Original Article

# YAP-based nomogram predicts poor prognosis in patients with hepatocellular carcinoma after curative surgery

**Wenxuan Zhou[1#], Feiyang Ye[1#], Gaowei Yang[1#], Chenghu Liu[1#], Zeya Pan[1], Chengjing Zhang[2], Hui Liu[1]**

[1]The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital (Second Military Medical University), Naval Medical University, Shanghai, China; [2]Department of Nutrition, Eastern Hepatobiliary Surgery Hospital (Second Military Medical University), Naval Medical University, Shanghai, China

*Contributions:* (I) Conception and design: H Liu, C Zhang, Z Pan; (II) Administrative support: H Liu; (III) Provision of study materials or patients: W Zhou, F Ye, G Yang, C Liu; (IV) Collection and assembly of data: W Zhou, F Ye, G Yang, C Liu; (V) Data analysis and interpretation: W Zhou, F Ye, G Yang, C Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

*Correspondence to:* Hui Liu, MD. The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital (Second Military Medical University), Naval Medical University, No. 225 Changhai Road, Shanghai 200438, China. Email: liuhui@smmu.edu.cn; Chengjing Zhang, MD. Department of Nutrition, Eastern Hepatobiliary Surgery Hospital (Second Military Medical University), Naval Medical University, No. 225 Changhai Road, Shanghai 200438, China. Email: xin.ning@163.com; Zeya Pan, MD. The Third Department of Hepatic Surgery, Eastern Hepatobiliary Surgery Hospital (Second Military Medical University), Naval Medical University, No. 225 Changhai Road, Shanghai 200438, China. Email: panzeya700705@hotmail.com.

**Background:** Hepatocellular carcinoma (HCC) ranks prominently in cancer-related mortality globally. Surgery remains the main therapeutic option for the treatment of HCC, but high post-operative recurrence rate makes prognostic prediction challenging. The quest for a reliable model to predict HCC recurrence continues to enhance prognosis. We aim to develop a nomogram with multiple factors to accurately estimate the risk of post-operative recurrence in patients with HCC.

**Methods:** A single-center retrospective study on 262 patients who underwent partial hepatectomy for HCC at the Eastern Hepatobiliary Surgery Hospital from May 2010 to April 2013 was conducted where immunohistochemistry assessed Yes-associated protein (YAP) expression in HCC. In the training cohort, a nomogram that incorporated YAP expression and clinicopathological features was constructed to predict 2-, 3-, and 5-year recurrence-free survival (RFS). The performance of the nomogram was assessed with respect to discrimination calibration, and clinical usefulness with external validation.

**Results:** A total of 262 patients who underwent partial hepatectomy for HCC at the Eastern Hepatobiliary Surgery Hospital were included in our study. HCC patients with high YAP expression exhibited significantly higher recurrence and reduced overall survival (OS) rates compared to those with low YAP expression ($P<0.001$). YAP was significantly associated with alpha-fetoprotein (AFP) ($P=0.03$), microvascular invasion (MVI) ($P<0.001$), and tumor differentiation grade ($P<0.001$). In the training cohort, factors like YAP expression, hepatitis B surface antigen (HBsAg), hepatitis B virus deoxyribonucleic acid (HBV-DNA), Child-Pugh stage, tumor size, MVI, and tumor differentiation were identified as key elements for the predictive model. Two YAP-centric Nomograms were developed, with one focused on predicting postoperative OS and the other on RFS. The calibration curve further confirmed the model's accuracy in the training cohort. The validation cohort confirmed the model's predictive accuracy.

**Conclusions:** The proposed nomogram combining the YAP, a predictor of HCC progression, and clinical features achieved more-accurate prognostic prediction for patients with HCC after partial hepatectomy, which may help clinicians implement more appropriate interventions.

**Keywords:** Hepatocellular carcinoma (HCC); Yes-associated protein (YAP); nomogram; prognosis

 

Submitted Jan 13, 2024. Accepted for publication Jun 14, 2024. Published online Aug 05, 2024.
doi: 10.21037/jgo-24-36
**View this article at:** https://dx.doi.org/10.21037/jgo-24-36

## Introduction

Hepatocellular carcinoma (HCC) stands as the third most lethal malignancy globally, marking itself as a leading cause of cancer-related deaths. This prominence is attributed to late diagnoses, high recurrence rates post-operation, and a scarcity of effective chemotherapy options (1,2). Despite the pressing need, the underlying mechanisms of HCC recurrence are yet to be fully understood, and there remains a significant gap in the development of effective models to predict its recurrence.

Yes-associated protein (YAP), a crucial growth promoter within the Hippo signaling pathway, plays a pivotal role in the tumorigenesis, development, and progression of various cancers (3,4). Studies have demonstrated that high YAP expression is closely associated with advanced stages and poor prognosis in HCC (5,6). YAP has been identified as an independent factor influencing HCC recurrence in patients undergoing hepatectomy or liver transplantation, subsequently impacting overall survival (OS) time (5,7). Prior studies (8) revealed YAP's correlation with HCC patient outcomes, firmly establishing its link to individual prognoses. However, these studies often overlook the role of clinical factors in the prognosis of HCC. In two studies by Liu *et al.* investigating the association between YAP expression and prognosis in HCC, the included common clinical factors were limited to tumor size and alkaline phosphatase (ALP). Currently recognized adverse prognostic factors such as microvascular invasion (MVI) and tumor grade were not included, while YAP expression is closely related to tumor invasion, metastasis, and vascular invasion (9,10). Therefore, there is still a lack of predictive models centered around YAP expression that encompass various common clinical risk factors. The absence of a YAP-centric clinical model to predict the likelihood of HCC recurrence post-curative surgery is a notable gap in the field.

Nomograms, as statistical models, have been developed to enhance the predictive accuracy of individual outcomes, particularly in forecasting the prognosis of malignant tumors (11,12). These models offer a more personalized prediction of outcomes by integrating a combination of variables, standing in contrast to other models that assign prognosis based on risk groups. With their high predictive accuracy, nomograms have been increasingly reported and considered superior to traditional staging systems across various cancer populations (13-15). Consequently, they have been proposed as an alternative, or even a new standard, for predicting the prognosis of diverse cancers. However, a common limitation is that many nomograms primarily integrate clinicopathologic variables, often overlooking molecular biomarkers.

Addressing this, our study employs an immunohistochemistry (IHC) approach to examine YAP expression in HCC and assess its association with clinicopathologic features and prognosis. Given the established role of YAP in cancer progression, it is reasonable to hypothesize that its expression in HCC could be indicative of poor prognosis. Furthermore, we aim to develop a YAP-inclusive nomogram and compare its prognostic predictive accuracy with the Barcelona Clinic Liver Cancer (BCLC) staging system in patients with HCC who have undergone curative resection. We present this article in accordance with the TRIPOD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-36/rc).

### Highlight box

**Key findings**

- Yes-associated protein (YAP) overexpresses in hepatocellular carcinoma (HCC) and is associated with several clinical features. A nomogram incorporating YAP expression and five prognostic clinical indicators was developed, providing an effective prediction for the prognosis of HCC.

**What is known and what is new?**

- One nomogram incorporating YAP expression, alkaline phosphatase (ALP) levels and tumor diameter, while another incorporating tumor size, serotonin levels, and the YAP/VGLL4 ratio, were used to predict postoperative prognosis in patients with HCC.
- A nomogram comprising YAP expression and five clinical features was proposed to predict the prognosis of HCC.

**What is the implication, and what should change now?**

- Our study offers a tailored risk assessment tool for predicting post-operative recurrence in HCC patients following liver resection and can aid surgeons in devising effective follow-up monitoring strategies and identifying patients who may benefit from additional adjuvant therapies.

 

## Methods

### *Patients and specimens*

A total of 262 paired formalin-fixed, paraffin-embedded (FFPE) HCC tissues alongside their corresponding normal tissues were included in this study, collected from May 2010 to April 2013 from the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University. The inclusion criteria were as follows: (I) accurate pathological diagnosis of HCC with no other malignancies; (II) absence of extrahepatic metastasis and portal/hepatic veins invasion; (III) liver resection performed with curative intent, with no other therapies administered pre-surgery. The data were randomly allocated into a training cohort and a validation cohort at a ratio of 1:2. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University (No. EHBHKY2018-K-002) and written informed consent was acquired from all participants.

### *Follow-up investigation*

To obtain comprehensive physical information of the enrolled HCC patients, follow-up visits were conducted every 3 months during the first-year post-surgery, and biannually thereafter. The precise dates of post-operative HCC recurrence were recorded. Additionally, the dates and primary causes of death during the follow-up were documented. At the conclusion of the study period, the surviving patients were censored. HCC recurrence was characterized by the emergence of a newly identified tumor validated through two radiologic images, with or without an increase in serum tumor markers. Overall survival (OS) was used as primary end point and recurrence-free survival (RFS) was used as secondary end point. OS was the duration from partial hepatectomy to death or the last follow-up date. RFS was calculated from the surgery date to the diagnosis of recurrence/metastasis.

### *Immunohistochemical staining and scoring method*

For antigen retrieval, slides were heated in citrate buffer via microwave, followed by incubation with YAP antibody (Cell Signaling Technology, USA) at 37 ℃ for one hour, and then overnight at 4 ℃ in a moist condition. Following the Immunohistochemical (IHC) staining kit instructions (Dako, Denmark), the primary antibody was detected using the corresponding secondary antibody from the kit. Reaction products were visualized with the kit's DAB reagent and counterstained with haematoxylin. Negative controls were concurrently performed. Four random views (400× magnification) per sample were selected to classify staining intensity. Based on the percentage of positive staining cells (0–25%, 26–50%, 51–75%, and 76–100%), percentage grade scores of 1, 2, 3, and 4 were assigned. Similarly, staining intensity scores of 1, 2, 3, and 4 were assigned based on negative, weak, moderate, and strong staining, respectively. The final YAP expression level scores were obtained by multiplying the percentage grade score by the intensity staining score, categorized as + [0–4], ++ [5–8], +++ [9–12], ++++ [13–16], based of which + to ++ represent YAP low expression (YAP-low) and +++ to ++++ represent YAP high expression (YAP-high). All results were validated using a blind method by at least two pathologists.

### *Statistical analyses*

The association between YAP expression levels and clinicopathological variables of HCC patients was evaluated using the Chi-square test. Cox univariate and multivariate analysis models were employed to identify potential independent factors related to RFS and OS. Calibration curves were generated to assess the model's calibration, while the area under the curve (AUC) was calculated to estimate the model's discrimination performance. Decision curve analysis (DCA) was further performed to ascertain the clinical utility of the model by quantifying the net benefits at different threshold probabilities. Statistical analysis was conducted using R software (version 4.2.0), with all tests being two-tailed and significance set at a level of $<0.05$.

## Results

### *YAP overexpression in HCC*

IHC was employed on HCC tumor samples and adjacent non-tumor tissues to investigate YAP expression. The IHC results indicated a pronounced overexpression of YAP in HCC samples compared to adjacent non-cancerous tissues. Further analysis revealed that YAP predominantly localized in the nuclei of cancer cells, with a minor presence in the cytoplasm. Notably, HCC patients with high YAP expression exhibited a significantly elevated recurrence rate and reduced OS rate compared to those with low YAP expression ($P<0.001$, *Figure 1*).

 

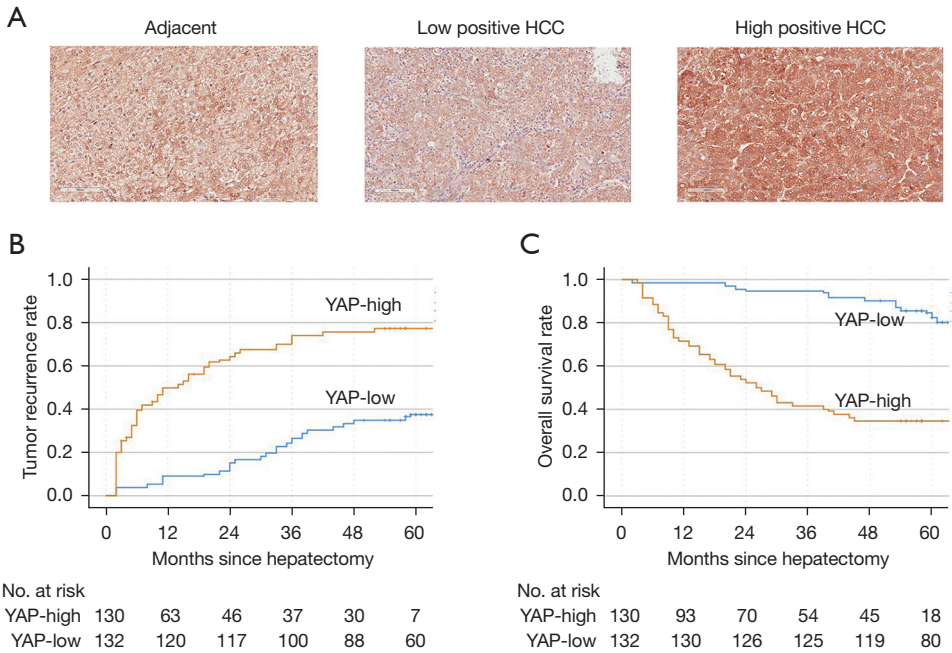


**Figure 1** Immunohistochemical analysis of YAP overexpression in HCC clinical samples. High YAP expression was detected in HCC clinical samples, correlating with poor prognosis, low overall survival, and short recurrence-free survival. (A) Representative immunohistochemical staining of anti-YAP antibody in paired tumor and adjacent nontumor tissue sections (scale bar, 100 μm). (B,C) HCC patients with elevated YAP levels exhibited inferior recurrence-free survival (B) and overall survival (C). HCC, hepatocellular carcinoma; YAP, Yes-associated protein.

### *Correlations between YAP expression and clinicopathological features*

To delve deeper into the relationship between YAP expression and clinicopathological features, HCC samples were categorized into high and low YAP expression groups. The Chi-square test was utilized to determine correlations, with results summarized in *Table 1*. Notably, a high positive rate of MVI (P<0.001) and differentiation grade (P<0.001) were linked to elevated YAP expression. Concurrently, YAP expression was associated with alpha-fetoprotein (AFP) (P=0.03), hepatitis B e antigen (HBeAg) (P=0.04), and a more severe Child-Pugh grade (P=0.03).

### *Development of a prediction model for RFS and OS in training cohort*

In the training cohort, several factors, including YAP expression, hepatitis B surface antigen (HBsAg), Child-Pugh stage, tumor diameter >5 cm, MVI, and tumor differentiation, emerged as potential predictors for RFS in post-surgery HCC patients based on univariate cox regression analysis (*Table 2*). Subsequent multivariate cox regression analysis identified the aforementioned factors as independent predictors. A RFS prediction nomogram model integrating these predictors was developed (*Figure 2A*). Similarly, YAP expression, identified as an independent predictor for HCC OS, was incorporated into a nomogram model predicting 2-, 3-, and 5-year OS rates. This OS prediction nomogram model included factors like HBsAg, HBV-DNA, MVI, and tumor grade (*Figure 2B*). The model's predictive performance for RFS was represented by an AUC of 0.824 in the training set while for OS was 0.837 (*Figure 3*).

### *Validation of the nomogram model in validation cohort*

The predictive efficacy of the nomogram model was further assessed using 103 patient tissues from the validation cohort. Despite differences between the training and validation cohorts (Table S1), the model maintained a consistent AUC prediction level (*Figure 3*). The calibration curve further confirmed the model's accuracy in the training cohort (*Figure 4*).

 

**Table 1** Clinical features of HCC patients based on YAP expression

| Characteristics | YAP-high set (n=130), n (%) | YAP-low set (n=132), n (%) | P value |
|---|---|---|---|
| Male | 117 (90.00) | 117 (88.64) | 0.72 |
| Age >50 years | 77 (59.23) | 82 (62.12) | 0.63 |
| TBIL >17.1 μmol/L | 21 (16.15) | 15 (11.36) | 0.26 |
| ALT >44 U/L | 58 (44.62) | 53 (40.15) | 0.47 |
| AST >40 U/L | 80 (61.54) | 69 (52.27) | 0.13 |
| HBsAg positive | 116 (89.23) | 113 (85.61) | 0.38 |
| HBeAg positive | 28 (21.54) | 16 (12.12) | 0.04 |
| HBV-DNA ≥2,000 IU/mL | 76 (58.46) | 74 (56.06) | 0.69 |
| Child-Pugh B stage | 17 (13.08) | 7 (5.30) | 0.03 |
| AFP >400 ng/mL | 97 (74.62) | 82 (62.12) | 0.03 |
| Non-anatomical hepatectomy | 2 (1.54) | 15 (11.36) | 0.20 |
| Surgical margin <1 cm | 9 (6.92) | 9 (6.82) | 0.97 |
| Bilateral tumor distribution | 12 (9.23) | 12 (9.09) | 0.97 |
| Tumor diameter >5 cm | 69 (53.08) | 72 (54.55) | 0.81 |
| Tumor number >1 | 32 (24.62) | 35 (26.52) | 0.73 |
| Satellite nodules | 97 (74.62) | 103 (78.03) | 0.52 |
| Microvascular invasion | 90 (69.23) | 33 (25.00) | <0.001 |
| Edmondson-Steiner grade III–IV | 121 (93.08) | 85 (64.39) | <0.001 |
| Cirrhosis | 95 (73.08) | 95 (71.97) | 0.84 |
| BCLC stage: A–B | 54 (41.54) | 71 (53.79) | 0.047 |

HCC, hepatocellular carcinoma; YAP, Yes-associated protein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

### *Clinical application*

The DCA discerned the advantages of the developed nomogram model over other conventional evaluation systems (16). The BCLC stage, a widely accepted staging system for HCC, was compared against other traditional systems. The DCA for models with and without YAP integration is depicted in *Figure 5*. The decision curve revealed that for threshold probabilities ranging from 0.25 to 0.80, the YAP-integrated nomogram model offers greater benefits than the BCLC staging system in predicting RFS post-surgery in HCC patients (*Figure 5A*). This was further corroborated in the validation cohort, where the YAP-integrated model outperformed the BCLC system across a range of 0.10 to 0.85 (*Figure 5B*).

## Discussion

The pronounced overexpression of YAP has been identified as a substantial contributor to the deterioration of surgical outcomes in patients with HCC. In our present investigation, elevated YAP expression emerges as a formidable independent risk factor, notably impacting both tumor recurrence and OS rates. Our study further highlights the intricate interplay between YAP expression levels and key clinical parameters, encompassing HBeAg status, Child-Pugh classification, AFP levels, the presence of MVI, tumor differentiation grade, and BCLC staging.

In recent times, there has been a growing understanding of the molecular mechanisms governing the development of liver cancer, with a particular focus on the pivotal role

 

**Table 2** Uni- and multivariate Cox regression analysis of factors associated with survival and recurrence in HCC patients

| Characteristics | OS | | | | | | RFS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate | | | Multivariate analysis | | | Univariate | | | Multivariate analysis | | |
| | HR | 95% CI | P value | HR | 95% CI | P value | HR | 95% CI | P value | HR | 95% CI | P value |
| YAP | 7.23 | 3.58–14.6 | <0.001 | 4.84 | 2.34–10.05 | <0.001 | 3.64 | 2.27–5.82 | <0.001 | 2.47 | 1.47–4.14 | 0.001 |
| Gender, male *vs.* female | 1.22 | 0.53–2.8 | 0.64 | | | | 1.75 | 0.81–3.77 | 0.15 | | | |
| Age, >50 *vs.* ≤50 years | 1.21 | 0.77–1.92 | 0.41 | | | | 1.04 | 0.7–1.54 | 0.85 | | | |
| TBIL, >17.1 *vs.* ≤17.1 μmol/L | 0.98 | 0.5–1.9 | 0.95 | | | | 1.01 | 0.57–1.77 | 0.98 | | | |
| ALT, >44 *vs.* ≤44 U/L | 1.14 | 0.73–1.77 | 0.57 | | | | 0.87 | 0.59–1.28 | 0.49 | | | |
| AST, >40 *vs.* ≤40 U/L | 1.31 | 0.82–2.09 | 0.26 | | | | 1.18 | 0.79–1.77 | 0.43 | | | |
| HBsAg, positive *vs*. negative | 2.51 | 1.01–6.21 | 0.046 | 2.64 | 1.05–6.6 | 0.04 | 2.06 | 1.04–4.07 | 0.04 | 3.08 | 1.53–6.23 | 0.002 |
| HBeAg, positive *vs*. negative | 1.3 | 0.73–2.33 | 0.37 | | | | 1.57 | 0.97–2.53 | 0.07 | | | |
| HBV-DNA, ≥2,000 *vs*. <2,000 IU/mL | 1.59 | 1–2.51 | 0.048 | 2.21 | 1.37–3.56 | 0.001 | 1.16 | 0.79–1.71 | 0.46 | | | |
| Child-Pugh, B *vs.* A | 1.58 | 0.83–2.98 | 0.16 | | | | 2.87 | 1.68–4.93 | <0.001 | 3.76 | 2.14–6.62 | <0.001 |
| AFP, >400 *vs.* ≤ 400 ng/mL | 1.53 | 0.92–2.54 | 0.10 | | | | 1.26 | 0.83–1.91 | 0.29 | | | |
| Hepatectomy, nonanatomical *vs.* anatomical | 0.9 | 0.47–1.76 | 0.77 | | | | 1.08 | 0.63–1.87 | 0.78 | | | |
| Surgical margin, <1 *vs.* ≥1 cm | 0.35 | 0.09–1.44 | 0.15 | | | | 0.78 | 0.32–1.92 | 0.59 | | | |
| Tumor distribution, ipsilateral *vs.* bilateral | 0.98 | 0.43–2.25 | 0.96 | | | | 1.19 | 0.6–2.36 | 0.61 | | | |
| Tumor diameter, >5 *vs.* ≤5 cm | 1.59 | 1.01–2.51 | 0.045 | 1.66 | 1–2.75 | 0.051 | 1.48 | 1–2.19 | 0.048 | 1.66 | 1.08–2.55 | 0.02 |
| Tumor number, >1 *vs.* 1 | 1.15 | 0.7–1.88 | 0.58 | | | | 1.06 | 0.69–1.63 | 0.80 | | | |
| Satellite nodules, presence *vs.* absence | 1 | 0.58–1.71 | >0.99 | | | | 1.01 | 0.63–1.61 | 0.98 | | | |
| Microvascular invasion, presence *vs.* absence | 3.95 | 2.39–6.54 | <0.001 | 2.09 | 1.17–3.74 | 0.01 | 4.14 | 2.72–6.31 | <0.001 | 2.8 | 1.73–4.51 | <0.001 |
| Edmondson-Steiner grade, III–IV *vs.* I–II | 12.17 | 2.98–49.71 | 0.001 | 4.74 | 1.12–20.09 | 0.04 | 5.15 | 2.38–11.12 | <0.001 | 2.61 | 1.15–5.91 | 0.02 |
| Cirrhosis, yes *vs.* no | 0.96 | 0.58–1.58 | 0.86 | | | | 0.86 | 0.56–1.31 | 0.48 | | | |

HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; HR, hazard ratio; CI, confidence Interval; YAP, Yes-associated protein; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; AFP, alpha-fetoprotein.

played by YAP (8,17). Previous research efforts have shed light on the correlation between YAP and clinical outcomes in patients, unequivocally establishing its close relationship with the prognosis of individuals suffering from HCC (18-20). However, these studies have often been limited in scope, failing to comprehensively consider the influence of other clinical factors and neglecting the establishment of a robust predictive model for the prognosis of HCC patients. A noteworthy study, for instance, explored the regulatory role of serotonin (5-HT) in modulating YAP expression and formulated a nomogram based on prognostic data encompassing a 3-year timespan (9). This nomogram incorporated three variables, namely, ALP levels, tumor diameter, and YAP expression. Subsequently, the same research team extended their efforts by constructing another nomogram predictive model, which incorporated three factors: tumor size, serotonin levels, and the YAP/VGLL4 ratio, to predict post-operative prognosis in HCC patients (10). However, it is essential to underscore that these predictive models did not encompass additional factors

 

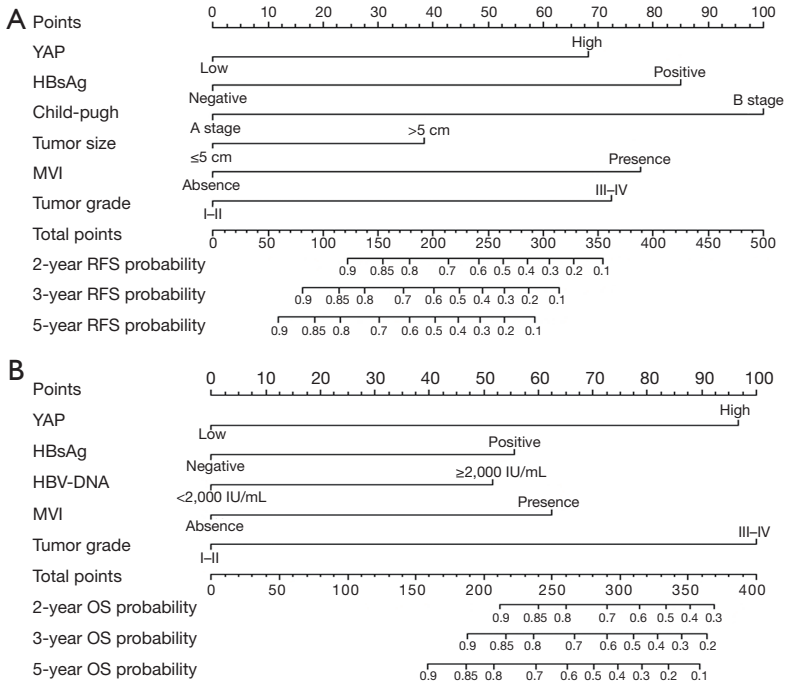


**Figure 2** Development of a prediction model for RFS and OS. The RFS prediction nomogram model (A) incorporating YAP expression, HBsAg status, Child-Pugh stage, tumor size, MVI, and tumor grade. The OS prediction nomogram model (B) incorporating YAP expression, HBsAg status, Child-Pugh stage, MVI, and tumor grade. Both of them was developed in the training cohort. YAP, Yes-associated protein; RFS, recurrence-free survival; OS, overall survival; HBsAg, hepatitis B surface antigen; MVI, microvascular invasion.

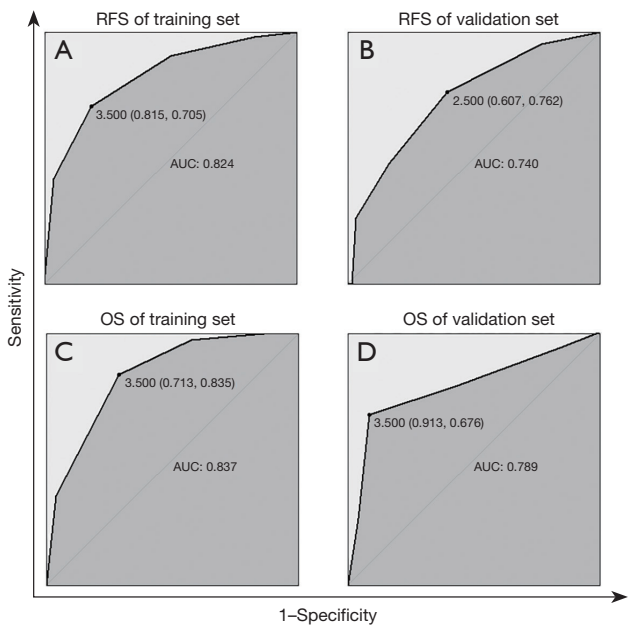


**Figure 3** ROC curves and AUC for the YAP-centric nomogram to predict RFS and OS. ROC curves and AUC values demonstrate the predictive performance of the YAP-centric nomogram for RFS (A,B) and OS (C,D) in both the training and validation cohorts. Data are presented as optimal cutoff value (specificity, sensitivity). ROC, receiver operating characteristic; AUC, area under the curve; YAP, Yes-associated protein; RFS, recurrence-free survival; OS, overall survival.

 

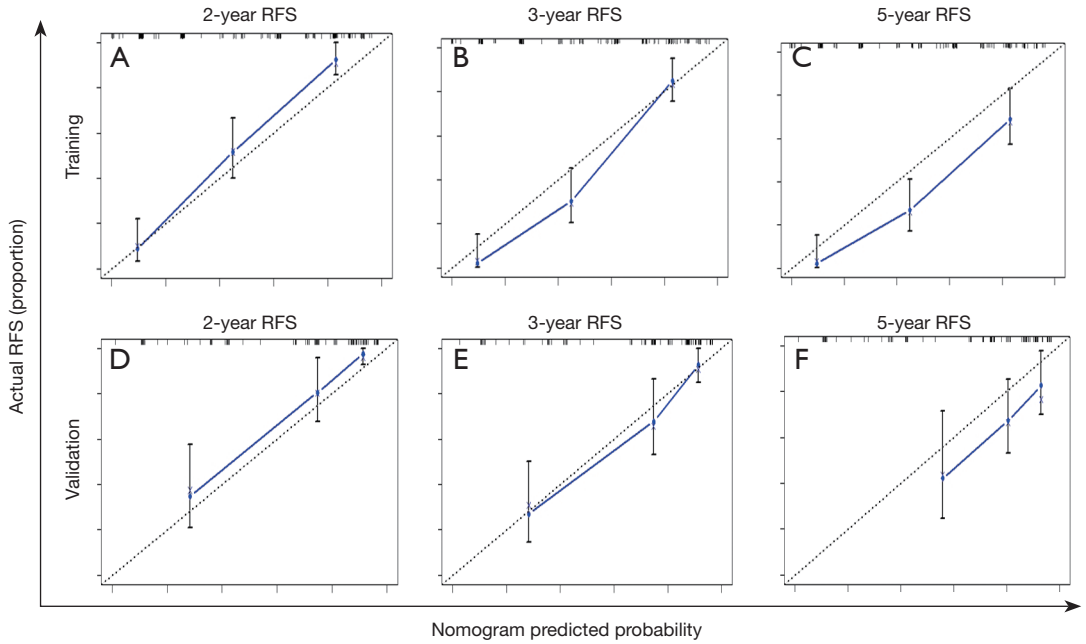


**Figure 4** Calibration curves of the YAP-centric nomogram. (A-C) Calibration curves for the YAP-centric nomogram in the training cohort at 2 (A), 3 (B), and 5 years (C). (D-F) Calibration curves for the YAP-centric nomogram in the validation cohort at 2 (D), 3 (E), and 5 years (F). These curves illustrate the agreement between predicted risks of RFS and observed RFS outcomes. The diagonal dotted line represents an ideal model, while the blue solid line represents the nomogram's performance, with a closer fit to the diagonal line indicating better prediction accuracy. YAP, Yes-associated protein; RFS, recurrence-free survival.

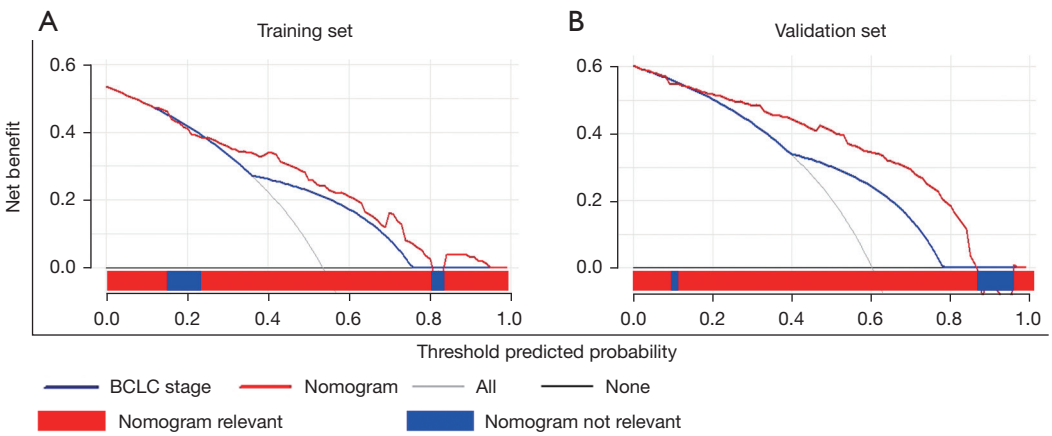


**Figure 5** DCA for predictive model of RFS. DCA shows the net benefit of the predictive model compared to different assumptions. The x-axis typically represents the decision threshold probability, which refers to the critical probability value in medical decision-making where a particular test or prediction result is considered positive or warrants intervention. The y-axis represents the net benefit, a comprehensive measure assessing the utility of model predictions for decision-making across different decision thresholds. The slope represents how the net benefit changes with varying thresholds at a given threshold value. The blue line represents the model with BCLC stage, the grey line assumes all patients have recurrence, and the thin black line assumes no patients have recurrence. DCA, decision curve analysis; RFS, recurrence-free survival; BCLC, Barcelona Clinic Liver Cancer.

 

that have been widely recognized as closely associated with YAP expression levels. In our comprehensive study, we propose a nomogram comprising six variables that bear direct relevance to prognosis and are readily accessible in clinical practice. Importantly, this nomogram demonstrates robust and reliable performance, a fact substantiated by its excellent calibration curves, which consistently align model predictions with actual observations across both the training and validation cohorts.

Within the prognostic nomogram, apart from considering YAP expression levels, certain clinical factors such as elevated HBsAg levels, poorer Child-Pugh classification, tumor diameter exceeding 5 cm, positive MVI, and lower tumor differentiation serve as indicators for an elevated risk of post-surgery recurrence and a shortened survival period for patients. Our investigation has unveiled a notable correlation between YAP expression levels and these clinical parameters, which is consistent with the findings of previous studies (21,22). Moreover, our findings suggest that heightened YAP expression might also be associated with elevated AFP levels surpassing 400 ng/mL, a phenomenon consistent with prior research discoveries. Existing literature posits the existence of AFP binding sites that are subject to regulation by YAP, thereby hinting at a potential direct influence of YAP on AFP expression (7,19). However, it is important to highlight that our study did not establish a clear-cut correlation between AFP levels and patient prognosis. This observation could be attributed to various contributing factors, including the robust associations between AFP and specific inclusion criteria, as well as the inherent limitations in the sensitivity and specificity of AFP in monitoring HCC (23,24). Furthermore, our study did not ascertain a significant relationship between YAP levels and tumor diameter. Prior research has proposed that YAP engages in a competitive binding mechanism with hepatocyte nuclear factor 4 alpha (HNF-4α) for the TEA domain transcription factor 4 (TEAD4), resulting in the inhibition of HCC cell differentiation and the promotion of cell proliferation upon YAP overexpression (25). The incongruence in tumor staging at the time of resection among the patients in our study may have contributed to the absence of a discernible association between YAP levels and tumor diameter. Nonetheless, it is worth noting that disparities in tumor size between patients with high and low YAP expression have been documented in previous investigations (7,26). An intriguing finding in our study is the suggested link between YAP expression levels and HBsAg. The existing literature reports on the association between HBsAg transgenic mice and liver expression signals that are related to YAP response, cell cycle control, DNA damage, and spindle events. This intriguing observation hints at the possibility that hepatitis B virus (HBV) infection could exert regulatory control over the development of liver cancer through its interaction with the YAP pathway (27,28). Nevertheless, it is imperative to emphasize that further validation and exploration of this relationship are warranted.

The decision curves depicted earlier offer a visual roadmap for clinicians and patients, aiding them in making an informed choice regarding the adoption of our model at the opportune moment. This can maximize the advantages associated with predicting the timing of cancer recurrence. Should the threshold probability of a patient or physician surpass the 10% mark, employing the decision curve derived from our present study to forecast the date of recurrence can serve as a valuable tool for healthcare practitioners and patients alike. It aids in the selection of the most appropriate treatment strategies and optimal timing for follow-up procedures. In the YAP-centric nomogram, individuals with high scores could undergo strengthened postoperative review and follow-up frequency, allowing for timely intervention in potential recurrent lesions. Furthermore, the predictive model incorporates clinical factors recognized as high-risk for postoperative recurrence, such as MVI, tumor size, and tumor grade. For such individuals postoperatively, selective adjuvant therapies aimed at reducing tumor recurrence, such as transarterial chemoembolization (TACE), targeted therapy, and immune checkpoint inhibition (ICI) therapy, can be considered.

Our study is subject to certain limitations. Firstly, the analysis relies on data from a single institution, underscoring the importance of validating the results across multiple centers. Secondly, to bolster the reliability of the nomogram, a prospective study is warranted. Thirdly, despite the nomogram's commendable predictive accuracy, it continues to display a relatively elevated false-positive rate when forecasting patient prognoses. These limitations should be taken into account when interpreting our findings.

## Conclusions

In summary, our YAP-based nomogram, when combined with clinical features, offers a tailored risk assessment tool for predicting post-operative recurrence in HCC patients following liver resection. This valuable tool can

 

aid surgeons in devising effective follow-up monitoring strategies and identifying patients who may benefit from additional adjuvant therapies.

## Acknowledgments

*Funding:* This study was supported by Pilot Talents Program of Naval Medical University (to H.L.), National Natural Science Foundation of China (82270634), Shanghai Municipal Health Commission Health Science Popularization Leading Talent Capacity Enhancement Special Project (JKKPYL-2023-B03) and Shanghai Science and Technology Innovation Action Plan Project (20XD1405100).

## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-36/rc

*Data Sharing Statement:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-36/dss

*Peer Review File:* Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-36/prf

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-36/coif). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University (No. EHBHKY2018-K-002) and written informed consent was acquired from all participants.



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**Cite this article as:** Zhou W, Ye F, Yang G, Liu C, Pan Z, Zhang C, Liu H. YAP-based nomogram predicts poor prognosis in patients with hepatocellular carcinoma after curative surgery. J Gastrointest Oncol 2024;15(4):1712-1722. doi: 10.21037/jgo-24-36

 