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The role of non-invasive biomarker M2BPGi in managing liver disease in Vietnamese patients

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Abstract

Chronic liver disease has a high global burden and death toll. Early diagnosis is important to halt disease progression to cirrhosis, hepatocellular carcinoma, and eventually death. At present, there are many methods used for liver disease assessment, such as liver biopsy, elastography, serum biomarkers, and surrogate markers. However, shortcomings of these methods include invasiveness, costly equipment, requirements for skilled technicians, long turnaround and waiting times, which limit their usefulness, particularly in developing countries in the world that lack resources and skilled technicians. Vietnam is a developing country with a high burden of hepatitis B and C, and liver disease-related mortality is expected to increase in 2025. A recent study in Vietnam found that the Mac-2 binding protein glycosylation isomer (M2BPGi) levels are correlated with elastography used for liver fibrosis staging. In this review, we examined the challenges and prevalence of liver disease in Vietnam. We also reviewed the literature on the use of M2BPGi in liver disease in other countries and discussed how this marker can be used to improve the detection and management of liver disease as well as the challenges and problems faced.

Keywords: Hepatitis B; Hepatitis C; Mac-2 binding protein glycosylation isomer; chronic liver disease; Vietnam

Introduction

Liver disease causes 2 million deaths globally, of which 1 million are due to cirrhosis and 1 million are due to viral hepatitis and hepatocellular carcinoma [1]. There is also an intricate link between viral hepatitis and liver disease. Of note, the global burden of liver cancer and cirrhosis has increased from 2012 to 2017 [2]. Chronic inflammation occurs during hepatitis B (HBV) and C (HCV) infections, resulting in liver damage and subsequently liver fibrosis to develop. This decrease hepatic function and may eventually progress to cirrhosis and hepatocellular carcinoma.

Early diagnosis and treatment can halt progression of chronic hepatitis to liver fibrosis, cirrhosis and hepatocellular carcinoma. With proper control, this allows patients' disease to be effectively managed. At present, pan-genotypic combinations of direct-acting antiviral drugs have shown high efficacy in the treatment of HCV caused by different genotypes and antiviral drugs are available to treat HBV [3,4]. These has demonstrated clear efficacy to drive better disease treatment strategies. More tools are needed to tackle initial liver disease assessments and for long term management of patients with hepatic fibrosis.

Liver disease assessment methods

Currently, there are many methods used for liver fibrosis screening, of which liver biopsy is considered the gold standard [5]. However, this is an invasive procedure and it is not feasible to carry out repeated biopsies, particularly in advanced stage patients (>F3) in which evaluation is required every 3-6 months. It is also difficult to gain approval in early stage patients as well, given these patients appear generally healthy without significant symptoms. Besides being invasive, liver biopsies are prone to sampling errors and inter- and intra-observer variability. These can cause errors in staging [6]. In rare but possible situations, liver biopsy can also result in life-threatening complications and causes pain in 40% of patients [7,8].

Besides liver biopsy, elastography methods such as transient elastography, magnetic resonance elastography, and ultrasound-based elastography are used to assess liver fibrosis stages. However, elastography has its limitations, such as unreliability in obese patients, patients with ascites, and requires high operator skills [9-13]. In magnetic resonance elastography, patients need to hold their breath and respiratory cooperation with the patient is required. Also, this method is not suitable for claustrophobic patients.

Serum biomarkers such as type III-procollagen-N-peptide, lincRNA-p21, hyaluronic acid (HA), platelet count, aspartate transaminase, gamma-glutamyltransferase, are used alone or as biomarker panels [14-16]. However, these markers have poor specificity to distinguish between early and intermediate stages of fibrosis. Some biomarkers may also be affected by other diseases, such as food intake causing an increase in HA [17]. Also, lincRNA-p21 level is not correlated with markers of viral replication, liver inflammation, and liver function and hence non-specific to the liver. These shortcomings limit their clinical application.

Current challenges and prevalence of liver disease in Vietnam

Vietnam has a high prevalence of HBV and HCV as seen in the hepatitis B surface antigen (HBsAg) rate of 8.8%-19.0% and high anti-HCV antibody rate of 1.0%-3.3% [18]. In central and southern Vietnam, cirrhosis was found in 30%-40% of chronic HBC and HCV patients and the incidence of hepatocellular carcinoma increased from 2010 to 2016 [19]. 31.2% and 19.2% of liver disease patients in Ho Chi Minh city are positive for HBV and HCV, respectively, showing that these viruses are important causative agents of liver disease in this city

[20]. It is estimated that HBV-related hepatocellular carcinoma and mortality will increase to 25,000 and 40,000, respectively in 2025 [21]. The prevalence of non-alcoholic fatty liver disease was found to be 73.3% in type 2 diabetics in Vietnam [22].

Currently, HBV prevention and control programs require more support to be adequately funded to tackle the disease [23]. It is also estimated that 65% and 18% of hepatocellular carcinoma cases are caused by HBV and HCV, respectively, in Southeast Asia. The healthcare burden is significant and early detection is the key to provide both qualities of life for patients and manage healthcare budgets. A review of HCV in Vietnam found that there is a paucity of data on the nature and burden of HCV in Vietnam [24]. There is also heavy alcohol consumption in men in Vietnam. These factors have caused liver cancer to be the leading cause of deaths due to cancer in Vietnam [25]. The 2018 global cancer statistics showed that Vietnam has the 4th highest incidence of hepatocellular carcinoma in the world, after Mongolia, Egypt, and Gambia [26]. Most hepatocellular carcinoma patients are diagnosed at advanced stages, resulting in expensive treatments and is a major economic problem for Vietnam.

Therefore, it is imperative to diagnose liver fibrosis at an early stage to prevent progression to cirrhosis and hepatocellular carcinoma. However, the shortcomings of the aforementioned liver assessment methods have hindered early screening and monitoring of liver disease in Vietnam and an inexpensive and patient compliant marker is urgently required.

Use of Mac-2 binding protein glycosylation isomer (M2BPGi) as a non-invasive biomarker for liver disease

In 2013, Mac-2 binding protein glycosylation isomer (M2BPGi) was first described by Kuno et al. as a non-invasive biomarker for fibrosis evaluation [27]. Serum M2BPGi levels are correlated with liver fibrosis stages and liver stiffness [28,29].

In our previous work, we studied M2BPGi levels in a Vietnamese population with mixed etiologies. In profiling patients, the biomarker measurements are statistically different between patients with F0-1, F2 and F>3 liver fibrosis [30]. M2BPBi levels were observed to be higher in patients with viral hepatitis infections than other etiologies. The changes in biomarker levels are a direct result of the presence of abnormal hepatic cells that offers a convenient marker to understand the extend of liver damage due to different etiologies of liver disease. Within HBV patients of differing viral load, M2BPGi levels were lower in HBV patients with a viral load <2000 IU/mL compared with those with a viral load >2000 IU/mL. This indicated a close correlation to viral load testing, has the potential to monitor treatment response and risk profiling in patients. We have demonstrated that M2BPBi levels are correlated with other serum markers and staging by transient elastography. The marker provides complementarity to existing testing methods and will significantly reduce the need for patients to undergo invasive biopsy procedures. Our previous results showed that M2BPGi can be a good marker of viral load levels in HBV, is correlated with liver disease staging, and provides understanding of etiology-specific trend of M2BPGi levels.

The marker has received widespread acceptance in various independent studies. Investigative work in China, South Korea, Japan, Taiwan and USA have demonstrated the usefulness of M2BPGi to manage patients better. These studies addressed similar considerations in developing and finding better tools for liver disease management [31-34]. In the reported work, M2BPGi was shown to be useful in health screening of the general population for liver disease, determination of liver fibrosis staging, and as a surrogate to determine responses to antiviral therapy. Majority of the studies focused on a specific etiology in the liver disease patient population, with the exception of one report [35]. Bulk of data are derived from the Asian population, having extensive testing on viral hepatitis related liver disease causes. In our current use, M2BPGi establishes a niche need for widespread testing of liver disease among the Vietnamese population using a straightforward blood test. This allows patients in distant provinces to receive early access to healthcare services to better manage the disease, where specialized instruments for liver assessment are not available.

Conclusion and outlook

We envision with better testing and treatment available for liver disease, this will benefit patients greatly. From this review, it can be seen that M2BPGi has significant value as a surrogate marker for liver fibrosis and cirrhosis. Operationally, this biomarker provides automated testing with rapid result turnaround time, reduces the need for skilled technicians to operate sophisticated instrumentation (in contrast to elastography) and wider coverage for liver disease detection using centralized laboratory testing by sending blood samples from distant locations. For the patients, specimen collection is non-invasive, reduce the need to travel to specialized clinics for initial assessments, procedures have less requirement for patient compliance as compared to magnetic resonance imaging or elastography that needs patients to hold their breath or lie in a certain direction allows and high correlation with other markers of liver fibrosis and cirrhosis.

However, as mentioned above, most studies were carried out in East Asian populations and there is a need to conduct more studies in different populations with mixed etiologies to determine the specific M2BPGi cutoff values for different liver fibrosis stages and etiologies. We are currently embarking on a comprehensive study to profile Vietnamese patients to derive these medical decision limits to integrate into our healthcare management of these patients.

The future perspectives for liver disease patients are positive and promising with the advent of these new tools and myriad treatment options. For unique assays such as M2BPGi, we believe this can be expanded to other developing countries where the burden of liver disease is high. With more patients getting access to testing, this can be employed in epidemiological studies on the prevalence of liver fibrosis and cirrhosis in Vietnam to obtain a clearer picture of the liver disease situation in Vietnam. This will aid healthcare officials to better plan resources to support the control and management of this disease. We believe having more testing is advantageous, especially to include in national control programs in order to reduce the incidence of hepatocellular carcinoma by treating liver fibrosis at early stages to slow or halt progression. Although Vietnam has a high prevalence of liver disease, we are poised to tackle the challenges with new tools and treatment options.

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