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# Prediction of Early Recurrence of Hepatocellular Carcinoma in Patients with Cirrhosis Who Had Received Deceased Donor Liver Transplantation: A Multicenter Study

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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**Background:** Early recurrence after liver transplantation (LT) is still a clinical problem. This multicenter study evaluated the Milan, Hangzhou, and AFP model-based criteria for prediction of early recurrence of HCC in patients with cirrhosis who had undergone LT.

**Material/Methods:** From the China Liver Transplant Registry (CLTR) database, we analyzed data of 589 HCC patients who had undergone LT between Jan 2015 and Jan 2019. Imaging data and AFP levels were evaluated immediately before LT. Recurrence and overall survival rates at 2 years were tested using the Kaplan-Meier estimate. The Milan criteria, Hangzhou criteria, and AFP model-based criteria were evaluated.

**Results:** We found that 62.0%, 91.2%, and 67.6% of patients were within the Milan criteria, Hangzhou criteria, and AFP model-based criteria, respectively. The 2-year recurrence rate was 8.9%, 15.8%, and 11.8% with corresponding overall survival of 85.3%, 82.7%, and 86.5%, respectively. The 2-year recurrence rate was different in patients fulfilling and exceeding the AFP model-based criteria among patients who met either the Milan criteria (7.9% *vs.* 18.8%, HR=3.83, p=0.006) or Hangzhou criteria (12.0% *vs.* 27.6%, HR=2.95, p<0.001). However, the 2-year recurrence rate was not significantly different among patients who were beyond either the Milan or Hangzhou criteria.

**Conclusions:** For the prediction of early recurrence of HCC in patients with cirrhosis after liver transplantation, Milan criteria, Hangzhou criteria, and AFP model-based criteria are effective predictive tools for stratification of patients into low- and high-risk groups of recurrence with different prognoses. The AFP model-based criteria can identify a subgroup of patients with high risk of recurrence among patients who met either Milan or Hangzhou criteria.

**MeSH Keywords:** **Carcinoma, Hepatocellular • Liver Cirrhosis • Liver Transplantation • Prognosis • Recurrence**

**Abbreviations:** **AFP** – alfa-fetoprotein; **HCC** – hepatocellular carcinoma; **LT** – liver transplantation

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## Background

Generally, liver transplantation (LT) is one of the most effective therapeutic modalities for hepatocellular carcinoma (HCC) as it can cure cancer along with its underlying causative disease. Even with the careful selection of HCC candidates, tumor recurrence after LT is still a clinical challenge, with a rate of about 10–47% [1–9]. HCC recurrence has 2 different types – early recurrence occurs within 2 years of surgery and it arises due to metastasis of pre-existing cancer cells, while late recurrence occurs after 2 years of surgery and is usually due to the formation of *de novo* tumors [2].

Since the introduction of the Milan criteria in 1996, the recurrence and survival of HCC candidates after LT were improved, so it has been adopted globally and is still recommended as a benchmark for selection of HCC candidates for transplantation [1,3,4]. However, the Milan criteria were considered to be very restrictive as it depends only on the morphological assessment of the tumor, but not on the biological assessment. Thus, many researchers are trying to combine both biological and morphological factors, but there is no consensus between these novel models that lack comparability to the Milan criteria.

AFP is a surrogate biological biomarker and a risk factor for HCC recurrence after LT, and AFP has a prognostic significance better than cancer morphology alone [5,6]. By adding the prognostic features of AFP to tumor grade and tumor size, the Hangzhou criteria were proposed for the selection of HCC patients for LT and it was unique in that it expands the Milan criteria by combining the biological and morphological features of the tumor without affecting the long-term survival of patients [7]. Nowadays, the Hangzhou criteria have been widely accepted as a selection tool of HCC candidates for LT in mainland China. Similarly, Duvoux et al. introduce the French AFP model as a predictive model for HCC recurrence by incorporation of pre-LT AFP levels to tumor size and number, and it was shown that the AFP model-based criteria is better than the Milan criteria for predicting HCC recurrence [8].

Identification of the patients at high risk of recurrence will allow for more accurate selection of HCC candidates for LT and better management of this patient group. To date, no study has evaluated the Milan criteria, Hangzhou criteria, and AFP model-based criteria together for prediction of HCC early recurrence, especially among populations where hepatitis B virus infection (HBV) is a predominant cause, such as China. Therefore, the present multicenter study aimed to evaluate these 3 criteria for prediction of early recurrence of HCC in patients with cirrhosis who had undergone LT.

## Material and Methods

Patients

The subjects of this retrospective cohort study consisted of all adult cirrhotic patients with a known HCC who had undergone LT between January 2015 and January 2019. The required data were retrieved from a prospectively maintained database of the Chinese liver transplantation registry (CLTR). The inclusion criteria for the study subjects were: (1) cirrhotic patients who had undergone LT, (2) adult patients ≥18 years, (3) HCC patients diagnosed preoperatively by radiological assessment depending on guidelines of the American Association for the Study of Liver Diseases (AASLD) [9], (4) no vascular invasion on preoperative imaging of the liver (mainly CT scan, and MRI), (5) no re-transplantation or combined renal transplantation, and (6) all the essential laboratory and clinical data required for analysis are available.

After applying the inclusion criteria, 589 subjects were included for the final analysis. This study was authorized by the Scientific Committee of CLTR (*http://www.cltr.org/* approval No. K19001) in accordance with ethical guidelines of the Helsinki Declaration 1975, as revised in 2013. Every participant provided consent before being included in this study.

### Study variables

The required data for the analysis were extracted by independent researchers who were blinded to further steps of the study. The variables of this study included: age, sex, body mass index (BMI), diabetes and hypertension status, blood group, Model for End-stage Liver Disease (MELD) score, Child-Pugh score, presence of HBV infection, and pre-LT neoadjuvant therapies. The pre-LT characteristics of HCC were obtained from radiological assessment (mainly CT and MRI), including the total tumor diameter, largest tumor diameter, number of nodules, and the last pre-LT measurements of AFP. Post-LT features of HCC were obtained from the pathology reports, including tumor differentiation and vascular invasion. Data on survival and recurrence, including death cause, last follow-up dates, recurrence, and death dates, were also obtained. The last censoring date of this study was 21 January 2019. After the implementation of liver transplantation, all patients were monitored until death or last censoring date. In the first year post-LT, subjects were examined routinely every 2 months and at least every 3–4 months thereafter. During follow-up, serum AFP assay was performed independently. Abdominal computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed every 6 months, or immediately in case of recurrence suspicion.





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### Definitions and outcome measures

The main goal of this study was to evaluate Milan criteria, Hangzhou criteria, and AFP model-based criteria for prediction of HCC early recurrence (within 2 years) in patients with cirrhosis who had undergone LT.

The Milan criteria require, in addition to the absence of macrovascular invasion and metastasis, a single nodule ≤5 cm or no more than 3 nodules (each nodule ≤3 cm) [3]. While the Hangzhou criteria require, in addition to the absence of macrovascular invasion, (a) a total tumor size ≤8 cm, (b) total tumor diameter >8 cm, well-differentiated to moderately-differentiated tumor, and preoperative AFP level ≤400 ng/mL, simultaneously [7].

The tumor metrics were extracted from pre-LT radiological assessment. Then, the Hangzhou criteria were calculated by utilizing these data; however, part (b) of the Hangzhou criteria required 1 pathological factor (tumor differentiation), which was retrieved from the posttransplant explant reports.

The AFP model-based criteria were calculated for every patient using the simplified version of the AFP model-based criteria, in which patients with ≤2 total points are considered to be "within the AFP model-based criteria", while those with >2 total points are considered to be "exceeding the AFP model-based criteria" [8].

The 2-year recurrence and overall survival rates were estimated based on pre-LT imaging and AFP levels. Overall survival (OS) was defined as time interval by months between the surgery date and the dates of death or last follow-up.

### Statistical methodology

HCC recurrence and OS were calculated using Kaplan-Meier (KM) survival estimates. The Milan criteria, Hangzhou criteria, and AFP model-based criteria were compared by log-rank test. Univariate and multivariate Cox analyses were performed to calculate the hazard ratio (HR) between risk groups and to identify the risk factors of early recurrence. Categorical data are described as number and percentages and were compared using Fisher's test or the chi-square test. Continuous data are described as mean ±SD or median and interquartile range (IQR) and were compared by t test or Wilcoxon rank sum test, according to their distribution. Stata version 14 and SPSS version 25 were used for all statistical analyses, with a 5% level of significance.

## Results

### Baseline characteristics

All patients included in this study underwent LT for HCC treatment. Of the 589 patients, 521 were male (88.5%) and 68 were female (11.5%). The mean age was 52.2± 8.7 years. The median pre-LT MELD score was 12 (IQR, 9-19). All subjects in this cohort had cirrhosis and most (n=554) presented with HBV (94.1%). Among the 314 patients who had received neoadjuvant therapies before undergoing LT (53.3%), 235 had transcatheter arterial chemoembolization (TACE) (39.9%), 111 patients had radiofrequency ablation (RFA) (18.9%), 89 patients had hepatectomy (15.1%), and 121(38.5%) had received more than 1 neoadjuvant therapy. Overall, before transplantation, 365 patients were within the Milan criteria (62%), 537 patients were within the Hangzhou criteria (91.2%), and 398 patients were within the AFP model-based criteria (67.6%). The overall median follow-up period was 280 days (IQR, 99–594 days). Post-LT overall mortality and recurrence rate was 12.4% and 9.3%, respectively. Other baseline features of the study subjects are listed in Table 1.

### Milan and Hangzhou criteria assessment

Regarding the Milan criteria, the 2-year recurrence rate was significantly lower in 365 patients who met Milan than in 224 patients who exceeded the Milan criteria (8.9% *vs.* 32.2%, p<0.001, HR=3.81, 95% CI: 2.14–6.78) (Figure 1A).The corresponding 2-year OS rate were also significantly different (85.3% *vs.* 75.8%, respectively) (p=0.035, HR=1.67, 95% CI: 1.03–2.67) (Figure 1B), whereas the 2-year recurrence rate for 537 patients within the Hangzhou criteria was 15.8% and for 52 patients exceeding the Hangzhou criteria it was 32.1% (p=0.002, HR=2.83, 95% CI: 1.42–5.63) (Figure 1C). The corresponding 2-year OS rate was 82.7% and 71.6%, respectively (p=0.019, HR=2.13, 95% CI: 1.12–4.07) (Figure 1D).

### AFP model assessment

By using the AFP model-based criteria, the 2-year recurrence rate was significantly different between the 398 patients who met the AFP model-based criteria and the 191 patients beyond the AFP model-based criteria (11.8% *vs.* 30.3% respectively, p<0.001, HR=3.5, 95% CI: 2.00–5.97) (Figure 1E). The corresponding 2-year OS rate was also significantly different (86.5% *vs.* 71.3%, respectively (p=0.005, HR=1.94, 95% CI: 1.20–3.12) (Figure 1F).

Of note, among the patients who fulfilled or exceeded either of these 3 criteria, the 2-year recurrence rate was not significantly different, except for patients who met either the Milan or Hangzhou criteria, for whom the 2-year recurrence rate was significantly different (8.9% *vs.* 15.8%, p=0.030) (Figure 2).





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**Table 1.** Characteristics of the study population.

| Variable | Study group |
|---|---|
| Age* | 52.2± 8.7 |
| Sex (M/F) n (%) | 521 (88.5)/68 (11.5) |
| BMI* | 24.1±11.8 |
| Hypertension (yes/no) n (%) | 69 (11.7)/520 (88.2) |
| Diabetes (yes/no) n (%) | 90 (15.2)/499 (84.7) |
| Blood group n (%) A/B/O/AB | 174 (29.5)/176 (29.9)/ 179 (30.4)/60 (10.2) |
| MELD score** | 12 [9–19], (6–47) |
| Child score n (%) A/B/C | 379 (64.4)/168 (28.5)/ 42 (7.1) |
| HBV/non-HBV n (%) | 554 (94.1)/35 (5.9) |
| Number of nodules** | 1 [1–2], (1–10) |
| Largest tumor diameter (cm)** | 3.3 [2–5], (0.3–23) |
| Milan criteria in/out (n,%) | 365 (62.0)/224 (38.0) |
| Hangzhou criteria in/out (n,%) | 537 (91.2)/52 (8.8) |
| AFP model in/out (n,%) | 398 (67.6)/191 (32.4) |
| Pre-LT neoadjuvant therapies (n,%) | |
| TACE (yes/no)# | 235 (39.9)/353 (59.9) |
| RFA (yes/no) | 111 (18.9)/478 (81.2) |
| Hepatectomy (yes/no) | 89 (15.1)/500 (84.9) |
| Donor type (n,%) | |
| DBD | 169 (28.7) |
| DCD | 241 (40.9) |
| DBCD | 179 (30.4) |
| Donor death cause (n,%) | |
| Trauma | 351 (59.6) |
| CVA | 166 (28.2) |
| Tumor | 34 (5.8) |
| Anoxia | 25 (4.2) |
| Others | 13 (2.2) |
| Post-LT mortality (n,%) | |
| Alive | 516 (87.6) |
| HCC-related death | 36 (6.1) |
| HCC-unrelated death | 37 (6.3) |
| Overall Recurrence rate (n,%) | 55 (9.3) |
| Follow-up (days)** | 280 [99–594], (1–1428) |

M – Male; F – Female; BMI – body mass index; MELD – Model for End-Stage Liver Disease; HCC – hepatocellular carcinoma; LT – liver transplantation; TACE – transarterial chemoembolization; RFA – radiofrequency ablation; DBD – donation after brain death; DCD – donation after circulatory death; DBCD – donation after brain death followed by circulatory death; CVA – cerebrovascular accident. * Mean ±SD; ** (median, [IQR, interquartile range]),(range), # missing value.

All the above results indicate that Milan criteria, Hangzhou criteria, and AFP model-based criteria are effective tools for stratification of patients into high- and low-risk groups of early recurrence after LT with different prognoses.

### AFP model-based criteria *vs.* Milan criteria

Among 365 patients who met the Milan criteria, the 2-year recurrence rate was different in patients fulfilling *vs.* those exceeding the AFP model-based criteria (7.9% *vs.* 18.8%, HR=3.83, p=0.006) (Figure 3A). However, among 224 patients exceeding the Milan criteria, the 2-year recurrence rate was not different in patients fulfilling and exceeding the AFP model-based criteria (p=0.259) (Figure 3B). These results indicate that the AFP model-based criteria can identify patients at high and low risk of recurrence among patients fulfilling the Milan criteria.

### AFP model-based criteria *vs.* Hangzhou criteria

Among 537 patients fulfilling the Hangzhou criteria, the 2-year risk of recurrence was 12.0% in patients within the AFP model-based criteria and 27.6% in patients beyond the AFP model-based criteria, (p <0.001, HR=2.95 95% CI: 1.62–5.37) (Figure 3C). However, among 52 patients exceeding the Hangzhou criteria, the risk of recurrence was not significantly different among patients within and beyond the AFP model-based criteria (p=0.213) (Figure 3D). These findings indicate that the AFP model-based criteria can identify patients with high and low risk of recurrence among patients who meet the Hangzhou criteria.

### Evaluation of clinical features according to Milan, Hangzhou, and AFP model-based criteria

Comparative analysis of clinical features according to the Milan, Hangzhou, and AFP model-based criteria showed that nodule number was higher and total and largest tumor size were larger in patients exceeding AFP model-based criteria than in patients within the AFP model-based criteria. Interestingly, the same results were observed for patients exceeding either the Hangzhou or Milan criteria (Table 2).





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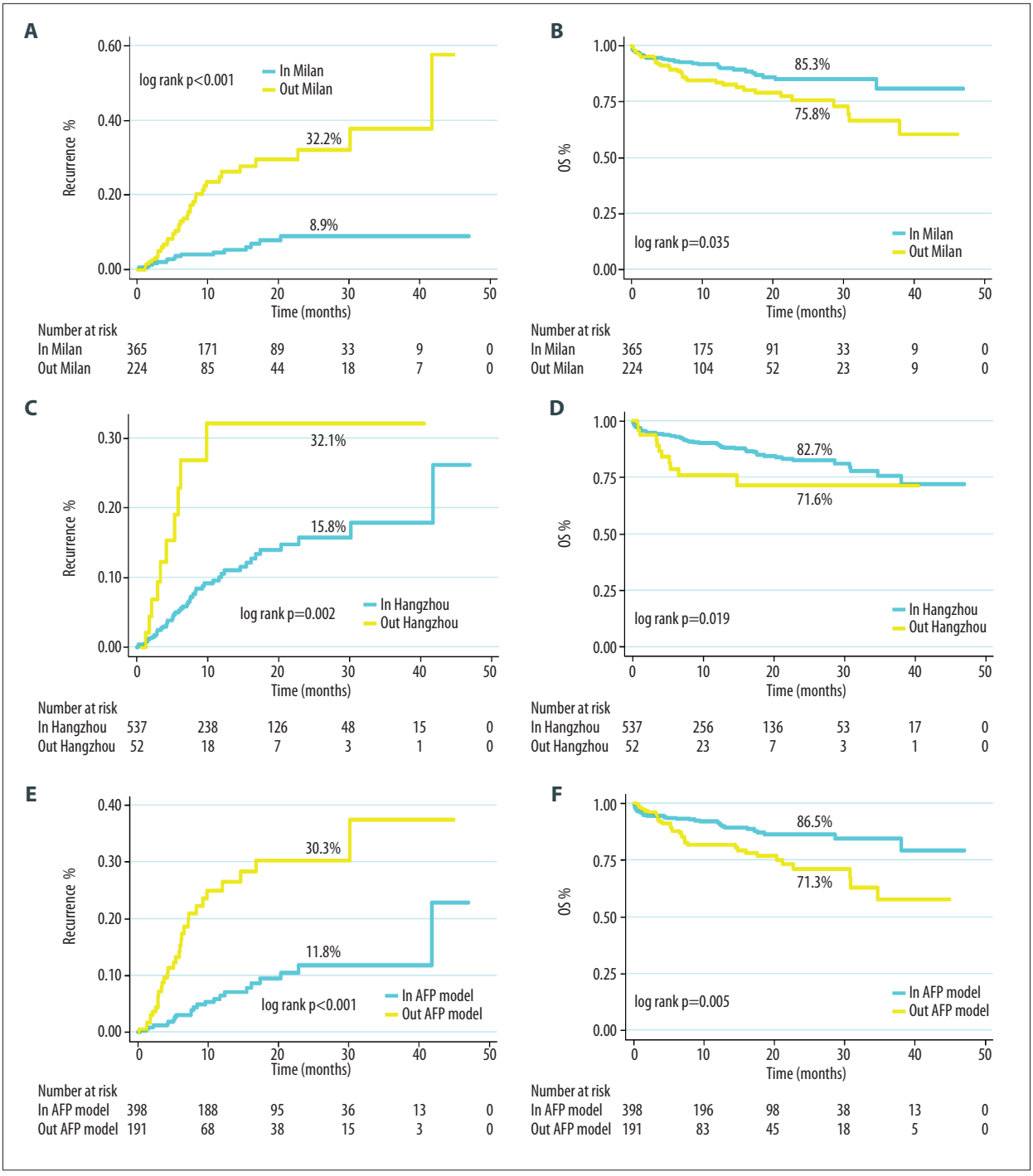


**Figure 1.** Two-year recurrence and survival rates according to Milan criteria (**A, B**) according to Hangzhou criteria (**C, D**) and according to AFP model-based criteria (**E, F**).

Univariate analysis of recurrence showed that blood group, MELD score, AFP >100 ng/mL, number of nodules, the largest size of the nodule, the total tumor size, neoadjuvant therapy before LT, and presence of post-LT macrovascular invasions were predictors of early recurrence of HCC. However, multivariate analysis showed that MELD score, total tumor diameter, and presence of macrovascular invasion after transplantation were independent predictors of post-LT HCC recurrence (Table 3).





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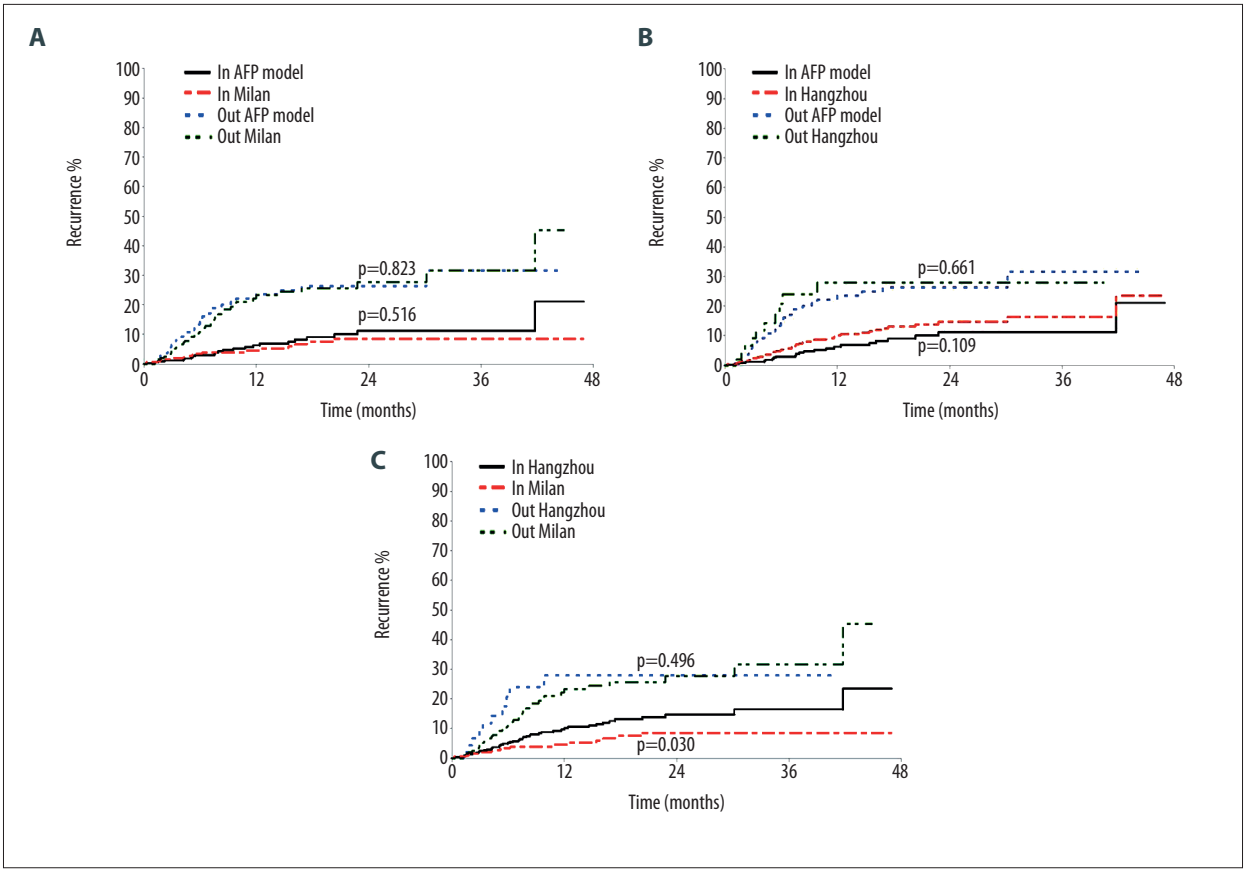


**Figure 2.** (**A**) Two-year recurrence rates of patients fulfilling (p=0.516) or exceeding (p=0.823) either Milan criteria or AFP model-based criteria. (**B**) Two-year recurrence rates of patients fulfilling (p=0.109) or exceeding (p=0.661) either Hangzhou criteria or AFP model-based criteria. (**C**) Two-year recurrence rates of patients fulfilling (p=0.030) or exceeding (p=0.496) either Milan or Hangzhou criteria.

## Discussion

To the best of our knowledge, this is the first multicenter study to evaluate the well validated and widely recognized selection criteria in clinical practice of LT for HCC; Milan, Hangzhou, and AFP model-based criteria for prediction of early recurrence of HCC. A total of 589 HCC patients with cirrhosis from centers scattered throughout mainland China were evaluated in our cohort. The main strength of our study is that the evaluation was based on preoperative imaging of the selection criteria and AFP levels for prediction of early recurrence of HCC after transplantation.

In Italy 1996, the Milan criteria were proposed by incorporation of the tumor number, tumor size, and the absence of vascular invasion. The prospective, single-center study evaluated 48 HCC patients with cirrhosis who received LT, and they achieved a survival rate of 75% and recurrence risk of about 10% at 4 years after LT [3]. Since then, the Milan criteria have been validated and used worldwide as a selection tool for LT in HCC patients and is still recommended as a benchmark [4,9,10]. However, the Milan criteria are challenged by their restrictiveness and absence of biological indices of tumor behavior [11]. Therefore, many novel criteria and models were developed for expanding HCC indications for LT, but these expansions were at the expense of recurrence rate, which ranges between 8% and 47% [1,7,12–19]. In the present study, all patients were also HCC patients who had cirrhosis, and the 2-year cumulative recurrence rate was 8.9% with an OS rate of 85.3% among patients who met the Milan criteria.

In China 2008, Zheng et al. combined the biological and pathological indices of HCC and proposed the Hangzhou criteria. These criteria were different from the previous criteria in that they were not limited to the tumor morphology and did not affect long-term survival. The Hangzhou criteria have been validated by many clinical studies in China, France, and Germany. All these studies confirmed that HCC patients who fulfill the Hangzhou criteria have achieved an acceptable post-LT 5-year survival of 72–76% and recurrence rate of 20–23% [7,20–24]. In accordance with these studies, our study showed that the early recurrence rate was 15.8% with an OS rate of 71.6% for patients who met the Hangzhou criteria.





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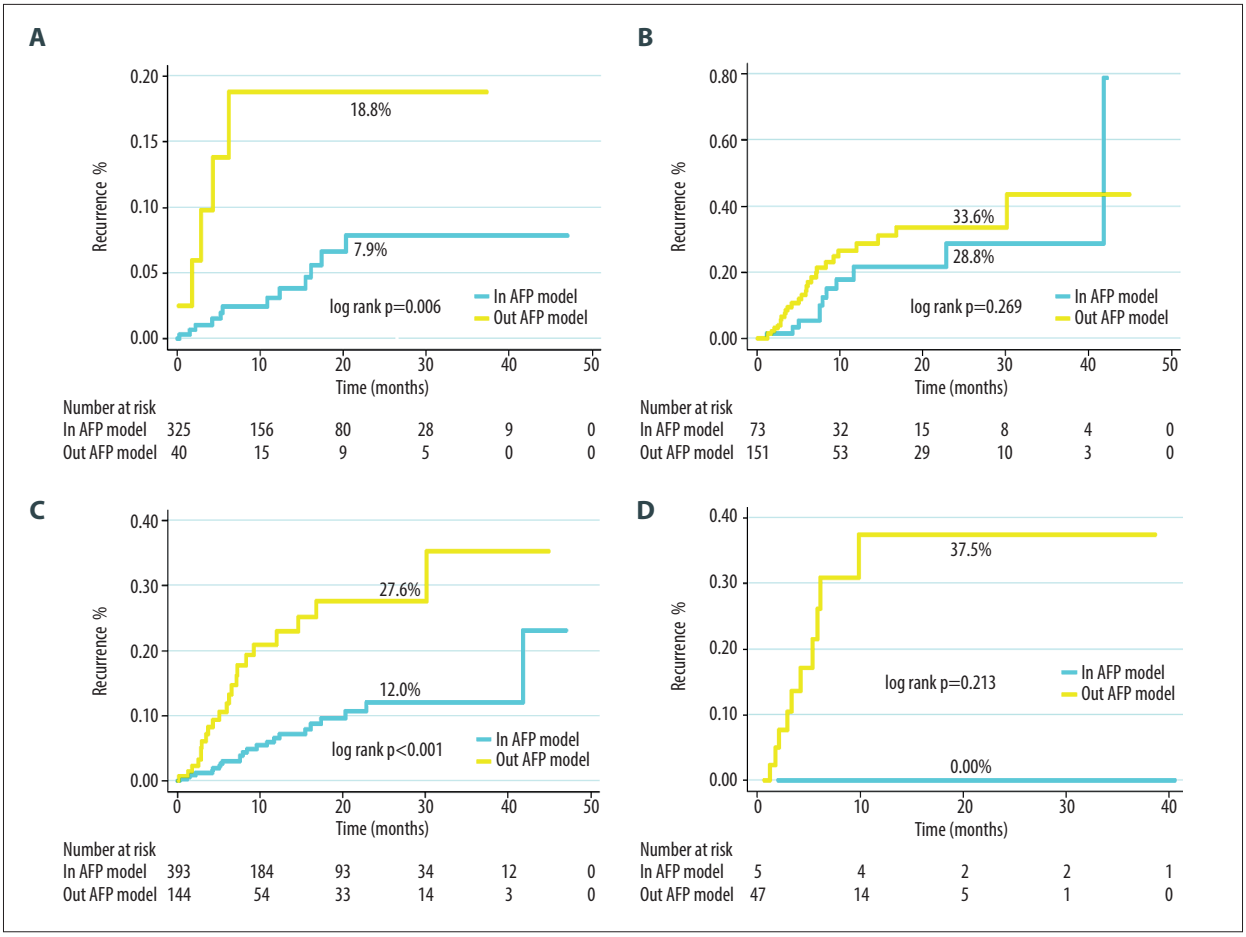


**Figure 3.** Two-year recurrence rates according to AFP model-based criteria in patients fulfilling Milan criteria (**A**), in patients exceeding Milan criteria (**B**), in patients fulfilling Hangzhou criteria (**C**), and in patients exceeding Hangzhou criteria (**D**).

In France 2012, Duvoux et al. established a binary prognostic score depending on the AFP level, number of nodules, and tumor size. This model allowed more patients who are beyond the Milan criteria to be transplanted and survive. The AFP model-based criteria were superior to the Milan criteria for selection of HCC subjects and thus were adopted as an authorized selection tool in France. Subsequently, the AFP model-based criteria have been validated in separate cohorts from Italy and Latin America, and the 5-years survival rate was 66–72% with a recurrence rate of 8–13% [8,25,26]. In accordance with these studies, our findings showed that the early recurrence rate was 11.8% and OS was 86.5% for patients within the AFP model-based criteria at 2 years after LT.

All the selection criteria included in this multicenter study confirmed their ability to significantly discriminate between high- and low-risk groups of patients for early recurrence after transplantation with a different prognosis. In addition, the AFP model-based criteria can recognize a subgroup of patients within the Milan criteria with a recurrence rate of 18.8%, and a subgroup within the Hangzhou criteria with a recurrence rate of 27.6%. These findings indicate that this subgroup of patients should be assessed carefully before implantation of LT to avoid postoperative recurrence.

According to the current guidelines of the Chinese Society of Organ Transplantation, the Milan and Hangzhou criteria are the 2 recommended tools for HCC recurrence risk stratification and selection of HCC candidates for LT. However, based on our study results, the AFP model-based criteria can play a complementary role in further stratification of HCC recurrence risk alongside the conventional (Hangzhou and Milan) selection criteria.

We also conducted univariate and multivariate analyses to determine the factors associated with early recurrence of HCC after LT, showing that MELD score and total tumor diameter were the preoperative independent factors for early recurrence of HCC after LT. Thus, meticulous evaluation of these factors is very important because it is accessible to diagnostic work-up before transplantation. It also showed that macrovascular invasion was the postoperative independent factor for early





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**Table 2.** Comparative analysis of clinical features according to AFP model-based criteria, Milan, and Hangzhou criteria.

| Variable | Milan | | | Hangzhou | | | AFP model | | |
|---|---|---|---|---|---|---|---|---|---|
| | In (n=365) | Out (n=224) | P | In (n=537) | Out (n=52) | P | In (n=398) | Out (n=191) | P |
| Age* | 52.1±8.52 | 52.3±9.1 | 0.895 | 52.2±8.7 | 52.5±9.0 | 0.831 | 52.1±8.2 | 52.5±9.7 | 0.597 |
| Sex (M/F) n | 316/49 | 205/19 | 0.068 | 474/63 | 47/5 | 0.648 | 351/47 | 170/21 | 0.772 |
| BMI* | 24.4±14.9 | 23.6± 3.3 | 0.426 | 24.1± 12.4 | 23.9±4.1 | 0.893 | 24.1±12.8 | 24.1± 9.8 | 0.990 |
| Hypertension (yes/no) n | 323/42 | 197/27 | 0.841 | 476/61 | 44/8 | 0.389 | 358/40 | 162/29 | 0.070 |
| Diabetes (yes/no) n | 303/62 | 196/28 | 0.142 | 455/82 | 44/8 | 0.983 | 336/62 | 163/28 | 0.772 |
| Blood group (A/B/O/AB) n | 100/105/ 116/44 | 74/71/ 63/16 | 0.122 | 155/163 162/57 | 19/13 17/3 | 0.459 | 113/118 120/47 | 61/58 59/13 | 0.288 |
| MELD score** | 12 [8–19], (6–51) | 13 [9–19.5], (6–47) | 0.451 | 12 [9–19], (6–51) | 14 [9–25.5], (6–42) | 0.130 | 12 [9–18], (6–51) | 13 [9–22], (6–47) | 0.177 |
| Child score** | 5 [4–7], (4–12) | 6 [4–7.5], (4–11) | 0.288 | 5 [4–7], (4–12) | 6.5 [5–8], (4–11) | 0.014 | 5 [4–7], (4–12) | 6 [4–8], (4–12) | 0.043 |
| HBV/non-HBV n | 345/20 | 209/15 | 0.544 | 502/35 | 52/0 | 0.058 | 374/24 | 180/11 | 0.896 |
| Number of nodules** | 1 [1–2], (1–3) | 2 [1–3], (1–10) | <0.001 | 1 [1–2], (1–8) | 2 [1–3], (1–10) | 0.005 | 1 [1–2], (1–8) | 2 [1–3], (1–10) | <0.001 |
| Largest tumor diameter (cm)** | 2.5 [1.63], (0.5–5.1) | 5.5 [4–8], (0.6–17) | <0.001 | 3 [2–4.5], (0.5–15.5) | 8 [5–11.55], (2.2–17) | <0.001 | 2.5 [1.8–3.5], (0.5–6) | 5.5 [4–8], (1–17) | <0.001 |
| Total tumor diameter (cm)** | 3 [2–4], (0.5–8.5) | 8 [6–10.3], (1.3–17.5) | <0.001 | 4 [2.5–6], (0.5–17.5) | 10.7 [9.2–12.5], (3–17) | <0.001 | 3 [2–4.5], (0.5–12) | 8 [5.3–10.5], (1.5–17.5) | <0.001 |
| Pre-LT neoadjuvant therapies (yes/no) n | 176/189 | 138/86 | 0.002 | 281/256 | 33/19 | 0.124 | 205/193 | 109/82 | 0.205 |
| Post-LT macrovascular invasion(yes/no) n | 55/310 | 43/141 | 0.192 | 87/450 | 11/41 | 0.360 | 67/331 | 31/160 | 0.854 |
| Tumor differentiation (well, moderate, poor) n | 60/266/39 | 31/157/36 | 0.141 | 85/398/54 | 6/25/21 | <0.001 | 69/290/39 | 22/133/36 | 0.003 |
| Follow-up (days)** | 280 [98–602], (1–1428) | 264 [100.5–573], (2–1404) | 0.821 | 282 [99–617], (1–1428) | 203.5 [101.5–510.5], (20–1231) | 0.418 | 299.5 [101–599, (1–1428) | 220 [94–587], (2 1366) | 0.295 |

* Mean ±SD; ** (median, [IQR, interquartile range]), (range).

recurrence of HCC after transplantation. Pre-LT macrovascular invasion can be identified radiologically and is considered a contraindication for LT. However, post-LT macrovascular invasion can be coexisting with microvascular invasion on the explant. Our study showed that post-LT macrovascular invasion is a strong predictor of HCC recurrence, and this is in accordance with previous studies [1,25,27].

The present study is limited in that it was a retrospective and the subjects were Chinese citizens and mainly males, with hepatitis B virus infection. The small sample size and lack of data on some parameters such as microvascular invasion precluded us from including other prominent scores in this study.

## Conclusions

In conclusion, for prediction of early recurrence of HCC in patients with cirrhosis who underwent LT, we showed that the Milan, Hangzhou, and AFP model-based criteria are effective





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**Table 3.** Univariate and multivariate analysis of factors associated with HCC early recurrence.

| Variable | Recurrence-free survival | | | |
|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | |
| | HR (95%CI) | P | HR (95%CI) | P |
| Age (years) | 1.01 (.97–1.03) | 0.995 | | |
| Sex (M/F) | 1.20 (0.48–3.01) | 0.689 | | |
| BMI | 0.99 (0.93–1.05) | 0.515 | | |
| Hypertension (yes/no) | 1.01 (0.43–2.36) | 0.978 | | |
| Diabetes (yes/no) | 1.09 (0.51–2.30) | 0.832 | | |
| Blood group | 1.33 (1.02–1.74) | 0.035 | | |
| MELD score | 0.97 (0.94–1.00) | 0.043 | 0.97 (.94–1.01) | 0.034 |
| Child score | 0.88 (0.76–1.02) | 0.073 | | |
| Pre-LT AFP | | | | |
| ≤100 | | | | |
| 100–1000 | 1.41 (0.73–2.72) | 0.005 | | |
| >1000 | 3.18 (1.67–6.04) | | | |
| Number of nodules | 1.23 (1.06–1.43) | 0.015 | | |
| Largest tumor diameter (cm) | 1.19 (1.11–1.27) | <0.001 | | |
| Total tumor diameter (cm) | 1.20 (1.14–1.27) | <0.001 | 1.20 (1.13–1.28) | <0.001 |
| Pre-LT neoadjuvant therapies (yes/no) | 2.16 (1.21–3.87) | 0.007 | | |
| Post-LT macrovascular invasion (yes/no) | 2.83 (1.64–4.88) | <0.001 | 0.39 (0.22–0.67) | 0.001 |
| Tumor differentiation (well, moderate, poor) | 1.57 (0.98–2.51) | 0.058 | | |

prognostic tools for stratification of patients into high- and low-risk recurrence groups with different prognoses. AFP model-based criteria help to identify a subgroup of patients with high risk of recurrence among patients who meet either the Milan or Hangzhou criteria.

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**Conflicts of interest**

None.

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