mL *vs.* 67.79 ng/mL *vs.* 67.70 ng/mL, respectively; $P < 0.001$), implying that the measurement of serum GP73 may represent a means of identifying patients with significant/advanced fibrosis or cirrhosis. The potential utility of serum GP73 for the identification of patients with significant/advanced liver fibrosis and cirrhosis was further evaluated using receiver operating characteristic (ROC) analysis. The area under the ROC curve of serum GP73 for the identification of significant/advanced liver fibrosis and cirrhosis was 0.605 (95% confidence interval: 0.58–0.64, $P < 0.001$), and the sensitivity and specificity were 62.6% and 56.6%, respectively. There were no significant differences in the screening efficiencies of serum GP73 *vs.* the aspartate aminotransferase-to-platelet ratio index and fibrosis-4 index, two established non-invasive diagnostic indices of liver fibrosis ($P = 0.338$ and 0.925, respectively).

The findings of community screening were also consistent with serum GP73 concentration reflecting liver inflammation. The participants were allocated to three groups, using ALT levels of >40 U/L and >80 U/L as cutoff values, and the serum GP73 concentrations of each group were compared. The serum GP73 concentration increased significantly with increases in ALT levels (60.63 ng/mL *vs.* 78.46 ng/mL *vs.* 103.1 ng/mL, respectively; $P < 0.001$). Further correlation analysis also showed that serum GP73 positively correlated with ALT serum concentrations, albeit relatively weakly ($r = 0.275$, $P < 0.001$).

Serum GP73 could not only be used as a serum marker of significant fibrosis and cirrhosis but also for the evaluation of the severity of liver inflammation in patients with CHB. In this community-based study, we also evaluated the utility of serum GP73 for the screening of a population to identify patients who require antiviral therapy. The results showed that patients that needed antiviral therapy had significantly higher serum GP73 concentrations than those who did not (68.99 ng/mL *vs.* 53.17 ng/mL; $P < 0.001$). In addition, the ROC curve yielded a cut-off value of serum GP73 for the screening of patients for a requirement for antiviral therapy was 59.08 ng/mL, with a true-positive rate (TPR) and false-negative rate (FNR) of 62.8% and 37.2%, respectively. When ALT >40 U/L alone was used to screen such patients, the TPR and FNR were only 50.2% and 49.8%, and the screening efficacy slightly lower than that of serum GP73 (62.8% *vs.* 50.2%). When serum GP73 was combined with ALT for the screening of the patients, the TPR increased to 78.9%, the FNR decreased to 21.1%, and the patient detection rate was further improved [Table 1].

Table 1: Use of serum GP73 concentration, ALT activity, and a combination for the screening of patients with CHB for a requirement for antiviral therapy.

Indicators	Needing antiviral therapy, *n* (%)	
	Yes	No
Serum GP73 alone (+)	265 (62.8)	452 (40.8)
Serum GP73 alone (−)	157 (37.2)	655 (59.2)
ALT alone (+)	212 (50.2)	10 (0.9)
ALT alone (−)	210 (49.8)	1097 (99.1)
GP73 (+) and/or ALT (+)	333 (78.9)	458 (41.4)
GP73 (−) and ALT (−)	89 (21.1)	649 (58.6)
Total	422 (100)	1107 (100)

Serum GP73 (+): GP73 > 59.08 ng/mL; serum GP73 (−): GP73 ≤ 59.08 ng/mL; ALT (+): ALT > 40 U/L; ALT (−): ALT ≤ 40 U/L. ALT: Alanine aminotransferase; CHB: Chronic hepatitis B; GP73: Golgi protein 73.

Timely detection and the administration of antivirals are important ways of delaying the development of end-stage liver disease in and improving the quality of life of patients with CHB. In 2015, the World Health Organization produced its first set of guidelines regarding the prevention, care, and management of chronic HBV infection, in which it advocated the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment. The current mainstream guidelines for CHB state that HBV DNA and abnormal ALT levels should be used to evaluate liver injury and serve as the marker to start antiviral treatment. However, previous studies have shown that 13.8% to 47.5% of HBsAg-positive individuals have ongoing liver damage but normal ALT levels,[7] which implies that the conventional means of identifying patients that require antiviral therapy is inadequate. Thus, new non-invasive biomarkers of liver injury are still required to identify patients who need antiviral treatment.

Serum GP73 is an emerging serological marker in recent years, but its biological significance and clinical application value remain to be further investigated. In this community screening study, although limited by the availability of trials using LSM and ALT as criteria to identify patients requiring antiviral therapy, the results

confirm serum GP73 not only reflects the severity of liver injury but also identifies more patients in need of antiviral treatment than ALT. In particular, a combination of serum GP73 and ALT significantly improved the efficacy of screening, which should help clinicians identify more patients with CHB who require antiviral treatment, improve the antiviral treatment rate, and contribute to achieving the goal of eliminating HBV infection by 2030.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81902115), the National Key Research and Development Program of China (No. SQ2020YFF0426358), and the National S and T Major Project for Infectious Diseases (No. 2017ZX10201201).

Conflicts of interest

None.

References

1. WHO. Global Hepatitis Report. Geneva: World Health Organization; 2017.
2. Tan M, Bhadoria AS, Cui F, Tan A, Van Holten J, Easterbrook P, *et al*. Estimating the proportion of people with chronic hepatitis B virus infection eligible for hepatitis B antiviral treatment worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2021;6:106–119. doi: 10.1016/S2468-1253(20)30307-1.
3. Bachert C, Fimmel C, Linstedt AD. Endosomal trafficking and proprotein convertase cleavage of cis Golgi protein GP73 produces marker for hepatocellular carcinoma. Traffic 2007;8:1415–1423. doi: 10.1111/j.1600-0854.2007.00621.x.
4. Yao M, Wang L, You H, Wang J, Liao H, Yang D, *et al*. Serum GP73 combined AST and GGT reflects moderate to severe liver inflammation in chronic hepatitis B. Clin Chim Acta 2019;493:92–97. doi: 10.1016/j.cca.2019.02.019.
5. Wang G, Duan Z. Guidelines for prevention and treatment of chronic hepatitis B. J Clin Transl Hepatol 2021;9:769–791. doi: 10.14218/JCTH.2021.00209.
6. Chinese Society of Hepatology, Chinese Medical Association; Chinese Society of Infectious Diseases; Chinese Society of Gastroenterology; Chinese Medical Association. Consensus on the diagnosis and treatment of hepatic fibrosis (2019). J Dig Dis 2020;21:127–138. doi: 10.1111/1751-2980.12854.
7. Sarin SK, Kumar M. Should chronic HBV infected patients with normal ALT treated: debate. Hepatol Int 2008;2:179–184. doi: 10.1007/s12072-008-9065-2.

How to cite this article: Duan J, Wen X, Wang H, Chen W, Gao P, Yuan Q, Zheng H, Liu Y, Wu J, Wang J, Yao M, Lu F. Use of serum Golgi protein 73 for screening chronic hepatitis B virus infection patients needing antiviral therapy in the community. Chin Med J 2022;135:2741–2743. doi: 10.1097/CM9.0000000000002051