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THE ROLE OF PIVKA-II TUMOR MARKER IN HEPATOCELLULAR CARCINOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Hepatocellular carcinoma (HCC) ranks sixth among the most common malignant neoplasms in the world and accounts for about 5.6% of all human malignant neoplasms. Despite encouraging progress in the diagnosis and treatment of HCC, the prognosis remains unsatisfactory, i.e., with a 5-year overall survival rate below 10.3%. However, the survival rate can reach 50-74% if early detection and therapeutic intervention are carried out on time. However, unfortunately, about 50% of HCC cases are diagnosed at a late stage.*

The protein induced by the absence of vitamin K or antagonist-II (PIVKA-II), also known as Dez-γ-carboxyprothrombin (DCP), is another marker specific to HCC. In several studies, elevated PIVKA-II serum levels were associated with HCC. Many authors have proven the PIVKA-II applicability for HCC monitoring.

This study aimed to *compare the efficiency of alpha-fetoprotein and des-gamma-carboxyprothrombin serological markers in HCC.*

Methods: *The study included reviewing published articles on the causes of HCC and analyzing literature to compare cancer markers' efficacy, including PIVKA-II and alpha-fetoprotein (AFP), in detecting HCC.*

Results: *The published results evidence an important role of PIVKA-II in HCC early detection since PIVKA-II elevation in risk-group patients predicts HCC development in two years. Higher PIVKA-II levels can indicate a bigger tumor or a higher clinical stage. Besides, HCC patients with metastasis to the lymph nodes and distant metastasis had much higher PIVKA-II levels than non-metastatic patients. So, high PIVKA-II levels can, to a certain extent, reflect poor prognosis in HCC patients.*

Conclusion: *The reviewed publications report much higher PIVKA-II serum levels in patients with HCC than in patients with benign liver diseases or healthy people. Besides, PIVKA-II has a higher diagnostic capacity than AFP due to its higher levels, sensitivity, and specificity. Thus, we can expect high sensitivity and efficiency of the PIVKA-II tumor marker in early HCC diagnostics.*

Keywords: *Hepatocellular carcinoma, protein, liver, biomarker, serum.*

Introduction: Hepatocellular carcinoma (HCC) is the most common primary liver tumor with an aggressive course and adverse prognosis. In the case of late diagnosis and untimely treatment, the 5-year survival rate is below 15% [1]. HCC ranks 5th among the most common malignant tumors and 2nd in cancer mortality [2]. According to GLOBOCAN 2018, Kazakhstan ranks second and third in HCC incidence and mortality among Central Asian countries [3]. The highest HCC incidence and mortality are observed in the West Kazakhstan, Kyzylorda, and East Kazakhstan regions in Kazakhstan. In men, HCC incidence and mortality are twice higher as in women. HCC incidence is significantly higher in men aged 50 to 74 and women aged 55 to 79 with viral hepatitis C [4].

Due to the absence of clinical symptoms at early stages, 60% of patients are diagnosed late, often against the background of multiorgan metastasis [1, 4]. However, in early detection, the prognosis is relatively good, and the 5-year survival exceeds 70% [4-5].

There are several hypotheses for HCC carcinogenesis, but the viral theory is still dominant. Thus, the hepatitis B virus (HBV) initiates the disease development by incorporating the viral genome into the host cells of DNA, leading to translocation, point mutations, and deletions in the embedding of the virus genome. In this case, the hepatocyte DNA is reconstructed with an increase in tissue malignancy due to lower cell differentiation. The Hepatitis B surface antigen (HBsAg) suppresses the apoptosis gene p53, which is responsible for cell division suppression, leading to uncontrolled cell division. Commonly, hepatocytes express a transforming factor that induces apoptosis. In hepatitis, tumor cells lack the transforming factor α, which is suppressed by HBsAg, which leads to cell cycle disruption [6].

The prevalence of viral hepatitis B from screening in 2012 in Kazakhstan was 16.3 per 100,000 population [6]. Serological signs of past or current HBV infection are detected in about 1/3 of the global population, and 350-400 million people are chronic carriers of HBsAg [3].

The hepatitis C virus supports degenerative and necrotic hepatocyte activity. HCC is more common in patients with 1b genotype chronic viral hepatitis C, as NS5A 1b genotype HCV blocks interferon-dependent protein kinase, typically providing antiviral activity and tumor suppression. In addition, HCC can occur against congenital

liver diseases, such as hemochromatosis, α-1-antitrypsin deficiency, and tyrosinemia. Patients with these pathologies have mutations in hepatocytes genes responsible for DNA repair, cell division control, and cell apoptosis [7].

Viral hepatitis C is the leading cause of HCC in Japan, the United States, Latin America, and Europe. Every year, 2-8% of patients with chronic hepatitis C and diagnosed liver cirrhosis develop HCC. In Japan, current HCC mortality is more than threefold higher than in the mid-1970s [8, 9].

More than 6,000 cases of chronic viral hepatitis are registered annually in Kazakhstan. Of them, chronic viral hepatitis B accounts for 48%, and chronic viral hepatitis C makes up 52% of cases. The highest incidence of viral hepatitis established forms (about 87%) is registered at 30 to 60 years [7].

The third most common cause of HCC is liver alcoholic cirrhosis. In the U.S., HCC occurs in 15% of patients who consume alcohol regularly and in large doses. The main factor leading to HCC is the inflammatory process in the liver, accompanied by oxidative damage to hepatocytes [7].

Risk factors for developing HCC include:

– HBV+HCV co-infection, which increases the cumulative risk of developing HCC by 35%. HBV infection itself can lead to malignancy, even without liver cirrhosis. The five-year HCC cumulative risk in these patients ranges from 10% in the West to 15% in countries with high HCV prevalence [10];

– HCV infection, which is present in every third patient with HCC [7].

A literature review was conducted to determine the PIVKA-II efficiency as a tumor marker since early diagnosis increases the HCC treatment efficacy. The HCC prognosis depends on the tumor stage. If liver cancer is detected early, therapy after liver resection or transplantation can improve survival rates by up to 70%. However, only palliative treatment is available in advanced malignant processes, increasing patient survival by no more than one year [11].

The study aimed to compare the efficiency of alpha-fetoprotein and des-gamma-carboxyprothrombin serological markers in HCC.

Materials and methods: The study included reviewing published articles on the causes of HCC and analyzing literature to compare the efficacy of tumor markers, including PIVKA-II and alpha-fetoprotein (AFP), in detecting HCC. The sources published in English over the last five years were obtained from PubMed and Scopus databases; the review also involved domestic publications and cases interesting for evaluating the tumor markers' efficacy from a 2004 publication.

Results: Although the serum AFP is the most studied HCC marker and is considered the gold standard against which other markers are compared, about 30% of patients, especially in the disease's early stages, had an average AFP level [12]. Elevated AFP is sometimes observed in patients with liver cirrhosis or chronic hepatitis [13]. Ultrasound is an essential diagnostic tool, but its effectiveness depends on the operator's experience [12]. Accordingly, the significance of other biomarkers in diagnosing HCC, including PIVKA-II, needs to be investigated.

Currently, extrahepatic HCC lesions or multifocal tumor growth at the diagnosis is recorded in about 15% and 75% of cases, respectively. In addition, randomized controlled studies have shown that with an adequate screening at least twice a year, deaths decrease by 37% [12].

Screening methods include ultrasound, computed tomography, magnetic resonance imaging, and serological markers. In addition, we can increase the proportion of diagnosed HCC patients at an early stage and thereby increase treatment efficiency using PIVKA-II as a tumor marker.

AFP is a glycoprotein produced in the fetus's embryonic yolk sac, liver, and intestinal epithelium. This protein has a molecular mass of about 70,000 daltons and a half-life of 5-7 days. In the fetus, it performs the adult albumin functions: it transports certain substances necessary for the development of the fetus, binds estrogens, limiting their effect on the developing body, and protects against adverse impacts of the mother's immune system [13].

The reasons for AFP formation in adult patients with liver cancer have not yet been established. Embryo-specific cells are assumed to appear in a malignant tumor due to a violation of intercellular-matrix interactions. Thus, low differentiation of a new tumor cell generation resumes the process through AFP synthesis [14].

AFP has been used as a marker for diagnosing HCC since the 1970s. An increase in AFP levels of over 10 μg/L was observed in almost 75% of HCCs [15]. Serum AFP analysis is still considered the most critical marker for HCC diagnosis. This method can be used in conjunction with ultrasonography to increase diagnostic value. However, AFP values may be high in some non-malignant liver diseases (hepatitis, cirrhosis without HCC nodules) and low in some patients with HCC [16].

One of the new markers is des-gamma-carboxyprothrombin (DCT). Its level is increased in 67% of HCC patients and only 8% of patients with small tumors (<2 cm). This marker, also known as PIVKA-II (vitamin K deficiency or antagonist-II induced protein), is a pathological inactive prothrombin with insufficient carboxylation of 10 glutamic acid residues on the N-terminus, resulting from a post-translational defect of the prothrombin precursor in HCC cells. Desacarboxylated prothrombin is functionally defective due to the inability to bind calcium and phospholipids. In the case of malignant transformation in hepatocytes, the vitamin K-dependent carboxylation pathway of γ-glutamic acid is disrupted, leading to des-gamma-carboxyprothrombin (DCT) formation. Typically, PIVKA-II is absent in human serum. PIVKA-II effectively increases the detection rate of hepatocellular carcinoma so that it can be used as an adjunct to AFP. PIVKA-II is also used in the prognosis of hepatocellular carcinoma. If HCC is present, the level of this protein is much higher

than in patients with chronic hepatitis or liver cirrhosis. It has previously been argued that the sensitivity of the DCT depends on the tumor size. For example, in the case of a neoplasm larger than 5 cm, it is comparable to the sensitivity of AFP [17]. For the first time in 1984, Liebman et al. described a high level of PIVKA II in patients with initially diagnosed HCC and its recurrence. Some researchers believed that PIVKA-II was superior to AFP and could replace it in diagnosing HCC [16], but most studies did not come to that conclusion. They suggested that the combined detection of PIVKA-II and AFP could improve HCC diagnostics compared to using each biomarker separately [18].

Recently, much attention has been paid to the diagnostic role of PIVKA-II. Typically, vitamin K is necessary for synthesizing blood coagulation factors II, VII, IX, and X in the liver. The absence of vitamin K or the presence of antagonists suppresses the activity of vitamin K-dependent carboxylase, leading to impaired carboxylation of the N-terminal glutamic acid residues of blood coagulation factors. This abnormal coagulation factor cannot function as a blood clotting and is known as vitamin K deficiency prothrombin or antagonist-II (PIVKA-II) [19].

In 2009, the Japanese physicians M. Kobayashi, K. Ikeda, Y. Kawamura, et al. showed that serum levels of PIVKA-II in HCC patients were significantly higher than in patients with benign liver diseases or healthy people. Moreover, the diagnostic ability of PIVKA-II was higher than that of AFP. PIVKA-II showed higher values and greater sensitivity and specificity than AFP, as indicated by diagnostic efficacy indicators [17]. A specific increase in PIVKA-II in HCC showed PIVKA-II as a potential HCC marker. Some researchers suggested that the increased PIVKA-II levels could be caused by abnormal enzymes associated with vitamin K metabolism and generated during malignant hepatocyte transformation [18].

The studies of tumor markers showed the possibility of using PrEP for early HCC diagnosis since an increase in PrEP was observed in 67% of HCC patients. As we know, early diagnosis of HCC increases the survival rate by up to 70%.

PIVKA-II could play an important additional role for AFP, so combining PIVKA-II and AFP is more desirable. Some researchers evaluated the diagnostic value of PIVKA-II in the AFP-deficient group. In the study, PIVKA-II showed a moderate diagnostic ability for AFP-negative HCC patients, which once again proved the additional role of PIVKA-II for AFP in HCC diagnostics [18-20].

According to the articles presented in the review, PIVKA-II is more effective in HCC than other tumor markers. The collected data also suggest that PrEP with AFP might be the most efficient tumor marker.

According to the reviewed publications, a high PIVKA-II level in patients at risk indicates the development of HCC after two years. A higher PIVKA-II concentration may indicate a larger tumor volume and a higher clinical stage. Besides, HCC patients with metastasis to the lymph nodes and distant metastasis had much higher PIVKA-II levels than non-metastatic patients [21]. So, high PIVKA-II levels can reflect poor prognosis in HCC patients [22, 23].

Discussion: Thus, the diagnostic value of PIVKA-II is debatable. A correlation between PIVKA-II and AFP and whether PIVKA-II can completely replace or supplement the role of AFP in diagnosing HCC [20]. In addition, the relationship between PIVKA-II and clinical pathological characteristics, as well as the role of PIVKA-II in assessing HCC therapeutic effects, are yet to be studied. These results may contribute to a better understanding of PIVKA-II significance in HCC.

The relationship between PIVKA-II and HCC progression and prognosis has been studied. Thus, in 2017, Chinese researchers analyzed clinical and pathological characteristics, including sex, age, tumor size, number and stage, metastases, general classification, differentiation, and complications in HCC patients, and found that serum levels of PIVKA-II positively correlated with tumor stage and size. This suggests that PIVKA-II may play a role in predicting disease severity. A total of 1,016 HCC patients were detected using PIVKA-II in this study. Using the PIVKA-II tumor marker helped identify patients with primary tumors (88.7% of all examined patients); 61.3% of them had HCC metastases. PIVKA-II levels were significantly higher in patients with an advanced stage (4,650.0 mIU/mL, 667.0-33,438.0 mIU/mL) than with an early stage (104.5 mIU/mL, 61.0-348.8 Mme/mL, $P<0.001$). PIVKA-II levels were significantly higher in the relapse group than in the recovery group ($P<0.001$). A total of 1,054 PIVKA-II-positive patients without HCC were selected. Most of them had liver cirrhosis (46.3%), followed by hepatitis (20.6%) and benign nodules (15.3%).

Several studies of PIVKA-II have mentioned its role in assessing the treatment effect. Analysis of changes in serum levels of PIVKA-II in HCC patients treated surgically showed a significant difference in serum levels of PIVKA-II in HCC patients before and after surgery. This suggests the possibility of using PIVKA-II as an indicator for assessing the therapeutic effects of liver cancer surgery. In addition, changes in PIVKA-II levels after surgery were more significant than changes in AFP levels, which may be due to a shorter serum half-life of PIVKA-II (40-72 h) than that of AFP (5-7 days) [24, 25]. This evidence suggests that PIVKA-II may better reflect the treatment effects of liver cancer surgery.

Thus, PIVKA-II can be considered a promising biomarker for diagnosing HCC. However, most studies have shown no correlation between PIVKA-II and AFP in HCC, and some have shown little correlation.

Conclusion: The presented literature review on laboratory diagnostics of HCC and the use of PIVKA-II as a screening biomarker showed the relevance and timeliness of PIVKA-II determination in HCC and its significance in this disease diagnosis and prognosis. For the first time, this method was introduced into clinical diagnostics at the «National Scientific Center of Surgery named after A.N. Syzganov» JSC

at the end of 2021. Currently, the material is being collected for a complete analysis of the use of PIVKA-II in HCC. We hope to obtain and publish statistically reliable and scientifically based HCC diagnosis and prognosis results.

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АҢДАТПА

ГЕПАТОЦЕЛЛЮЛЯРЛЫҚ КАРЦИНОМАДАҒЫ PIVKAII ОНКОМАРКЕРІНІҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *гепатоцеллюлярлық карцинома (ГЦК) әлемдегі ең көп таралған қатерлі ісіктердің арасында алтыншы орын алады және адамның барлық қатерлі ісіктерінің 5,6%-ын құрайды. ЦКБ диагностикасы мен емдеудегі үміт күттіретін прогреске қарамастан, болжам қанағаттанарлықсыз болып қалуда, яғни 5 жылдық жалпы өмір сүру деңгейі 10,3%-дан төмен. Алайда, егер ерте анықтау және емдік араласу уақтылы жүргізілсе, өмір сүру деңгейі 50-74% жетуі мүмкін. Бірақ, өкінішке орай, ЦКБ жағдайларының шамамен 50%-ы кеш сатысында диагноз қойылады.*

Зерттеу мақсаты: *ГЦК жанындағы альфа-фетопротеин және дес-гамма-карбоксипротромбин серологиялық маркерлерінің тиімділігін салыстыру.*

Әдістері: *скрининг, ультрадыбыстық зерттеу, гепатоцеллюлярлық карциноманы ерте диагностикалау үшін онкомаркерлерді қолдану.*

Нәтижелері: *онкомаркерлерге жүргізілген зерттеулер кезінде дес-гамма-карбоксипротромбин (ДКП) пайдалану кезінде деңгейінің жоғарылауы ГЦК-мен ауыратын науқастардың 67%-ында байқалатын ерте диагностика жүргізуге болатындығы атап өтілді. Гепатоцеллюлярлық карциноманы ерте диагностикалау кезінде біз білетіндей, пациенттердің өмір сүру деңгейі 70%-га дейін артады. DCP PIVKA-II ретінде де белгілі (К дәрумені немесе антагонист-II болмауынан туындаған ақуыз).*

Қорытынды: *К дәрумені немесе антагонист-II (PIVKA-II) болмауынан туындаған ақуыз, сонымен қатар дез-γ-карбоксипротромбин (DCP)-бұл ГЦК-ге тән тағы бір маркер. Сарысудағы PIVKA-II деңгейінің жоғарылауы ГЦК-мен байланысты болатын зерттеулер бар. Көптеген зерттеулер PIVKA-II ГЦК-ны бақылау үшін қолданылатынын және ұсыныста ұсынылғанын көрсетті жапондық бауыр қоғамы, PIVKA-II биомаркерінің анықтамасы өте жақсы нәтижелерге қол жеткізуге мүмкіндік береді.*

Түйінді сөздер: *гепатоцеллюлярлық карцинома, ақуыз, бауыр, биомаркер, сарысу.*

АННОТАЦИЯ

РОЛЬ ОНКОМАРКЕРА PIVKA-II ПРИ ГЕПАТОЦЕЛЛЮЛЯРНОЙ КАРЦИНОМЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Гепатоцеллюлярная карцинома (ГЦК) занимает шестое место по распространенности среди злокачественных новообразований в мире и составляет около 5,6% всех злокачественных новообразований человека. Несмотря на обнадеживающий прогресс в диагностике и лечении ГЦК, прогноз остается неудовлетворительным, поскольку 5-летняя общая выживаемость не превышает 10,3%. Однако при раннем выявлении и своевременном лечебном вмешательстве выживаемость может достигать 50-74%. К сожалению, около 50% случаев ГЦК диагностируется на поздней стадии.*

Белок, индуцируемый отсутствием витамина К или антагонистом-II (PIVKA-II), также известный как дез-γ-карбоксипротромбин (ДКП), является маркером, специфичным для ГЦК. Есть исследования, где повышенный уровень PIVKA-II в сыворотке был связан с ГЦК. Многие авторы показали, что PIVKA-II применим для наблюдения за ГЦК.

Цель исследования *– сравнение эффективности серологических маркеров альфа-фетопротеина и дес-гамма-карбоксипротромбина при ГЦК.*

Методы: *Был проведен обзор опубликованных статей о причине возникновения ГЦК и анализ литературных данных для сравнения эффективности онкомаркеров, в частности сероlогического маркера PIVKA-II и альфа-фетопротеина (АФП), в определении ГЦК.*

Результаты: *Опубликованные данные показывают важную роль онкомаркера PIVKA-II для ранней диагностики ГЦК, поскольку повышение уровня PIVKA-II у пациентов из группы риска является индикатором развития ГЦК через два года. Более высокая концентрация PIVKA-II может указывать на больший объем опухоли и более высокую клиническую стадию. Кроме того, уровни PIVKA-II у пациентов с ГЦК с метастазами в лимфатические узлы и отдаленными метастазами были значительно выше, чем у пациентов без метастазов, поэтому высокая концентрация PIVKA-II может в некоторой степени отражать плохой прогноз у пациентов с ГЦК.*

Заключение: *Согласно включённым в анализ публикациям, уровни PIVKA-II в сыворотке у пациентов с ГЦК были значительно выше, чем уровни, наблюдаемые у пациентов с доброкачественными заболеваниями печени и у здоровых людей. Более того, диагностическая способность PIVKA-II выше, чем у АФП: PIVKA-II показал более высокие значения и большую чувствительность и специфичность, чем у АФП. Таким образом, можно предположить высокую чувствительность и эффективность онкомаркера PIVKA-II при ранней диагностике ГЦК.*

Ключевые слова: *гепатоцеллюлярная карцинома (ГЦК), белок, печень, биомаркер, сыворотка.*

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