Letter

Combination of triple biomarkers AFP, AFP-L3, and PIVAKII for early detection of hepatocellular carcinoma in China: Expectation

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Summary	Hepatocellular carcinoma (HCC) remains a severe health threat in China. Early tumor detection is crucial for improving the prognosis of patients. Currently, ultrasound plus biomarker alpha fetoprotein (AFP) is recommended by Chinese Liver Cancer Diagnosis and Treatment Guidelines in China. However, most HCC continues to be diagnosed beyond an early stage due to insufficient sensitivity and specificity of current surveillance tools, highlighting the need for more accurate biomarkers to improve early HCC detection. In Japan, ultrasound plus triple biomarkers AFP, *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), and prothrombin induced by vitamin K absence II (PIVKA II) has been routinely used for HCC surveillance and achieved increased early HCC detection rate. Very recently, the assay of triple biomarkers AFP, AFP-L3, and PIVKA II using µTASWako i30 immuno-analyzer was brought into China. The prospect of the modality of ultrasound plus triple biomarkers for early HCC detection in China is expected in the future.

Keywords: AFP, AFP-L3, PIVKA II, DCP, HCC

Liver cancer is the fourth most common cancer in China and the third most common cause of death from cancer in China in 2015 (*1*). It is estimated that over 50% of new cases of liver cancer in the world occurred in China each year (*2*). As the most common type of liver cancer, hepatocellular carcinoma (HCC) has a dismal prognosis because most patients (about two thirds) had lost the opportunity of surgical therapy when HCC was detected at advanced stage (*3*). Surveillance at regular intervals and early diagnosis of HCC is crucial for improving the patients' survival.

Currently, early detection of HCC is primarily based on noninvasive imaging methods, such as ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) and expression patterns of serologic tumor markers such as alpha-fetoprotein (AFP) (*4*). Guidelines from the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend surveillance using ultrasound alone. Chinese Liver Cancer Diagnosis and Treatment Guidelines recommend ultrasound and serum AFP level as monitoring methods for surveilling high-risk groups. However, most HCC continues to be diagnosed beyond an early stage due to insufficient sensitivity and specificity of current surveillance tools, highlighting the need for more accurate biomarkers to improve early HCC detection.

Lens culinaris agglutinin-reactive fraction of AFP (AFP-L3), the glycosylated isoform of AFP, has been suggested as a biomarker for HCC early detection given its higher specificity than AFP. Clinical studies revealed a specificity of 92% and a sensitivity of 37-49% of AFP-L3 for early stage HCC detection when used alone (*5-7*). Prothrombin induced by vitamin K absence II (PIVKA II), also known as des-γ-carboxy prothrombin (DCP), is an abnormal prothrombin protein that is generated as a result of an acquired defect in posttranslational carboxylation (*8*). Several studies suggested that DCP had a high specificity of approx. 90% and a sensitivity of 56% for early stage HCC detection when used alone (*6,9*). Although AFP-L3 or PIVKA II appears to have insufficient sensitivity when used alone, it may have potential additive benefit to AFP which may cause false

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positives with non-HCC malignancies. A recent clinical study showed that the combination of AFP, AFP-L3 and PIVKA II is superior to a single biomarker in HCC detection (*10*). The GALAD scoring algorithm based on AFP, AFP-L3, and PIVKA II significantly improves detection of BCLC early stage HCC, with a specificity of 93.3% and sensitivity of 85.6% (*11*). Thus far, ultrasound examination plus simultaneous measurement of triple tumor biomarkers AFP, AFP-L3, and PIVKA II has been recommended for surveillance of high-risk populations by Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology (JSH-HCC Guidelines). Studies showed that early HCC detection rate and patients' 5-year survival in Japan was 68% and 45.2% (*12,13*), which are obviously higher than those in the US and China, suggesting the promising value of combination of triple biomarkers in early HCC detection.

On June 28, 2017, Wako Pure Chemical Industries, Ltd. (Japan), the developer of μTASWako i30 immuno-analyzer for detection of AFP, AFP-L3, and PIVKA II, and Techpool Bio-pharma Co., Ltd. (China) announced in Shanghai, China that the two companies would cooperate to promote the application of the triple biomarkers detection assay in China. The prospect of improved HCC early detection in China is expected in the future.

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