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FIELD OF VISION

Alpha-fetoprotein: A controversial prognostic biomarker for small hepatocellular carcinoma

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Abstract

The assessment of the prognosis in patients with early hepatocellular carcinoma represents a hot-topic issue that requires further improvements and clarifications. The life expectancy of the patients has been shown to depend on several clinical and histological parameters (such as patient's general conditions, macroscopic tumor morphology and histopathology). Recently, the prognostic role of some biomarkers [i.e., alpha-fetoprotein (AFP)] has been also investigated with controversial findings mainly on the assessment of patient survival. The study by Giannini *et al* failed to show a prognostic value of AFP on survival of patients with well-compensated cirrhosis and small hepatocellular carcinoma. Since the study presents some limitations, a larger clinical trial is needed to clarify the potential prognostic role of serum AFP levels in these patients.

Key words: Hepatocellular carcinoma; Alpha-fetoprotein; Prognosis; Cirrhosis; Biomarker

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INVITED COMMENTARY ON HOT ARTICLES

The incidence of hepatocellular carcinoma (HCC) has rapidly increased in the last decade to reach the sixth most common cancers worldwide[1]. HCC most often develops in patients with chronic liver disease, usually cirrhosis. Several therapies for HCC have been developed and can be divided into four categories: surgical interventions (tumor resection and liver transplantation), percutaneous interventions (ethanol injection, radiofrequency thermal ablation), transarterial interventions (embolization, chemoperfusion, or chemoembolization) and drugs including gene and immune therapy. However, the diagnosis and treatment of a HCC at an early stage remain the most relevant strategies to improve prognosis[2]. Several pathophysiological biomarkers have been investigated to predict HCC recurrence after liver transplantation[3]. In particular, among different gene, RNA and protein targets, the circulating levels of alpha-fetoprotein (AFP) before the liver transplantation have been recently shown to be independent predictors of HCC recurrence[3]. Firstly described by Abelev *et al*[4], AFP is a large serum glycoprotein, belonging to the class of onco-development protein[5]. It is synthesized by embryonic liver, the fetal intestinal tract and the vitelline sac cells. Similar to albumin, AFP binds and transports a large variety of ligands, such as fatty

acids, retinoids, steroids, heavy metals, dyes, flavonoids, phytoestrogens, dioxin, and various others drugs[6,7]. Previous findings by Toso *et al*[8], showing that a combined score with total tumor volume (TTV) and AFP levels (> 400 ng/mL) was capable of predicting posttransplant survival, further supported the clinical prognostic use of this biomarker in transplanted patients. In this analysis of 6478 adult recipients of an isolated first liver transplant included in the Scientific Registry of Transplant Recipients database, the authors suggested that more traditional Milan criteria might be less efficient especially in patients with large TTV[8]. Despite these promising results, the clinical use of AFP has been also shown to present some important limitations in sensitivity and specificity. In fact, low AFP levels have been described in HCC patients, while high levels might be detected in hepatic cirrhosis without HCC[2]. For instance, Sangiovanni *et al*[9] have found that the level of AFP was increased in only 38% patients developing small HCC nodules. Indeed, AFP might be also useful in detecting other tumors (such as germ cell tumors of the ovary and testis and colorectal cancer)[10,11]. Thus, although currently recommended as a fundamental parameter for HCC screening in patients with cirrhosis[2,12], the prognostic capability of AFP in patients with HCC remains controversial and with important limitations.

The article by Giannini *et al*[13] performed a retrospective analysis from the Italian Liver Cancer group and showed that serum AFP levels did not predict survival in a prospective cohort of 205 patients with well-compensated cirrhosis and small (< 3 cm) hepatocellular carcinoma (Child-Pugh class A and Eastern Cooperative Group Performance Status 0) treated with curative intent. Therefore, accordingly to the Child-Pugh score, which is used to assess the prognostic of the liver disease, and the status that indicates the severity of the disease, the patients for this study exhibit a very early stage of HCC. Interestingly, AFP failed to predict survival also when patients were sub-divided into three groups and analyzed accordingly to their alpha-fetoprotein serum levels (normal: 0-20 ng/mL, n = 116; altered: 21-200 ng/mL, n = 71; diagnostic: > 200 ng/mL, n = 18) at the time of HCC diagnosis. Authors also indicate some potential limitations underlying the study results. AFP levels were within the normal range in a large portion of the cohort, thus confirming the previously discussed limitations in sensitivity of this marker in patients with early HCC and cirrhosis[14]. These low AFP levels also contributed to determine a very low statistical power (22%) to detect differences in survival rates between patient groups. In addition, the stratification from AFP levels revealed a statistically significant difference in male gender between groups. Since AFP levels have been shown to be potentially influenced by the patient gender (increased values in women)[15], this point might represent a critical concern affecting the relevance of the negative results. Finally, potential comorbidities (such as human immunodeficiency virus co-infection previously shown to potentially influence AFP levels) were also not reported[16]. These limitations have been correctly considered by authors, who concluded that the evaluation of more accurate biomarkers (other than AFP) might improve the assessment of prognosis in patients with early HCC. We believe that the study by Giannini *et al*[13] critically confirmed important concerns on strategies targeting a single prognostic biomarker in early HCC. In fact, given several existing confounders and its potential association with HCC nodule size, AFP levels might be more perceptible and relevant in patients with advanced HCC[17]. In particular, the changes from AFP basal levels might be also useful for monitoring the treatment efficacy[18]. In agreement with Giannini *et al*[13], we support a multifactorial approach to improve the prognostic prediction in patients with early HCC. In addition, we would also suggest that larger prospective studies with appropriate statistical power are needed to really evaluate the role of AFP and other biomarkers in these patients.

In conclusion, we believe that the study by Giannini *et al*[13], focused on a hot-topic issue in the hepatological field, importantly contributed to the current debate on the clinical use of serum biomarkers in disease prognosis. Considering the substantial study limitations, larger clinical trials are needed to better evaluate the prognostic role of AFP in early HCC. The matter is opened for future studies and discussion.

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