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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Retrospective Study

Novel model combining contrast-enhanced ultrasound with serology predicts hepatocellular carcinoma recurrence after hepatectomy

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Abstract

BACKGROUND

Surgery is the primary curative option in patients with hepatocellular carcinoma (HCC). However, recurrence within 2 years is observed in 30%-50% of patients, being a major cause of mortality.

AIM

To construct and verify a non-invasive prediction model combining contrast-enhanced ultrasound (CEUS) with serology biomarkers to predict the early recurrence of HCC.

METHODS

Records of 744 consecutive patients undergoing first-line curative surgery for HCC in one institution from 2016-2018 were reviewed, and 292 local patients were selected for analysis. General characteristics including gender and age, CEUS liver imaging reporting and data system (LIRADS) parameters including wash-in time, wash-in type, wash-out time, and wash-out type, and serology biomarkers including alanine aminotransferase, aspartate aminotransferase, platelets, and alpha-fetoprotein (AFP) were collected. Univariate analysis and multivariate Cox proportional hazards regression model were used to evaluate the independent prognostic factors for tumor recurrence. Then a nomogram called CEUS model was constructed. The CEUS model was then used to predict recurrence at 6 mo, 12 mo, and 24 mo, the cut-off value was calculate by X-tile, and each C-index was calculated. Then Kaplan-Meier curve was compared by log-rank test. The calibration curves of each time were depicted.

RESULTS

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A nomogram predicting early recurrence (ER), named CEUS model, was formulated based on the results of the multivariate Cox regression analysis. This nomogram incorporated tumor diameter, preoperative AFP level, and LIRADS, and the hazard ratio was 1.123 (95% confidence interval [CI]: 1.041-1.211), 1.547 (95% CI: 1.245-1.922), and 1.428 (95% CI: 1.059-1.925), respectively. The cut-off value at 6 mo, 12 mo, and 24 mo was 100, 80, and 50, and the C-index was 0.748 (95% CI: 0.683-0.813), 0.762 (95% CI: 0.704-0.820), and 0.762 (95% CI: 0.706-0.819), respectively. The model showed satisfactory results, and the calibration at 6 mo was desirable; however, the calibration at 12 and 24 mo should be improved.

CONCLUSION

The CEUS model enables the well-calibrated individualized prediction of ER before surgery and may represent a novel tool for biomarker research and individual counseling.

Key Words: Hepatocellular carcinoma; Recurrence; Prediction; Contrast-enhanced ultrasound; Liver imaging reporting and data system; Alpha-fetoprotein

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Core Tip: This study aimed to construct and verify a non-invasive prediction model combining contrast-enhanced ultrasound with serology biomarkers to predict the early recurrence of hepatocellular carcinoma. Records of 292 local patients of hepatocellular carcinoma (HCC) were selected for analysis. A nomogram predicting early recurrence (ER) named contrasted-enhanced ultrasound (CEUS) model, incorporating tumor diameter, preoperative alpha-fetoprotein level, and LIRADS, was developed. The model showed satisfactory results, and the C-index was 0.762 (95%CI: 0.706–0.819). The calibration at 6 mo was desirable. The CEUS model enables the well-calibrated individualized prediction of ER before surgery and may represent a novel tool for biomarker research and individual counseling.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related deaths worldwide[1]. Surgery is the primary curative option in patients with HCC. However, recurrence within 2 years occurs in 30%–50% of patients and is the major cause of mortality[2,3]. Identifying patients with a high recurrence risk after surgery is important so that clinicians can provide appropriate monitoring to detect the earliest stage of recurrent HCC in time and treatment may still be feasible.

The widely used tumor staging system, such as tumor node metastasis (TNM) and Barcelona clinic liver cancer (BCLC) staging, is useful for guiding surgery; however, their ability to predict recurrence has not been fully evaluated. Some models, such as the Singapore Liver Cancer Recurrence score[4], the Korean model[5], and the Surgery-Specific Cancer of the Liver Italian Program[6], have been specially developed to detect tumor recurrence after surgical resection; however, the most important parameter, that is, microvascular invasion, can only be evaluated pathologically on the resected specimens. A prognostic model that only requires preoperative available parameters may assist surgeons in planning a reasonable treatment strategy.

With the development of radiology technology and serology detection ability, predicting postoperative recurrence noninvasively is possible. Many scholars have used radiology technology or serological biomarkers to achieve this goal[7,8], but only a few have combined the two technologies; the combination of ultrasound and

serological biomarkers has not been used for preoperative prediction. Ultrasound examination is favored by clinicians and patients for its lack of radiation, repeatability, and real-time monitoring. Contrast-enhanced ultrasound (CEUS) can observe tumor hemodynamics in real time, which plays an important role in evaluating the nature of a tumor. In this study, a nomogram model was constructed by fusing CEUS and a serological biomarker. The predictive ability of the model was evaluated and validated by internal resampling.

MATERIALS AND METHODS

Patient selection and study design

This study was approved by the hospital's ethics committee (No. 2020-010-01), and all participating patients provided written informed consent. Between January 2016 and January 2018, 744 consecutive patients meeting the study's criteria who underwent curative resection at our institution were retrospectively recruited. The exclusion criteria were as follows: (1) CEUS of the liver was unavailable; (2) CEUS was performed more than 1 mo before surgery; (3) macrovascular invasion or extrahepatic metastasis was present; (4) previous treatment (*i.e.*, local ablation, repeated liver resection, transarterial chemoembolization, chemotherapy, and radiotherapy) before surgery; (5) liver resection was performed for a ruptured tumor or non-R0 resection; and (6) clinicopathologic or follow-up data were not available. A total of 292 patients were enrolled in this study (Figure 1).

CEUS technique

Ultrasound scanning was performed by a radiologist (LJL) who had 30 years of conventional ultrasound experience and 15 years of CEUS experience. She used a multi-frequency (5–2 MHz) convex array probe (C5-2) (Esaote) on a Mylab 90 system, and digital storage was recorded at the same time. Before CEUS, the whole liver must be thoroughly examined using a gray-scale ultrasound. Baseline scan included evaluation of lesions on B-mode imaging and color Doppler ultrasound in combination with tissue harmonic imaging.

Before CEUS was performed, each patient rested for 10 min and received breathing training to obtain the best image. In CEUS, 2.4 mL of a microbubble contrast agent (Sonovue, Bracco, Milan, Italy) was rapidly injected *via* an antecubital vein followed by a 10 mL saline flush. A sufficiently large needle (20-gauge minimum diameter) was used to avoid bubble rupture. A low mechanical index (< 0.1) was used for CEUS examination. Different dynamic phases of contrast enhancement were identified in the liver study after a microbubble-based contrast agent was injected. The contrast side-by-side mode was used *via* a live dual-image display. The CEUS terminology follows the ACR CEUS LI-RADS working group standard[9]. Continuous scanning was used to observe the tumor. The duration of the study included the arterial phase (0–30 s), portal phase (31–120 s), and late phase (121–300 s). Three radiologists with 5 years of working experience with CEUS classified the tumor according to the LI-RADS (Figure 2)[10], and 5v was defined as 6. If more than one tumor was detected, the biggest one was reviewed. The following parameters were also collected: (1) The maximum diameter of the lesion; (2) Starting time (the time from injection to entering the tumor); (3) Peak time (the time from the injection to the maximum intensity of the tumor); (4) Iso-time (the time from the injection to tumor enhancement was equal to peripheral); (5) Washout time (the time from the injection to the tumor enhancement lower than peripheral); (6) Enhancement type (fast-in fast-out and non-fast-in fast-out); (7) Wash-in type (fast-in and non-fast-in); (8) Washout type (fast-out, < 30 s, and non-fast-out, ≥ 30 s); (9) Enhancement echogenicity (homogeneous and inhomogeneous); and (10) Tumor location (half liver and non-half-liver, half-liver means that the tumor was located only in the left or right liver).

Serology parameters

Laboratory data within 3 d of morning fasting blood before curative treatment were obtained from medical records, which included alanine aminotransferase, aspartate aminotransferase, platelet, albumin, total bilirubin, serum creatinine, prothrombin time, prothrombin time activity, and international normalized ratio. Alpha-fetoprotein (AFP) was divided into 0–20 µg/L, 20–200 µg/L, and > 200 µg/L.

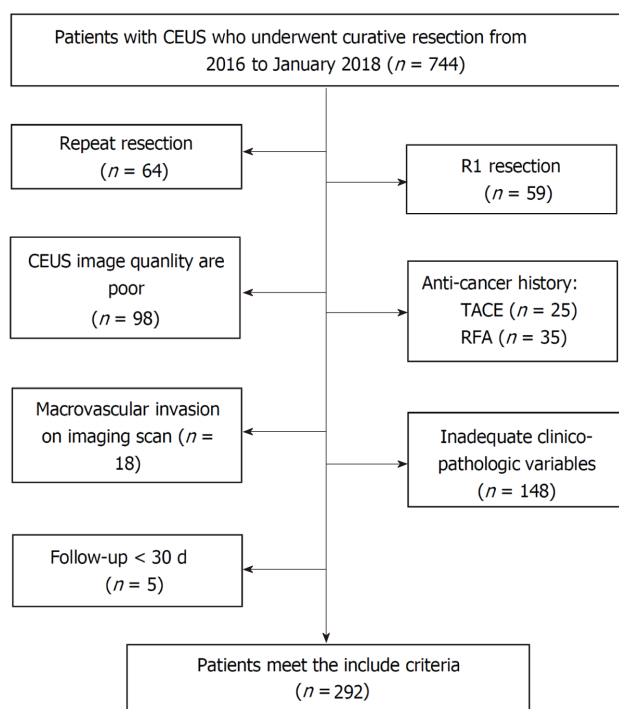


Figure 1 Flow program for patient inclusion. CEUS: Contrast-enhanced ultrasound.

Follow-up surveillance

After resection, follow-up examination was performed every 3 mo during the study period, and data on serum AFP, liver function tests, contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the chest and abdomen, and ultrasound of the abdomen were obtained. The data were censored on January 3, 2020. Recurrence-free survival was defined as the time from the date of surgery to the date of first recurrence, metastasis, or last follow-up.

Statistical analysis

Continuous variables are expressed as the mean $\pm$ SD and were compared using an unpaired, 2-tailed *t*-test or Mann-Whitney test. Categorical variables were compared using the χ^2 test or Fisher exact test. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox proportional hazards regression model was used to evaluate the independent prognostic factors for tumor recurrence. All variables associated with recurrence at a significant level were candidates for stepwise multivariate analysis. A nomogram was formulated based on the results of multivariate Cox regression analysis and by using the rms package of R, version 3.6.3 (<http://www.r-project.org/>). The nomogram is based on proportionally converting each regression coefficient in Cox regression to a 0-to-100-point scale. The effect of the variable with the highest β coefficient (absolute value) is assigned 100 points. The points are added across independent variables to derive the total points, which are converted to predict recurrence probabilities. The predictive performance of the nomogram was measured using C-index and calibration with 1000 bootstrap samples to decrease the over fit bias. For clinical use of the model, we tested the model's prediction ability at 6, 12, and 24 mo and used X-tile, version 3.6.1 to calculate the optimal cut-off values. Then, Kaplan-Meier curve was analyzed [11]. The prediction error of the CEUS model and variables was assessed using the "Boot632plus" split method with 1000 iterations to calculate estimates of prediction error curves and is summarized as the integrated Brier score, which reflects a weighted average of the squared distances between observed recurrence status and predicted recurrence probability of a model; the integrated Brier score represents a valid measure of overall model performance and can range from 0, for a perfect model, to 0.25, for a noninformative model with a 50% incidence of the outcome [12]. In all analyses, $P < 0.05$ was considered statistically significant. All analyses were performed using R, version 3.6.3.

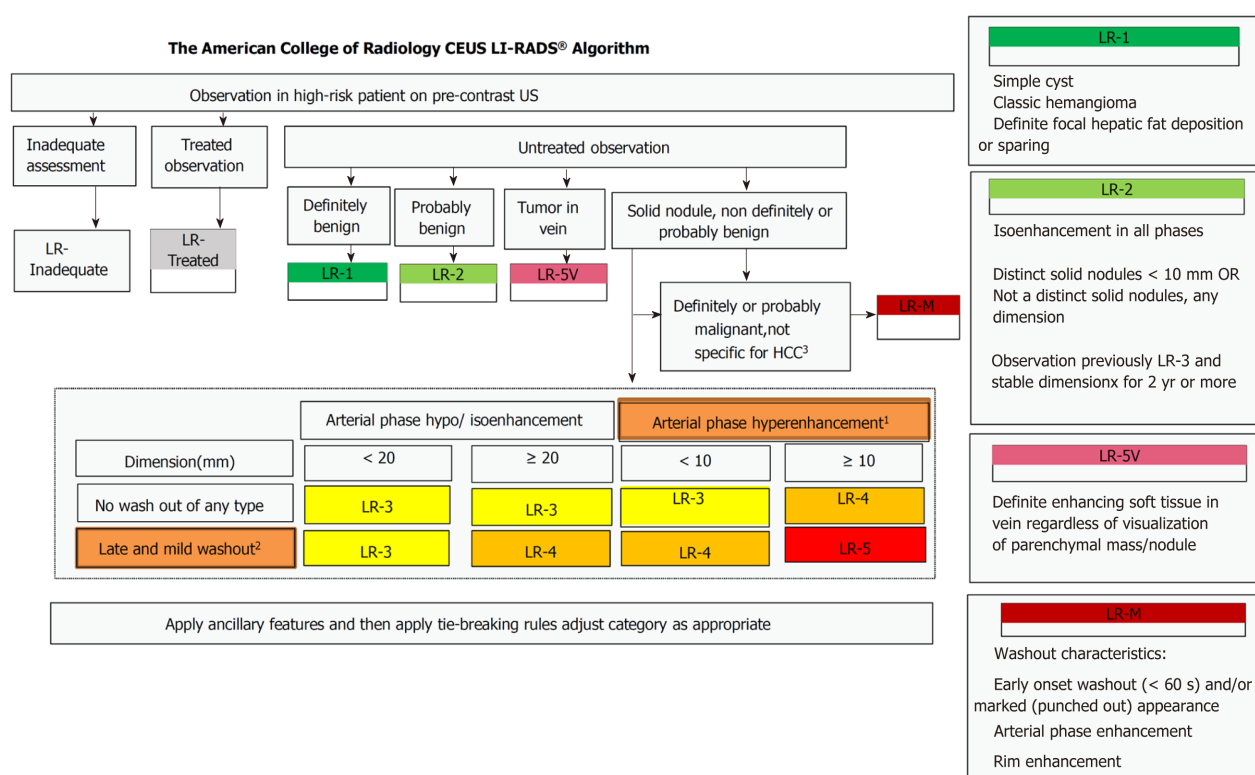


Figure 2 Official ACR algorithmic display for contrasted-enhanced ultrasound model and liver imaging reporting and data system. ¹Arterial phase hyperenhancement: Whole or in part, no rim or peripheral discontinuous globular enhancement. ²Late in onset (≥ 60 s) and mild in degree: Whole or in part, with no part showing early or marked washout. ³Early onset washout (< 60 s) and/or marked (punched out) appearance and/or arterial phase rim enhancement. CEUS: Contrast-enhanced ultrasound; LI-RADS: Liver imaging reporting and data system; US: Ultrasound; HCC: Hepatocellular carcinoma.

RESULTS

Basic characteristics

The basic characteristics are shown in Table 1. We collected 292 patients, including 238 males and 54 females, with a mean age of 55.7 ± 11.2 years.

Cox regression results

Cox regression results are shown in Table 2. LI-RADS, AFP level, and tumor diameter were entered into the final model. The hazard ratio (HR) was 1.428, 1.547, and 1.123, respectively. A prediction model, named CEUS model, was constructed. The CEUS model's integrated Brier score of prediction error was the lowest (Figure 3).

Nomogram structure

The nomogram is shown in Figure 4. Every patient's score was calculated and divided into three subgroups: 6, 12, and 24 mo.

For the 6-mo recurrence, 100 was the optimal cut-off. It can distinguish the high-risk group from the low-risk group (Figure 5A). The C-index was 0.748 (95%CI: 0.683–0.813), and the calibration curve was satisfactory (Figure 6A). For the 12-mo recurrence, 80 was the optimal cut-off. It can distinguish the high-risk group from the low-risk group (Figure 5B). The C-index was 0.762 (95%CI: 0.704–0.820), and the calibration curve was insufficient (Figure 6B). For the 24-mo recurrence, 50 was the optimal cut-off. It can distinguish the high-risk group from the low-risk group (Figure 5C). The C-index was 0.762 (95%CI: 0.706–0.819), and the calibration curve was insufficient (Figure 6C).

DISCUSSION

This study aimed to construct and validate an early recurrence risk model before surgery, called the CEUS model, based on CEUS and serology for HCC. The CEUS

Table 1 Basic characteristics

	Total	Non-recurrence	Recurrence	P value
Diameter (mean ± SD, cm)	3.9 ± 2.3	3.2 ± 1.5	4.8 ± 2.8	< 0.001
Age (mean ± SD, yr)	55.7 ± 11.2	54.9 ± 11.3	56.7 ± 11.1	0.17
ALT (mean ± SD, U/L)	35.5 ± 30.1	31.5 ± 21.4	40.7 ± 38.1	0.016
AST (mean ± SD, U/L)	36.1 ± 34.6	30.4 ± 15.3	43.5 ± 48.9	0.11
PLT (mean ± SD, /L)	150.2 ± 66.4	145.0 ± 62.9	157.2 ± 70.4	0.16
ALB (mean ± SD, g/L)	38.8 ± 4.6	38.7 ± 4.8	38.9 ± 4.3	0.94
TBIL (mean ± SD, μmol/L)	17.6 ± 8.9	16.9 ± 8.3	18.6 ± 9.6	0.16
Cr (mean ± SD, μmol/L)	74.0 ± 17.5	74.3 ± 19.8	73.6 ± 14.0	0.42
PT (mean ± SD, s)	13.8 ± 1.2	13.9 ± 1.2	13.8 ± 1.3	0.49
PTA(mean ± SD,)	92.6 ± 14.9	92.3 ± 13.7	92.9 ± 16.3	0.91
INR (mean ± SD)	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	0.97
Start time (mean ± SD, s)	16.8 ± 3.7	17.1 ± 3.9	16.5 ± 3.5	0.17
Peak time (mean ± SD, s)	24.1 ± 5.6	24.1 ± 5.3	24.0 ± 6.0	0.45
Iso-time (mean ± SD, s)	39.1 ± 16.9	40.9 ± 19.8	36.8 ± 11.7	0.079
Washout time (mean ± SD, s)	94.8 ± 63.3	98.5 ± 63.3	89.8 ± 63.3	0.11
Sex, n (%)				
Male	238 (81.5)	129 (77.7)	109 (86.5)	0.068
Female	54 (18.5)	37 (22.3)	17 (13.5)	
LIRADS, n (%)				
3	10 (3.4)	8 (4.8)	2 (1.6)	< 0.001
4	176 (60.3)	118 (71.1)	58 (46.0)	
5	95 (32.5)	37 (22.3)	58 (46.0)	
6	11 (3.8)	3 (1.8)	8 (6.3)	
AFP [n (%), μg/L]				
< 20	193 (66.1)	133 (80.1)	60 (47.6)	< 0.001
20-200	32 (11.0)	13 (7.8)	19 (15.1)	
> 200	67 (22.9)	20 (12.0)	47 (37.3)	
Enhancement type, n (%)				
Non-fast-in fast-out	42 (14.4)	24 (14.5)	18 (14.3)	1.00
Fast-in fast-out	250 (85.6)	142 (85.5)	108 (85.7)	
Wash-in type, n (%)				
Non-fast-in	4 (1.4)	2 (1.2)	2 (1.6)	1.00
Fast-in	288 (98.6)	164 (98.8)	124 (98.4)	
Washout type, n (%)				
Non-fast-out	80 (27.4)	41 (24.7)	39 (31.0)	0.29
Fast-out	212 (72.6)	125 (75.3)	87 (69.0)	
Enhancement type, n (%)				
Homogeneous enhancement	223 (76.4)	127 (76.5)	96 (76.2)	1.00
Inhomogeneous enhancement	69 (23.6)	39 (23.5)	30 (23.8)	
Location, n (%)				
Half liver	261 (89.4)	148 (89.2)	113 (89.7)	1.00

Non-half liver	31 (10.6)	18 (10.8)	13 (10.3)
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ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet; AFP: Alpha-fetoprotein; ALB: Albumin; TBIL: Total bilirubin; Cr: Serum creatinine; PT: Prothrombin time; PTA: Prothrombin time activity; INR: International normalized ratio; LIRADS: Liver imaging reporting and data system.

Table 2 Cox model

	β	P value	HR	95.0%CI	
				Lower	Upper
LIRADS	0.356	0.019	1.428	1.059	1.925
AFP	0.436	0.000	1.547	1.245	1.922
Diameter	0.116	0.003	1.123	1.041	1.211
Age	0.009	0.319	1.009	0.991	1.027
ALT	0.007	0.075	1.007	0.999	1.014
AST	0.003	0.322	1.003	0.997	1.008
PLT	0.002	0.225	1.002	0.999	1.005
TBIL	0.019	0.052	1.019	1.000	1.039
Start time	-0.032	0.229	0.968	0.918	1.021
Out time	-0.001	0.595	0.999	0.996	1.002
Sex	-0.270	0.312	0.763	0.453	1.288

LIRADS: Liver imaging reporting and data system; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; PLT: Platelet; TBIL: Total bilirubin.

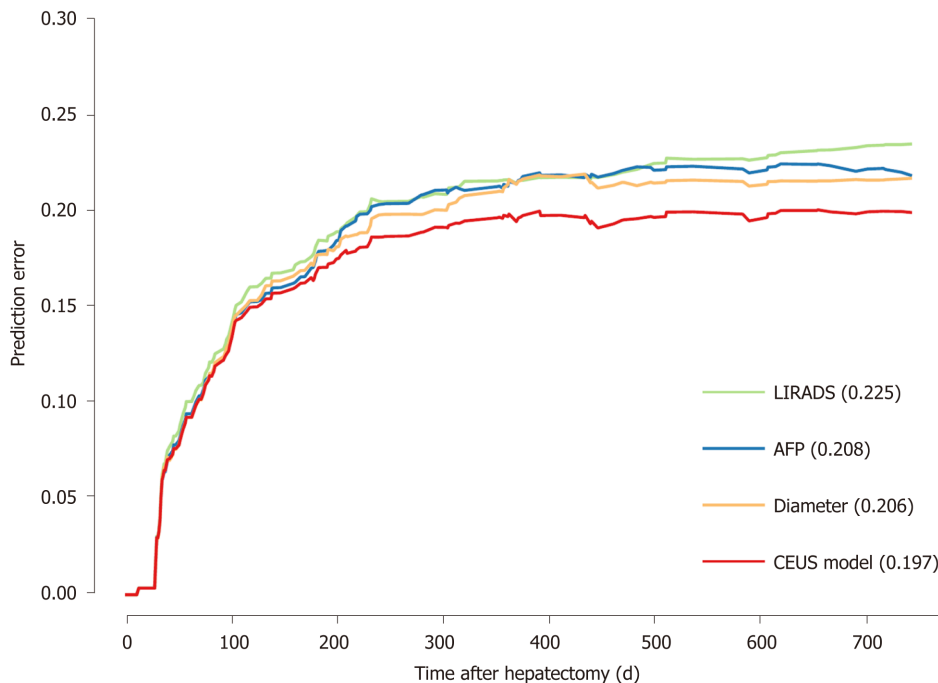


Figure 3 Prediction error of contrasted-enhanced ultrasound model and liver imaging reporting and data system, alpha-fetoprotein, and diameter. AFP: Alpha-fetoprotein; LIRADS: Liver imaging reporting and data system; CEUS: Contrast-enhanced ultrasound.

model showed satisfactory results. The C-index at 6, 12, and 24 mo was 0.683–0.820. The calibration at 6 mo is good, although a 12- and 24-mo improvement is still needed. The CEUS model showed lower prediction error than a single indicator, with an

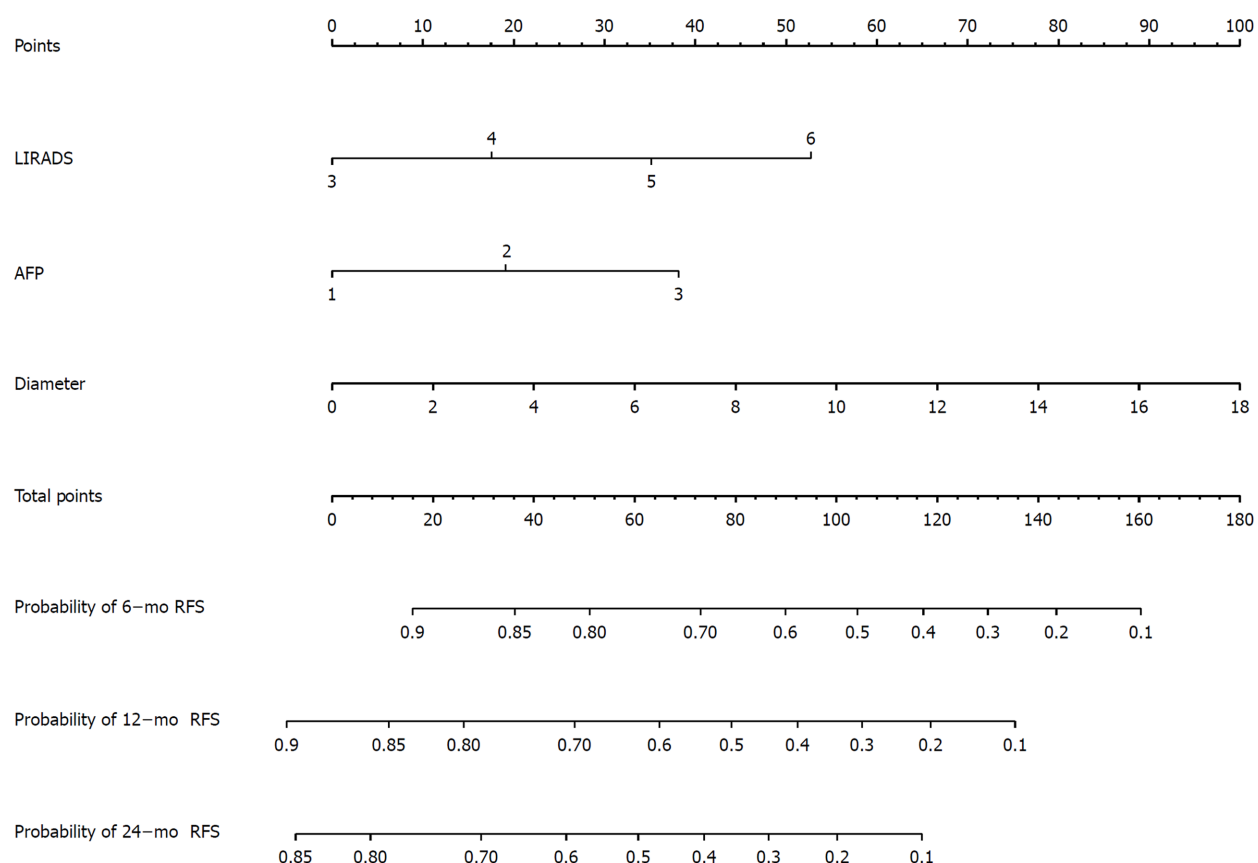


Figure 4 Nomogram structure based on liver imaging reporting and data system, alpha-fetoprotein, and tumor diameter. LIRADS: Liver imaging reporting and data system; AFP: Alpha-fetoprotein; RFS: Relapse free survival.

integrated Brier score of 0.197. In addition, at the three study time points, using appropriate cut-off value can well distinguish high-risk groups from low-risk groups.

Resection for patients with HCC is still plagued by high recurrence, especially early recurrence[2]. This rate is approximately 30%–50% in early reports[13,14]; similar to a previous report, tumor relapse occurred in approximately half of the patients in the present study. Gene signatures may promote prognosis scoring; however, they are not used in routine clinical process[15]. Conversely, the potential and power of radiological image data, which include CT, MRI, PET, and ultrasound, are increasingly recognized in the field of oncology[16–19]. Meanwhile, serology indicators, such as albumin-to-alkaline phosphatase ratio[7], AFP[20], and neutrophil-lymphocyte ratio [21], are also widely used in this domain. In our study, parameters that may predict recurrence pre-operation were collected, rigorous statistical analysis was performed, and unimportant parameters were excluded. Finally, LIRADS, AFP level, and the maximum tumor diameter were confirmed as independent hazard factors. These factors were combined, and a novel model named the CEUS model was established.

In the past, many imaging techniques have been used for the noninvasive prediction of postoperative recurrence, and satisfactory results have been obtained. However, the use of ultrasound combined with serological biomarkers to build a prediction model is rare. The present study fully explored the advantages of CEUS and serological biomarkers and constructed the CEUS model through a series of rigorous test. We used LI-RADS because of its better accuracy compared with most previous noninvasive prediction models[8]. The overall prediction ability in the present study was as anticipated and was similar to that in previous studies[14,22]. However, the 1- and 2-year calibration degree was slightly insufficient. The main reasons are as follows: (1) The subjects included in the two studies are different. Ji *et al*'s study only included patients who met the Milan criteria, but our study included all patients with radical resection. Thus, our model may have a wider applicable population; and (2) Ji *et al*'s study recruited external validation queue, while only internal resampling was performed in our study. Although the calibration was insufficient, we used LI-RADS as the operation specification, which was more objective and convenient.

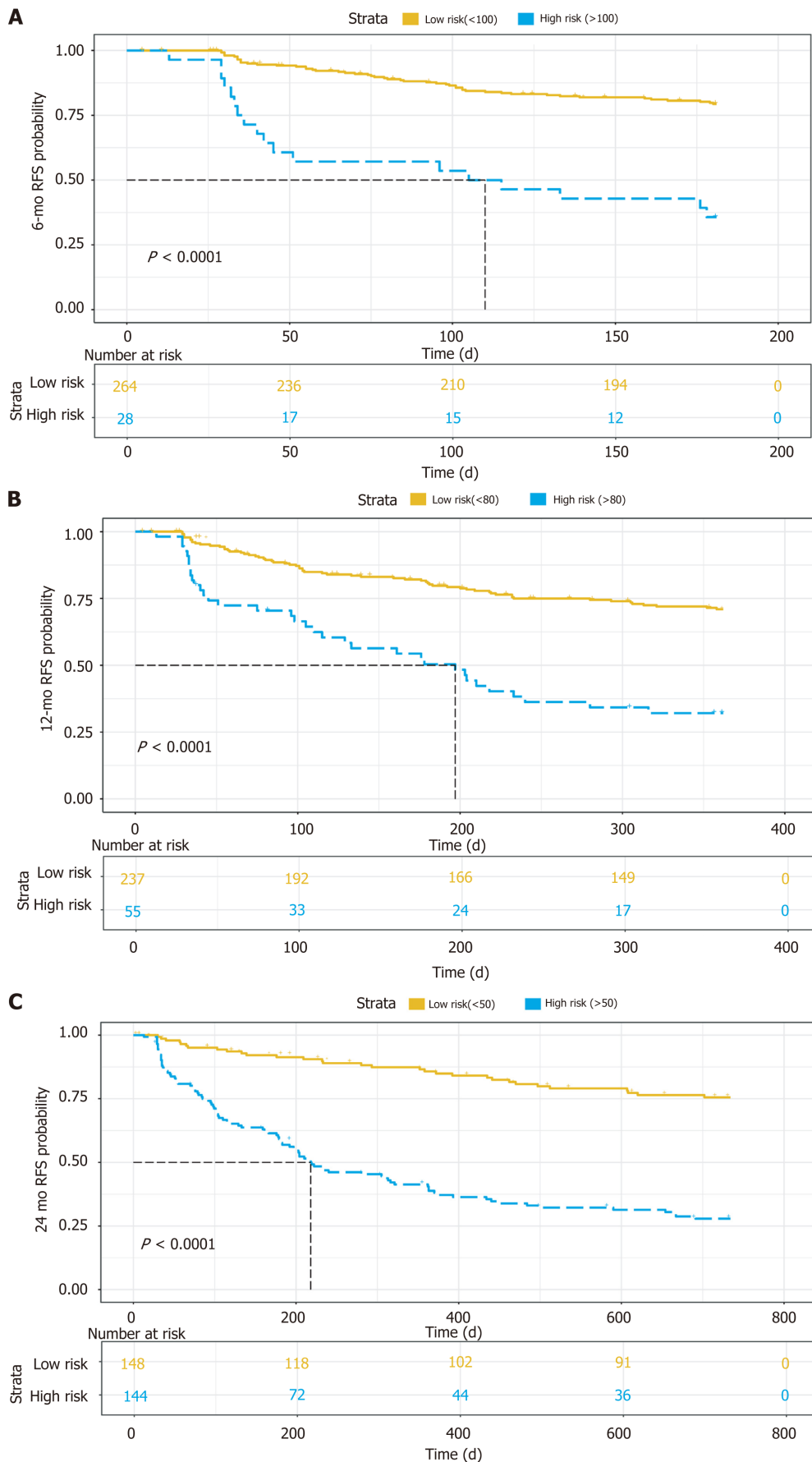


Figure 5 Kaplan–Meier curves for survival at 6 mo (A), 12 mo (B), and 24 mo (C). RFS: Relapse free survival.

CEUS can dynamically display microvascular and tissue perfusion in real time, and it has good resolution and simple operation, without risk of nephrotoxicity and

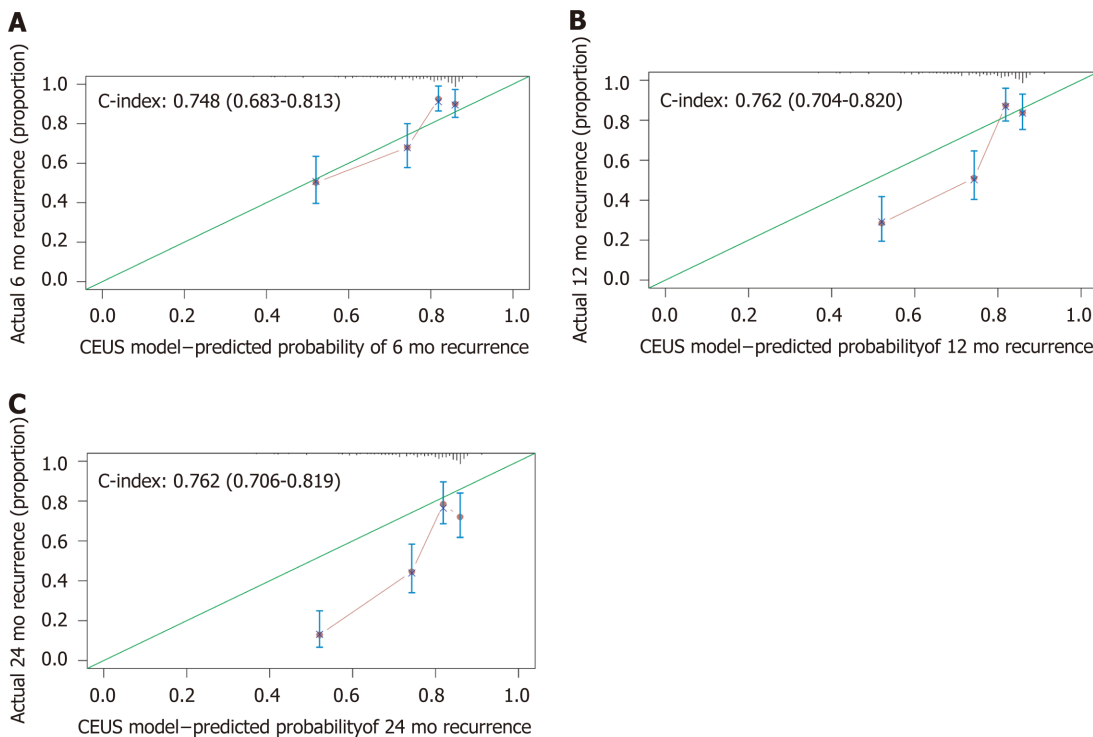


Figure 6 Calibrated curves for recurrence at 6 mo (A), 12 mo (B), and 24 mo (C). CEUS: Contrast-enhanced ultrasound.

radiation. It is widely used in the diagnosis of clinical liver diseases. Different contrast patterns reveal varying tumor differentiation[23]. Qin *et al* found that the faster the washout, the higher the recurrence rate, and the C-index of this parameter was 0.756 [24]. In our study, the difference in the washout time and type was not statistically significant. This result may be attributed to the following reasons: (1) The primary study end point was different. Qin *et al* defined early recurrence as 1 year, and in our study, the early recurrence was 2 years; (2) The definition of washout rate was different. Qin *et al* divided the washout rate into four grades (120 s, 60–120 s, 30–60 s, and < 30 s), but in our study, the washout time was less than 30 s and defined as fast-out in contrast to others that were non-fast-out; (3) The research subjects were different; Qin *et al*'s study enrolled the patients who were first discovered and after radical resection, which was pathologically confirmed; and (4) Qin *et al*'s study only enrolled patients with a single tumor, but our study enrolled patients with single and multiple tumors.

In the past, CEUS evaluation was mainly based on the subjective evaluation of an operator, and it lacked objective criteria. Thus, the American College of Radiology (ACR) convened a working group of international experts to develop the ACR CEUS Liver Imaging Reporting and Data System (LI-RADS) in 2014, which was implemented in 2016[10]. CEUS LI-RADS is highly specific for HCC, enabling its use for a confident non-invasive diagnosis[25]. In our study, we divided patients into different categories according to CEUS LI-RADS, which is objective and suitable for general applications. Our study also showed that LI-RADS can be used as an independent hazard factor for recurrence. The higher the LI-RADS grade, the higher the recurrence rate.

Tumor diameter can be used as an independent risk factor for postoperative recurrence and has been proven by many previous studies[26–28]; tumor size was significantly related to the outcomes in our cohort with an HR per centimeter of 1.12 for recurrence. Our findings are similar to those of Agopian *et al*[29], and this result supports the use of the Milan and UCSF criteria, which include the tumor size. The increase in tumor diameter suggests that the local proliferation of tumor is in an active state, resulting in the recurrence of liver cancer. The increase in tumor diameter prolongs the whole operation process, affecting the immune system of patients, heightening the response state of the body to tumor cells, and further accelerating recurrence.

AFP is an established and routine tumor marker in patients with HCC and is readily available for patients who are AFP-positive before surgery. AFP values > 1000 ng/mL before surgery have been associated with the risk of HCC recurrence after

hepatectomy. High AFP serum levels may be a surrogate parameter for vascular invasion and is a well-characterized predictor of HCC recurrence after surgery[20]. A high serum AFP level suggests that HCC is highly invasive. Elevated preoperative AFP levels indicate an increased risk of tumor cell metastasis *via* blood route. Therefore, predicting the malignant characteristics and prognosis of HCC through the pre-operative serum AFP level is important. Nowadays, the cut-off value of preoperative serum AFP level for predicting recurrence and survival of HCC has not been standardized. Our observation is consistent with that of another study[23]; we divided AFP into three levels and the HR per grade was 1.547 for recurrence. In general, serum AFP levels may be associated with HCC tumors, but not all patients with HCC have AFP levels higher than 250–400 ng/mL. In addition, mildly to moderately elevated AFP may be associated with necrotizing inflammation of the liver but not with malignant tumors[30], which should be given attention.

Limitations

As this work was a single-center and retrospective cohort study, some limitations should be noted due to the inherent defects of the study design. First, selection and management bias is unavoidable. In general, if liver ultrasound examination is not enough, CEUS examination is also insufficient. In addition, the quality of an examination still depends on the skills of the operators. However, the ability of CEUS to observe some parts of the liver is limited, especially for patients with obesity. Further limitations are related to the width of the acoustic window and motion artifacts. The model has not been validated by external cohorts, thereby limiting its wide application. We hope that in the future, we can conduct a multi-center study, with an expanded sample size and prospective verification.

CONCLUSION

In summary, early recurrence of liver cancer after operation seriously affects the health of patients. Our non-invasive prediction model based on CEUS and serological biomarkers can achieve a high prediction efficiency with few indicators and is helpful in planning an appropriate treatment schedule.

ARTICLE HIGHLIGHTS

Research background

Surgery is the main treatment for hepatocellular carcinoma (HCC). However, 30%-50% of patients develop recurrence within 2 years, which is the main cause of death.

Research motivation

Screening patients with high recurrence risk plays an important role in making reasonable clinical decisions.

Research objectives

To combine contrast-enhanced ultrasound (CEUS) liver imaging reporting and data system (LIRADS) with serology biomarkers to construct a non-invasive model predicting the early recurrence of HCC, and verify the model.

Research methods

Records of 744 consecutive patients undergoing first-line curative surgery for HCC in one institution from 2016–2018 were reviewed, and 292 local patients were selected for analysis. General characteristics, CEUS liver imaging reporting and data system (LIRADS) parameters, and serology biomarkers were collected. Univariate analysis and multivariate analyses were performed to evaluate the independent prognostic factors for tumor recurrence. Then, a nomogram called CEUS model was constructed. The CEUS model was then used to predict recurrence at 6 mo, 12 mo, and 24 mo.

Research results

Tumor diameter, preoperative alpha-fetoprotein (AFP) level, and LIRADS were identified to be independent hazard factors, with a hazard ratio of 1.123 (95% confidence interval [CI]: 1.041-1.211), 1.547 (95%CI: 1.245-1.922), and 1.428 (95%CI:

1.059-1.925), separately. A nomogram based on them was constructed; the cut-off value at 6 mo, 12 mo, and 24 mo was 100, 80, and 50, and the C-index was 0.748 (95%CI: 0.683-0.813), 0.762 (95%CI: 0.704-0.820), and 0.762 (95%CI: 0.706-0.819), separately. The calibration at 6 mo was desirable; however, the calibration at 12 and 24 mo should be improved.

Research conclusions

The CEUS model can screen out patients who have a high recurrence risk, it is helpful for making reasonable treatment strategy.

Research perspectives

A multi-center study, with an expanded sample size and prospective verification, is required.

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