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RESEARCH ARTICLE

HCV BIOMARKERS UPDATES AND HEPATOCELLULAR CARCINOMA

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ABSTRACT

Hepatocellular carcinoma (HCC) is considered a cause of cancer-related death across the globe. Numerous improvements have been achieved in treating the early and advanced HCC stages. HCC biomarkers play a significant role in the prognosis of HCC. However, there has not been predictable clinically important data for surveillance and early diagnosis of HCC. Diagnosis of alpha-fetoprotein (AFP) negative hepatic cancer (ANHC) is challenging in clinical practice. For the clinical detection of ANHC, a single biomarker alone is usually insufficient in sensitivity and specificity. Combining different types of biomarkers could enhance the diagnostic performance for ANHC detection.

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INTRODUCTION

Hepatitis C virus (HCV) causes acute hepatitis in around 15%-20% of cases. Subsequently, acute infection is followed by chronic conditions in 50% to 80% of HCV patients. [31] In 30% (15–45%) of infected individuals, spontaneous clearance of HCV occurs within six months of infection without any treatment.[31]The remaining 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years. (http://www.who.int).[28,29] Chronic hepatitis C (CHC) patients are at substantial risk of developing life-threatening complications, including cirrhosis in 20% of cases and hepatocellular carcinoma (HCC) with an incidence of 4%-5% per year in cirrhotic patients.[28,29] Hepatocellular carcinoma (HCC) is considered a cause of cancer-related death across the globe..[1]Considering liver cancer, HCC is the most encountered form in approximately 90 % of cases.[1]Hepatitis B virus and Hepatitis C virus are the predominant risk factors contributing to the development of HCC. However, non-alcoholic steatohepatitis associated with metabolic syndrome or Diabetes Mellitus is a relatively frequent risk factor in the West for causing HCC.[1]Chronic hepatitis C (CHC) patients are at high risk of developing life-threatening complications, including cirrhosis in 20% of cases, and hepatocellular carcinoma (HCC) with an incidence of 4-5% per year in cirrhotic patients.[28,29]During the last few decades, numerous improvements have been achieved in treating the early and advanced HCC stages.[1]HCC biomarkers play a significant role in the prognosis of HCC. However, there has not been predictable clinically important data available for surveillance and early diagnosis of HCC.[1]

The study of virus-dysregulated signaling pathways may, therefore, contribute to identifying reliable minimally invasive biomarkers for detecting patients with early-stage liver disease, potentially complementing existing non-invasive methods in clinics. [30] Using an appropriate single or combination of tumor markers might improve the effectiveness in screening HCC patients.[2]Serum tumor markers are categorized into four significant types: oncofetal antigens and glycoprotein antigens; enzymes and isoenzymes; genes; and cytokines.[2] Serum alpha-fetoprotein (AFP) is the predominant tumor marker in detecting patients with hepatocellular carcinoma. Furthermore, other tumor markers, including glypican-3, gamma-glutamyl transferase II, alpha-l- fucosidase, transforming growth factor-beta1, and tumor-specific growth factor, have also been considered supplementaries to AFP in the detection.[2] The challenge is to develop biomarkers that can improve early diagnosis and aid in adequate treatment selection of patients and post-treatment prognosis.[3]

Objective: This review aims to discuss various biomarkers that effectively improve the early diagnosis and prognosis of HCC patients.

Overview: Biomarkers are measurable indicators for physiological or pathological processes secreted in response to various diagnostic or therapeutic procedures. In the case of HCC, the development is characterized by multiple genetic and epigenetic events alterations. Liver cells in HCC are likely to present different molecular signatures and release specific tumor-associated molecules into body fluids.[32]

The developed liver-related biomarkers are explicitly validated in patients suffering from chronic hepatitis C due to chronic liver injury. They require no invasive procedure, are reproducible, and require minimum training.[33]Biomarkers provide implications for screening, diagnosis, treatment, and prognosis of chronic hepatitis. Therefore, studying virus-dysregulated signaling pathways may contribute to showing minimally invasive biomarkers for detecting patients with early-stage liver disease, potentially complementing existing non-invasive methods in clinics.[34]However, the mechanisms of carcinogenesis in chronic HCV infection have not been fully understood, which involve complex epigenetic regulation and cellular signaling pathways.[31]Recent studies have proved the involvement of circRNAs in HCC diagnosis, prognosis, development, and drug resistance, suggesting that circRNAs may be a class of novel targets for improving HCC diagnosis, prognosis, and treatments. [35]Also, they concentrated on the role of the Liver-Specific microRNA, miRNA-122, in the HCV Replication Cycle.[36]Other studies showed that HCV infection initiates genome-wide epigenetic changes in both active and repressed chromatin, where altered histone modifications and DNA methylation of the host gene command mRNA levels and expression.[31] And then, these changes influence the downstream signaling pathways associated with the HCV life cycle and HCC.[31]

Conventional Serum Biomarkers: The early diagnosis of HCC is a critical issue, as all the curative measures work well in the early stages of HCC. Early screening of HCC is an essential tool for early detection and treatment.[4] Abdominal ultrasound is the only tool used in the screening process due to its cost-effectiveness. AFP is restricted to the diagnosis or screening of high-risk populations (the European Association for the Study of the Liver (EASL), the American Association of Study of Liver Disease (AASLD)).[4] In Japan, high-risk populations for HCC are screened, by abdominal ultrasound, for three months, and AFP, along with another two biomarkers, AFP*Lens culinaris*, which is an agglutinin-reactive fraction, and a protein-induced by vitamin K absence or antagonist-II called PIVKA-II.[4]

Dickkopf-1 and descarboxy prothrombin are the other biomarkers considered for HCC diagnosis. Dickkopf-1 is a good biomarker for HCC with negative AFP.[4]Descarboxy prothrombin has higher sensitivity than AFP; it can be used more effectively for screening HCC.[4]AFP, however, due to cost-effectiveness, difficult availability, or high variability across studies,is not considered an addition to any clinical practice guidelines.[4] Body fluids could be a possible source for several biomarkers, e.g., plasma, serum, urine, or stool, which may contribute to HCC surveillance and diagnosis if measured.[32] The most well-studied non-invasive HCC biomarkers are alpha-fetoprotein (AFP), AFP-L3, and des- -carboxy prothrombin (DCP).[32] Other molecules such as Glypican 3 (GPC-3), Alpha-l fucosidase (AFU), Golgi protein-73 (GP73), and Squamous cell carcinoma antigen (SCCA), or tumor-associated signatures such as DNA mutation DNA methylation are still investigated.[32] The diagnosis of HCC is predictable when significantly increased serum AFP levels and definitive imaging features are present simultaneously. Moreover, AFP-negative hepatic cancer (ANHC) is not diagnosed easily, as most ANHCs are early and small HCCs, often without typical imaging characteristics.[5]Perhaps a single biomarker has insufficient sensitivity or specificity for diagnosing ANHC; combining multiple biomarkers is usually recommended to improve diagnostic efficacy effectively.[5]

Recently Discovered Serum Protein Biomarkers: Traditional biomarkers are known to have specific diagnostic values for HCC; however, new biomarkers are continuing to be explored.[6]

Aldo-keto reductase (AKR1B10): Aldo-keto reductase family member B10 (AKRB10) is a novel secretory protein overexpressed in multiple tumors. It can be considered a potential diagnostic and prognostic biomarker for HCC.[5,7,8] A multicenter study with 1,244 participants found that serum AKRB10 levels were significantly increased in HCC patients in relevance to those in non-HCC patients. AKRB10 exhibited a promising diagnostic value (AUROC 0.891, sensitivity 71.2%, and specificity 92.6%).[5,8]

Midkine (MDK): This is a growth factor with a heparin-binding site havingmultiple functions. A large-scale, multicenter validation study found that serum MDK is expressed higher in HCC patients thanin other gastrointestinal malignant tumors.[5,9] MDK possesses higher sensitivity, but similar specificity for HCC diagnosis relative to AFP even in early-stage HCC.[5,9] MDK exhibits an outstanding performance for distinguishing ANHC from non-HCC controls.[5,9]

Heat shock protein 90alpha, abbreviated as Hsp90α: It isa conserved molecular chaperone that significantly increases in various tumors.[5]Hsp90α was found more valuable for distinguishing HCC from non-liver cancer controls than that of AFP.[5,10]

Angiopoietin-like protein 2 (ANGPTL2): Chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection is associated with an increase in the acute-phase proteins, mostly glycoproteins.[37] The interactivity between viral glycoproteins and cellular receptors, stated by one study, showed that glycoproteins determine the possibility of whether the virus penetrates the host cells or not. So, these glycans are possible targets for developing novel treatment strategies for viral hepatitis.[37]Angiopoietin-like protein 2 (ANGPTL2) is a secretory glycoprotein detected in inflammation and tumor development. [5,11]In the case of AFP-negative HBV-related HCC,ANGPTL2 is overexpressed in HCC tissues and may be considered a potential diagnostic biomarker.[5,11]

Serum paraoxonase 1 (PON1): It is a highly fucosylated glycoprotein in HCC.[5,12]

Cyclase-associated protein 2 (CAP2): Cyclase-associated protein 2 (CAP2), a conserved protein, regulatesthe actin cytoskeleton. CAP2 is upregulated in multiple tumors, including HCC.[5,13]

CCT3 and IQGAP3: This is aChaperonin containing TCP1 complex subunit 3 (CCT3) is involved in tumor cell proliferation and tumorigenesis. Overexpressed CCT3 was foundin HCC progression.[5,14]

Thioredoxin: Thioredoxin is a thiol oxidoreductase and is highly expressed in various malignancies. Serum thioredoxin levels were found to be higher in HCC compared with chronic liver diseases.[5,15]

Tyrosine kinase is known as sAxl: It isa transforming receptor tyrosine kinase (Axl), is a member of the tumor-associated macrophage family and upregulates in several types of cancer.[5,16] HCC patients with high serum sAxl levels exhibited a significantly reduced overall survival compared with low-level sAxl patients.[5]sAxl outperformed AFP for the detection of very early HCC.[5,16]

Osteopontin (it is known as OPN): It is a secreted phosphoprotein associated with tumor invasion, progression, or metastasis in multiple types of cancer. Although HCC patients with elevated plasma levels of OPN were more likely to exhibit intrahepatic metastasis, early recurrence, and a worse prognosis[5,17.]

Minichromosome maintenance complex component 6 (MCM6): This is present inPlasma in the form of MCM6 mRNA. The protein levels were significantly upregulated in HCC and correlated with vascular invasion, tumor progression, and lymph node metastasis.[5,18]

C-reactive protein (known as CRP): This is a non-specific acute-phase protein secreted by the liver in response to acute and chronic inflammation. Thus,elevated CRP expression has been detected in multiple tumors.[5,19]

Vasorin (abbreviated as VASN): It is a secreted cell surface protein. Higher VASN levels were detected in HCC serum compared to control cohorts.[5,20]

Annexin A2: This is a calcium-dependent, phospholipid-binding protein expressed on the surface of endothelial cells and most epithelial cells.[5]Serum annexin A2 levels were significantly higher in

HCC patientswith better performance than AFP for distinguishing HCC from hepatitis and cirrhosis. It also had a better diagnostic performance for early-stage HCC.[5,21]

Human cervical cancer oncogene 1 (HCCR-1): It isa relatively novel human oncoprotein associated with human cervical cancer. Moreover, HCCR-1 can be complementary to AFP for ANHC diagnosis.[5,22]

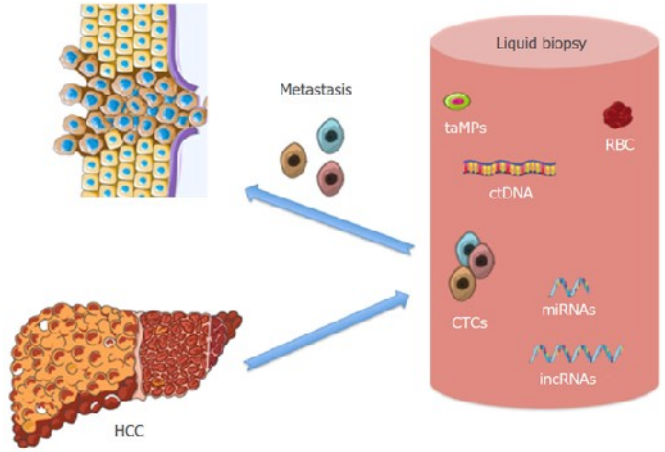
CYP17A1: The cytochrome P450, coming from family 17 and subsequently subfamily A, polypeptide 1 (CYP17A1), is a secretory protein overexpressed in human HCC tissues at preneoplastic and neoplastic stages.[5,23]CYP17A1 is a promising diagnostic biomarker for ANHC detection.

Glutamine synthetase (GS): It is a metabolic enzyme that catalyzes glutamine synthesis and has been revealed as a sensitive and specific indicator for developing HCC. It may be a valuable biomarker for HCC diagnosis, especially for ANHC.[5,24]

Alpha-1 acid glycoprotein (AGP): This is an acute-phase glycoprotein and can be used as a novel biomarker for HCC.[5,25]

New Protein Biomarkers Identified by "omics": Tumor cells can secret proteins from their surface into body fluids as a source for the discovery of potential cancer biomarkers. For the early detection of ANHC, numerous proteomic studies have been performed to examine specific protein profiles. Wu et al. found 45 differentially changed serum protein/peptide peaks in HCC.[5,26] Moreover, Tissue interstitial fluid was also used to identify differentially expressed proteins. Zhang et al. found that two overexpressed extracellular matrix proteins from interstitial tissue fluid, SPARC, and thrombospondin-2 (THBS2), were valuable for HCC diagnosis.[5,27]

miRNAs: The miRNAs (figure 1) biomarkers are endogenous RNA, small, non-coding, about 19–25 nucleotides in length.[36] They regulate gene expression by degrading messenger RNAs (mRNAs) or inhibiting translation. [36] Also, they control cell proliferation, migration, invasion, and development in HCC by acting as tumor promoters or suppressors. [36] The discovery of miRNA-484, 524, 615, and 628 in HCV-mediated HCC patients are possibly significant biomarkers for diagnosing fibrosis and cirrhosis.[32]Oncogenic miRNAs (OncomiRs) and tumor-suppressive miRNAs can result in carcinogenesis and malignant transformation.[36] Figure 1.



Liquid biopsy of hepatocellular carcinoma (HCC): circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), epigenetic non-coding RNA (miRNAS and lncRNA), and tumor-associated circulating microparticles (taMPs) Rojas et al. Hepatoma[39]

Hepatic stellate cells (HSCs): Hepatic stellate cells (HSCs) are vital immune cell populations activated during HCV infection. [40] With the concentration of (HSCs), which are closely related to HCV-infected liver fibrosis, analysis of the alterations in the HSCs in terms of their surface-specific markers, cytokine release, activation, cell function, and morphological components is essential.[40]

CONCLUSION

Although the diagnosis of ANHC is a challenge in clinical practice, a single biomarker alone is relatively insufficient in sensitivity and specificity for the clinical detection of ANHC. Therefore, combining several biomarkers could enhance the diagnostic performance for ANHC detection. It is essential to mention that more studies and extensive research is required to discover more tools to diagnose HCC and provide better outcomes accurately.

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