scientific reports

Check for updates

OPEN

Prothrombin-induced by vitamin K absence II as a prognostic factor in living donor liver transplantation for hepatocellular carcinoma

Abu Bakar Hafeez Bhatti[1,2]✉, Usman Shafique[1], Nazish Ahmed[1], Ghazanfar Abbas[3], Muslim Atiq[4], Haseeb Haider Zia[1], Nusrat Yar Khan[1] & Atif Rana[5]

In hepatocellular carcinoma (HCC), there is a need for novel tumor markers to enhance patient selection for liver transplantation. This study evaluates the prognostic value of Prothrombin Induced by Vitamin K Absence-II (PIVKA-II) in predicting microvascular invasion (MVI) and post-transplant recurrence, either alone or in combination with alpha-fetoprotein (AFP), following living donor liver transplantation (LDLT). We reviewed 400 patients who underwent LDLT under expanded criteria (largest tumor diameter ≤ 10 cm, any tumor number, AFP < 1000 ng/ml). PIVKAII outperformed AFP and tumor size in predicting MVI, with a C-statistic of 0.777 compared to 0.579 and 0.631. On multivariate analysis, AFP > 20 ng/ml [HR 3.3, *P* = 0.003] and PIVKAII > 1000 mAU/ml [HR 3.5, *P* = 0.001] were predictors of recurrence. PIVKAII > 1000 mAU/ml was associated with MVI (21.6% vs. 65.7%, *P* < 0.001) and lower 5-year RFS (79% vs. 50%, *P* < 0.001). A combination of AFP > 20 ng/ml and PIVKAII > 1000 mAU/ml predicted 47.1% of recurrences, whereas HCC recurred in 6.1% of patients not meeting this threshold. The 5-year RFS was 45% for dual tumor marker positive HCC versus 77% for all others (*P* < 0.001). PIVKAII is a strong predictor of MVI and post-transplant recurrence. Dual tumor marker-positive HCC can serve as an exclusion criterion for upfront LDLT.

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide[1]. Due to underlying liver cirrhosis, liver transplantation (LT) represents the most effective treatment in carefully selected patients[2]. Even though Milan Criteria (MC) is considered restrictive, it is associated with low recurrence rates and favorable post-transplant outcomes[3,4]. Liberal expansion outside the MC is associated with high recurrence rates unless additional markers of tumor biology are used for patient selection[5]. Alpha-fetoprotein (AFP) is a key marker and has been extensively studied in LT. An AFP level exceeding 1000 ng/ml is a strong indicator of microvascular invasion (MVI) and post-transplant recurrence, leading the United Network for Organ Sharing (UNOS) to use it as an exclusion criterion[6,7].

Tradeoffs between tumor size, tumor number, and AFP levels in the expanded criteria improve patient selection by keeping the rates of MVI and post-transplant recurrence within acceptable limits[5,8,9]. However, AFP is not a perfect tumor marker as some patients with AFP non-secreting HCC still experience post-transplant recurrence[7]. Prothrombin induced by vitamin K absence or antagonist II (PIVKAII), also known as des-gamma-carboxy prothrombin (DCP), is a form of prothrombin lacking carboxylation due to some HCC cells not expressing the vitamin K-dependent carboxylase enzyme. It has a role in the diagnosis and surveillance of HCC, and its association with unfavorable biology including poor grade, MVI, and post-transplant recurrence is being actively investigated[7,10,11].

Living donor liver transplantation (LDLT) provides a unique opportunity to perform LT outside the MC due to the low risk of waitlist mortality and lack of competition for donor organs[12]. The International Liver Transplant Society (ILTS) working group on HCC recommends that a 5-year overall survival (OS) of 60% should be achieved in waitlisted patients who undergo LDLT[13]. To achieve these outcomes in expanded criteria, balancing tumor morphometrics with tumor markers is a valuable approach, although it may be challenging in

[1]Department of HPB Surgery and Liver Transplantation , Shifa International Hospital Islamabad , Islamabad, Pakistan. [2]Department of Surgery , Shifa Tameer-e-Millat University Islamabad , Islamabad , Pakistan. [3]Department of Pathology , Shifa International Hospital Islamabad , Islamabad , Pakistan. [4]Department of Gastroenterology and Hepatology , Shifa International Hospital Islamabad , Islamabad , Pakistan. [5]Department of Radiology , Shifa International Hospital Islamabad , Islamabad , Pakistan. ✉email: abubakar.hafeez@yahoo.com; abubakar.hafeez@shifa.com.pk

cases of low AFP HCC[14]. Although, few studies from Japan have previously evaluated pre-transplant PIVKAII levels in LDLT, there was only moderate expansion beyond the MC[15–17].

Since 2018, we have been regularly monitoring PIVKAII levels in HCC patients, and this study aimed to evaluate its effectiveness in predicting MVI and post-transplant recurrence, either alone or in combination with AFP.

Methods

Study population

In this single-center retrospective cohort study, patients who underwent LDLT with a pre-transplant diagnosis of HCC between April 2012 and March 2024 were reviewed. Out of 400 patients with a pre-transplant diagnosis of HCC, 81 were excluded, as shown in Fig. 1, and the final cohort included 319 patients.

The diagnosis of HCC was based on a liver dynamic computed tomography (CT) or magnetic resonance imaging (MRI) scan showing characteristic features of HCC[18]. Tumor marker levels were performed within 3 months of LDLT. Upfront LDLT was considered for patients with HCC meeting the University of California San Francisco (UCSF) criteria[19]. Given the short waiting time, typically less than four weeks, no additional oncologic treatment was administered during this period. For patients outside the UCSF criteria but fulfilling our center-specific selection parameters (i.e., largest tumor < 10 cm, any number of tumors, and alpha-fetoprotein [AFP] < 1000 ng/mL), downstaging with trans arterial chemoembolization (TACE) or ablation was recommended. In cases where loco regional therapy (LRT) was not feasible, due to decompensated liver disease or patient's decision to proceed with transplantation, upfront LDLT was offered[19,20]. Patients not meeting our center-specific criteria were required to undergo downstaging for a period of 3–6 months with LRT and systemic therapy, if there was no evidence of extrahepatic disease. LDLT was considered if radiological response was achieved and AFP levels decreased to below 1000 ng/ml. Lenvatinib is our preferred systemic agent owing to its favorable side effect profile, ease of administration, and cost-effectiveness. LRT was employed as a bridging strategy if a delay in LT of approximately three months was anticipated. The Modified Response Evaluation Criteria in Solid Tumors (mRECIST) was used to assess response to LRT and patients with complete or partial response were considered good responders, while those with progressive or stable disease were considered poor responders[20,21]. All transplants were performed following comprehensive evaluation and consensus in multidisciplinary and transplant assessment meetings, with subsequent approval from the Human Organ and Tissue Transplant Authority (HOTA). All donors were related to their respective recipients, either legally or by blood.

Patient demographics, etiology of liver disease, tumor morphometrics, Model for end-stage liver disease-sodium (MELD-Na) score, tumor marker levels, neutrophil to lymphocyte ratio (NLR), response to LRT, and explant features including poor differentiation and MVI were assessed. Pre-transplant AFP levels were available for all patients, but PIVKAII levels were performed from 2018 onwards and were available for 146 patients. Regarding post-transplant immunosuppression, tacrolimus monotherapy is the preferred regimen for patients with hepatocellular carcinoma (HCC) within the Milan criteria (MC). In cases of HCC beyond MC, or those exhibiting poor differentiation or microvascular invasion, a combination regimen comprising low-dose tacrolimus with either Mycophenolate Mofetil or Everolimus is employed. Additionally, these patients receive adjuvant therapy with Sorafenib or Lenvatinib for a duration of 3 to 6 months. Post-transplant surveillance includes assessment of tumor markers every three months during the first year and biannually thereafter. Cross-sectional imaging with computed tomography (CT) is performed at 6 months post-transplant and subsequently on an annual basis for five years.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 22 (IBM). The primary outcome of the study was to determine 5-year recurrence-free survival (RFS) and overall survival (OS) in

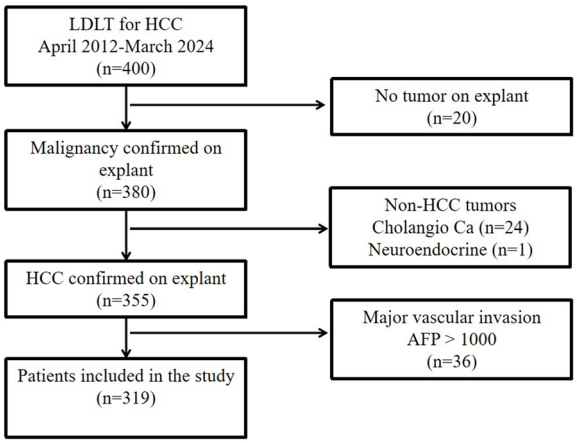

Fig. 1. Flowchart of patients included in the study.

patients who underwent LDLT within and outside MC. In addition, we evaluated pre-transplant PIVKAII levels in predicting microvascular invasion (MVI) and post-transplant recurrence. The sample size for this study was calculated to detect a significant difference in the prevalence of MVI between patients with low and high pre-transplant tumor marker levels. Using a power of 80% and a two-sided alpha level of 0.05 (corresponding to a 95% confidence interval), and assuming a 1:3 ratio of exposed (high AFP and/or PIVKA-II) to unexposed (low AFP and PIVKA-II) patients, MVI rates were estimated at 20% in the unexposed group and 50% in the exposed group, as reported previously [14]. Based on these parameters, the minimum required sample size was calculated to be 115 patients.

Receiver operator curves (ROC) and Concordance statistics (C-statistic) were used to quantify the ability to predict MVI, looking for cutoffs with high specificity. Categorical variables were compared using Chi-square and Fisher's test, while the t-test and Mann-Whitney U test were used for continuous variables. OS was calculated by subtracting the date of death or last follow-up from the date of transplant and RFS was calculated by subtracting the date of recurrence from the date of transplant. The 5-year RFS and OS were calculated using Kaplan-Meier curves, and the log-rank test was used to determine significance. After the exclusion of tumor morphometrics, response to LRT, NLR > 5, pre-transplant AFP, and PIVKAII cutoffs were analyzed in univariate and multivariate analysis. The study was performed in accordance with the Declaration of Helsinki. The institutional review board at Shifa International Hospital approved the study and informed consent was waived due to the study's retrospective nature (IRB# 489 – 24).

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. Hepatitis C was the etiology of liver disease in 222 (69.6%) patients, and 201 (63%) patients had HCC within MC. Ninety patients (28.2%) had LRT with a good response in 62/90 (68.9%) patients. Sixty-four (20%) patients had poorly differentiated HCC, and 98 (30.7%) had MVI on explant histopathology.

With a median follow-up of 46.8 (18.5–82.6) months, the 5-year OS and RFS were 68% and 75% respectively. Sixty-three (19.7%) patients had recurrence, 27/201 (13.4%) within the MC and 36/118 (30.5%) outside the MC ($P < 0.001$). The 5-year OS within and outside MC was 71% and 62% (P 0.053), and the 5-year RFS was 83% vs. 62% ($P < 0.001$) (Fig. 2a and b).

Pre-transplant variables	Patients ($n = 319$)
Median age (years, IQR)	54(48–59)
Sex (n, %)	
Men	269(84.3)
Women	50(15.7)
Etiology of liver disease (n, %)	
Hepatitis c	222(69.6)
Hepatitis B	71(22.3)
Others	26(8.1)
Transplant criteria (n, %)	
Within Milan criteria	201(63)
Outside Milan criteria	118(37)
Median largest tumor diameter (cm, IQR)	3(2–4.4)
Median tumor number (n, IQR)	2(1–3)
Locoregional therapy (n, %)	90(28.2)
Type of locoregional therapy	
Transarterial chemoembolization	78(86.7)
Radiofrequency or microwave ablation	13(14.5)
Percutaneous ethanol ablation	5(5.6)
Response to locoregional therapy	
Good	62(68.9)
Poor	28(31.1)
Median MELD score at transplant (n, IQR)	12(10–18)
Median neutrophil to lymphocyte ratio (n, IQR)	2.5(1.6–3.8)
Median AFP at transplant (n, IQR)	11.6(4.7–67.1)
AFP < 7.0 ng/ml (n, %)	116(36.4)
Median PIVKAII at transplant (n, IQR) ($n = 146$)	281(77.7–947)

Table 1. Baseline patient characteristics.

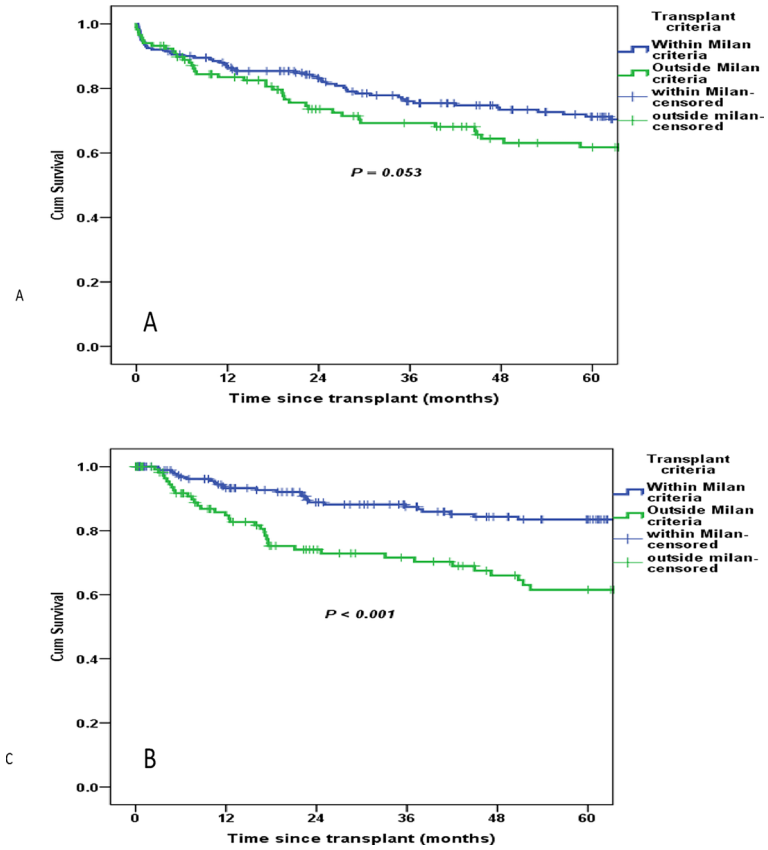

Fig. 2. (**a**) Estimated 5-year overall survival in 319 patients within and outside Milan criteria. (**b**) Estimated 5-year recurrence-free survival within and outside Milan criteria.

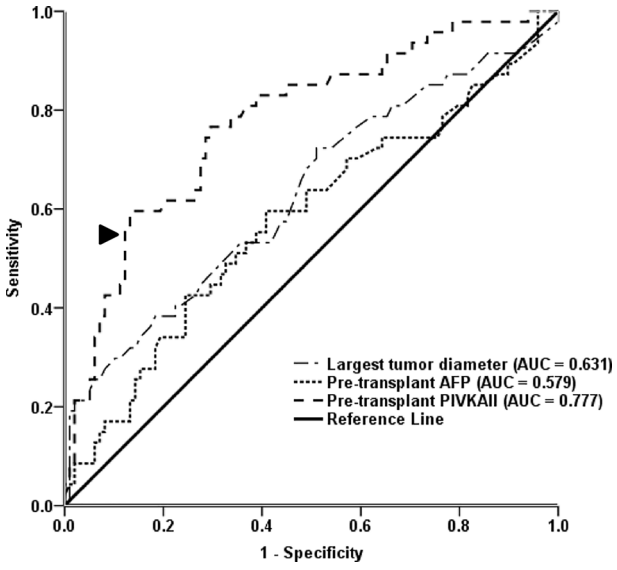

Fig. 3. Receiver operator curves for microvascular invasion.

PIVKAII and microvascular invasion

Among 146 patients with documented pre-transplant PIVKAII levels, ROC curves were used to quantify the ability to predict MVI. PIVKAII outperformed tumor size and AFP, with a C-statistic of 0.777 compared with 0.631 and 0.579, respectively (Fig. 3).

In addition, The NLR and tumor number were not associated with MVI (AUC < 0.6) (Supplementary digital content Table 1). A PIVKAII threshold of 1000 mAU/ml had a sensitivity of 55% and specificity of 88.8% for MVI. MVI was present in a significantly higher number of patients with PIVKAII > 1000 mAU/ml (21.6% vs. 65.7%)($P < 0.001$) (Supplementary digital content Table 2).

PIVKAII and post-transplant recurrence

On univariate analysis, AFP > 20 ng/ml, PIVKAII > 400 mAU/ml, and PIVKAII > 1000 mAU/ml were associated with recurrence (Supplementary Digital Content Table 3). PIVKAII > 1000 mAU/ml was included in the multivariate analysis due to a higher hazard ratio. AFP > 20 ng/ml [HR 3.3, CI 1.4–7.4, $P = 0.003$] and PIVKA II > 1000 mAU/ml [HR 3.5, CI 1.6–7.5, $P = 0.001$] were independent predictors of recurrence on multivariate analysis. The 5-year RFS was 79% and 50% for PIVKAII cutoff of 1000 mAU/ml ($P < 0.001$). (Supplementary digital content Fig. 1).

Post-transplant recurrence in the expanded criteria

Out of 146, 59(40.4%) patients underwent LDLT outside MC and 36(61%) of these 59 patients had PIVKAII < 1000 mAU/ml (Fig. 4). The 5-year RFS was significantly lower in patients with PIVKAII > 1000 mAU/ml both within and outside MC ($P < 0.05$). Next, we looked at recurrence rates for tumor marker combinations of AFP > 20 ng/ml (AFP +) or AFP < 20 ng/ml (AFP -) and PIVKAII > 1000 mAU/ml (PIVKAII +) or PIVKAII < 1000 mAU/ml (PIVKAII -). A dual tumor marker positive HCC (AFP +/PIVKAII +) predicted 47.1% of recurrences in 17 patients, whereas HCC recurred only in 6.1% of 66 patients not meeting the threshold (AFP-/PIVKAII-) ($P < 0.001$) (Fig. 5). The 5-year RFS was 45% for dual tumor marker positive HCC versus 77% for all others ($P < 0.001$).

Discussion

Herein, we report post-transplant outcomes of LDLT for expanded HCC criteria and show that pre-transplant PIVKAII is a strong predictor of MVI and post-transplant recurrence. Regardless of MC, PIVKAII > 1000 mAU/ml was associated with high recurrence rates despite excluding patients with AFP > 1000 ng/ml. When combined with AFP, PIKAII provided useful prognostic information, and patients with a high-risk tumor marker profile of AFP > 20 ng/ml and PIVKAII > 1000 mAU/ml were not suitable candidates for upfront LT.

In the "no competition" situation unique to LDLT, there is a scientific and ethical rationale to offer LT beyond traditional tumor morphometrics. The ILTS has recently proposed that a 5-year survival of 60% must be achieved in LDLT, particularly in waitlisted patients[13,22]. We have previously reported 5- and 10-year OS of 67% and 61% for our expanded criteria. Despite comparable OS, the recurrence rate was high outside MC[12]. DS was prioritized in patients with AFP > 600 ng/ml but was only feasible in a small number of patients due to high MELD scores,

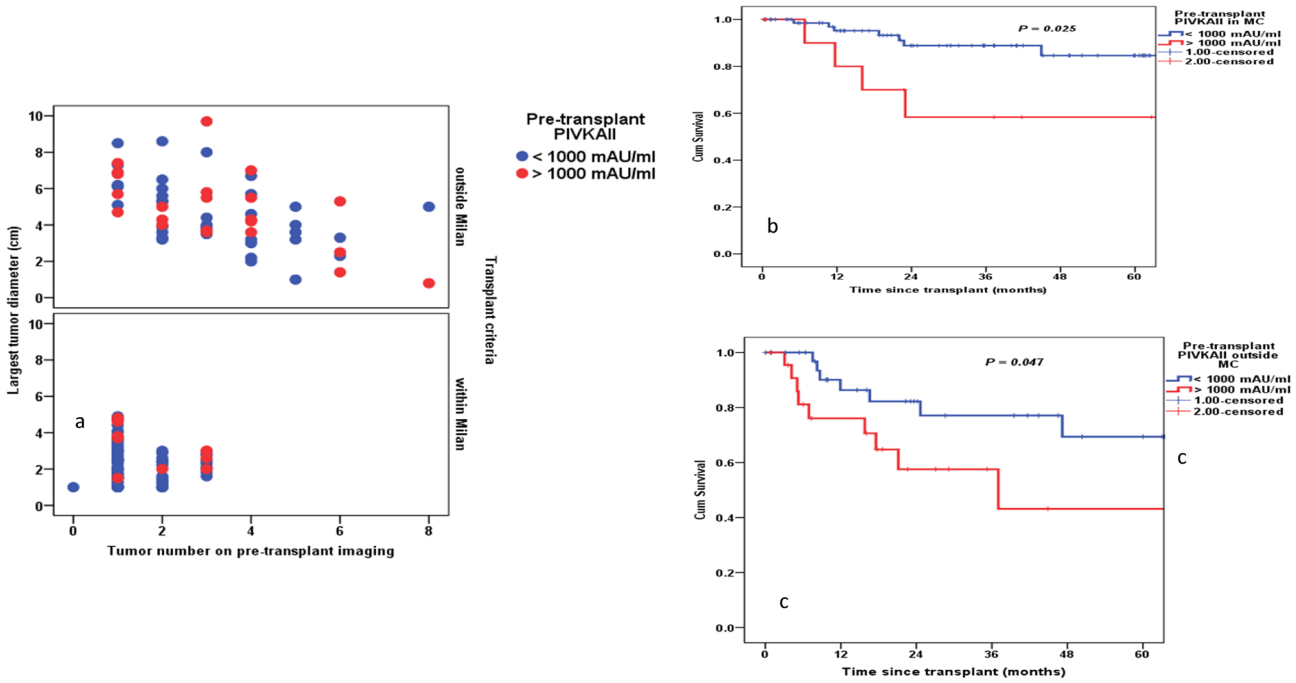

Fig. 4. (**a**) Tumor number and largest tumor diameter distribution within and outside Milan criteria with PIVKAII threshold of 1000 mAU/ml. (**b**) Estimated 5-year recurrence-free survival in Milan criteria with PIVKAII cutoff of 1000 mAU/ml ($n = 87$). (**c**) Estimated 5-year recurrence-free survival outside Milan criteria with PIVKAII cutoff of 1000 mAU/ml ($n = 59$).

Tumor marker groups (N=146)	Recurrence n(%)	P Value
AFP - /PIVKAII - (n=66)	4(6.1)	P < 0.001
AFP - / PIVKAII + (n= 18)	5(27.8)	
AFP +/ PIVKAII - (n=45)	10(22.2)	
AFP + / PIVKAII + (n=17)	8(47.1)	

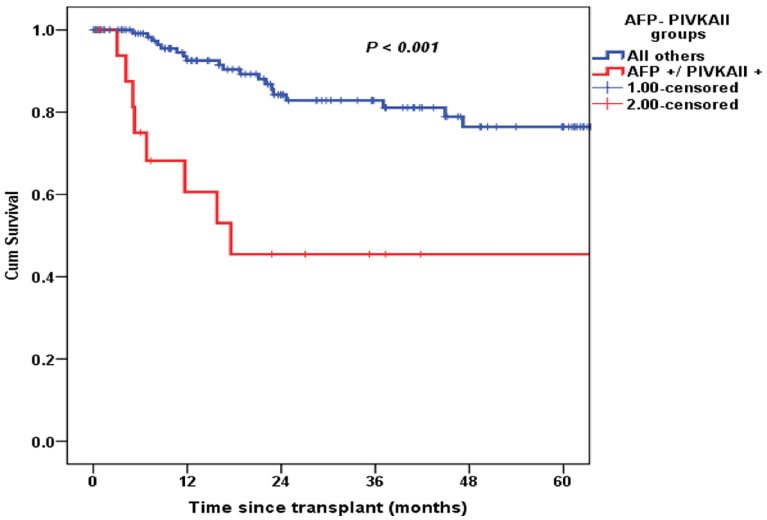

Fig. 5. Recurrence rates in 146 patients with various tumor marker combinations, *AFP* +, AFP > 20 ng/ml, *PIVKAII* +, PIVKAII > 1000 mAU/ml and estimated 5-year recurrence-free survival in dual tumor marker positive HCC (AFP+/PIVKAII +) versus all others.

underlying acute-on-chronic liver failure, and decompensated liver disease[20,23]. For this group, a pre-transplant PIVKA-II level can enhance informed decision-making when considering LDLT.

Despite the established role of AFP > 1000 ng/ml as a predictor of MVI and post-transplant recurrence, many patients with lower AFP levels experience post-transplant recurrence[6,14]. In the expanded criteria for LDLT, no universally agreed-upon AFP cutoffs exist, and exclusion criteria remain center-specific[13]. On the other hand, the role of PIVKAII in the management of HCC continues to evolve, and new data support its routine use in pre-transplant evaluation. In a recent study from the United States, a combination of PIVKAII (DCP) ≥ 7.5 ng/dl and AFP-L3 ≥ 15% predicted 61.1% recurrences, whereas HCC only occurred in 2.6% of patients not meeting this threshold[7]. Regarding expanded criteria, in a multicenter retrospective analysis, patients with far advanced HCC (tumor size > 10 cm, tumor number > 10) had 5-year OS and RFS of 47.8% and 53.4%, when a combined AFP and PIVKAII cutoff of 300 was used[24]. After excluding tumor morphometrics, we evaluated established AFP cutoffs, PIVKAII cutoffs, NLR > 5, and response to LRT in univariate analysis[3,9,12,15–17,19,25]. Only AFP levels > 20 ng/ml and PIVKAII levels > 1000 mAU/ml were independent predictors of recurrence. This corresponds with recent evidence where artificial intelligence-based models have shown that tumor size, AFP, and PIVKAII levels are the larger weighted factors with high Shapley Additive exPlanations value for recurrence[26–28]. Tumor size and number are well-established prognostic factors in LT. However, these morphological parameters were deliberately excluded in order to evaluate the prognostic significance of biological factors such as tumor markers, response to LRT, and the NLR in predicting post-transplant recurrence under our expanded criteria.

It is widely accepted that the 5-year survival threshold in LDLT can be lower than DDLT[13,29,30]. Using AFP and PIVKAII thresholds of 20 ng/ml and 1000 mAU/ml respectively, we identified a small but high-risk group of 17 patients with a 5-year RFS of only 45%. The exclusion of these 17 patients could potentially improve the 5-year RFS of our cohort from 62 to 77% (Fig. 4). Previously, few studies from Japan have evaluated pre-transplant PIVKAII levels in LDLT using cutoffs between 300 and 450 mAU/ml and moderate expansion in tumor dimensions[15,16,31,32]. We used a liberal PIVKAII cutoff of 1000 mAU/ml to achieve high specificity, hoping to maximize transplant eligibility, with a 5-year survival > 60% as the benchmark.

The limitations of the present study include its retrospective design and the exclusion of patients with AFP levels exceeding 1000 ng/ml. While this exclusion criterion aligns with current practices in the transplant community, it also serves to ensure a more uniform and homogeneous study cohort by eliminating potential outliers. Additionally, the impact of LRT on post-transplant recurrence was not found to be significant, likely due to the limited number of patients who underwent such treatment.

In conclusion, pre-transplant PIVKA-II serves as a valuable prognostic marker, demonstrating associations with MVI and post-transplant recurrence. In this study, the combination of AFP > 20 ng/mL and PIVKA-II > 1000 mAU/mL was linked to unacceptably high recurrence rates. These findings suggest that patients exhibiting this tumor marker profile may not be suitable candidates for upfront LT unless a favorable biochemical response to downstaging therapy is achieved. To enhance clinical utility and consistency, a more reliable and universally accepted PIVKA-II threshold is needed for incorporation into liver transplantation selection criteria.

Data availability

Data is available from the corresponding author upon reasonable request.

Received: 31 January 2025; Accepted: 19 June 2025
Published online: 01 July 2025

References

1. Sung, H. et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **71** (3), 209–249. https://doi.org/10.3322/caac.21660 (2021).
2. Sapisochin, G. & Bruix, J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat. Rev. Gastroenterol. Hepatol.* **14** (4), 203–217. https://doi.org/10.1038/nrgastro.2016.193 (2017).
3. Mazzaferro, V. et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl. J. Med.* **14** (11), 693–699. https://doi.org/10.1056/NEJM199603143341104 (1996).
4. Rudnick, S. R. & Russo, M. W. Liver transplantation beyond or downstaging within the Milan criteria for hepatocellular carcinoma. *Expert Rev. Gastroenterol. Hepatol.* **12**, 265–275 (2018). 17474124. 2018.1417035.
5. Lingiah, V. A. et al. Liver Transplantation Beyond Milan Criteria. J. Clin. Transl. Hepatol. 28;8(1):69–75. (2020). https://doi.org/10.14218/JCTH.2019.00050
6. Hameed, B. et al. Alpha-fetoprotein level > 1000 ng/ml as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl.* **20** (8), 945–951. https://doi.org/10.1002/lt.23904 (2014).
7. Norman, J. S. et al. AFP-L3 and DCP strongly predict early hepatocellular carcinoma recurrence after liver transplantation. *J. Hepatol.* **79** (6), 1469–1477. https://doi.org/10.1016/j.jhep.2023.08.020 (2023).
8. Wang, W. et al. The clinical significance of microvascular invasion in the surgical planning and postoperative sequential treatment in hepatocellular carcinoma. *Sci. Rep.* **28** (1), 2415. https://doi.org/10.1038/s41598-021-82058-x (2021).
9. Mazzaferro, V. et al. Metroticket 2.0 model for analysis of competing risks of death after liver transplantation for hepatocellular carcinoma. *Gastroenterology* **154** (1), 128–139. https://doi.org/10.1053/j.gastro.2017.09.025 (2018).
10. De, J. et al. A systematic review of des-γ-carboxy prothrombin for the diagnosis of primary hepatocellular carcinoma. *Med. (Baltim).* **95** (17), e3448. https://doi.org/10.1097/MD.0000000000003448 (2016).
11. Johnson, P. J. et al. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. *Cancer Epidemiol. Biomarkers Prev.* **23** (1), 144–153. https://doi.org/10.1158/1055–9965.EPI-13-0870 (2014).
12. Bhatti, A. B. H. et al. Living donor liver transplantation for hepatocellular carcinoma using expanded criteria and alpha-fetoprotein threshold of 1000ng/ml. J Gastrointest Surg. 8: S1091-255X (24)00669-3. (2024). https://doi.org/10.1016/j.gassur.2024.10.008
13. Mehta, N. et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation.104(6):1136–1142. (2020). https://doi.org/10.1097/TP.0000000000003174
14. Devillers, M. J. C. et al. The Role of PIVKA-II as a Predictor of Early Hepatocellular Carcinoma Recurrence-Free Survival after Liver Transplantation in a Low Alpha-Fetoprotein Population. Cancers (Basel).19;16(1):4. (2023). https://doi.org/10.3390/cancers16010004
15. Shindoh, J. et al. Evaluation methods for pretransplant oncologic markers and their prognostic impacts in patient undergoing living donor liver transplantation for hepatocellular carcinoma. *Transpl. Int.* **27** (4), 391–398 (2014).
16. Takada, Y. & Uemoto, S. Liver transplantation for hepatocellular carcinoma: the Kyoto experience. *J. Hepatobiliary Pancreat. Sci.* **17** (5), 527–532 (2010).
17. Shirabe, K. et al. Prognostic importance of the gross classification of hepatocellular carcinoma in living donor-related liver transplantation. *Br. J. Surg.* **98** (2), 261–267 (2011).
18. Bruix, J. & Sherman, M. American association for the study of liver diseases. Management of hepatocellular carcinoma: an update. *Hepatology* **53**, 1020–1022. https://doi.org/10.1002/hep.24199 (2011).
19. Yao, F. Y. et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* **33** (6), 1394–1403. https://doi.org/10.1053/jhep.2001.24563 (2001).
20. Bhatti, A. B. H. et al. Living donor liver transplantation for advanced hepatocellular carcinoma including macrovascular invasion. *J. Cancer Res. Clin. Oncol.* **148**(1):245–253. https://doi.org/10.1007/s00432-021-03665-99(2022).
21. Lencioni, R. & Llovet, J. M. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* **30** (1), 52–60. https://doi.org/10.1055/s-0030-12471329 (2010).
22. Llovet, J. M., Burroughs, A. & Bruix *J. Hepatocellular Carcinoma Lancet* **362**:1907–1917 (2003).
23. Bhatti, A. B. H. et al. Patient selection for living donor liver transplantation in Acute-on-chronic liver failure. *J. Clin. Exp. Hepatol.* **14** (5), 101403. https://doi.org/10.1016/j.jceh.2024.101403 (2024).
24. Lee, H. W. et al. Patient selection by tumor markers in liver transplantation for advanced hepatocellular carcinoma. *Liver Transpl.* **24** (9), 1243–1251. https://doi.org/10.1002/lt.250569 (2018).
25. Halazun, K. J. et al. Recurrence after liver transplantation for hepatocellular carcinoma: A new MORAL to the story. *Ann. Surg.* **265** (3), 557–564. https://doi.org/10.1097/SLA.0000000000001966 (2017).
26. Kaido, T. et al. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery* **154** (5), 1053–1060. https://doi.org/10.1016/j.surg.2013.04.056 (2013).
27. Nam, J. Y. et al. Novel model to predict HCC recurrence after liver transplantation obtained using deep learning: A multicenter study. *Cancers (Basel).* **12** (10), 2791. https://doi.org/10.3390/cancers12102791 (2020).
28. Altaf, A. et al. Artificial intelligence-based model for the recurrence of hepatocellular carcinoma after liver transplantation. *Surgery* **176** (5), 1500–1506. https://doi.org/10.1016/j.surg.2024.07.039 (2024).
29. Pomfret, E. A. et al. Should we use living donor grafts for patients with hepatocellular carcinoma? Ethical considerations. *Liver Transpl. 17 Suppl.* (2), S128–S132. https://doi.org/10.1002/lt.22356 (2011).
30. Kim, D. S. & for Asian Pacific Association for Study of Liver (APASL). Asian Pacific association for the study of the liver clinical practice guidelines on liver transplantation. *Hepatol. Int.* **18** (2), 299–383. https://doi.org/10.1007/s12072-023-10629-3 (2024).
31. Lai, Q. et al. Des-gamma-carboxy prothrombin in hepatocellular cancer patients waiting for liver transplant: a systematic review and meta-analysis. *Int. J. Biol. Markers.* **32**, e370–e374 (2017).
32. Kim, D. Y. et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. *Clin. Mol. Hepatol.* **29** (2), 277–292. https://doi.org/10.3350/cmh.2022.0212 (2023).

Author contributions

A.H.B. contributed to research design, writing, data analysis; U.S. and N.A. contributed to data collection, analysis, and writing G.A. and N.Y.K. contributed to the research design and critical review; M.A., H.H.Z., and A.R. contributed to data collection and critical review.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-08103-1.

Correspondence and requests for materials should be addressed to A.B.H.B.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.