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Serum Protein Kinase C delta: New Kid on the Block for Early Detection of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related deaths in the world.\textsuperscript{1} Age-standardized incidence rates of HCC are highest in Asia and Africa, however, both incidence and mortality are rapidly rising in the United States and Europe due to a shift in epidemiology of HCC from viral hepatitis to nonalcoholic fatty liver disease-related cancer.\textsuperscript{2} Given the dual clinical challenges of detection at late stages and high incidence-to-mortality ratio of HCC,\textsuperscript{3} major hepatology societies have recommended abdominal ultrasound with or without alpha fetoprotein (AFP) as the primary HCC surveillance strategy for at-risk patients.\textsuperscript{4} However, ultrasound suffers from low sensitivity for detecting early-stage HCC, with factors such as operator experience and patient factors, such as obesity, decreasing its diagnostic accuracy.\textsuperscript{5-7} At present, only limited data exist on the cost-effectiveness of other imaging modalities, such as computed tomography and magnetic resonance imaging.\textsuperscript{8,9}

Given the limitations of imaging-based strategies, serum-based biomarkers have an important role in HCC surveillance. Alpha fetoprotein (AFP) has been widely used in combination with ultrasound for HCC surveillance. AFP has significant limitations as a biomarker for detection of HCC due to low specificity when used alone, but combining it with ultrasound improves sensitivity from 45% with ultrasound alone to 63% with ultrasound plus AFP.\textsuperscript{5} However, it is obvious that no single serum biomarker may be sufficient due to HCC tumor heterogeneity and need to predict response to therapy.\textsuperscript{10} Thus, other serum biomarkers such as des-γ-carboxy prothrombin ([DCP), GALAD (gender, age, AFP-L3, AFP, and DCP), and methylated DNA markers panel are being investigated in HCC surveillance strategies.\textsuperscript{10-12}
In this issue of Gastro Hep Advances, Oikawa et al report on the potential of serum protein kinase C delta (PKCδ) as a novel biomarker for HCC complementary to biomarkers currently used in clinical practice.\textsuperscript{13} These investigators previously reported that while PKCδ is an intracellular serine/threonine kinase, HCC cells secrete PKCδ into extracellular space, where it acts as a growth factor for HCC progression, while neither normal hepatocytes nor non-HCC gastrointestinal cancer cells secrete PKCδ.\textsuperscript{14} They also demonstrated that HCC patients had higher serum PKCδ compared with patients with chronic liver disease or healthy controls. Here, they extend their observations on serum PKCδ in a larger group of patients with chronic liver disease with or without HCC.

Serum PKCδ levels were found to be higher in chronic liver disease patients with HCC compared with those without HCC. They also report that in their cohort, the diagnostic performance of PKCδ was comparable to AFP and DCP. However, a particularly intriguing observation is that serum PKCδ levels were elevated in a subset of patients that were double-negative for AFP/DCP, and serum PKCδ levels were not correlated with AFP/DCP levels. This finding suggests that serum PKCδ may detect tumors with distinct biology and serve as a complementary biomarker to the GALAD, which includes both AFP and DCP.\textsuperscript{15} A second observation that deserves further investigation is that serum PKCδ performed better than AFP/DCP in detecting very early-stage (solitary and small) tumors.
Despite the promise serum PKCδ holds as a biomarker of early-stage HCC, several questions need to be addressed before it can be adopted in clinical practice. First, this study will need to be replicated in a larger, more diverse group of patients. Second, given the rapidly changing epidemiology of HCC from a viral hepatitis-related to NAFLD-related cancer, diagnostic performance of PKCδ will need validation in NAFLD subjects with and without coexisting obesity. Third, the role of serum PKCδ as a complementary test to conventional biomarkers will need validation. Fourth, determining the diagnostic performance of serum PKCδ levels in combination with abdominal ultrasound will be needed, and compared with other emerging biomarker panels such as the GALAD score and circulating cell-free DNA. Fifth, the ability of PKCδ to identify tumors with distinct biology and/or response to specific treatments will need additional exploration.

In summary, there is an urgent need to improve surveillance strategies for HCC, a common cancer with increasing incidence and high mortality, as the current strategy consisting of ultrasound with or without AFP has significant limitations. Serum PKCδ represents a novel biomarker for HCC detection that may prove to be complementary to other serum biomarkers, particularly in cases of AFP/DCP double-negative tumors, and in detection of small, early-stage HCC.
References


