# Midkine as a new diagnostic tool in hepatocellular carcinoma

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**Abstract:** In the field of hepatocellular carcinoma (HCC), new biomarkers are needed in order to refine diagnosis of small tumors accessible to curative treatments. However, most of biomarkers (AFP, AFPL3, DCP, PIVKA-II, etc.) have failed to show any additional value for the diagnostic of early HCC. A recent study published in *Clinical Cancer Research* by Zhu WW *et al*. has identified serum midkine as an interesting diagnostic tool for HCC. Despite some limitations, this study has paved the way for a potential use of serum midkine in clinical care.

**Keywords:** Hepatocellular carcinoma (HCC); diagnosis; midkine; biomarker

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Despite several advances in both curative and palliative treatment, hepatocellular carcinoma (HCC) remains a dreadful disease with a dismal prognosis (1). Along this line, the need for new biomarkers is crucial for improving screening, diagnosis and treatment of HCC patients (2,3). One of the unresolved issues is that of diagnosing early HCC in order to inaugurate curative treatment and consequently increase patient survival. Diagnosis of HCC on cirrhosis may be difficult when confronted with small nodules of less than 2 cm. Diagnosis of small nodules of less than 1 cm is virtually impossible, and those of 1 to 2 cm often difficult. In this particular clinical setting, AFP is useless; its sensitivity is insufficient using the usual cut-off (2). In addition, from a diagnostic point of view, specificity must be high in order to avoid false-positive results and overdiagnosis. Several new biomarkers have shown initial promising results (lectin-bound alpha-fetoprotein AFP L3, des-gamma carboxyprothrombin DCP, prothrombin induced by the absence of vitamin K or antagonist-II PIVKA-II), but have failed to perform satisfactorily, at least in western countries (4). In the clinical setting of western scientific societies, AFP have, for the most part, been rejected for screening of cirrhotic patients for HCC and, at present, only ultrasonography every six months is recommended (5). In general, AFP is proposed only as a prognostic biomarker, and major efforts are required to identify new and robust diagnostic biomarkers. A new candidate biomarker, midkine, has emerged from a gene expression study of HCC (6) and has been extensively examined in a study recently published by Zhu WW *et al*. in *Clinical Cancer Research* (7). Midkine is a heparin-binding growth factor expressed during early embryogenesis (8). In adults, midkine is expressed only at very low levels in the kidney. However, midkine is involved in the inflammatory response, in wound repair and also in carcinogenesis (9). Midkine is overexpressed in several types of cancer, including gastric, pancreatic and colorectal cancer (10,11). Midkine acts as a ligand and uses several transmembrane receptors—ALK, LRP1, NGC or NOTCH2—to transduce the signal into the cell (9). In vitro studies suggested a role for midkine in proliferation and protection of cancer cells from drugs and autophagy, in addition to a role in neo-angiogenesis (8). A previous study by the team of XW Wang using microarray identified several genes, including GPC3, PEG10, SERPIN1, QP-C and MDK (coding for the midkine protein) as being specifically overexpressed in HCC compared to non-cancerous hepatic tissues (6). Following that study, a recent paper published by Zhu WW

*et al.* in *Clinical Cancer Research* assessed the diagnostic value of serum midkine in HCC in Chinese patient cohorts (7). First, they confirmed an increase in midkine expression in hepatocellular cell lines and in a set of HCC analyzed by immunohistochemistry. Interestingly, the serum level of midkine was correlated with the corresponding tumor level. Next, they found that the serum level of midkine was increased in patients with HCC compared to healthy patients, patients with cirrhosis, patients with benign liver tumor and patients with gastrointestinal cancer. One strength of the study lies in the validation of midkine diagnostic value and its related cut-off (0.654 ng/mL) in a second set of patients. In contrast to AFP, midkine was not significantly associated with advanced HCC or prognosis. This suggests that midkine could be used for diagnosis of early HCC. Supporting this hypothesis, the authors reported a sensitivity of 86% with a specificity of 90% in BCLC 0/A. Interestingly, serum midkine retains it diagnostic performance in AFP-negative HCC. Despite this impressive performance, some important points should be verified before translation into clinical practice. First, biomarkers should be prospectively and externally validated by another team to avoid overstatement of the discovery team. Next, most HCC included in this study developed in patients infected by chronic hepatitis B. Validation in other underlying liver diseases, including alcohol, NASH and hepatitis C, should be mandatory. Previous biomarkers (including PIV3KA, AFPL3, DCP, etc.) failed the validation step in western countries (4). This may reflect a differing carcinogenic process in non-HBV etiology. Moreover, several new diagnostic biomarkers have been recently identified by other teams, including serum DKK1, serum osteopontin and a combination of plasma microRNA (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801) (12-14). The performance of serum midkine in the diagnosis of HCC should be compared to these new biomarkers. Finally, one of the major issues is the usefulness of this biomarker in a clinical setting. The authors reported high sensitivity and specificity for diagnosis of BCLC 0/A HCC. However, diagnosis using non-invasive criteria of BCLC A (>2 cm) HCC is not difficult and the usefulness of a diagnostic biomarker in this setting is limited. The main diagnostic problem remains that of BCLC 0 HCC smaller than 2 cm, and the usefulness of a new biomarker should be tested in that particular clinical setting. In their study, Zhu WW *et al.* did not validate the diagnostic value of midkine in BCLC 0 HCC in their second set of patients (7). Moreover, we are unaware of its potential utility for small nodules of indeterminate origin, less than 2 cm and uncharacterized at imaging. Despite this limitation, the study of Zhu WW *et al.* has identified a new serum biomarker, midkine, that gives an attractive diagnostic performance for HCC (7). Additional studies are warranted in order to confirm the robustness of this data and to elucidate the potential role of serum midkine in HCC diagnosis. Consequently, there remains a long and winding road before midkine can be endorsed as a diagnostic biomarker in daily practice.

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