Protein induced by vitamin K absence-II for the surveillance and monitoring of hepatocellular carcinoma in Hong Kong

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Introduction

In Hong Kong, primary liver cancer is the fifth most common cancer and third leading cause of cancer-related deaths.[1] Moreover, the age- and sex-adjusted prevalence of hepatitis B virus (HBV) infection is 6.2%.[2] Locally, >75% of liver cancers are linked to chronic HBV infection.[3] Although cirrhosis remains the leading risk factor for hepatocellular carcinoma (HCC) worldwide, its epidemiology is transitioning from viral to non-viral factors because of increases in metabolic dysfunction–associated steatotic liver disease (MASLD) and alcohol-associated liver disease.[4] It is estimated that three-quarters of global deaths related to HCC occur in the Asia-Pacific region.[5]

Unmet needs in Hong Kong

In 2016, the World Health Organization published an advocacy brief aimed at combating viral hepatitis.[6] This brief set ambitious global targets, including a 90% reduction in the number of new cases and a 65% decrease in deaths by 2030.[6] In recognition of the public health threat posed by viral hepatitis, the Hong Kong SAR Government introduced the Hong Kong Viral Hepatitis Action Plan 2020–2024, which provides a comprehensive strategy for reducing the local public health burden of the disease.[7] Considering that most HBV-related deaths are caused by HCC, it is important for at-risk individuals to undergo surveillance for the early detection of cancer; this approach enables potentially curative therapies.[8] The most widely used modalities include liver ultrasonography (USG), either alone or in combination with alpha-fetoprotein (AFP) monitoring.[9] The overall sensitivity of these methods in patients with HBV is reported to exceed 80% for any stage of HCC. However, they exhibit suboptimal sensitivity for early-stage HCC, cirrhosis, obesity, MASLD, and alcohol-related disease.[10] Alpha-fetoprotein is the most widely used serologic biomarker for HCC surveillance. However, almost one-third of HCCs do not secrete AFP.[11] Additionally, AFP may be elevated in benign conditions such as active hepatitis and liver cirrhosis, as well as non-HCC malignancies (eg, cholangiocarcinoma).[9] Despite these limitations, studies conducted in Hong Kong using USG and AFP every 6 months, primarily in patients with HBV, have shown that this approach can detect smaller and earlier-stage HCCs; it is also associated with improved survival.[12,13] The situation is less clear for MASLD, where HCC surveillance is not yet routinely recommended.[14]

The Hong Kong Association for the Study of Liver Diseases convened an HCC Surveillance Expert Meeting on 29 June 2023. Eleven hepatologists

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from academia and the public sector participated to explore new strategies for HCC surveillance in at-risk individuals. The relevant discussion points and recommendations from this meeting are presented below.

Value and application of new biomarkers in hepatocellular carcinoma surveillance

Protein induced by vitamin K absence-II (PIVKA-II) is an abnormal form of the coagulation protein prothrombin. Elevated levels of PIVKA-II can be detected in individuals with vitamin K deficiency and individuals taking vitamin K antagonists (eg, warfarin). In the context of HCC, PIVKA-II is an abnormal prothrombin molecule known as des-gamma-carboxyprothrombin, which is thought to arise from an acquired defect in the post-translational carboxylation of the prothrombin precursor in malignant cells. Protein induced by vitamin K absence-II has been identified as an HCC-associated serum biomarker and serves as an independent predictor of microvascular invasion in HCC (Fig).[15]

When a PIVKA-II cut-off value of 28.4 ng/mL was used, the sensitivity of HCC detection was 86.9%, and the specificity was 83.7%.[16] For early-stage HCC detection, the sensitivity and specificity were 77.9% and 83.7%, respectively.[16] In contrast, when an AFP cut-off value of 20 ng/mL was used, the sensitivity and specificity for early-stage HCC were 36.4% and 98.1%, respectively.[16] These findings indicate that PIVKA-II has greater sensitivity for early-stage HCC. The use of PIVKA-II in combination with AFP increases the HCC detection sensitivity to 92%.[16] There may also be a role for the combined use of PIVKA-II and AFP in detecting HCC in non-viral chronic liver diseases, such as MASLD or alcoholic liver disease.[17] Consequently, a panel of experts from the Asia-Pacific region strongly agreed that PIVKA-II in combination with AFP enables optimal detection of HCC; they also agreed that PIVKA-II is valuable for HCC detection in AFP-negative patients,[18] and it may be useful when monitoring treatment response and recurrence. Notably, PIVKA-II assays generally are not affected by renal impairment or haemodialysis.[19]

A health economics study from Hong Kong[20] showed that PIVKA-II-based surveillance strategies are feasible options for the local healthcare system. The combination of PIVKA-II and AFP exhibited greater sensitivity for early-stage HCC compared with the combination of USG and AFP. In patients who had compensated liver cirrhosis, the use of PIVKA-II and AFP for HCC detection resulted in cost savings of HK$3328 and a gain of 0.016 in quality-adjusted life years compared with the use of USG and AFP.[20] It was projected that an additional 521 cases of early-stage HCC per 100 000 patients could be detected by the combination of PIVKA-II and AFP compared with the combination of USG and AFP.[20] Among patients with chronic hepatitis B, the combination of PIVKA-II and AFP for HCC detection led to cost savings of HK$4351 and a gain of 0.008 in quality-adjusted life years compared with the use of USG and AFP.[20] It was projected that an additional 247 cases of early-stage HCC per 100 000 patients could be detected by the combination of PIVKA-II and AFP compared with the combination of USG and AFP.[20] The study concluded that all PIVKA-II–based surveillance strategies, including the GAAD (gender, age, AFP, and des-gamma-carboxyprothrombin) score, provided superior early-stage HCC detection compared with the current approach of USG in combination with AFP.[20]

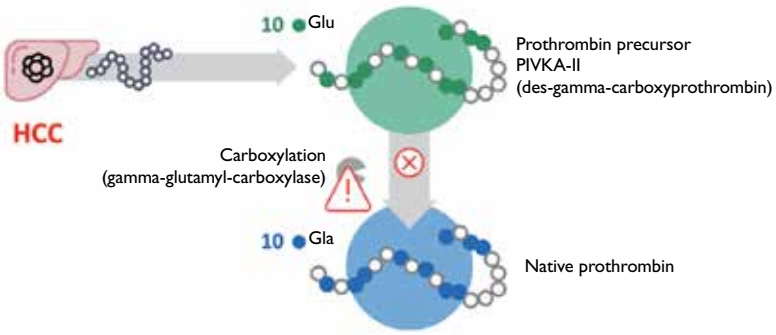

FIG. Abnormal production of protein induced by vitamin K absence-II by hepatocellular carcinoma

Abbreviations: Gla = gamma-carboxylated glutamic acid; Glu = glutamic acid; HCC = hepatocellular carcinoma; PIVKA-II = protein induced by vitamin K absence-II

Local experience using protein induced by vitamin K absence-II in clinical practice

In Hong Kong, a pilot programme involving the use of PIVKA-II in combination with AFP was conducted in several acute hospitals from 2022 to 2023. Generally, patients in this programme were HBV carriers, had advanced fibrosis or cirrhosis, and/or had a high index of suspicion for HCC with chronically elevated AFP levels or abnormal imaging findings.

We carried out a clinical audit of 165 patients who underwent PIVKA-II testing. The pooled analysis revealed an overall sensitivity of 85.7%, specificity of 96.2%, positive predictive value of 50% and negative predictive value of 99.3%, consistent with findings reported in the literature[16] (Table). Among the six patients with false-positive results,

TABLE. Performance of protein induced by vitamin K absence-II and alpha-fetoprotein in Hong Kong (n=165)

	HCC		No HCC	
	AFP-positive	AFP-negative	AFP-positive	AFP-negative
PIVKA-II–positive	2	4	2	4
PIVKA-II–negative	1	0	40	112

Abbreviations: AFP = alpha-fetoprotein; HCC = hepatocellular carcinoma; PIVKA-II = protein induced by vitamin K absence-II

five had chronic hepatitis B (two of whom also had cirrhosis), and one had alcoholic liver cirrhosis. One patient with non-cirrhotic chronic HBV experienced a non-icteric flare with alanine transaminase level reaching 159 U/L. In the single patient with false-negative results, the AFP level showed an increasing trend, rising from 8.6 μg/L in July 2022 to 180 μg/L in June 2023. The patient's initial triphasic computed tomography scan only showed a non-specific lesion; 2 months later, the lesion was identified as a 1.4-cm HCC on a follow-up scan. This case provides real-world evidence to support the use of PIVKA-II in combination with AFP.

Recommendations of the Expert Meeting

Based on the above data and local experience with PIVKA-II, the Expert Meeting established the following recommendations:

1. Most experts recommended using PIVKA-II in addition to AFP because this combination has better diagnostic performance compared with either biomarker alone. However, PIVKA-II cannot entirely replace AFP due to limited evidence and differing biological mechanisms.
2. Regardless of the biomarker(s) used, this approach cannot serve as a substitute for semi-annual liver USG in HCC surveillance. This recommendation is particularly pertinent considering the long wait times for USG in the public sector. Protein induced by vitamin K absence-II may be useful in prioritising patient referrals to the private sector for imaging.
3. Protein induced by vitamin K absence-II is recommended for special patient populations, such as those with cirrhosis, normal AFP levels, and non-viral aetiologies of chronic liver disease (eg, MASLD and alcoholic liver disease), particularly when accompanied by cirrhosis.
4. The utility of the GAAD score has been demonstrated, but it is considered difficult to interpret for continuous monitoring because age increases each year.[21]
5. Other potential roles for PIVKA-II include its use in difficult or borderline cases, where it may serve as a helpful adjunct to clarify the diagnosis, and for monitoring HCC recurrence in patients who have undergone HCC resection.

Practical considerations and future directions

Currently, most experts in Hong Kong would consider using PIVKA-II for surveillance in patients who exhibit MASLD-related cirrhosis or newly diagnosed HCC with normal AFP levels. The cost of the PIVKA-II test is perceived as a substantial barrier to wider implementation of this surveillance and monitoring strategy. More evidence, such as a cost-effectiveness study, is needed to justify its use as a replacement for USG and facilitate broader adoption. It was suggested that the test should initially be made available to a small group of high-risk patients before expansion to a larger population. In the near future, additional data regarding PIVKA-II-based detection of MASLD-related HCC should be collected and analysed.

Conclusion

The PIVKA-II test, when used in combination with AFP, is likely to be both cost-effective and clinically useful for HCC surveillance in Hong Kong, particularly among patients with small and AFP-negative HCC. Use of this test should be prioritised in certain at-risk patient groups, such as those with cirrhosis and non-viral aetiologies. Considering the existing service gaps in providing timely USG surveillance within the public sector, better diagnostic, surveillance, and risk stratification tools (eg, PIVKA-II) are needed to meet the targets established by the World Health Organization and the Hong Kong Viral Hepatitis Action Plan.

Author contributions

Concept or design: All authors.
Acquisition of data: All authors.
Analysis or interpretation of data: All authors.
Drafting of the manuscript: RNS Lui, LLY Mak.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

RNS Lui has served as an advisory board member for Gilead Sciences and speaker for GenieBiome; he also holds equity in Pfizer. As an editor of the journal, RNS Lui was not involved in the peer review process. LLY Mak has served as a speaker for Roche. HLY Chan is an advisor for Aligos, GlaxoSmithKline, Roche, Vaccitech, and Virion Therapeutics; a speaker for Echosens, Gilead Sciences, Roche, and Viatris; and a data management board member for Aligos, Arbutus, Roche, Vaccitech, and Zhimeng Therapeutics. MF Yuen has served

as an advisor/consultant for and/or received grant/research support from AbbVie, Aligos, AiCuris, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Bristol Myers Squibb, ClearB Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Roche, Silverback Therapeutics, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology, and Visirna Therapeutics. GLH Wong has served as an advisory board member for AstraZeneca, Gilead Sciences, and Janssen, as well as a speaker for Abbott, AbbVie, Ascletis, Bristol Myers Squibb, Echosens, Gilead Sciences, Janssen, and Roche; she has also received a research grant from Gilead Sciences. Other authors have disclosed no conflicts of interest.

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