

Application of serum Golgi protein-73 in the management of chronic liver disease

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Chronic liver disease (CLD) causes approximately 2.14 million (2.06–2.30) deaths annually, and; therefore, represents a heavy global health burden.^[1] Currently, chronic hepatitis B (CHB), hepatitis C, alcohol-related liver disease, and non-alcoholic liver disease (NAFLD) account for 29%, 26%, 25%, and 9% of cirrhosis-related deaths worldwide, respectively.^[1] Although vaccination has resulted in reductions in the seroprevalence of hepatitis B surface antigen and the overall prevalence of liver-related mortality, CHB remains the principal cause of liver disease, especially in China.^[2] However, in recent years, the prevalence of NAFLD has increased dramatically, both in China and worldwide. Furthermore, the evaluation of hepatitis C virus (HCV) inflammation-associated liver fibrosis is important for the management and prognosis of CLD. Although liver biopsy can be used to simultaneously evaluate the inflammatory features and fibrosis score of patients, its invasiveness and the relatively high frequency of sampling errors hinder its repeated use in routine clinical practice. Circulating biomarkers are considered to be an attractive and affordable surrogate that reflect the severity of liver inflammation and fibrosis.

Golgi protein-73 (GP73), also known as Golgi membrane protein-1 (GOLM1) or Golgi phosphorylation protein-2, is a transmembrane glycoprotein that has a relative molecular weight of 73,000. The *GOLM1* gene, which encodes GP73, was first cloned by Kladney *et al*^[3] via differential screening of a cDNA library derived from the liver of a patient with adult giant-cell hepatitis, a rare form of hepatitis that has a presumed viral etiology. GP73 is mainly expressed in bile duct epithelial cells and is rarely expressed in hepatocytes in normal livers. Furthermore, serum GP73 concentration has been suggested to be useful

for the diagnosis of human hepatocellular carcinoma (HCC).^[4] However, in recent years, studies from our own group and others^[5,6] have indicated that the serum GP73 concentration in HCC patients is comparable to or even lower than that in CLD patients with cirrhosis. Indeed, high serum GP73 was found in HCC patients with a background of cirrhosis, but not in HCC patients without cirrhosis, and the serum GP73 concentration in cirrhotic HCC patients was comparable to that in compensated cirrhosis patients. This implies that serum GP73 is not a useful biomarker for the differentiation of HCC from cirrhosis.^[7] Consistent with this, immunohistochemical analysis revealed that, although GP73 protein is aberrantly expressed in tumor tissues, it is also highly expressed in dysplastic nodules in HCC patients with cirrhosis and is expressed at very low levels in the paracancerous liver tissue of HCC patients who do not have cirrhosis. Moreover, the serum GP73 concentration in HCC patients was found to be related to the number of GP73-positive cells and the staining intensity in paracancerous tissues, but not to these parameters in HCC tumor tissue.^[7] The serum GP73 concentration, in contrast to the steep decline in the serum alpha-fetoprotein concentration in HCC patients after tumor resection, remains largely unchanged following the curative resection of a tumor. Finally and most importantly, correlation analysis showed that serum GP73 concentration positively correlates with the severity of cirrhosis.^[7] Taken together, these results suggest that a high serum GP73 concentration in an HCC patient is likely to be associated with the presence of cirrhosis.

The correlation between the serum GP73 concentration and its protein expression in cirrhotic nodules, revealed by immunohistochemical staining of liver samples from HCC

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patients, prompted us to speculate that serum GP73 may be of diagnostic value for cirrhosis. Its diagnostic performance was first evaluated in a large, well-defined cohort of 3044 patients who had compensated cirrhosis ($n = 1247$), decompensated cirrhosis ($n = 841$), or pre-cirrhotic CLD ($n = 956$).^[5] The area under the curve of serum GP73 concentration for the diagnosis of compensated cirrhosis was 0.909 (95% confidence interval: 0.896–0.921, $P < 0.001$), which was superior to that of the aspartate aminotransferase-to-platelet ratio index and the fibrosis index based on four factors (FIB-4), and comparable to that of liver stiffness measurement (LSM). Furthermore, a receiver operating characteristic curve (ROC) analysis was performed for a previously reported clinical cohort in which all the patients had been diagnosed based on pathology, and the severity of fibrosis/cirrhosis had been scored. The result indicated that serum GP73 could legitimately be used as a serological indicator of the severity of liver fibrosis.^[5]

To further optimize the diagnostic potential of serum GP73 for cirrhosis, Cao *et al*^[6] assessed the use of this marker in parallel with LSM. They showed that the combination of serum GP73 concentration and LSM yielded a diagnostic accuracy that was better than those of the currently available approaches. Specifically, >60% of antiviral treatment-naïve CHB patients could be diagnosed as having significant liver fibrosis or not using this algorithm, thereby avoiding the necessity for liver biopsy. In addition, to improve the diagnostic performance of this approach for fibrosis/cirrhosis, we assessed the use of a combination of serum GP73 with the patient's age, platelet count (PLT), and alkaline phosphatase (ALP) activity in the GAPA model (Logit $P = 1/[1 + \exp(1.614 - 0.054 \times \text{GP73} - 0.045 \times \text{Age} + 0.030 \times \text{PLT} - 0.015 \times \text{ALP})]$), which was associated with much better diagnostic performance for cirrhosis in patients who had been diagnosed either on the basis of clinical or pathological findings.^[8] These findings confirm that GP73 has potential value for the diagnosis of fibrosis/cirrhosis and the monitoring of CLD progression.

Accumulating evidence demonstrates that serum GP73 concentration not only reflects the severity of cirrhosis but also provides information regarding inflammation in the livers of CLD patients with differing etiologies. It is well-known that hepatic inflammation is a major risk factor for fibrosis and that fibrosis is a critical stage in the progression of CLD. Indeed, all the major guidelines recommend the presence of moderate-to-severe inflammation and/or fibrosis as triggers for intervention. For example, the presence of histological lesions in the livers of patients with CHB is an important indication for the initiation of antiviral treatment.^[9] However, the availability of non-invasive serum biomarkers would represent a step forward in the identification of moderate liver injury, especially in CHB patients with normal serum ALT activity. In a previous study, we demonstrated that serum GP73 represents an auxiliary biomarker of moderate liver necroinflammation, especially in individuals with ALT activities of <40 U/L^[10]: 66.67% of patients who had a level of inflammation $\geq A2$ could be identified using serum GP73 concentration, with a negative predictive value of 85.3%. However, the complex mechanism that underlies

high serum GP73 concentration in CHB patients means that the simple use of GP73 as a biomarker of liver necroinflammation may lead to confusion, especially for patients with fibrosis but no active liver necroinflammation.

To minimize this confusion, a series of diagnostic models were explored in the study. Among these, the use of the hepatic inflammation model (HIM), which combined serum GP73, gamma-glutamyltransferase, and aspartate aminotransferase, was associated with a significantly higher diagnostic accuracy for liver necroinflammation (area under the ROC curve [AUROC]: 0.890) than that of any of the three serum biomarkers alone. More importantly, the HIM also exhibited excellent diagnostic value (AUROC: 0.873) for the identification of patients with at least moderate liver necroinflammation but with ALT activity <40 U/L. The diagnostic potential of this model has been confirmed in a treatment-naïve cohort with significant liver fibrosis ($n = 82$). Another study^[11] showed that by combining ALT and GP73, 77.4% to 78.9% of patients with at least moderate liver lesions ($G \geq 2$ and/or $S \geq 2$) can be identified. In addition, it has been shown that serum GP73 is a useful biomarker for the evaluation and monitoring of disease progression, including with regard to liver necroinflammation and fibrosis, in patients with chronic HCV infection, but that its value is limited for the diagnosis of advanced fibrosis and cirrhosis, compared to those of aspartate aminotransferase-platelet ratio index and FIB-4.^[12]

Unlike for patients with viral hepatitis, for whom many serum biomarkers are available for the diagnosis and evaluation of hepatic necroinflammation, there are few serum biomarkers of hepatic necroinflammation for patients with non-alcoholic steatohepatitis (NASH). We recently reported that the GP73 concentrations in both the serum and liver are higher in NASH patients with a high liver necroinflammation grade than in those with no or mild inflammation.^[13] Furthermore, the serum GP73 concentration strongly correlates with its protein expression in inflamed liver tissue, and both the serum and liver GP73 concentrations are closely related to the severity of liver necroinflammation.

Given that the presence of NASH is an important prognostic factor in patients with NAFLD, the use of serum GP73 for the diagnosis of hepatic necroinflammation could be of great clinical significance. In our previous study,^[13,14] the AUROC of serum GP73 (0.742) was superior to those of ALT (0.609) and AST (0.667) for the diagnosis of moderate inflammation ($G \geq 2$). Serum GP73 also exhibited excellent performance for the identification of severe inflammation ($G \geq 3$), with an AUROC of 0.891. Recently, Zheng *et al*^[14] showed that the G-NASH model (composed of GP73 and CK18-M30) performed better than the other established non-invasive scoring systems: using the proposed sequential, non-invasive approach, 82.9% of patients with NASH could be correctly identified.

The mechanisms responsible for the increase in GP73 expression by hepatocytes that occurs in parallel with liver

inflammation are largely unknown. However, previous studies have shown that GP73 expression can be induced by various cytokines, including interleukin (IL)-6, which is involved in liver necroinflammation. Study of a lipopolysaccharide-induced mouse^[10] liver injury model demonstrated that hepatic GP73 expression increased immediately after the increase in the expression of IL-6, and the increase in serum GP73 could be inhibited either by blocking the action of IL-6 using a neutralizing antibody or antagonizing the effects of IL-6 using the janus kinase-signal transducer and activator of transcription 3 (STAT) signaling pathway inhibitor ruxolitinib. Based on these findings,^[15] we developed a mechanical model to explain the increase of GP73 expression that occurs in liver inflammation. In this model, once liver inflammation occurs, the increase in IL-6 affects GP73 expression at transcriptional or post-transcriptional levels via the STAT3 signaling pathway. In addition, furin, the principal enzyme of the GP73 protein section, can also be upregulated by IL-6, which permits the high hepatic GP73 expression to be reflected in the serum.^[5]

In summary, the roles of GP73 and its regulation in physiological and pathological processes are still not completely clear. At present, research on GP73 mainly focuses on the diagnosis and prognosis of liver-related diseases. However, the potential clinical utility of serum GP73 for the prediction of temporal changes in liver disease should be explored in a prospective study. Furthermore, large, multi-center clinical studies are warranted to verify the clinical value of serum GP73 measurement.

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Conflicts of interest

None.

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