Liver Cancer

Editorial

Liver Cancer 2024;13:113–118
DOI: 10.1159/000537897

Received: December 14, 2023
Accepted: January 31, 2024
Published online: February 20, 2024

Urgent Global Need for PIVKA-II and AFP-L3 Measurements for Surveillance and Management of Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · PIVKA-II · DCP · AFP-L3 · Immunotherapy

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Editor *Liver Cancer*

Introduction

The incidence of hepatocellular carcinoma (HCC) is increasing worldwide [1]; therefore, early detection and treatment are critical to improve prognosis and outcomes. To ensure early diagnosis, it is essential to identify patients at high risk for HCC and to conduct surveillance through regular ultrasound (US) examinations and measurement of tumor markers. In Japan, a nationwide surveillance program based on US examinations and measurement of alpha-fetoprotein (AFP) was established during the 1980s. In 1989, measurement of protein induced by vitamin K absence or antagonist II (PIVKA-II) was approved by insurance, followed by *Lens culinaris*-agglutinin-reactive fraction of AFP (AFP-L3) in 1996. Therefore, since 1996, surveillance has been based on measurement of three tumor markers (AFP, AFP-L3, and PIVKA-II), coupled with US examination [2]. Recently, high-sensitivity AFP-L3 measurement has become extremely important for surveillance, diagnosis, and evaluation of treatment responses in patients with HCC since more HCC patients can be detected with high-sensitivity AFP-L3 while high specificity is maintained [3]. Thus, more than 60% of all HCC cases are diagnosed at the BCLC-0 and A stages. In addition, a recent report revealed that 48% of patients undergo hepatic resection as the initial treatment, and 19% of patients undergo ablation; therefore, 67% of patients receive potentially curative treatment [2]. A nationwide registry survey conducted by the Japan Liver Cancer Association during 2010–2013 revealed that the 5-year survival rate for HCC patients in Japan is 58%, with a median overall survival of 80 months (based on 58,418 HCC patients) [2]. This is the best HCC treatment outcome in the world [2, 4]. However, an increasing number of patients are being diagnosed with very large HCC tumors because they have not been captured by the surveillance program. Many of

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these cases are HCCs of nonviral etiology. Indeed, HCC of nonviral etiology accounts for more than 40% of all HCC cases in Japan; most of these are metabolic dysfunction-associated steatotic liver disease (MASLD)/metabolic dysfunction-associated steatohepatitis (MASH)-related HCC [2, 5]. Simultaneously, the number of surgical resections has increased in recent years due to identification of many more MASLD/MASH-related HCC tumors presenting with mild fibrosis (these tumors are good candidates for surgical resection) [2]. This increase in detection is likely due to the fact that Japanese practice guidelines [6, 7] do not define non-cirrhotic MASLD/MASH patients as high risk or super high risk for developing HCC; thus, even the established and successful Japanese surveillance program may not be sufficient to identify cases of non-cirrhotic MASLD/MASH-related HCC.

Recent Increasing Incidence of AFP-Negative HCC Cases: The Value of Measuring PIVKA-II

Because there is no correlation between AFP, AFP-L3, and PIVKA-II (Fig. 1), measuring two or three tumor markers rather than one increases the sensitivity of HCC detection [8, 9]. In addition, the incidence of AFP-negative HCC is increasing worldwide, particularly HCCs of nonviral etiology (Fig. 2). Alcoholic liver disease is considered high risk for development of HCC because it is often accompanied by cirrhosis; such patients are therefore a target population for HCC surveillance. However, MASLD/MASH-related HCC is a problem. In Japan, the number of MASLD/MASH-related HCC cases diagnosed with a large tumor has increased; this may be because, as mentioned above, the guideline-recommended surveillance program does not define MASLD/MASH patients without cirrhosis as a high-risk group. As has been well known, a high percentage of patients with MASLD/MASH-related HCC are positive for PIVKA-II, even those who are negative for AFP [10] (Fig. 2, 3). Higher levels of AFP-L3 have also been reported in cases of MASLD/MASH-related HCC [3]. Thus, the role of PIVKA-II and AFP-L3 measurements in HCC surveillance and diagnosis of AFP-negative HCCs has become more important.

Relevance to Evaluation and Monitoring of Treatment Responses

Traditionally, in countries other than Japan, only AFP has been used to determine responses to resection, transplantation, and locoregional therapy; however,

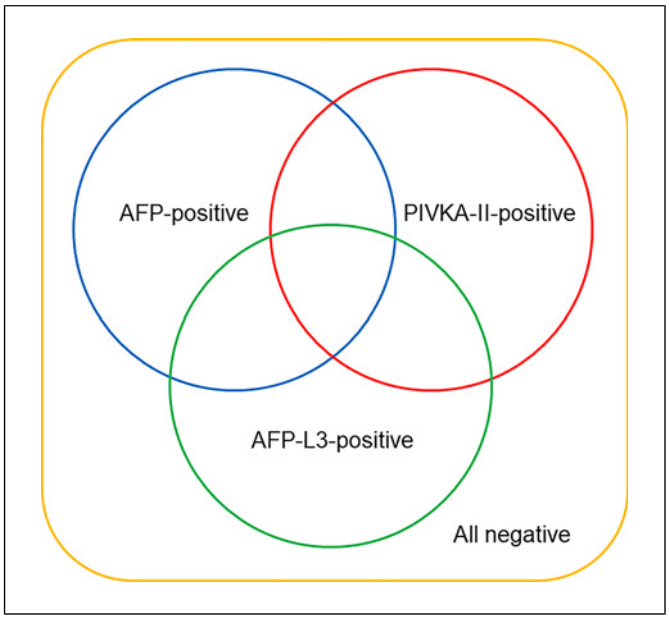

Fig. 1. There is no correlation between three tumor markers, AFP, PIVKA-II, and AFP-L3. Thus, they play a complementary role. Modified from ref #9.

diagnosis of a pathological complete response (CR) cannot be made clinically without confirmation that elevated pre-treatment PIVKA-II or AFP-L3, as well as AFP, levels have returned to normal [11–15]. By contrast, if tumor markers that were high before treatment do not return to normal or become negative, it is assumed that viable HCC remains; therefore, if any residual tumor can be located and identified, additional treatment can improve outcomes. This point is critical in countries that do not or cannot measure PIVKA-II/AFP-L3, particularly in patients who are AFP-negative. Routine assessment of these three tumor markers as a readout for treatment response is one of the reasons why the prognosis of HCC patients in Japan is better than that in other countries, even for the same BCLC-A, BCLC-B, and BCLC-C stages [4].

Particular Relevance to Systemic Therapy for HCC

Systemic therapy has progressed significantly over recent years: in addition to molecular targeted agents (MTAs) such as sorafenib, lenvatinib, regorafenib, cabozantinib, and ramucirumab, immuno-oncology agents (IOs) such as atezolizumab + bevacizumab (Atezo/Bev), durvalumab + tremelimumab (Durva/Treme), durvalumab, nivolumab, pembrolizumab, and nivolumab +

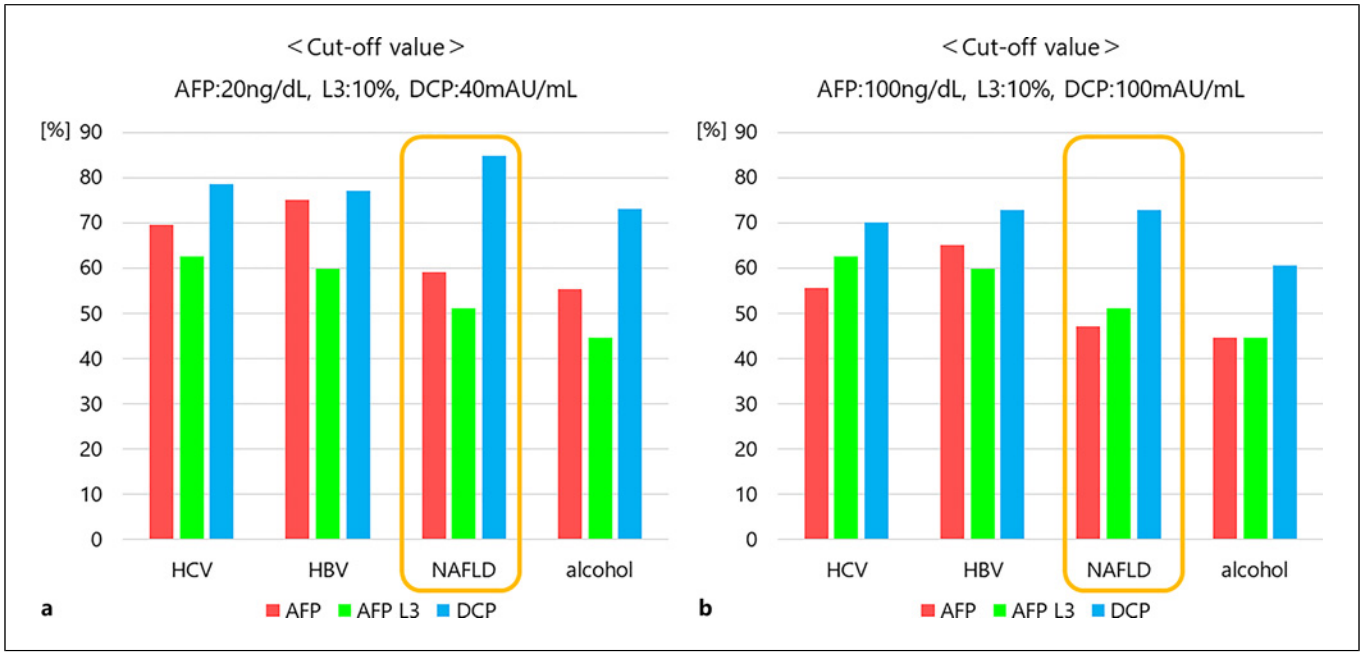

Fig. 2. Relationship between tumor marker positivity and etiology. In NAFLD-related HCC, the PIVKA-II (DCP) level is higher than that of AFP or AFP-L3. Blood samples were taken right before systemic therapy was initiated at Kindai University Hospital. **a** The cut-off values for AFP, AFP-L3, and DCP are 10 ng/mL, 10%, and 40 mAU/mL, respectively. **b** The cut-off values of AFP, AFP-L3, and DCP are 100 ng/mL, 10%, and 100 mAU/mL, respectively. NAFLD, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist II; DCP, des-gamma-carboxy-prothrombin; AFP, alpha-fetoprotein; AFP-L3, *L. culinaris*-agglutinin-reactive fraction of AFP.

ipilimumab (Nivo/Ipi) have been approved by many countries. In this era of combination immunotherapy, tumor markers and imaging play significant roles in monitoring the efficacy of these systemic therapies [16]. Measurement of PIVKA-II and AFP-L3 in routine clinical practice, in addition to imaging, is critical for evaluating treatment responses, particularly in AFP-negative HCC cases. In such cases, normalization of AFP-L3 or PIVKA-II can confirm CR or an objective response.

Duality of PIVKA-II as a Marker of Treatment Response in HCC Cases Treated with Anti-VEGF Agents

It should be noted that PIVKA-II has a duality with respect to all MTAs that exert anti-VEGF activity, including sorafenib and lenvatinib [16, 17]. In other words, PIVKA-II levels in some cases responding to anti-VEGF therapy may be elevated because the anti-VEGF agents create a hypoxic environment within a tumor, which results in vitamin K deficiency [16, 17]. This means that when PIVKA-II is elevated it can suggest one of two things: either that systemic therapy is effective or that it is ineffective and the cancer is progressing. Of course, it is essential to note that a fall in PIVKA-II to below baseline levels is considered to be an excellent response to systemic therapy. This duality is also true in cases receiving Atezo/Bev but is different in cases receiving IO monotherapy or IO-IO combination therapy (e.g., Durva/Treme and Nivo/Ipi). Since these regimens do not have anti-VEGF activity, an elevation or reduction in PIVKA-II is a reliable indicator of disease progression and treatment response, respectively.

Relevance of PIVKA-II in the Context of "Drug-Off Criteria"

Recent studies report that lenvatinib and Atezo/Bev show high objective response rates such as CR (i.e., the patient is cancer-free) in an increasing number of cases, either when used alone or in combination with locoregional therapy [18, 19]. In such cases, the question of how long to continue systemic therapy, or what criteria must be met to discontinue the drug, has

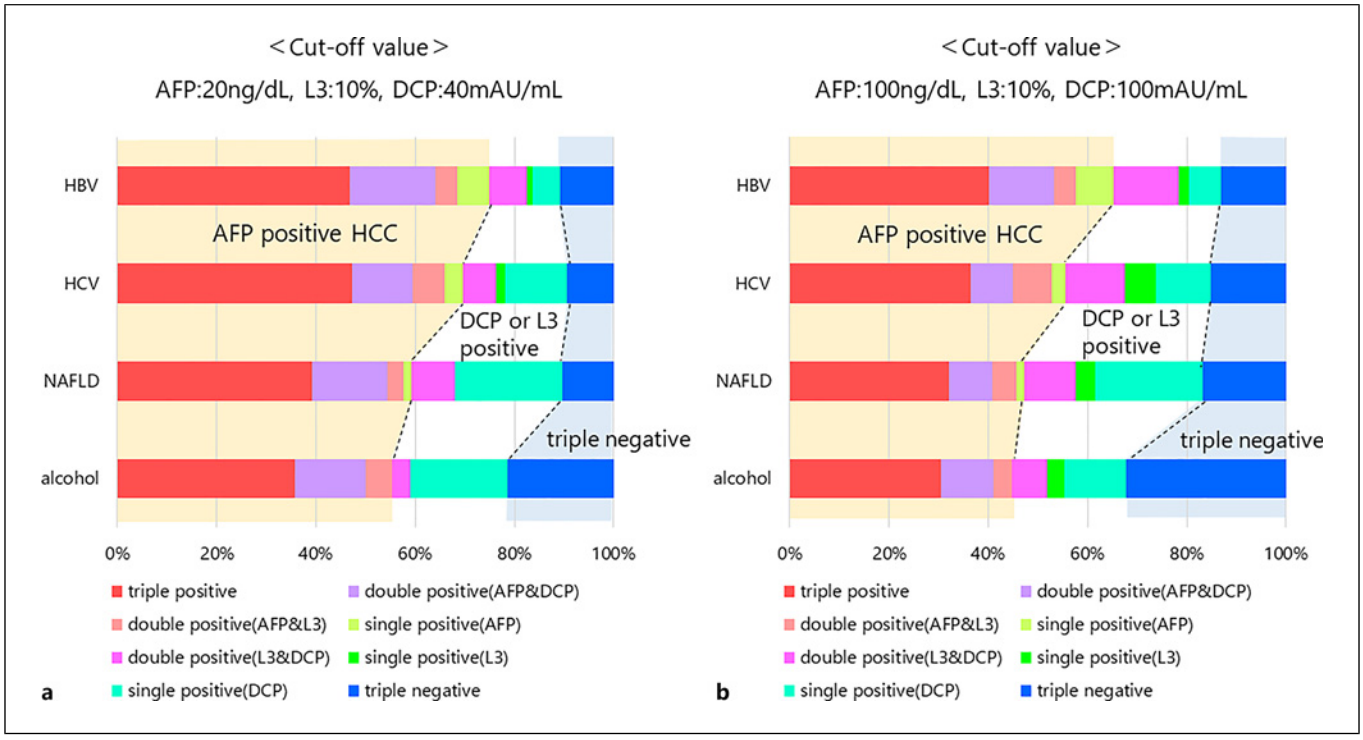

Fig. 3. Relationship between tumor marker-positive rates in cases of AFP-negative HCC and etiology. AFP-negative HCCs are positive for PIVKA-II (DCP) and AFP-L3; this is particularly true for NAFLD-related HCCs. Blood samples were taken right before systemic therapy was initiated at Kindai University Hospital. **a** The cut-off values of AFP, AFP-L3, and DCP are 10 ng/mL, 10%, and 40 mAU/mL, respectively. **b** The cut-off values of AFP, AFP-L3, and DCP are 100 ng/mL, 10%, and 100 mAU/mL, respectively. NAFLD, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma, PIVKA-II, protein induced by vitamin K absence or antagonist II; DCP, des-gamma-carboxy-prothrombin; AFP, alpha-fetoprotein; AFP-L3, *L. culinaris*-agglutinin-reactive fraction of AFP.

become significant. Recently, one "drug-off criterion" for treatment discontinuation has been proposed [19, 20]. The critical point is that at least two prerequisites should be met: CR on imaging and normalization of all three tumor markers. Normalization of AFP alone is not sufficient. Many patients achieved CR and were drug-free after treatment with Atezo/Bev, followed by curative conversion (ABC conversion) [19]. In such cases, AFP and AFP-L3 normalize relatively easily; however, PIVKA-II tends not to normalize; thus, it is essential to include PIVKA-II as a criterion for drug-off. If PIVKA-II is not normalized and remains slightly elevated, it is essential to carefully detect tumor blood flow by contrast-enhanced US (CEUS). CEUS is more sensitive than CT, MRI, DSA, or CT during hepatic arterial angiography (CTHA) for detecting intratumoural arterial blood flow [19, 20].

The relevance of achieving drug-free status in unresectable HCC is as follows: (1) even if the drug is effective at first, the tumor will eventually become resistant; (2) the treatment duration of intermediate-stage HCC is exceptionally long, and once adverse events (AEs) such as proteinuria occur, sequential treatment with other MTAs becomes difficult (in this respect, it is essential for the patient to achieve CR and become drug-free at least once; (3) even if recurrence occurs after drug-off, it is possible to achieve CR again by providing locoregional therapy, or a combination of immunotherapy and locoregional therapy; (4) there is always a risk of immune-related AEs if IO is used for a long-term period; and (5) intermediate-stage HCC has a high chance of being cured by a combination of systemic and locoregional therapies. Hence, attempting to achieve CR and drug-free status is a reasonable goal.

Pseud-Positive Cases of PIVKA-II

It should be noted that PIVKA-II can be elevated even in the absence of HCC, particularly in the population targeted for surveillance and diagnosis. PIVKA-II is

elevated in cases of vitamin K deficiency. The following conditions can give rise to a false-positive PIVKA-II result: (1) warfarin intake; (2) antibiotics with a N-methylthiotetrazole substrate; (3) obstructive jaundice associated with pancreatic head cancer, biliary tract cancer, or benign stricture of the bile duct; and (4) heavy drinking. PIVKA-II-producing tumors other than HCC are rare, but some PIVKA-II-producing gastrointestinal tract cancers (e.g., hepatoid adenocarcinoma) have been identified.

Role of the GALAD or GAAD Scores

The GALAD score, a good index for surveillance of HCC, was developed by Johnson et al. [21]. The GALAD score is calculated using a formula based on five factors: gender, age, AFP-L3, AFP, and des-gamma-carboxy-prothrombin (DCP), e.g., PIVKA-II. The utility of the GALAD score has been established by many studies; it is a more efficient marker of HCC than AFP, AFP-L3, or PIVKA-II alone [22]. The GAAD score, which excludes AFP-L3, was proposed recently due to the low probability of elevated AFP-L3 in early-stage HCC. These indices may be helpful in many Asian, and indeed some Western countries in which access to imaging tests is restricted; however, it is a well-known fact that older age and male gender are important risk factors for HCC. Japan has established a system through which patients are referred immediately for imaging tests such as CT, MRI, or CEUS if any of the three tumor markers show abnormal values, even though the GALAD score is automatically calculated by the central clinical laboratory. Therefore, the GALAD score is used rarely in Japan in practice. Instead, a rising trend in each of the three tumor markers is used as a reference, and if a clear rising trend is observed in one of these, imaging tests are performed without delay.

Conclusion and Proposals

In countries where measurement of all three tumor markers is not possible, a system that measures PIVKA-II in addition to AFP should be established as soon as possible. Also, in countries where immediate access to imaging tests is restricted, the GALAD score or GAAD score may be helpful; therefore, this system should be established first. In addition, measurement of tumor markers other than AFP should be recommended by national HCC treatment guidelines. In the USA, both PIVKA-II and AFP-L3 have been tested in detection of HCC in the phase 3 trial [23]; indeed, tests for both PIVKA-II and AFP-L3 are currently covered by insurance. Nevertheless, the reality is that tumor markers other than AFP have yet to be measured routinely. One of the reasons for this is that the Clinical Practice Guidelines of the American Association for the Study of Liver Diseases (AASLD) have not yet recommended routine measurement of PIVKA-II and AFP-L3, and some hepatologists point out that clear evidence of their efficacy is still needed. However, Japan has 35 years of experience since 1989, and many published papers show the efficacy and effectiveness of PIVKA-II and AFP-L3 measurements. The USA has also accumulated a considerable amount of data. From the first edition of the Japanese HCC treatment guidelines in 2009 until the fifth edition in 2021, it has been stated consistently that "Surveillance should be conducted using two or more tumor markers." While it is essential to develop new effective biomarkers for HCC, such as ctDNA, there is an urgent global need to establish systems that routinely measure well-established biomarkers such as PIVKA-II and AFP-L3 to detect early-stage HCC and to evaluate treatment response accurately in locoregional and systemic therapy, especially immunotherapy.

Statement of Ethics

No statement is needed because this study is based exclusively on data from the published literatures.

Conflict of Interest Statement

Lectures: Eli Lilly, Bayer, Eisai, Chugai, Takeda, and AstraZeneca. Grants: Taiho, Otsuka, EA Pharma, AbbVie, Eisai, Chugai, and GE Healthcare. Consulting: Chugai, Roche, AstraZeneca, and Eisai. Masatoshi Kudo is the Editor-in-Chief of Liver Cancer.

Funding Sources

There is no funding for this editorial.

Author Contributions

Masatoshi Kudo conceived, wrote, and approved the final manuscript.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2 Kudo M. Surveillance, diagnosis, and treatment outcome of hepatocellular carcinoma in Japan: 2023 update. Liver Cancer. 2023;12(2):95–102.

3 Nouso K, Furubayashi Y, Kariyama K, Wakuta A, Miyake N, Inoue K, et al. Abnormal fucosylation of alpha-fetoprotein in patients with nonalcoholic steatohepatitis. Hepatol Res. 2021;51(5):548–53.

4 Kudo M, Lencioni R, Marrero JA, Venook AP, Bronowicki JP, Chen XP, et al. Regional differences in sorafenib-treated patients with hepatocellular carcinoma: GIDEON observational study. Liver Int. 2016;36(8):1196–205.

5 Tateishi R, Uchino K, Fujiwara N, Takehara T, Okanoue T, Seike M, et al. A nationwide survey on non-B, non-C hepatocellular carcinoma in Japan: 2011-2015 update. J Gastroenterol. 2019;54(4):367–76.

6 Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. Liver Cancer. 2021;10(3):181–223.

7 Hasegawa K, Takemura N, Yamashita T, Watadani T, Kaibori M, Kubo S, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan society of hepatology 2021 version (5th JSH-HCC guidelines). Hepatol Res. 2023;53(5):383–90.

8 Toyoda H, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Tumor markers for hepatocellular carcinoma: simple and significant predictors of outcome in patients with HCC. Liver Cancer. 2015;4(2):126–36.

9 Toyoda H, Kumada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Prognostic significance of simultaneous measurement of three tumor markers in patients with hepatocellular carcinoma. Clin Gastroenterol Hepatol. 2006;4(1):111–7.

10 Best J, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol. 2020;18(3):728–35.e4.

11 Toyoda H, Kumada T, Tada T, Niinomi T, Ito T, Kaneoka Y, et al. Prognostic significance of a combination of pre- and post-treatment tumor markers for hepatocellular carcinoma curatively treated with hepatectomy. J Hepatol. 2012;57(6):1251–7.

12 Hayashi K, Kumada T, Nakano S, Takeda I, Sugiyama K, Kiriyama S, et al. Usefulness of measurement of Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein as a marker of prognosis and recurrence of small hepatocellular carcinoma. Am J Gastroenterol. 1999;94(10):3028–33.

13 Yamashita F, Tanaka M, Satomura S, Tanikawa K. Prognostic significance of Lens culinaris agglutinin A-reactive alpha-fetoprotein in small hepatocellular carcinomas. Gastroenterology. 1996;111(4):996–1001.

14 Toyoda H, Kumada T, Kaneoka Y, Osaki Y, Kimura T, Arimoto A, et al. Prognostic value of pretreatment levels of tumor markers for hepatocellular carcinoma on survival after curative treatment of patients with HCC. J Hepatol. 2008;49(2):223–32.

15 Kobayashi M, Ikeda K, Kawamura Y, Yatsuji H, Hosaka T, Sezaki H, et al. High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. Cancer. 2009;115(3):571–80.

16 Kodama K, Kawaoka T, Namba M, Uchikawa S, Ohya K, Morio K, et al. Correlation between early tumor marker response and imaging response in patients with advanced hepatocellular carcinoma treated with Lenvatinib. Oncology. 2019;97(2):75–81.

17 Murata K, Suzuki H, Okano H, Oyamada T, Yasuda Y, Sakamoto A. Cytoskeletal changes during epithelial-to-fibroblastoid conversion as a crucial mechanism of des-gamma-carboxy prothrombin production in hepatocellular carcinoma. Int J Oncol. 2009;35(5):1005–14.

18 Kudo M, Ueshima K, Saeki I, Ishikawa T, Inaba Y, Morimoto N, et al. A Phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with Lenvatinib in patients with unresectable intermediate-stage hepatocellular carcinoma: TACTICS-L trial. Liver Cancer. 2023;13(1):99–112.

19 Kudo M, Aoki T, Ueshima K, Tsuchiya K, Morita M, Chishina H, et al. Achievement of complete response and drug-free status by Atezolizumab plus Bevacizumab combined with or without curative conversion in patients with transarterial chemoembolization-unsuitable, intermediate-stage hepatocellular carcinoma: a multicenter proof-of-concept study. Liver cancer. 2023;12(4):321–38.

20 Kudo M. Drug-off criteria in patients with hepatocellular carcinoma who achieved clinical complete response after combination immunotherapy combined with locoregional therapy. Liver cancer. 2023;12(4):289–96.

21 Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev. 2014;23(1):144–53.

22 Berhane S, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S, et al. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. Clin Gastroenterol Hepatol. 2016;14(6):875–86.e6.

23 Tayob N, Kanwal F, Alsarraj A, Hernaez R, El-Serag HB. The performance of AFP, AFP-3, DCP as biomarkers for detection of Hepatocellular Carcinoma (HCC): a Phase 3 biomarker study in the United States. Clin Gastroenterol Hepatol. 2023;21(2):415–23.e4.