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Review article

Research progress of protein induced by vitamin K absence or antagonist II in liver transplantation for hepatocellular carcinoma

Zheyu Zhou [a,1], Qiaoyu Liu [b,1], Jinsong Liu [c,d,1], Wenwen Li [e], Shuya Cao [f], Jiawei Xu [g], Jun Chen [h,**], Xiaoliang Xu [b,*], Chaobo Chen [i,***]

[a] *Department of General Surgery, Nanjing Drum Tower Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Graduate School of Peking Union Medical College, Nanjing, China*
[b] *Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China*
[c] *Department of Colorectal and Anal Surgery, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*
[d] *Shanghai Colorectal Cancer Research Center, Shanghai, China*
[e] *Jiangsu Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, Nanjing University of Chinese Medicine, Nanjing, China*
[f] *Hepatobiliary Center, The First Affiliated Hospital of Nanjing Medical University, Key Laboratory of Liver Transplantation, Chinese Academy of Medical Science, NHC Key Laboratory of Living Donor Liver Transplantation (Nanjing Medical University), Nanjing, China*
[g] *Department of Hepatobiliary and Transplantation Surgery, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China*
[h] *Department of Pathology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China*
[i] *Department of General Surgery, Xishan People's Hospital of Wuxi City, Wuxi, China*

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ABSTRACT

Hepatocellular carcinoma (HCC) is the most common pathologic type of primary liver cancer. Liver transplantation (LT) is a radical strategy for treating patients with early-stage HCC, which may lead to a better prognosis compared to hepatectomy and ablation. However, survival of patients who develop HCC recurrence after LT is short, and early recurrence is the most common cause of death. Thus, efficient biomarkers are also needed in LT to guide precision therapy to improve patient prognosis and 5-year survival. Protein induced by vitamin K absence or antagonist II (PIVKA-II) is an abnormal prothrombin that cannot activate coagulation, and it is significantly increased in patients with HCC, obstructive jaundice, and those taking vitamin K antagonists. Over the past decades, substantial progress has been made in the study of PIVKA-II in diagnosing, surveilling, and treating HCC, but its role in LT still needs to be elaborated. In this review, we focused on the role of PIVKA-II as a biomarker in LT for HCC, especially its relationship with clinicopathologic features, early recurrence, long-term survival, and donor-recipient selection.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: ichenjun@qq.com (J. Chen), xuxiaoliang1990@yeah.net (X. Xu), bobo19820106@gmail.com (C. Chen).
[1] These authors contributed equally to this work.

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1. Introduction

Primary liver cancer is the third leading cause of cancer-related deaths worldwide, with hepatocellular carcinoma (HCC) being its most common pathologic type, accounting for 75–86% of all cases [1]. Despite the spread of hepatitis B virus (HBV) vaccines in regions such as Asia and the continued development of effective antiviral drugs, HBV and hepatitis C virus infections remain the leading cause of HCC in many parts of the world [2]. Notably, alcohol- and non-alcoholic fatty liver disease (NAFLD)-related HCC morbidity and mortality due to lifestyle changes continue to rise [3]. Furthermore, NAFLD-related HCC patients are now the fastest-growing population of LT candidates [4].

Liver transplantation (LT) can cure HCC and underlying liver disease and is the best treatment strategy for patients with early-stage HCC with multifocal tumors or hepatic dysfunction who are not candidates for hepatectomy [5]. Compared with hepatectomy or ablation, the risk of HCC recurrence is significantly reduced after undergoing LT (5-year recurrence rate: 0–10% vs. 50–60%), and the median survival time can reach ten years [6]. However, the median survival of patients with early recurrence of HCC after LT is less than one year due to the use of immunosuppressive agents and the low probability of re-resection after recurrence [5,7]. Therefore, early identification of risk factors affecting recurrence and long-term survival in LT recipients is essential to improve prognosis. Efficient biomarkers are also needed to guide precision therapy.

Protein induced by vitamin K absence or antagonist II (PIVKA-II), alpha-fetoprotein (AFP), and AFP-L3 are currently the three most commonly used tumor markers for HCC. AFP combined with ultrasound is a recommended screening strategy for HCC [5], but a meta-analysis reported that the sensitivity of the combined diagnosis was only 63% [8]. Meanwhile, the sensitivity and specificity of AFP alone for detecting HCC are low, especially for small HCC [9,10]. The most significant advantage of AFP may be its economic cost-effectiveness, with a detection price of about 1/5 of PIVKA-II and 1/6 of AFP-L3. AFP-L3% is an essential complement to AFP and can be used to identify the nature of liver lesions when AFP is elevated [11]. Besides, a prospective cohort study reported that 34.3% of HCC patients presented with elevated AFP-L3% one year before diagnosis when their AFP levels were low and imaging was

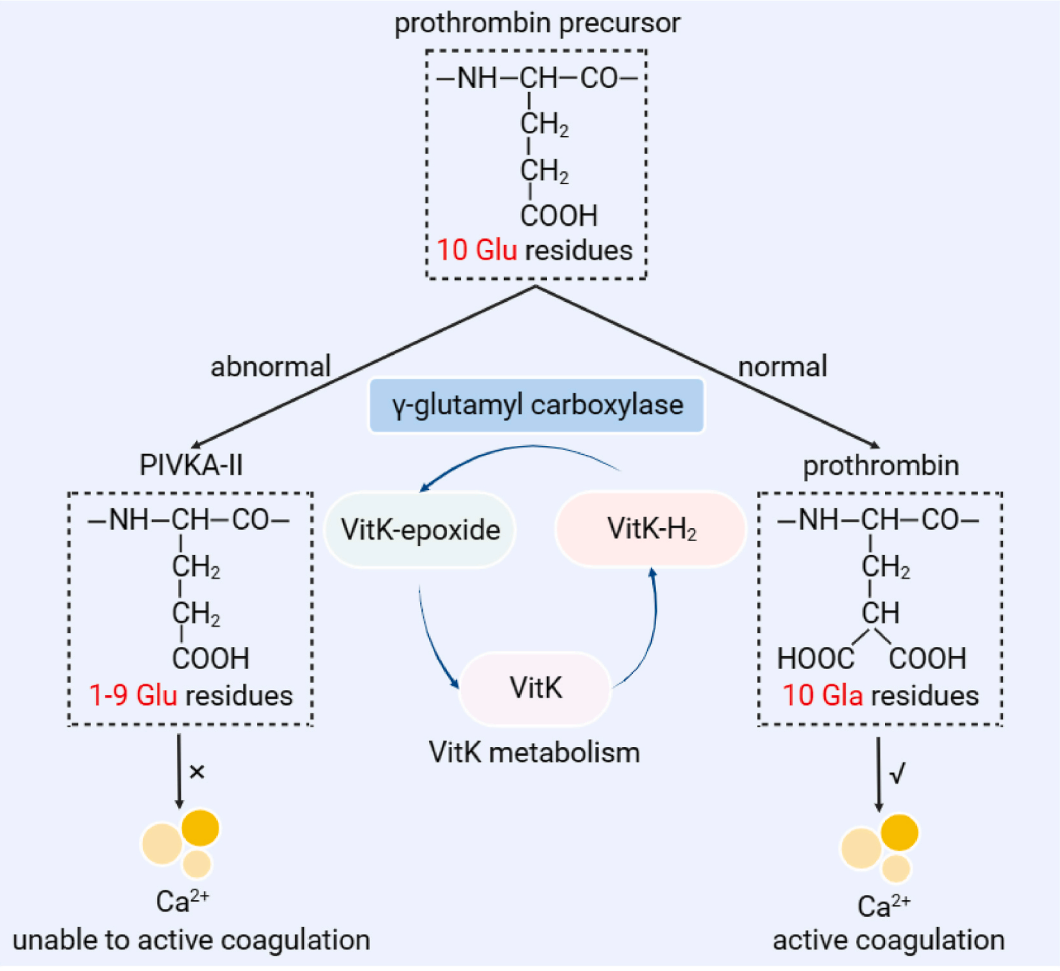

Fig. 1. Generation mechanism of PIVKA-II. PIVKA-II, protein induced by vitamin K absence or antagonist II; VitK, vitamin K; Glu, glutamic acid; Gla, γ-carboxy glutamic acid.

unremarkable [12]. However, simultaneous testing for AFP and AFP-L3 may add to the financial burden of patients. Previous studies showed that PIVKA-II had a higher positivity rate than AFP in detecting resectable HCC and predicting early recurrence of HCC after hepatectomy [13,14]. A recently published expert consensus also affirmed the clinical usefulness and value of PIVKA-II in monitoring treatment outcomes and recurrence after the operation [15]. Although the role of PIVKA-II in the diagnosis, surveillance, and treatment of HCC has been demonstrated [16], its role in LT requires further elaboration.

Herein, we summarized and discussed the clinical application of PIVKA-II in LT for HCC, especially its relationship with clinicopathologic features, early recurrence, long-term survival, and donor-recipient selection.

2. PIVKA-II and its specialized variant

2.1. Generation mechanism of PIVKA-II

The prothrombin precursor usually generates prothrombin (coagulation factor II) in the liver in a vitamin K-dependent manner [17]. This is a post-translational modification reaction in which the 10 glutamic acid (Glu) residues of the N-terminal domain of the prothrombin precursor are modified to 10 γ-carboxy glutamic acid (Gla) residues by γ-glutamyl carboxylase [18]. However, in HCC tissues, in the absence of vitamin K or the presence of vitamin K antagonists, this carboxylation reaction is disturbed, and an abnormal prothrombin (PIVKA-II) is formed. Thus, the N-terminal domain of PIVKA-II is present with 1–9 Glu residues and cannot bind Ca^{2+} [16] (Fig. 1).

2.2. Detection and clinical application of NX-DCP

Non-HCC patients with obstructive jaundice, vitamin K deficiency, taking vitamin K antagonists, or other diseases may produce a specific PIVKA-II variant called next-generation des-γ-carboxy prothrombin (NX-DCP) [19,20]. Previous studies have shown that PIVKA-II from HCC patients usually carries 6–9 Glu residues, whereas NX-DCP usually carries 1–5 Glu residues [21]. NX-DCP may play an important role in the differential diagnosis of HCC: the PIVKA-II/NX-DCP ratio > 1.5 suggests the presence of HCC, whereas ≤ 1.5

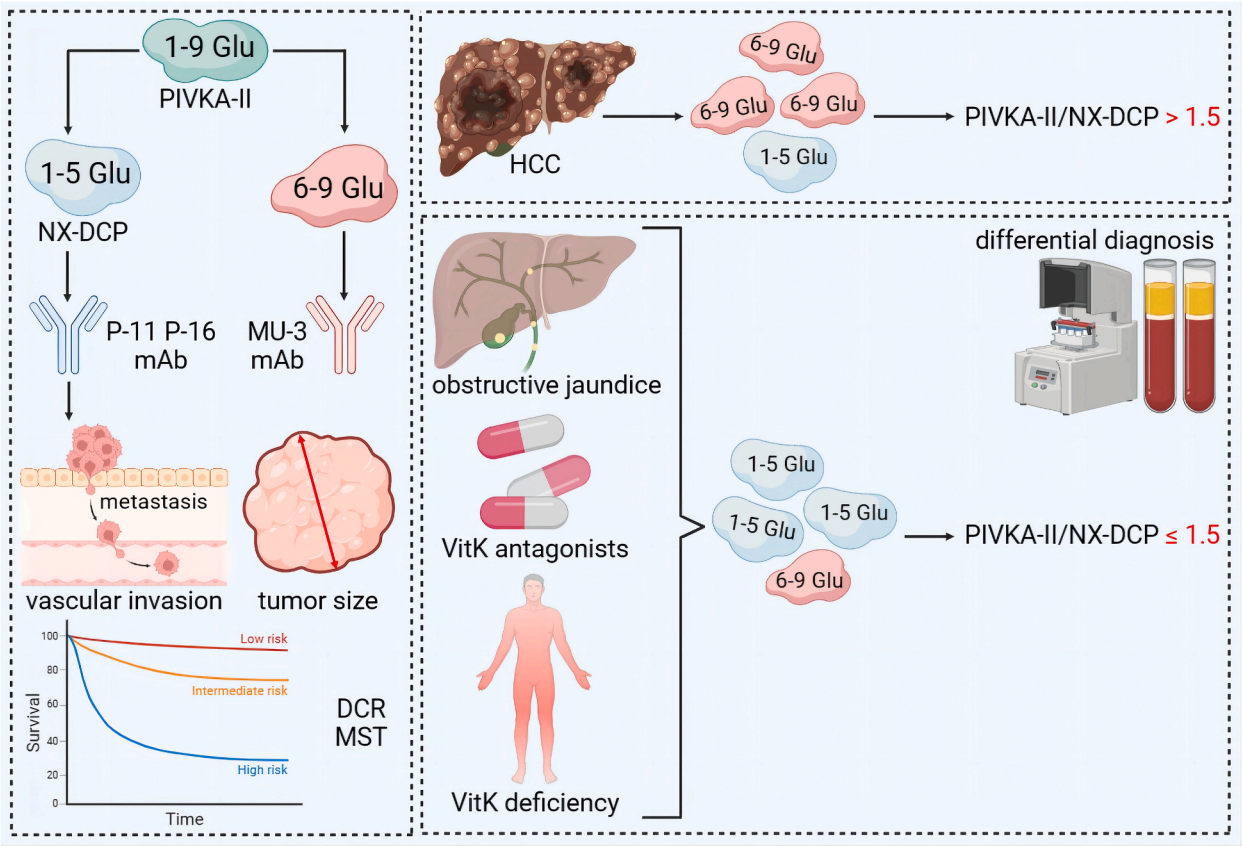

Fig. 2. Detection and clinical application of NX-DCP. NX-DCP, next-generation des-γ-carboxy prothrombin; PIVKA-II, protein induced by vitamin K absence or antagonist II; HCC, hepatocellular carcinoma; Glu, glutamic acid; mAb, monoclonal antibody; DCR, disease control rate; MST, median survival time; VitK, vitamin K.

suggests the presence of other non-HCC diseases such as obstructive jaundice [21,22].

In addition, NX-DCP expression may correlate with clinicopathologic features of HCC patients. Sumi A et al. [23] demonstrated that high NX-DCP expression in HCC tissues was associated with a significantly lower frequency of intrahepatic metastasis and portal vein (PV) invasion. Secondly, NX-DCP $\geq$ 90 mAU/mL and the PIVKA-II/NX-DCP ratio $\geq$ 1.5 were associated with significantly larger tumor size and more frequent PV invasion. Studies by Kurokawa T et al. [24] and Yamazaki S et al. [25] also found that NX-DCP had a higher sensitivity for detecting vascular invasion (VI) in HCC than PIVKA-II and AFP. Sorafenib was the first targeted drug used in treating HCC, and a Japanese retrospective study evaluated for the first time the effect of sorafenib on serum NX-DCP in HCC patients. The median serum NX-DCP and PIVKA-II increased 1.20-fold and 1.58-fold after treatment with sorafenib. Patients with more than a 2-fold increase in both markers had significantly higher rates of disease control and more prolonged median survival than patients with a more than 2-fold increase in PIVKA-II and a less than 2-fold increase in both markers [26]. This was associated with the inhibition of neovascularization by sorafenib, leading to hypoxia, which reduced vitamin K uptake and utilization [26,27] (Fig. 2). Hence, we speculated that when VI occurred in HCC, the blood supply to non-cancerous liver tissues was compromised, resulting in hypoxia and the generation of NX-DCP.

In summary, understanding the generation mechanism of PIVKA-II provides a theoretical basis for future therapies targeting PIVKA-II. Since the paucity of studies involving NX-DCP in HCC, further elucidation of the relationship and potential mechanisms of NX-DCP with treatment response, VI, and intrahepatic metastasis is needed in the future.

3. PIVKA-II and LT

3.1. PIVKA-II and clinicopathologic characteristics of LT recipients

Careful pathologic examination of explant livers in LT recipients can provide valuable prognostic information. Two previous studies have analyzed the relationship between PIVKA-II levels and VI occurrence in LT recipients. As a result, PIVKA-II levels were significantly higher in the high microvascular invasion (MVI) group (defined as having multiple invading vessels with more than 50 intravascular cancer cells) compared to the non-MVI group (mean $\pm$ standard deviation [SD]: 279.2 $\pm$ 1484.0 vs. 1219.8 $\pm$ 2540.1, $p = 0.018$). Besides, high MVI was an independent prognostic factor for recurrence-free survival (RFS) for all 142 included patients and 61 patients who exceeded the Milan criteria ($p = 0.030$ and 0.014) [28]. Similarly, Sakai K et al. [29] reported that living donor LT (LDLT) recipients with histologically confirmed hepatic vein or PV invasion had higher preoperative PIVKA-II levels than patients who were negative for VI (mean: 2511.7 vs. 134.8).

Tumor size in LT recipients has been proven to be an independent risk factor for HCC recurrence after LT [30]. A study that included 46 patients undergoing orthotopic LT (within the Milan criteria) revealed a significant positive correlation between PIVKA-II levels and tumor size ($p = 0.003$) [31]. Downstaging to LT is defined as using locoregional therapy (LRT) (such as ablation, transarterial chemoembolization [TACE], and transarterial radioembolization) to reduce tumor size to meet the LT criteria [32]. Most patients in the above study received at least one TACE before LT, and PIVKA-II levels significantly correlated with the number of preoperative TACE ($p = 0.011$) [31]. This reflected more advanced HCC in some LT recipients.

Complete pathological response (CPR) is an essential concept after LRT: $\geq$99% of the total HCC volume is extensively necrotic, with no live tumor cells in any node [33]. Due to the loss of live HCC cells led by CPR, it is considered a reliable indicator of a favorable prognosis after LT [34]. Follow-up data from Kim MJ et al. [33] also confirmed significantly lower HCC recurrence rates at 1, 3, and 5 years in CPR patients compared to pre-LT partial pathological response (PPR) patients (5.1%, 7.6%, and 7.6% vs. 15.3%, 20.9%, and 25.4%, $p < 0.001$). Importantly, preoperative PIVKA-II levels were significantly lower than those of patients in the PPR group (mean $\pm$ SD: 46.7 $\pm$ 126.2 vs. 77.4 $\pm$ 164.4, $p < 0.001$), and receiver operating characteristic curve analysis showed that the critical value of PIVKA-II between the two groups was 29 mAu/mL. Furthermore, the return to normalization of PIVKA-II and AFP after LRT was a marker for CPR [33].

Table 1
Effect of PIVKA-II on HCC recurrence after LT.

Study	LT type	Cohort size (No. of recurrence)	Cut-off value of PIVKA-II	RR/HR (95 % CI)	*p*
Shindoh J et al., 2014 [39]	LDLT	120 (11)	449 mAu/mL	1.03 (1.01–1.05)	0.004
Lee JY et al., 2014 [40]	LDLT and DDLT	93 (18)	100 mAu/mL	11.42 (2.04–63.83)	0.006
Chaiteerakij R et al., 2015 [41]	NM	127 (41)	7.5 ng/mL	3.50 (1.90–6.70)*	<0.001
Harimoto N et al., 2016 [42]	LDLT	190 (28)	300 mAu/mL	4.24 (1.64–10.93)	0.003
Togashi J et al., 2016 [43]	LDLT	139 (11)	200 mAu/mL	6.20 (1.31–29.45)	0.022
Kim SH et al., 2016 [44]	LDLT	461 (77)	100 mAu/mL	3.30 (1.80–6.06)	0.000
Wongjarupong N et al., 2018 [45]	NM	113 (38)	1.2 ng/mL	2.69 (1.28–5.64)	0.009
Yonemura Y et al., 2020 [46]	LDLT	43 (NM)	300 mAu/mL	9.36 (2.41–36.40)	0.001
Hwang HS et al., 2022 [47]	LDLT	25 (4)	100 mAu/mL	14.64 (1.08–198.20)	0.043
Norman JS et al., 2023 [48]	NM	285 (18)	7.5 ng/mL	24.2 (8.0–73.7)*	<0.001

Notes: PIVKA-II: 1 ng/mL = 52.6 mAu/mL; *Univariate cox proportional hazards analysis.
Abbreviations: PIVKA-II, protein induced by vitamin K absence or antagonist II; HCC, hepatocellular carcinoma; LT, liver transplantation; RR, relative risk; HR, hazard ratio; CI, confidence internal; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; NM, not mentioned.

The incidence of portal vein tumor thrombus (PVTT) is high in HCC patients, which is considered a poor prognostic factor for HCC and a contraindication for LT [35]. Meanwhile, the PIVKA-II level was verified to correlate with developing PVTT in HCC patients. When the cut-off value was 221.26 mAU/mL, PIVKA-II had a sensitivity of 83.7% to detect PVTT in HCC [36]. Nevertheless, several studies explored the prognosis of patients with PVTT undergoing LT [35,37]. HCC patients with type 1 or 2 PVTT (Cheng's classification, tumor thrombus is not expanded to the main PV) could consider LT an acceptable treatment option when preoperative AFP $\leq$ 100 ng/mL or AFP $\times$ PIVKA-II (AP) score $<$ 20000 [35,37].

In short, the close relationship between PIVKA-II and various prognosis-related clinicopathologic features suggests that it is a reliable biomarker in LT for HCC.

3.2. PIVKA-II and HCC recurrence after LT

The prognosis for patients with recurrent HCC after LT is usually poor, with $<$ 20% of patients eligible to undergo hepatectomy. Moreover, recurrent patients are not candidates for immune checkpoint inhibitors due to the use of immunosuppressive agents [5]. Of the 857 patients who underwent LT at the University of California-Los Angeles between 1984 and 2014, 106 patients experienced HCC recurrence, with a median survival of only 10.6 months after recurrence [38]. Therefore, recurrence after LT is the most common cause of death in HCC patients [5], and early identification of independent risk factors for recurrence is crucial for postoperative management and follow-up strategies. Previous studies have shown that preoperative PIVKA-II levels are vital for HCC recurrence in LDLT and deceased donor LT [39–48] (Table 1).

Lee JY et al. [40] reported a Korean cohort including 93 patients who underwent LT, of whom 84 (90.3%) underwent LDLT and 21 (22.6%) had preoperative PIVKA-II $>$ 100 mAU/mL. The mean follow-up of the cohort was 923 $\pm$ 344 days, and the 1- and 3-year recurrence rates of HCC were 12.9% and 19.4%. Multivariate Cox regression analysis certified that PIVKA-II $>$ 100 mAU/mL was an independent risk factor for 1- and 3-year recurrence after LT ($p = 0.006$ and 0.021, hazard ratio [HR] = 11.42 and 4.25). Norman JS et al. [48] established a prospective cohort including 285 patients undergoing LT. At a median follow-up of 3.1 years, 18 (6.3%) patients experienced HCC recurrence. The authors compared the ability of PIVKA-II, AFP, and AFP-L3 in predicting HCC recurrence, and the result indicated that PIVKA-II and AFP-L3 outperformed AFP (C-statistics were 0.86, 0.81, and 0.74, respectively). PIVKA-II $\geq$ 7.5 ng/mL and AFP-L3 $\geq$ 15% were able to predict 61.1% recurrence, and for patients with this biomarker combination, the 3-year RFS rate was only 43.7% compared to 97.0% for other patients ($p < 0.001$). At the same time, in another retrospective study that included a total of 639 LT patients from five transplant centers in Japan and Europe, PIVKA-II was found to be the most relevant independent risk factor for recurrence after LT after analysis by the inverse probability therapy weighting method (with the highest HR = 2.0, $p <$ 0.001). Additionally, a sub-analysis of AFP-negative ($\leq$ 20 ng/mL) HCC patients still confirmed the negative effect of PIVKA-II on recurrence (HR = 2.06, $p = 0.004$), suggesting that the role of PIVKA-II is independent of AFP status [49]. What is more, Devillers MJC et al. [50] also verified that PIVKA-II might be a better predictor for RFS rate in HCC patients with a low AFP level ($\leq$ 8 ng/mL) after LT.

Two previous meta-analyses published in 2016 evaluated whether PIVKA-II is a biomarker of LT recurrence. The study by Lai Q et al. [51] included three papers with disease-free survival (DFS) data with close thresholds for PIVKA-II (range 300–442 mAu/mL), and the results indicated a solid relationship between shorter DFS and elevated PIVKA-II levels (HR = 5.04, $p < 0.001$). Another meta-analysis included four comparable papers with thresholds for PIVKA-II of 100–400 mAu/mL, which also demonstrated a strong correlation between PIVKA-II and recurrence rate (HR = 5.99, $p < 0.001$) [52]. There was good homogeneity between the included studies (both $I^2 = 0\%$).

3.3. PIVKA-II and long-term survival after LT

5-year survival is an indicator of long-term survival in cancer patients, and the clinical cure of cancer is usually considered to be the absence of recurrence after five years of receiving treatment [53]. The effect of PIVKA-II on early recurrence after LT has been reviewed above, and the longer follow-up time makes it possible to study the effect of PIVKA-II on long-term survival in LT recipients [45,46,54–57] (Table 2).

Advanced HCC is defined as a maximum tumor diameter of $\geq$ 10 cm or the presence of $\geq$ 10 tumor nodules or with macrovascular invasion, and it is considered to be a contraindication to LT [58]. However, data from 146 patients with advanced HCC at 8 LT centers

Table 2
Effect of PIVKA-II on long-term survival of recipients after LT.

Study	LT type	Post-transplant survival	Cut-off value of PIVKA-II	OR/HR (95 % CI)	*p*
Harada N et al., 2012 [54]	LDLT	72.6% 5-year OS	300 mAu/mL	14.62 (1.16–185.10)	0.038
Harimoto N et al., 2015 [55]	LDLT	78.8% 5-year RFS	300 mAu/mL	4.08 (1.14–14.55)	0.030
Wongjarupong N et al., 2018 [45]	NM	66.3% 5-year OS	1.2 ng/mL	2.33 (1.31–4.13)	0.004
Toshima T et al., 2020 [56]	LDLT	81.3% 5-year OS	200 mAu/mL	2.68 (1.34–5.17)	0.006
Yonemura Y et al., 2020 [46]	LDLT	61.7% 5-year OS*	300 mAu/mL	13.8 (1.92–98.60)	0.010
Ishii M et al., 2023 [57]	LDLT, DDLT, and domino LT	39.2% 5-year CSS*	1976 mAu/mL	1.59 (1.07–2.36)	0.020

Notes: PIVKA-II: 1 ng/mL = 52.6 mAu/mL; *Beyond the Japan criteria.
Abbreviations: PIVKA-II, protein induced by vitamin K absence or antagonist II; LT, liver transplantation; OR, odd ratio; HR, hazard ratio; CI, confidence internal; LDLT, living donor liver transplantation; OS, overall survival; RFS, recurrence-free survival; NM, not mentioned; DDLT, deceased donor liver transplantation; CSS, cancer-specific survival.

in Korea showed that PIVKA-II and AFP could provide reliable information on tumor biology in this group of patients. Compared with patients with PIVKA-II (mAu/mL) + AFP (ng/mL) > 300, patients with PIVKA-II + AFP ≤ 300 (45 patients, 30.8%) had significantly higher 5-year overall survival (OS) and RFS rates (21.0% and 10.8% vs. 47.8% and 53.4%, $p < 0.001$) [58]. Salvage LT is a currently supported strategy for patients undergoing hepatectomy and developing HCC recurrence or residual hepatic decompensation. A research team from Kyushu University in Japan reported the outcomes of 114 patients who underwent salvage LDLT for HCC recurrence and achieved RFS rates of 80.4% and 78.8% at 3 and 5 years, respectively. Subsequent multivariate analysis revealed that PIVKA-II ≥ 300 mAu/mL was an independent predictor of RFS [55]. Furthermore, Toshima T et al. [56] retrospectively analyzed data from 193 patients who underwent LDLT, of whom death occurred in 42 patients. A nomogram based on the multivariate Cox regression model was established, and PIVKA-II > 200 mAu/mL (HR = 2.68, $p = 0.006$) was a significant influencer of 1- and 5-year OS.

The ADV score integrates three variables: PIVKA-II, AFP, and tumor volume. It is calculated as the logarithmic value of the product of the above metrics (log10), which is thought to reflect HCC aggressiveness. Previous studies have certified that HCC patients with ADV scores ≤ 4log10 benefit significantly from anatomic hepatectomy [59]. Studies of two Korean cohorts by Hwang S et al. [60] and Park GC et al. [61] demonstrated that an ADV score threshold of 5log10 could prognostically stratify HCC recurrence and OS in LT recipients. Moreover, the ADV score could further prognostically stratify patients within and outside other LT criteria (such as the Milan and UCSF). For instance, patients who met the Milan criteria with an ADV score of < 5log10 had a 5-year OS rate of 94.7%, whereas patients who met the Milan criteria or had an ADV score of < 5log10 and those who exceeded the Milan criteria and had an ADV score of ≥ 5log10 had 5-year OS rates of 86.2% and 60.4%, respectively ($p < 0.001$) [61].

3.4. PIVKA-II and selection of LT recipients

As is known, the Milan criteria is the best selection criteria for LT recipients, with the lowest recurrence rate (10–15%) after LT [62,63]. However, since the Milan criteria limitations on tumor size and number have deprived many HCC patients of LT, the liver transplant community is committed to expanding the indications for recipients in order to allow more HCC patients to benefit from this procedure. As mentioned above, PIVKA-II has become one of the critical variables for assessing early recurrence and long-term survival of HCC LT recipients. The role of PIVKA-II in the selection of LT recipients has also been investigated [30,60,61,64–70] (Table 3).

A recent retrospective study including 6 LT centers in China proved that the inclusion of PIVKA-II in the existing LT criteria could increase the number of eligible HCC patients without affecting the prognosis of LT. Multivariate Cox regression analysis identified PIVKA-II > 240 mAu/mL as an independent risk factor for DFS after LT (HR = 1.558, $p = 0.047$). This group of patients had significantly lower DFS rates at 1, 3, and 5 years compared with patients with PIVKA-II ≤ 240 mAu/mL (75.1%, 58.5%, and 50.5% vs. 83.2%, 77.3%, and 75.9%, $p < 0.001$). The authors established the new HC&PIVKA-II criteria after including PIVKA-II in the Hangzhou criteria: (i) tumor burden ≤ 8 cm; (ii) tumor burden > 8 cm, but with Edmondson-Steiner grade I/II and one eligible tumor marker (PIVKA-II ≤ 240 mAu/mL or AFP ≤ 400 ng/mL). Notably, the HC&PIVKA-II criteria increased the number of LT-eligible HCC recipients by 66 (21.6%) and 169 (83.7%) compared with the Hangzhou and Milan criteria. Subsequent prognostic analyses found no significant differences in 1- and 3-year DFS and 1-, 3-, and 5-year OS between patients who exceeded the Hangzhou/Milan criteria but were eligible for HC&PIVKA-II criteria compared with those who were eligible for Hangzhou/Milan criteria (the smallest $p = 0.245$) [64].

One Japanese LT center proposed the Kyushu criteria in 2009: PIVKA-II < 300 mAu/mL or maximum tumor diameter < 5 cm [30]. To confirm the rationality of the Kyushu criteria as a selection criterion for LDLT, a 7-year prospective study was carried out. For

Table 3
New LT expanded criteria incorporating PIVKA-II.

Expanded criteria		Post-transplant survival
HC&PIVKA-II criteria [64]	(i) tumor burden ≤ 8 cm (ii) tumor burden > 8 cm, but with Edmondson-Steiner grade I/II and one eligible tumor marker (**PIVKA-II ≤ 240 mAu/mL** or AFP ≤ 400 ng/mL)	73.7%–78.4% 3-year DFS 74.7%–82.3% 5-year OS
ADV score [60,61]	≤ 5 $\log_{10}$ [AFP (ng/mL) × **PIVKA-II (mAu/mL)** × tumor volume (mL)]	82.2% 10-year RFS 87.6% 10-year OS
A-P 200 criteria [65]	AFP ≤ 200 ng/mL and **PIVKA-II ≤ 200 mAu/mL**	88.5%–89.9% 3-year DFS 89.2% 3-year OS
New Kyoto criteria [66]	At least two eligible variables: number of tumors ≤ 5 with maximum tumor diameter ≤ 5 cm, or AFP ≤ 250 ng/mL, or **PIVKA-II ≤ 450 mAu/mL**	96.8% 5-year DFS 84.0% 5-year OS
Kyushu University criteria [30,67]	maximum tumor diameter < 5 cm or **PIVKA-II < 300 mAu/mL**	87.0% 5-year RFS 82.7%–89.4% 5-year OS
Kyoto criteria [68–70]	Number of tumors ≤ 10, maximum tumor diameter ≤ 5 cm, and **PIVKA-II ≤ 400 mAu/mL**	95.0%–97.0% 5-year RFS 87.0%–89.0% 5-year OS

Abbreviations: LT, liver transplantation; PIVKA-II, protein induced by vitamin K absence or antagonist II; HC: Hangzhou; AFP, alpha-fetoprotein; DFS, disease-free survival; OS, overall survival; RFS, recurrence-free survival.

patients who underwent LT in the pre-Kyushu era, whether or not within the Milan criteria had a significant effect on the RFS rate, disease-specific survival (DSS) rate, and OS rate (97.2% vs. 67.5%, $p < 0.001$; 100% vs. 74.8%, $p < 0.001$; 91.9% vs. 63.5%, $p < 0.001$). In contrast, the effect of the Milan criteria on prognosis disappeared in the post-Kyushu era (90.1% vs. 80.4%, $p = 0.218$; 96.7% vs. 92.3%, $p = 0.536$; 91.3% vs. 82.1%, $p = 0.272$) [67].

In a study published in 2007 by the University of Tokyo, which included 136 HCC patients who underwent LDLT, the authors proposed a new LT expanded criteria based on the results of the multivariate analysis of risk factors for recurrence: number of tumors $\leq$ 10, maximum tumor diameter $\leq$ 5 cm, and PIVKA-II $\leq$ 400 mAu/mL. The 83 patients who met the new criteria had a significantly higher 5-year survival rate (87% vs. 37%, $p < 0.0001$) and a lower 5-year recurrence rate (5% vs. 61%, $p < 0.0001$) than the 44 patients who exceeded the new criteria [68]. In a subsequent study published in 2009, the authors defined the above new criteria as the Tokyo criteria for the first time and compared them with the Milan criteria. The results revealed that the 28 patients who exceeded the Milan criteria but met the Tokyo criteria had a lower 5-year recurrence rate and higher 5-year survival rate (4% vs. 7% and 89% vs. 78%) than the 79 patients who met the Milan criteria [69]. With increasing sample size and longer follow-up, subsequent studies indicated that the 5-year OS rate of HCC patients meeting the Tokyo criteria remained more than 80%, which was not statistically different from that of the Milan criteria [70]. The above results confirmed that the Tokyo criteria was a useful expanded LT criteria.

Only one single-center prospective study from the United States evaluated the role of PIVKA-II, AFP, and AFP-L3 in predicting the waitlist dropout in LT. At a median follow-up of 19.3 months, 59 (22.1%) of the initial 267 HCC patients were still waiting for LT, 145 (54.3%) had received LT, and 63 (23.6%) had experienced the waitlist dropout. Multivariate modeling analysis demonstrated that PIVKA-II $\geq$ 7.5 ng/mL (HR = 2.20, $p = 0.02$) and AFP-L3 $\geq$ 35% (HR = 2.25, $p = 0.04$) were associated with the waitlist dropout. The subsequent Kaplan-Meier analysis showed that 100% of patients with a combination of both markers experienced a waitlist dropout ($p < 0.001$) [71]. This suggested that patients with PIVKA-II $\geq$ 7.5 ng/mL may not be ideal LT recipients.

In brief, selecting suitable LT recipients is essential for long-term survival and prevention of early recurrence. Routine dynamic testing of the PIVKA-II level for patients on the waiting list may be critical to the success of LT. Finally, particularly for HCC patients receiving downstaging therapies, there is a need to ensure that PIVKA-II is reduced to a low level.

3.5. PIVKA-II and LT donors

As with LT recipient factors, clinical characteristics of the LT donor have been proven to influence the prognosis of recipients. For instance, older donor age is a risk factor for LT failure, and a study including 80,347 LT patients in Europe demonstrated a higher survival rate for transplanted livers originating from donors under 55 years of age [72]. In addition, donor-to-recipient gender mismatch, especially Female-to-Male mismatch, had a deleterious role in transplanted liver survival (odds ratio [OR] = 1.83, $p = 0.005$) [73]. However, only two studies have focused on PIVKA-II levels in LT donors.

Suehiro T et al. [74] collected clinical data on 90 LT donors, of which 27 (30.0%) were positive for PIVKA-II (greater than 62.5 mAU/mL). The findings certified that recipients receiving positive PIVKA-II donor livers required more intraoperative transfusions (platelets, fresh frozen plasma, and packed red blood cells, $p = 0.0001$) and were more likely to develop postoperative hepatic insufficiency (significantly higher levels of alanine aminotransferase, aspartate aminotransferase, and prothrombin time). Multivariate analysis showed that donor PIVKA-II positivity was an independent preoperative risk factor for poor early graft function (OR = 6.58, $p = 0.0032$). In LDLT, donor liver regeneration is also essential in determining the procedure's success. A prospective study by Satilmis B et al. [75] analyzed preoperative and postoperative laboratory data from 63 donors. It indicated that PIVKA-II, one of the liver regeneration-associated markers, was significantly increased on the third postoperative day ($p = 0.007$).

In a word, the impact of donor factors on LT outcomes should receive more attention. As discussed above, non-tumor patients may also produce PIVKA-II and NX-DCP. Detecting their levels in LT donors may provide new insights into improving LT outcomes.

4. Conclusion and future prospective

In summary, PIVKA-II has become a validated biomarker in HCC and also plays a vital role in predicting clinicopathologic features, early recurrence, long-term survival, and donor/recipient selection in LT.

Elevated PIVKA-II levels can not only directly affect RFS and OS after LT but also significantly correlate with other independent risk factors for poor prognosis (e.g., VI, tumor size, and CPR). Differences in cohort size, race, and other aspects of different studies may have contributed to the differences in the PIVKA-II cut-off value. However, most results suggested that exceeding 100 mAu/mL significantly increased the risk of recurrence and other adverse events. Previous experiments have shown that PIVKA-II promotes the growth, invasion, and metastasis of HCC by enhancing tumor angiogenesis, cell proliferation, and extracellular matrix synthesis, among other mechanisms [76–78]. Besides, both Ohira M et al. [79] and Hwang HS et al. [47] reported that detectable circulating tumor cells and high levels of PIVKA-II were concurrently associated with HCC recurrence. This suggested that elevated PIVKA-II was associated with a higher degree of malignancy and tumor aggressiveness in HCC, which may be the reason for its unfavorable prognostic impact on LT.

Because donor livers are precious, it is crucial to identify HCC recipients who will benefit from LT more accurately. PIVKA-II showed the ability to further prognostic stratification for already recognized LT criteria (e.g., Milan and UCSF criteria). The new LT criteria incorporating PIVKA-II could increase the number of target recipients without affecting or even improving the prognosis, which helped to improve the fairness of graft allocation and the outcome after LT. It remains important to validate the new expanded criteria in multicenter prospective studies before being applied worldwide, like the Milan criteria.

Adjuvant therapy hepatic artery infusion chemotherapy with FOLFOX significantly improved DFS in HCC patients with MVI, a

high-risk factor for recurrence, after undergoing hepatectomy [80]. A previous meta-analysis evaluating the efficacy and necessity of adjuvant chemotherapy after LT demonstrated a significant benefit of adjuvant chemotherapy compared to controls on OS (HR = 0.34, $p = 0.000$) and DFS (HR = 0.87, $p = 0.004$) but did not significantly reduce the risk of HCC recurrence (HR = 1.26, $p = 0.696$) [81]. However, there are no recommendations for recurrence prevention after LT, and there is a lack of recognized adjuvant treatment options supported by evidence [82]. In future prospective clinical trials, high-risk populations with significantly elevated PIVKA-II levels and exceeding each LT criteria are essential criteria for screening the adjuvant treatment intention to treat population.

To our knowledge, no studies have reported clinical application of NX-DCP in LT for HCC. As a specialized variant of PIVKA-II, whether NX-DCP can be a new marker in LT is also worth investigating, especially in predicting clinicopathologic features, early recurrence, long-term survival, and donor/recipient selection.

In conclusion, the role of PIVKA-II in LT for HCC should be emphasized more. With a deeper understanding and more rational application of PIVKA-II, more LT recipients will benefit from individualized precision medicine in the future.

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Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed in this study.

CRediT authorship contribution statement

Zheyu Zhou: Writing – original draft, Conceptualization. **Qiaoyu Liu:** Writing – original draft. **Jinsong Liu:** Writing – original draft. **Wenwen Li:** Visualization. **Shuya Cao:** Visualization. **Jiawei Xu:** Visualization. **Jun Chen:** Writing – review & editing, Supervision. **Xiaoliang Xu:** Writing – review & editing, Supervision, Funding acquisition. **Chaobo Chen:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviation table

HCC	hepatocellular carcinoma
LT	liver transplantation
PIVKA-II	protein induced by vitamin K absence or antagonist II
HBV	hepatitis B virus
NAFLD	non-alcoholic fatty liver disease
AFP	alpha-fetoprotein
Glu	glutamic acid
Gla	γ-carboxy glutamic acid
NX-DCP	next-generation des-γ-carboxy prothrombin
PV	portal vein
VI	vascular invasion
MVI	microvascular invasion
SD	standard deviation
RFS	recurrence-free survival
LDLT	living donor liver transplantation
LRT	locoregional therapy
TACE	transarterial chemoembolization
CPR	complete pathological response
PPR	partial pathological response
PVTT	portal vein tumor thrombus
HR	hazard ratio
DFS	disease-free survival

OS	overall survival
DSS	disease-specific survival
OR	odds ratio

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