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ABOUT COVER

Associate editor of *World Journal of Hepatology*, Dr. Yong-Ping Yang is a Distinguished Professor at Peking University Health Science Center in Beijing, China. Having received his Bachelor's degree from Yanbian University in 1985, Dr. Yang undertook his postgraduate training at PLA Medical College, receiving his Master's degree in 1992. He rose to Chief Physician in the Hepatology Division of the Fifth Medical Center of the Chinese PLA General Hospital in 2003 and has held the position since. His ongoing research interests involve liver fibrosis, cirrhosis and hepatocellular carcinoma, with a particular focus on cryoablation and cryo-immunotherapy for hepatocellular carcinoma. Currently, he serves as Chairman of the Department of Liver Disease of the Chinese PLA General Hospital and as President of the Chinese Research Hospital Association for the Study of the Liver Disease. (L-Editor: Filipodia)

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WJH mainly publishes articles reporting research results and findings obtained in the field of hepatology and covering a wide range of topics including chronic cholestatic liver diseases, cirrhosis and its complications, clinical alcoholic liver disease, drug induced liver disease autoimmune, fatty liver disease, genetic and pediatric liver diseases, hepatocellular carcinoma, hepatic stellate cells and fibrosis, liver immunology, liver regeneration, hepatic surgery, liver transplantation, biliary tract pathophysiology, non-invasive markers of liver fibrosis, viral hepatitis.

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Retrospective Study

Real impact of tumor marker AFP and PIVKA-II in detecting very small hepatocellular carcinoma (≤ 2 cm, Barcelona stage 0) - assessment with large number of cases

Kazuo Tarao, Akito Nozaki, Hirokazu Komatsu, Tatsuji Komatsu, Masataka Taguri, Katsuaki Tanaka, Makoto Chuma, Kazushi Numata, Shin Maeda

ORCID number: Kazuo Tarao 0000-0002-7161-6748; Akito Nozaki 0000-0002-3310-6632; Hirokazu Komatsu 0000-0001-9613-6698; Tatsuji Komatsu 0000-0002-8293-3773; Masataka Taguri 0000-0001-8902-0056; Katsuaki Tanaka 0000-0003-4989-2073; Makoto Chuma 0000-0002-0963-9172; Kazushi Numata 0000-0003-4671-4431; Shin Maeda 0000-0002-0246-1594.

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Kazuo Tarao, Department of Gastroenterology, Tarao's Gastroenterological Clinic, Yokohama 241-0821, Japan

Akito Nozaki, Makoto Chuma, Kazushi Numata, Gastroenterological Center, Yokohama City University Medical Center, Yokohama 232-0024, Japan

Hirokazu Komatsu, Department of Gastroenterology, Yokohama Municipal Citizen's Hospital, Yokohama 221-0855, Japan

Tatsuji Komatsu, Department of Clinical Research, National Hospital Organization Yokohama Medical Center, Yokohama 245-8575, Japan

Masataka Taguri, Department of Data Science, Yokohama City University School of Data Science, Yokohama 236-0004, Japan

Katsuaki Tanaka, Department of Gastroenterology, Hadano Red Cross Hospital, Kanagawa 221-0045, Japan

Shin Maeda, Department of Gastroenterology, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan

Corresponding author: Kazuo Tarao, MD, PhD, Director, Department of Gastroenterology, Tarao's Gastroenterological Clinic, 2-58-6, Taiyo Building Futamatagawa, Asahi-ku, Yokohama 241-0821, Japan. duoluoweih7@gmail.com

Abstract**BACKGROUND**

In hepatocellular carcinoma (HCC), detection and treatment prior to growth beyond 2 cm are relevant as a larger tumor size is more frequently associated with microvascular invasion and/or satellites.

AIM

To examine the impact of the tumor marker alpha-fetoprotein (AFP) or PIVKA-II in detecting very small HCC nodules (≤ 2 cm in maximum diameter, Barcelona stage 0) in the large number of very small HCC. The difference in the behavior of

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Tanaka K has received research funding from Bristol-Myers Squibb and Abb Vie; Nozaki A has received research funding from Gilead Sciences; Tarao K, Komatsu H, Komatsu T, Taguri M, Chuma M, Numata K and Maeda S, declare that they have no conflict of interest.

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these tumor markers in HCC development was also examined.

METHODS

A total of 933 patients with single-nodule HCC were examined. They were subdivided into 394 patients with HCC nodules ≤ 2 cm in maximum diameter and 539 patients whose nodules were > 2 cm. The rates of patients whose AFP and PIVKA-II showed normal values were examined.

RESULTS

The positive ratio of the marker PIVKA-II was significantly different ($P < 0.0001$) between patients with nodules ≤ 2 cm in diameter and those with nodules > 2 cm, but there was no significant difference in AFP ($P = 0.4254$). In the patients whose tumor was ≤ 2 cm, 50.5% showed normal levels in AFP and 68.8% showed normal levels in PIVKA-II. In 36.4% of those patients, both AFP and PIVKA-II showed normal levels. The PIVKA-II-positive ratio was markedly increased with an increase in the tumor size. In contrast, the positivity in AFP was increased gradually and slowly.

CONCLUSION

In the surveillance of very small HCC nodules (≤ 2 cm in diameter, Barcelona clinical stage 0) the tumor markers AFP and PIVKA-II are not so useful.

Key Words: Hepatocellular carcinoma; AFP; PIVKA-II; Barcelona clinical stage; Tumor markers

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Core Tip: In hepatocellular carcinoma, detection and treatment prior to nodule growth of 2 cm (Barcelona stage 0) are relevant as a larger tumor size is more frequently associated with microvascular invasion and/or satellites. We surveyed the real impact of the tumor markers alpha-fetoprotein (AFP) or PIVKA-II in detecting very small hepatocellular carcinoma with a large number of cases (≤ 2 cm in diameter 394 cases) and found in AFP that 50.5% and in PIVKA-II that 68.8% showed normal levels. Moreover, 36.4% of the patients showed normal levels in both AFP and PIVKA-II. In the surveillance of very small hepatocellular carcinoma nodules, the tumor markers are not so useful.

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INTRODUCTION

For the detection of hepatocellular carcinoma (HCC) from various liver diseases, especially liver cirrhosis, surveillance with the tumor markers, alpha-fetoprotein (AFP) and PIVKA-II, or detection with the imaging modalities, ultrasonography (US) or magnetic resonance imaging (MRI) [computed tomography (CT)], is usually performed.

Detection and treatment prior to growth beyond 2 cm are relevant as a larger tumor size is more frequently associated with microvascular invasion and/or satellites, which are major predictors of recurrence after initial effective treatment^[1]. The same tendency was observed by Stravitz *et al*^[2], and they reported that the early detection of HCC improves the prognosis.

Therefore, we must identify minute HCC nodules (≤ 2 cm in diameter) in the surveillance of HCC. Previous reports concerning the tumor markers AFP and PIVKA-II in very small HCCs included a relatively small number of cases. In this retrospective

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analysis, we examined the precise levels of these markers in a large number of very small HCC cases (< 2 cm in diameter, 394 cases) and whether the tumor marker AFP or PIVKA-II is useful to find very small HCC (≤ 2 cm in maximum diameter, Barcelona clinic liver cancer staging 0)^[3,4]. Also, we examined the difference in the behavior of these tumor markers in relation to the tumor size of HCC nodules.

MATERIALS AND METHODS

Study population

This was a retrospective study that included 933 patients with single HCC nodules who entered the following three hospitals in Yokohama City for the first time, between January 2008 and January 2019: Gastroenterological Center, Yokohama City University Medical Center, Department of Gastroenterology, Yokohama Municipal Citizen's Hospital, Department of Clinical Research, National Hospital Organization Yokohama Medical Center. HCCs were diagnosed chiefly by dynamic CT and abdominal angiography, which showed early enhancement and early wash out. This work was performed in accordance with the Declaration of Helsinki.

Previously diagnosed HCC was excluded from the protocol. This study was performed after approval by the respective institutional review boards.

The patients were classified according to etiologies of liver diseases: 72 with hepatitis B (presence of hepatitis B surface antigen in serum), 540 with hepatitis C (presence of hepatitis C antibody in serum), 10 with primary biliary cholangitis, five with autoimmune hepatitis, 70 with alcoholic liver diseases, and others (Table 1).

Measurement of PIVKA-II and AFP

Samples were collected before the treatment for HCC. Concentrations of PIVKA-II and AFP in serum samples were determined by the chemiluminescent enzyme immunoassay in all three hospitals, and the cutoff values for PIVKA-II and AFP were 40 mAU/mL and 10 ng/mL, respectively, in every hospital. For PIVKA-II and AFP, ≤ 40 mAU/mL and ≤ 10 ng/mL were set as normal values, respectively.

HCC detection

The diagnosis of HCC was confirmed by US, MRI, CT, enhanced dynamic CT, and abdominal angiography. All patients underwent abdominal angiography to confirm the single nodules. The maximum diameter of the HCC nodules was scaled by US or MRI.

Helical dynamic CT and abdominal angiography were performed in almost all patients except the patients with hypersensitivity to iodine and with advanced kidney disease. In the helical dynamic CT, an intravenous bolus injection of contrast material and sequential scanning were performed, and intense homogenous arterial-phase (early enhancement) and early washout were thought to be characteristic of HCC^[5-7]. Abdominal angiography was also performed to exclude the benign nodular lesions and to exclude the HCC patients with macrovascular invasion.

The patients with macrovascular invasion or extrahepatic metastasis were excluded. In the hepatectomy performed patients, final decision of HCC was made by pathological diagnosis and cases of benign nodules were excluded.

Statistical analysis

For the comparisons of test-positive proportions between > 2 cm and ≤ 2 cm tumors, we conducted chi-squared tests for AFP and PIVKA-II, respectively. To understand the relationships between the tumor size and test-positive proportions for AFP and PIVKA-II, we applied logistic regression models using the tumor size as an independent variable and test results (positive or not) as the dependent variable. All reported *P* values correspond to two-sided tests, and $P < 0.05$ was considered significant. All analyses were performed with Statistics Analysis System, version 9.4 (Statistics Analysis System Institute, Cary, NC, United States).

RESULTS

The clinical characteristics of the patients are summarized in Table 1. Our study included 933 HCC patients with a single nodule. In total, 622 patients were male, and 311 patients were female. The average age was 72.0 ± 9.6 years. Concerning the tumor

Table 1 Background of the hepatocellular carcinoma patients

		Maximum diameter of nodules	
		≤ 20 mm	> 20 mm
Number of patients		394	539
Sex	Male	230 (58.4%)	392 (72.7%)
	Female	164 (41.6%)	147 (22.3%)
Age in yr		71.3 ± 8.8	72.5 ± 10.1
Etiology	HBV	33 (8.4%)	39 (7.2%)
	HCV	274 (69.5%)	266 (49.4%)
	PBC	4 (1.0%)	6 (1.1%)
	Alcohol	17 (4.3%)	53 (9.8%)
	NASH	4 (1.0%)	8 (1.5%)
	Autoimmune hepatitis	3 (0.8%)	2 (0.4%)
	Unknown	23 (5.8%)	62 (11.5%)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Non-alcoholic steatohepatitis; PBC: Primary biliary cirrhosis.

size at diagnosis, 394 patients had HCC nodules ≤ 2 cm in maximum diameter, and 539 patients had nodules larger than 2 cm in maximum diameter.

The positive rates of AFP and PIVKA-II in patients whose tumor was ≤ 2 cm and those whose tumor size was more than 2 cm are shown in [Table 2](#). The level of PIVKA-II showed a significant difference ($P < 0.0001$), but there was no difference in AFP ($P = 0.4254$).

[Table 3](#) shows the rates of patients whose AFP and PIVKA-II exhibited normal values in those with a maximum tumor size of ≤ 2 cm. In AFP, 50.5% showed normal levels, and in PIVKA-II, 68.8% showed normal levels. A more important finding was that, in 36.4% of the patients, both AFP and PIVKA-II showed normal levels.

[Table 4](#) shows the treatment methods of all HCC patients. In the very small HCC patients (≤ 2 cm), the radiofrequency ablation group occupied the majority. In the relatively large HCC group (> 2 cm), treatment by transcatheter arterial chemoembolization was the most frequent, followed by hepatectomy and radiofrequency ablation.

[Figure 1](#) shows the relationship between the tumor size and PIVKA-II and AFP positivity. The PIVKA-II positive ratio was markedly increased with an increase in tumor size. In contrast, the positivity in AFP was increased gradually and slowly.

[Figure 2](#) shows the correlation between the tumor size and PIVKA-II levels. The correlation ratio was 0.5691 ($P < 0.0001$).

[Figure 3](#) shows the correlation between the tumor size and AFP levels. The correlation ratio was 0.1895 ($P < 0.0001$).

DISCUSSION

Although the early detection of HCC with imaging modalities has been developed in recent years, tumor markers are still commonly used in HCC detection and follow-up.

We demonstrated in this study that 36.4% of the patients whose maximum diameter of HCC nodules was equal to or less than 2.0 cm (Barcelona stage 0) showed normal levels of both AFP and PIVKA-II. In support of our results, it was reported that about 30% of HCC patients show false-negative results regarding tumor markers, especially in its early stage^[4-10]. Moreover, it was demonstrated that AFP has a sensitivity of about 68% in the diagnosis of HCC, but the sensitivity decreased to about 59% in its early stage^[11,12].

In recent years, Huang *et al*^[13] demonstrated that PIVKA-II combined with AFP showed a better diagnostic ability than AFP alone for HCC diagnosis. However, our study confirmed the limitation in detecting HCC in patients with very small single HCC nodules (≤ 2 cm) (Barcelona clinic liver cancer staging 0)^[3,4], even in combination with AFP and PIVKA-II.

Table 2 Positive rates of alpha-fetoprotein and PIVKA-II in patients whose tumor size was ≤ 2 cm and those whose tumor size was more than 2 cm

		Maximum diameter of HCC nodules		P value ¹
		≤ 2 cm, n = 394	> 2 cm, n = 539	
AFP	(+)	195 (49.5%)	281 (52.1%)	0.4254
	(-)	199 (50.5%)	258 (47.9%)	
PIVKA	(+)	123 (31.2%)	385 (71.4%)	< 0.0001
	(-)	271 (68.8%)	154 (28.6%)	

¹ χ^2 tests. AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

Table 3 The rates of patients whose alpha-fetoprotein and PIVKA-II showed normal values in those whose maximum tumor size was ≤ 2 cm, n = 394 cases

HCC tumor marker	No. of cases (%)
AFP, normal cases	199 (50.5)
PIVKA-II, normal cases	271 (68.8)
Both AFP and PIVKA-II, normal cases	142 (36.4)

AFP: Alpha-fetoprotein; HCC: Hepatocellular carcinoma.

Table 4 Treatment methods of hepatocellular carcinoma patients

Therapy	No of treated patients	
	Group	
	≤ 2 cm, n = 394	> 2 cm, n = 539
Hepatectomy	45	110
RFA	223	107
TACE	56	136
TACE + RFA	6	32
TAI	2	10
Chemotherapy	9	21
BSC	10	60
Others	13	63

BSC: Best supportive care; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; TAI: Transcatheter arterial infusion.

We demonstrated that more than a third of the patients with minute HCC nodules (≤ 2 cm in diameter) were dropped from surveillance using the tumor markers AFP and PIVKA-II alone. Based on the results, we must depend on imaging modalities such as US or MRI (CT) for the surveillance of minute HCC.

Colli *et al*^[14] conducted a systemic review on this issue and found that pooled estimates of 14 US studies were 60.5% (95% confidence interval (CI): 44-76) for sensitivity^[13-29], and that nine MRI studies were 80.6% (95% CI: 70-91) for sensitivity^[27,30-37]. The difference in sensitivity between US and MRI may be due to the fact that MRI is less influenced by the operator's technique and patient's body type.

More recently, Kim *et al*^[38] compared MRI and US in a cohort of 407 patients with cirrhosis who underwent 1100 surveillance examinations and found that MRI had a sensitivity of 83.7% (95% CI: 69.7%-92.2%) for early HCC detection, which was significantly higher than US (25.6%, 95% CI: 14.8%-49.4%). Thus, we must follow-up

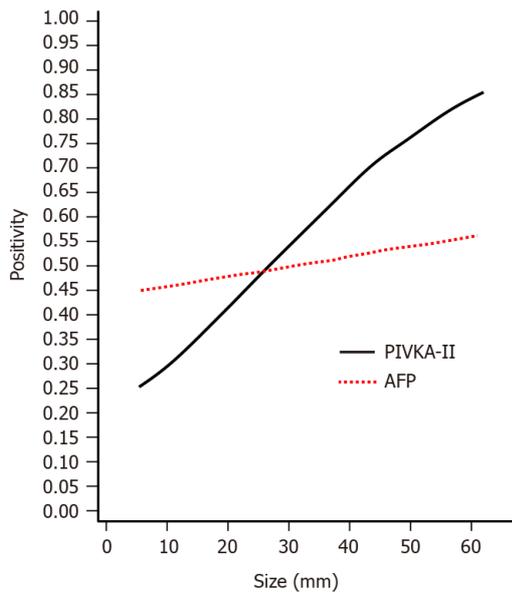


Figure 1 Relationship between tumor size and PIVKA-II and alpha-fetoprotein positivity. AFP: Alpha-fetoprotein.

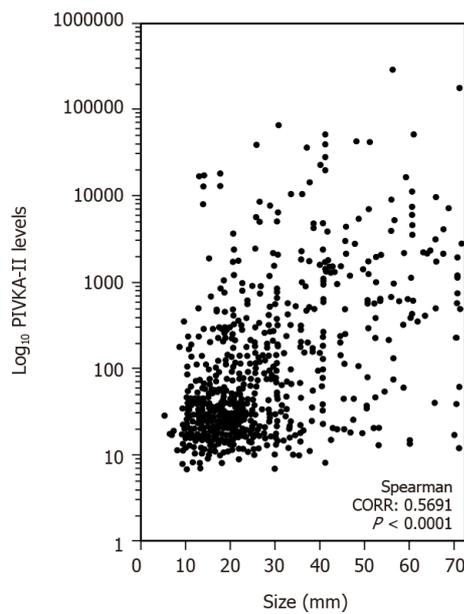


Figure 2 Correlation between tumor size and PIVKA-II levels.

patients with liver disease, especially liver cirrhosis, at regular intervals (at least every 6 mo) with MRI to detect very small HCC (diameter ≤ 2 cm).

Furthermore, we demonstrated that the PIVKA-II positive ratio was markedly increased with an increase in tumor size. In support of this phenomenon, previous studies established the correlation between the PIVKA-II level and tumor size^[16], and that PIVKA-II maintains the growth of HCC^[17]. Moreover, Ma *et al*^[18] reported direct clinical evidence of the correlation between PIVKA-II and cell proliferation.

CONCLUSION

More than one third of the patients with very small HCC nodule (≤ 2 cm in diameter, Barcelona stage 0) were dropped from the surveillance using the tumor markers AFP and PIVKA-II. So, we must survey patients with liver diseases by MRI at regular

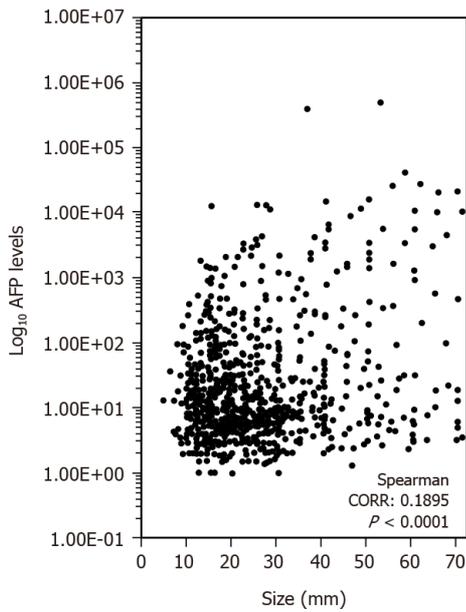


Figure 3 Correlation between tumor size and alpha-fetoprotein levels. AFP: Alpha-fetoprotein.

intervals to detect very small HCC nodules.

ARTICLE HIGHLIGHTS

Research background

In hepatocellular carcinoma (HCC), detection and treatment prior to growth of 2 cm are relevant as a larger tumor size is more frequently associated with microvascular invasion and/or satellites. However, we often experience cases whose tumor size was ≤ 2 cm and who showed normal values in both AFP and PIVKA-II.

Research motivation

Previous reports concerning the tumor markers AFP or PIVKA-II in very small HCC included relatively small number of cases, and a larger study is necessary in order to elucidate the precise levels of these markers.

Research objectives

In the present study, we surveyed the levels of AFP and PIVKA-II in a large number of very small HCC cases (≤ 2 cm in diameter, 394 cases).

Research methods

We analyzed 933 patients with single HCC nodules and surveyed the limitation of these tumor markers in the surveillance of very small HCC (≤ 2 cm, Barcelona stage 0, 394 cases).

Research results

It was found in patients with very small HCC (≤ 2 cm in diameter) that AFP and PIVKA-II levels were normal in 50.5% and 68.8%, respectively. Moreover, 36.4% of the patients showed normal levels of both AFP and PIVKA-II. We examined the difference in behavior of these tumor markers in relation to the size of HCC nodules and found that PIVKA-II positive ratio was markedly increased with an increase in tumor size, whereas the positivity in AFP was increased gradually and slowly.

Research conclusions

More than one third of the patients with very small HCC nodule (≤ 2 cm in diameter, Barcelona stage 0) were dropped from the surveillance using the tumor markers AFP and PIVKA-II.

Research perspectives

We propose that for detecting very small HCC nodules, we must survey patients with liver diseases by imaging modalities, especially by magnetic resonance imaging.

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