Commentary

Circulating microRNAs for early detection of hepatitis B-related hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is a major challenge for global health. Indeed, HCC represents the third leading and fastest rising cause of cancer death worldwide (1). About 90% of HCC cases can be associated with a well-characterized underlying risk factor including chronic hepatitis B, hepatitis C, ethanol consumption, aflatoxin exposure, non-alcoholic fatty liver disease, metabolic diseases like diabetes, and hereditary liver disease (1-3). Although the risk of developing HCC can be reduced in patients by treatment of the underlying cause, e.g., by viral clearance, strategies to prevent cancer development in patients with advanced fibrosis and established cirrhosis are still lacking (4). Furthermore, despite the recent improvements, treatment options for HCC remain largely unsatisfactory (5). Early diagnosis through surveillance of at-risk patients increases the chance of effective therapy. Clinical practice guidelines recommend periodic ultrasound-based surveillance of patients with cirrhosis (6). However, ultrasound detection of small liver tumors can be challenging and depends on the expertise of the operator. Therefore, several non-invasive biomarkers have been assessed for their utility in determining HCC risk and/or detecting HCC at early stages. Alpha-fetoprotein (AFP) is the most widely used diagnostic serum marker for HCC. However, since its diagnostic and predictive value is largely limited by the presence of AFP-negative HCC as well as the impact of the underlying liver disease (2,6), its use for HCC surveillance is currently not recommended by American and European guidelines. Thus there is an unmet need for novel serum biomarkers for HCC diagnosis capable of increasing the diagnostic and predictive power in surveillance programs.

Non-coding RNAs including microRNAs (miRNAs) provide a complex layer of the control of gene expression in virtually every biological process including development, immune response, aging and cell death (7). Accumulating evidence shows that altered regulation of miRNA expression contributes to disease pathogenesis including cancer (7,8). Moreover, miRNAs circulating in body fluids including blood have been suggested to hold promise as sensitive non-invasive biomarkers in clinical settings. However, only few clinical trials have been launched to validate the functional relevance of miRNAs as biomarkers (9). This paucity of clinical data also concerns the study of the involvement of miRNAs in HCC. Indeed, miRNA deregulation was indicated to contribute to the development of this disease by imparing key regulatory pathways in the tumor microenvironment (10). Additionally, circulating miRNAs were suggested as potential biomarkers useful for HCC diagnosis and prognosis (10,11). However, no previous study has evaluated whether circulating miRNAs could have a diagnostic performance in detecting early-stage HCC using prospectively collected HCC samples.

In their multicentre, longitudinal biomarker identification study including retrospective studies as well as a prospective nested case-control study, Lin and co-workers identified a novel miRNA classifier for hepatitis B virus (HBV)-associated HCC referred to as C_{mi} (12). This biomarker contains seven miRNAs (miR-29a, miR-29c, miR-133a, miR-143, miR-192 and miR-505) that display differential levels in the serum of Asian HCC patient cohorts versus non-HCC controls including healthy individuals, inactive HBV surface antigen (HBsAg) carriers, subjects with chronic hepatitis B and those with HBV-induced liver cirrhosis. Clinical diagnosis of HCC was based on at

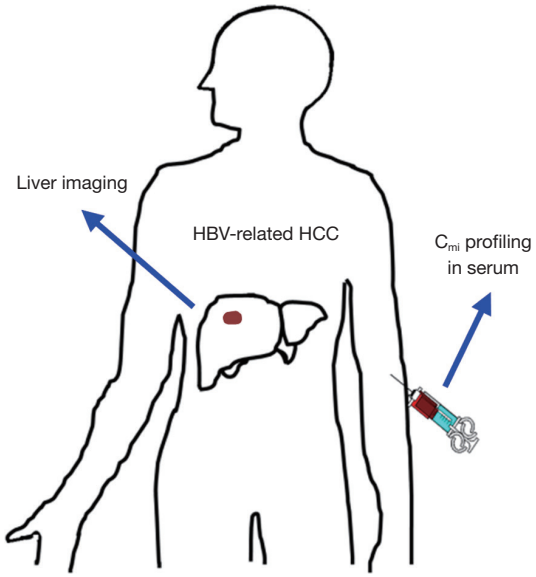

Figure 1 Schematic representation of the potential use of C_{mi} to complement current imaging-based surveillance for the management of HCC. HCC, hepatocellular carcinoma; HBV, hepatitis B virus.

least two imaging techniques and most of the cases were confirmed by histopathology. The C_{mi} was identified as follows: by TaqMan miRNA array, a pool of 754 miRNAs were screened in the discovery cohort that allowed detecting 19 differentially regulated miRNAs according to four distinct normalization methods. These candidate miRNAs were further assessed in the training cohort in order to establish the best miRNA classifier, whose sensitivity, specificity and performance to predict/diagnose HCC were validated in two independent cohorts and a nested case-control study with prospectively collected samples in a third validation cohort (12). By taking advantage of these large independent cohorts and robust statistical data analysis, the authors revealed that C_{mi} has greater sensitivity than AFP at a cutoff of 20 ng/mL (AFP20) in detecting HCC at the time of clinical diagnosis, while both biomarkers displayed similar sensitivity. Importantly, C_{mi} was shown to distinguish HCC 12 months before clinical diagnosis including small size, early-stage and AFP-negative HCC. Given that miRNA assessment in the serum is a pretty straight-forward non-invasive test that can be employed in clinical settings, the authors suggest C_{mi} as a tool for surveillance of HCC development in HBV-infected at-risk patients (12) (*Figure 1*).

This well conducted study that included several independent cohorts and thereby enabled large sample size provides a significant advancement in the early detection of HBV-related HCC. Given that quantitative detection of miRNAs by RT-PCR can be easily implemented in diagnostic laboratories, using C_{mi} for prediction and diagnosis of HCC could become a promising approach for routine application in clinics. In contrast to previous studies having assessed the correlation between circulating miRNAs and HCC, Lin and co-workers tested the diagnostic potential of C_{mi} by performing a nested case-control study with prospectively collected specimens in addition to the retrospectively assessed training and validation cohorts (12). Data from this prospective validation study showed that C_{mi} was more sensitive than AFP20 and could identify HCC irrespective of the presence of AFP several months earlier than imaging-based clinical diagnosis. This indicates that C_{mi} may be a valuable tool to identify at-risk patients developing HCC in order to complement and help interpretation of imaging-based surveillance of the liver. By increasing the chance of detecting early stage HCC and thus of successful curative surgery, the use of C_{mi} may enhance the overall survival for HCC.

The current study only focused on Asian patients and HBV-related HCC (12). In the future, it would be interesting to test whether C_{mi} can also be of relevance for other HCC etiologies as well as cohorts of non-Asian patients. A piece of increasing evidence likely supports this possibility. Indeed, several miRNAs among those of C_{mi} have been reported as being deregulated in HCC tissues from different etiologies including patients with hepatitis C (13-16) and/or have been suggested as potential biomarkers for HCC (17-19). In this picture C_{mi} holds potential as a universal miRNA classifier for HCC. Another unanswered question is about the potential role of C_{mi} in surveillance of HCC recurrence. Indeed, given the high recurrence rate of HCC following surgery, it would be very interesting to assess the ability of C_{mi} to detect HCC recurrence at an early stage in future studies.

In conclusion, the validation of the potential of C_{mi} for detection of early stage HCC using additional independent cohorts of patients with HCC related to chronic hepatitis C as well as non-alcoholic and alcoholic liver disease may ultimately provide a tool to improve the management of HCC patients by enabling detection of early stage, small size tumors irrespective of the presence of AFP. This may eventually increase the chance of successful curative operation and longer survival. Further studies are needed to define the role of C_{mi} in the management of patients at risk to develop HCC including HCC recurrence following surgery.

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Footnote

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