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Title

Factors predicting long-term outcome of early stage hepatocellular carcinoma after primary curative treatment–the role of surgical or nonsurgical methods

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Abstract

Background

The effect of putative factors on the clinical course of early hepatocellular carcinoma (HCC) after primary surgical or nonsurgical curative treatment, which remains elusive, was quantified.

Methods

Patients with newly diagnosed early HCC who received surgical resection (SR) or percutaneous radiofrequency ablation (RFA) with or without transcatheter arterial chemoembolization (TACE) from January 2003 to December 2016 were enrolled. The cumulative overall survival (OS) and disease-free survival (DFS) were compared. A polytomous logistic regression was used to estimate factors regarding early and late recurrence. Independent predictors of OS were identified using Cox proportional hazard regression.

Results

One hundred twenty-five patients underwent SR, and 176 patients underwent RFA, of whom 72 were treated with TACE followed by RFA. Either match analysis based on propensity score or multiple adjustment regression showed no significant difference in DFS and OS between the two groups. Multivariate

analysis showed high AFP (≥ 20 ng/mL), and multinodularity significantly increased risk of early recurrence (≤1year). In contrast, hepatitis B virus, hepatitis C virus and multinodularity were significantly associated with late recurrence (>1year). Multivariate Cox regression with recurrent events as time-varying covariates identified older age (HR=1.55, 95% CI:1.01-2.36), clinically significant portal hypertension (CSPH) (HR=1.97, 95% CI:1.26-3.08), early recurrence (HR=6.62, 95% CI:3.79-11.6) and late recurrence (HR=3.75, 95% CI:1.99-7.08) as independent risk factors of mortality. A simple risk score showed fair calibration and discrimination in early HCC patients after primary curative treatment. In the Barcelona Clinic Liver Cancer (BCLC) stage A subgroup, SR significantly improved DFS comparing to those received RFA with or without TACE.

Conclusion

Host and tumor factors rather than the initial treatment modalities determine the outcomes of early HCC after primary curative treatment. Statistical models based on recurrence types can predict early HCC prognosis but further external validation is necessary.

Key words: Early hepatocellular carcinoma; radiofrequency ablation; transcatheter arterial chemoembolization; surgical resection; prognosis; propensity score matching

Introduction

Hepatocellular carcinoma(HCC) is one of the most common cancers and one of the leading causes of malignancy-related death worldwide[1]. Since the launch of routine ultrasound and alpha-fetoprotein surveillance in high-risk populations, more and more patients are being diagnosed with HCC at an early stage, which is beneficial to curative therapies[2, 3]. Because of the shortage of donor organs, surgical resection (SR) and nonsurgical methods, including radiofrequency ablation (RFA) alone or the combined use of transcatheter arterial chemoembolization (TACE) remain the mainstay of curative HCC treatment in Asian-Pacific countries[4].

For patients with early HCC, S R has been proved to provide better clinical outcome than local ablation but was limited to impaired liver function[5, 6]. However, RFA has begun to challenge the status of SR as the optimal treatment for early HCC $\leq$ 2cm in terms of sustained local tumor control and survival [7]. Currently, the combined use of transcatheter arterial chemoembolization (TACE) and RFA has broaden this challenge and has widely accepted as the preferred strategy for intermediate size (3.0-5.0cm) HCC treatment. Given to the influence of various tumor and liver reserve factors, the choice of either a RFA with or without TACE (RFA-TACE) method or a SR method is of great interest to clinical physicians in the management of early stage HCC.

Recurrence after curative treatment is still a big challenge for clinical physicians. Intrahepatic metastasis and multicentric HCC developed through

accumulation of genetic alternations were previously thought to be major mechanisms for early and late HCC recurrence, respectively[8, 9]. Identification of patients after curative treatment who are at risk of recurrence allows clinicians to provide intensive surveillance to detect recurrent tumors at earlier stages, when curative treatment is still feasible. In addition, a few models from both eastern and western countries have been developed specifically to predict the long-term survival after curative HCC management but none of them have taken the influence of different recurrence types into consideration[10, 11].

The aim of our study is to determine if the initial treatment modalities or other clinical factors that could predict recurrence and overall survival of early HCC after primary curative treatment. A simple scoring system is also established for HCC outcome predictions.

Patients and methods

This is a cohort study conducted as a retrospective analysis of a prospective database at a single institution. The study cohort consists of patients who were newly diagnosed HCC from January 2003 to December 2016. The inclusion criteria were (1) a single HCC $\leq$ 50mm or up to 3 HCCs $\leq$30mm, (2) no previous treatment for HCC, (3) Child-Pugh class A or B cirrhosis, and (4) no vascular invasion or extrahepatic metastasis. Patients with an Eastern Cooperative Oncology Group performance status of 2 or greater, and those with the presence of an uncontrollable malignancy other than HCC were excluded. The diagnosis

of HCC was made using European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines[12, 13]. The study protocol was approved by the ethics committee of Show Chwan Memorial Hospital.

HCC management

The surgical resection (SR) composed of the mainstay of surgical method and was determined according to the location and extent of the tumor, hepatic reserve function, and the given patient's wishes. Liver reserve was assessed by Child-Pugh classification and indocyanine green retention rate at 15 minutes. The extent of SR was mainly based on the algorithm proposed by Makuuchi et al and anatomic resection was preformed if the liver function was fair[14]. The nonsurgical method included both RFA and sequential RFA after TACE treatment. All RFA procedures were performed percutaneously under general anesthesia. Real-time ultrasound was chosen as the guidance modality. RFA was done by two senior gastroenterologists with at least 10 years of experience. The RFA was performed with one of the following devices: monopolar expandable Boston LeVeen™ needles (RF 3000 Boston Scientific Corporate®); Cool-tip™ RFA system (Covidan®); Dual- Switching Systems (VIVA Multi®); or Separable clustered electrode (Octopus).

TACE was performed prior to the RFA procedures for patients with larger or multinodular HCC and relatively preserved liver function. Except for a few cases in which drug-eluting beads were used, most of our patients received

conventional TACE. The procedure is performed via intra-arterial injection of a viscous emulsion which consists of doxorubicin mixed with lipiodol, followed by embolization of the blood vessel with gelatin sponge particles. The influence of liver transplantation was little on our subjects not only because the organ resources were short in Taiwan but also because this therapeutic option was only available in limited centers.

Data collection and Follow-up

The main variable of interest was the type of HCC recurrence. Tumor recurrence was classified as no, early, and late phases by using 12 months as cutoff. The demographic and clinicopathological information of all the participants was collected via retrospective chart review by physicians. Subjects who were on antihyperglycaemic treatment were considered to be diabetics. Clinically significant portal hypertension (CSPH) was diagnosed if one of the following criteria was met: 1. esophageal or gastric varices confirmed by endoscopy. 2. splenomegaly on imaging and a platelet count less than 100,000/uL. Major complications were defined as those that led to prolongation of hospital stay, hospital admission or additional necessitated therapy.

Patients were assessed by serum biochemistry and ultrasonography every 3 months and by computed tomography scan or magnetic resonance imaging every 6 months after curative RFA or SR. Once recurrence was found, patients were managed with either SR, RFA or TACE. The duration of follow-up was recorded from the day of curative management until loss to follow-up, death or

Dec 31, 2017.

Statistical analysis

Chi-square tests and Student's t-tests were used to compare the differences between the two groups with regard to clinical characteristics. The Nelson-Aalen cumulative hazard estimate and the log-rank test were used to compare the OS and DFS rates of the HCC patients treated with SR or nonsurgical method. The propensity score was calculated by a multivariate logistic regression model which allows users to save the predicted probability of each patient being assigned to each option of curative treatment. Variables involving the recurrence or survival of HCC were entered in the propensity score model. One-to-one matching of propensity score was used to balance the baseline differences between the nonsurgical and SR groups. The difference between matched pairs was evaluated using signed rank test for continuous data and McNemar's test for binary data.

Polytomous logistic regression was used to assess independent risk factors for early or late recurrence of early HCC after curative treatment. Variables with values of $p < 0.1$ in the univariate analysis were further included in the multivariate regression analysis. Cox proportional hazards regression models were conducted to estimate the clinicopathologic factors associated with long-term survival. To establish a multivariate predicted model, we used forward selection with $p<0.15$ to evaluate the additive effects of risk factors. The final model was selected on the basis of log-likelihood test and Akaike

information criterion. By using the set of variables that were significant in the final model, a predicted risk score composed of time-invariant and time varying factors based on the regression coefficients estimated from the final model was developed. After we excluded enrolling subjects who did not complete 3 or 5 years of follow-up with censored observations, the discrimination capabilities were presented by receiver operating characteristic (ROC) curve and the optimal cut-off was estimated by using Youden index. All analysis was conducted with SAS version 9.4. All statistical tests were 2-sided and $p<0.05$ indicated significance.

Results

Patients

A total of 312 patients who underwent curative HCC management with pre-treatment serum and post-treatment pathology-verified HCC samples were collected as the target population. After excluding those with either residual tumors after nonsurgical therapy or those without free margin after SR, 301 patients who received SR, TACE followed by RFA, or RFA alone as the initial curative treatment for HCC were enrolled. One hundred twenty-five patients underwent SR. The operative procedure consisted of partial resections in 43 (34.4%) of those cases, segmentectomies/bisegmentectomies in 66 (52.8%) cases, and trisegmentectomy/lobectomy in 16 (12.8%) cases. On the other hand, 176 patients underwent RFA, of whom 72 (41%) were treated with TACE followed by

RFA. In our RFA-TACE cohort, 88% (29/33) of the patients with Barcelona Clinic Liver Cancer (BCLC) very early stage HCC received RFA monotherapy. In addition, more than sixty percent (49/81) of the patients with either multinodularity or a single tumor of more than 3cm in size underwent combined therapy (that is, TACE followed by RFA) for control of early HCC. The median follow-up times of the RFA-TACE (that is, those treated with RFA alone or with TACE followed by RFA) and SR groups were 32.2 months and 33.8 months, respectively.

Comparison of baseline characteristics of RFA-TACE and SR groups before and after propensity score matching

A comparison of all patients in our original cohort before propensity score matching revealed that there were no significant differences in gender, age, Ishak score, Edmonson grading, history of diabetes, CSPH, levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, total serum albumin and renal function impairment. However, the RFA-TACE group did include a larger proportion of patients with chronic hepatitis C virus infection. With regard to liver reserve factors, the SR patients were significantly more likely to have well-preserved liver function (Child-Pugh class A) ($P=0.04$). On the other hand, with regard to tumor factors, the patients who underwent RFA-TACE had higher levels of serum AFP, a larger proportion of multinodularity and Barcelona Clinic Liver Cancer (BCLC) stage 0. However, the SR patients had larger tumor size in comparison with the RFA-TACE patients ($P<0.0001$). The baseline characteristics

of the RFA-TACE and SR groups are listed in Table 1. Through propensity score matching, 66 matching pairs were generated. The confounding variables contributing to treatment selection were well matched and no significant differences were found between the SR and RFA-TACE groups (Table 1).

Survival analysis in both groups

Figure 1 illustrates the OS and DFS rates of the SR and RFA-TACE groups. In the RFA-TACE group, the 1-, 3-, and 5-year cumulative OS rates were 95.2%, 78.4%, and 60.9%, respectively, while the 1-, 3-, and 5-year DFS rates were 66.2%, 28.0% and 15.7%, respectively. On the other hand, the 1-, 3-, and 5-year cumulative OS rates of the SR group were 93.4%, 77.2%, and 64.5%, respectively, while the 1-, 3-, and 5-year DFS rates were 68.9%, 43.9%, and 34.4%, respectively. There were no significant differences in OS rates between the two groups (P=0.30) (Figure 1A). However, in comparison with the patients who underwent SR, the patients who underwent RFA-TACE had significantly more recurrence (P=0.0028) (Figure 1B).

After propensity score matching, the 1-, 3-, and 5-year OS rates of the RFA-TACE group were 98.3%, 81.5%, and 58.2%, respectively, compared to 1-, 3-, and 5-year OS rates of 89.0%, 74.7%, and 61.9%, respectively, for the SR group. There were thus no statistically significant differences in term of OS between the patients receiving RFA-TACE and SR (P=0.87) (Figure 1C). Similar results were obtained between the two groups in terms of recurrence. The 1-, 3-, and 5-year DFS rates of the RFA-TACE group were 66.4%, 27.1%, and 21.7%, respectively, compared to 1-, 3-, and 5-year DFS rates of 67.3%, 41.3%, and 29.4%, respectively,

for the SR group (P=0.54) (Figure 1D). Concerning the clinical course from recurrence to death, there were no statistical difference between RFA-TACE and SR groups in terms of post-recurrence survival (P=0.43).

Complications

There was no mortality during the initial hospital stays for either group. Two major complications (1.1%) occurred in two patients after RFA therapy. Specifically, one patient experienced intraperitoneal bleeding that required a blood transfusion and subsequent transcatheter arterial embolization, while the other patient had a hemobilia, such that an endoscopic sphinterotomy for the removal of blood clots was required. Three major complications (2.4%) were recorded after SR. One patient developed a postoperative abscess that required surgical debridement, while liver decompensation including jaundice, ascites, and encephalopathy occurred in two patients. There was no significant difference between the major complication rates of the two groups (P=0.65).

Predictors for HCC recurrence

Table 2 showed the results for the one-by-one testing of covariates for HCC early and late recurrence. It was found that CSPH, advanced fibrosis (FIB-4>3.25), multinodularity, higher AFP ($\geq$ 20 ng/mL) and chronic hepatitis C raised the likelihood of early recurrence. In contrast, elevated alanine aminotransferase (ALT), CSPH, advanced fibrosis, multinodularity, chronic hepatitis B and chronic hepatitis C were contributing to the development of late recurrence. In the multivariate analysis, multinodularity (OR=3.66, 95% CI=1.72-7.80) and higher

AFP (OR=2.06, 95% CI=1.12-3.81) were the factors that were found to contribute significantly to early recurrence. On the other hand, multinodularity (OR=2.50, 95% CI=1.14-5.50), chronic hepatitis B (OR=5.11, 95% CI=1.59-16.4) and chronic hepatitis C (OR=8.07, 95% CI=2.41-27.0) were associated with a significantly increased risk of late recurrence (Table 2).

Predictors for overall survival and derivation of predicted score

Univariate analysis by Cox regression revealed that the overall survival was significantly associated with early recurrence (≤ 1 year), late recurrence (>1year), older age (>65 years), hypoalbuminemia (≤ 3.0mg/dL), CSPH, ALBI grade 2 or 3, FIB-4 index>3.25, BCLC stage A and chronic viral hepatitis (Table 3). We further used forward selection to evaluate the additive effects of covariates on overall survival. The model I included the potential predictors without recurrence. The early and late recurrence were considered as time-invariant and time-varying covariates in model II and model III, respectively. On the basis of log-likelihood ratio and Akaike information criterion tests, the final model included early recurrence, late recurrence, older age and clinically significant portal hypertension (CSPH) (Table 3).

The clinical weight of each risk factor of the final model based on regression coefficients was 0.44 for older age, 0.68 for CSPH, 1.89 for early recurrence and 1.32 for late recurrence. The predicted risk score based on the clinical weight together with risk factor was:

Risk score= (0.44×older age)+(0.68×CSPH)+(1.89×early recurrence)+(1.32×late

recurrence)

After we excluded those who did not complete follow-up, the area under ROC of the predicted risk score of 3- and 5-year OS was 77.9% and 76.8%, respectively. The optimal cut-off was score 1.71 and 1.74 for 3- and 5-year OS. A more recent independent cohort of early HCC at our institute was used for internal validation. The C-indexes for 3-year and 5-year OS were 0.79 and 0.74, respectively. By using the cutoff score of 1.71, the overall sensitivity and specificity for 3-year OS were 92.3% and 50.0%, respectively. Meanwhile, the sensitivity and specificity for 5-year OS showed 90.0% and 63.2 % respectively on the basis of the cutoff score of 1.74. We also categorized our cohort into the three risk groups with cutoff scores of 1 and 2 by using previous estimated clinical weight (Figure 2). The difference of cumulative mortality among the risk categories was significant ($p<0.0001$). The 3- and 5-year overall mortality were 8.3% and 10.8% respectively in the low-risk category; 22.6% and 38.0% respectively in the intermediate-risk category (HR=2.71; 95% CI, 1.27–5.78); and 29.0% and 50.7% respectively in the high-risk category (HR=4.50; 95% CI, 2.22–9.10).

Subgroup analysis for HCC prognosis between surgical and nonsurgical methods

Figure 3 showed the relative risk of DFS and OS of HCC after curative treatment in associated with treatment modalities after adjusting for various clinical factors, stratified by various tumor and liver reserve status. Compared to SR, the HCC patients with tumor size <3 cm, single tumor, albumin-bilirubin (ALBI) grade 1

and those without CSPH who received RFA-TACE treatment had higher risks of recurrence in the univariate analysis (Supplementary Table S1). However, RFA-TACE was not significantly associated with DFS with addition of various clinical factors. Only those with BCLC stage A were beneficial from SR in terms of DFS (HR=1.58, 95% CI=1.12-2.22) (Figure 3A). On the other hand, RFA-TACE and SR showed similar effectiveness in terms of OS in all the subgroups (Figure 3B). Among those with BCLC stage A, the propensity score matching method with generation of 46 matching pairs also revealed the similar findings (Supplementary Figure S1).

Discussion

Transcatheter arterial chemoembolization (TACE) and radiofrequency ablation (RFA) are the mainstay of nonsurgical methods for early HCC and have provided minimally invasive options that may individually or in combination yield successful HCC eradication with maximal maintenance of liver reserve. In Japan, a large number of physicians have employed TACE before RFA treatment for 3cm or larger HCC with the concern of high likelihood of occult microsatellite lesions and microvascular invasion[15]. The other meta-analysis based on eight randomized controlled trials also revealed that combined TACE and RFA yielded better survival benefits than RFA monotherapy for patients with intermediate-size HCC (3 cm< tumor size $\leq$ 5 cm)[16]. There is some evidence supporting the synergic effects. Firstly, occlusion of the hepatic arterial flow by

embolization reduces the cooling effect of hepatic blood flow on thermal coagulation. Secondly, the iodized oil and gelatin sponge particles used in TACE fill the peripheral portal vein around the tumor by arterioportal shunting, thus compromising microscopic tumor spread[17, 18]. Thirdly, retained oil within HCC after TACE can also be helpful for targeting undetected liver tumors.

In our study, adjustment by propensity score matching indicated that the patients who underwent RFA-TACE had a similar OS and DFS rates as the patients who underwent SR. Yamakado et al. first compared the efficacy of RFA combined with TACE to that of SR in early stage HCC patients with Child-Pugh class A liver profiles[19]. The 5-year DFS and OS rates of the two groups were similar, a finding which was in accordance with the results of our study. Meanwhile, the 5-year OS rates of our cohort (61% in the RFA-TACE group and 65% in the SR group) were also similar to that of patients with early HCC who underwent RFA-TACE or SR, which were as high as 58-75% and 61-81%, respectively[19-21]. Although more and more research demonstrated the superiority of SR comparing to nonsurgical methods in the management of early HCC, the generalization was still limited to heterogeneity of baseline characteristics, relatively small sample size and single institute[21, 22]. Due to the ethical issues, it is difficult to establish a well-designed randomized trial to compare the effectiveness of nonsurgical treatment with that of SR. Our propensity score model balanced the baseline characteristics of the treatment groups and thus may have provided a suboptimal comparison between the two

groups.

To rule out the possibility of treatment discrepancy after HCC recurrence, we performed sensitivity test by comparing the post-recurrence survival between the two groups. A similar survival with no statistical difference after recurrence (P=0.43) may imply the outcomes in terms of recurrence and mortality in our study are largely attributed to the effects of modalities of initial treatments. The rate of major complications related to RFA-TACE in our study was 1.1%, which was inferior to the rate of SR and was comparable to previous reports which showed a range between 0 and 3.7%[16, 19, 20]. Since the nonsurgical treatment is much less invasive and was associated with shorter hospital stays, the results suggest that RFA-TACE could serve as a safe and less costly alternative form for early HCC treatment.

Both multinodularity and elevated AFP level are tumor factors which revealed their significant association with early recurrence in the present study. These findings suggest that dissemination of the primary tumor via microsatellite lesions and microvascular invasion was attributed to early type of recurrence[23, 24]. In addition, multinodulairty also appeared to be associated with late recurrence resulted from the field effect related multicentric metachronous tumors[25]. On the other hand, factors associated with late recurrence, such as chronic hepatitis B and chronic hepatitis C, are thought to be variables reflecting increased carcinogenicity of the background liver[26, 27]. As the occurrence of de novo tumor requires time, an early intervention, such as nucleoside analogs or

pegylated interferon plus ribavirin therapies have been proved to improve the tumor cascade of liver parenchyma, thus reducing the risk of HCC recurrence[28, 29].

Our finding showed that the presence of early and late recurrence was associated with a 6.62-time and 3.75-time higher likelihood of being mortality, respectively, compared with no recurrence. Intrahepatic metastasis and multicentric HCC development were previously thought to be the major mechanisms for early and late recurrence, respectively[8, 9]. Since the great influence of recurrence, it is important to consider treatment selection based on recurrence types because intrahepatic metastasis could be beneficial to targeted therapy based on the molecular profiles of the original tumor and multicentric occurrence might be prevented by managing underlying liver disease. In addition, CSPH and older age also made significant contribution on overall survival. Groups from various countries have documented that portal hypertension was positively associated with the risk of formation of liver decompensation and thus increased the risk of mortality[30, 31]. Similarly, the results of the present study demonstrated this point that CSPH was associated with increases in mortality of 1.97–fold. More and more evidence has suggested that antiviral therapies could reduce hepatic venous pressure gradient but these effects were limited to those with earlier stage of liver cirrhosis[32, 33]. The presence of CSPH in patients with early stage HCC may imply the consideration of liver transplantation before recurrence.

In the subgroup of BCLC stage A, our patients who underwent RFA-TACE had a similar OS rate but had poorer DFS when compared with patients who underwent SR. The difference between DFS rates may be mainly due to local tumor progression. Nearly sixty-five percent of our SR patients received anatomical segmentectomy. The advantage of complete resection of tumor tissue and portal territory containing the tumor may result in lower frequency of local tumor recurrence[34, 35]. The equivalent OS between RFA-TACE and SR may contribute to the higher repeatability of RFA-TACE procedures in the nonsurgical group for recurrence control. Meanwhile, many physicians had accepted that patients with good liver reserve should undergo SR while patients with poor liver reserve should receive nonsurgical therapy[36, 37]. In the present study, SR seemed to gain more advantages given to better liver reserve in the univariate analysis but failed to show this preference after adjustment with other clinical factors. Regarding to the long-term outcomes of early HCC, further research to assess the interaction between liver reserve and treatment modalities may be necessary.

There are several strengths of this study. Firstly, various pre- and post-operative factors in the past years have been used to predict the outcomes after curative early HCC treatment. The addition of recurrence information in our model not only quantify the influence of both early and late recurrence but also increase the predictive power. Secondly, a female receiving SR for early HCC, for example, who may undergo recurrence within one year. Recurrence at

either 3 or 12 months may both regard as the same indicator (early recurrence) in a time-fixed model but may imply different prognosis for clinical physicians. By using recurrence as a time-varying covariates, a new model can fit data better than a time-invariant one. Thirdly, previous reports only focused on the association between putative risk factors and outcomes after curative treatment. Our validated risk score with fair accuracy will be very helpful for general practitioners to identify patients prone to mortality for whom different management strategies may be indicated. Fourthly, risk factors associated with late recurrence were previously based on those who did not develop recurrence, hence subjects with early recurrence were abandoned in the analyses. A polytomous logistic regression model can simultaneously assess the risk factors of multiple outcome categories on the basis of a correct covariance matrix.

There were some limitations to the present study. Firstly, this study used a retrospective design and investigated patients in an endemic area of viral hepatitis. With the increasing evidence that antiviral therapies reduced recurrence after curative HCC treatment, further studies consisted of viral variables as well as treatment response may be warranted[28, 38]. Secondly, although we used the propensity score method to minimize the selection bias when comparing the survival rates of the patients who underwent RFA-TACE to those of the patients who underwent SR, the effective sample size in the propensity analysis was reduced and thus may have influenced the statistical power of the survival analysis. Finally, our predictive model was based on

Taiwanese residents in a single institute. Since the etiologies of HCC varied among different races, the predicted score needs to be validated in the near future before generalization to western populations.

In conclusion, our propensity score model provides evidence that, in comparison to SR, RFA with or without chemoembolization can result in comparable long-term overall survival for early HCC patients without increased safety concerns. However, SR yields better DFS than nonsurgical methods in the BCLC stage A subgroup. Our models on the basis of recurrence types are clinical relevant and provide fair accuracy to predict long-term survival. Further prospective studies to explore the external validity and applicability of our model are still required.

Table 1 Clinical characteristics of early hepatocellular carcinoma patients treated with RFA-TACE or with SR before and after propensity score matching

Variables	Before propensity score matching					After propensity score matching				
	RFA-TACE (n=176)		SR (n=125)		P value	RFA-TACE (n=66)		SR (n=66)		P value
	No.	%	No.	%		No.	%	No.	%	
Age(years)										
<65	90	51.1	74	59.2	0.17	35	53.0	35	53.0	1.0
≥65	86	48.9	51	40.8		31	47.0	31	47.0	
Mean±SD	64.0±10.4		62.2±10.7			63.7±12.6		64.0±10.3		
Gender										
Male	109	61.9	87	69.6	0.17	47	68.1	47	68.1	1.0
Female	67	38.1	38	30.4		22	31.9	22	31.9	
Child-Pugh										
A	162	92.1	122	97.6	0.04	61	92.4	65	98.5	0.10
B	14	7.9	3	2.4		5	7.6	1	1.5	
Etiology										
Seronegative	17	9.7	21	16.8	0.008	8	12.1	7	10.6	0.40
HBV	70	39.8	65	52.0		34	51.5	28	42.4	
HCV	82	46.6	36	28.8		22	33.3	29	43.9	
HBV+HCV	7	4.0	3	2.4		2	3.03	2	3.03	
Ishak score-fibrosis										
1-3	52	29.6	29	23.2	0.22	16	24.2	14	21.2	0.67
4-6	124	70.4	96	76.8		50	75.8	52	78.8	
Edmonson grading										
I and II	137	90.7	103	83.1	0.06	50	89.3	48	85.7	0.56
III and IV	14	9.3	21	16.9		6	10.7	8	14.3	
Diabetes										
No	123	69.9	92	73.6	0.48	47	71.2	48	72.7	0.85
Yes	53	30.1	33	26.4		19	28.8	18	27.3	
CSPH										
No	131	74.4	99	79.2	0.34	55	79.7	53	76.8	0.69
Yes	45	25.6	26	20.8		14	20.3	16	23.2	
No. of nodules										
Single	126	71.6	104	83.2	0.02	58	87.9	56	84.9	0.56
≥2 nodules	50	28.4	21	16.8		8	12.1	10	15.1	

Renal impairment (>1.5mg/dL)										
No	159	90.3	120	96.0	0.07	62	93.9	64	97.0	0.41
Yes	17	9.7	5	4.00		4	6.1	2	3.0	
AFP level (ng/mL)										
<20	96	54.6	85	68.0	0.02	40	60.6	42	63.6	0.59
≥20	80	45.4	40	32.0		26	39.4	24	36.4	
Albumin (mg/dL)										
>3.0	166	94.3	123	98.4	0.07	61	92.4	65	98.5	0.05
≤3.0	10	5.7	2	1.6		5	7.6	1	1.5	
Total bilirubin (mg/dL)										
≤1.5	161	91.5	117	95.1	0.22	60	90.9	61	92.4	0.74
>1.5	15	8.5	6	4.9		6	9.1	5	7.6	
Prothrombin time (INR)										
<1.3	164	93.2	122	97.6	0.11	62	93.9	65	98.5	0.18
≥1.3	12	6.8	3	2.4		4	6.1	1	1.5	
AST(IU/L)										
≤80	139	79.0	106	84.8	0.20	56	84.9	55	83.3	0.81
>80	37	21.0	19	15.2		10	15.1	11	16.7	
ALT(IU/L)										
≤80	140	79.6	99	79.2	0.94	54	81.8	53	80.3	0.81
>80	36	20.5	26	20.8		12	18.2	13	19.7	
Size(cm)										
<3.0	129	73.3	50	40.0	<0.0001	38	57.6	37	56.1	0.76
≥3.0	47	26.7	75	60.0		28	42.4	29	43.9	
Mean±SD	24.9±9.0		32.6±11.5			27.5±10.2		28.3±10.8		
BCLC stage										
0	47	26.7	18	14.4	0.01	17	25.8	16	24.2	0.71
A	129	73.3	109	85.6		49	74.2	50	75.8	

CSPH: clinically significant portal hypertension; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; INR: International normalized ratio; BCLC, Barcelona-Clınic Liver Cancer staging system; RFA-TACE: Radiofrequency ablation with or without transcatheter arterial chemoembolization; SR: surgical resection.

Table 2 Predictors for early and late recurrence after primary curative treatment by using polytomous logistic regression

Variables	Univariate model (OR,95%CI)		Multivariate model (OR, 95%CI)	
	Early recurrence (≤ 1yr) vs No	Late recurrence (>1yr) vs No	Early recurrence (≤ 1yr) vs No	Late recurrence (>1yr) vs No
Host-related factors				
Age > 65 years	1.08(0.62-1.89)	1.31(0.76-2.27)		
Male	1.26(0.70-2.27)	1.57(0.88-2.79)		
AST >80 IU/L	1.49(0.72-3.09)	1.62(0.79-3.33)		
ALT >80 IU/L	1.59(0.77-3.28)	2.15(1.07-4.31)		
Total bilirubin ≥1.5 (mg/dL)	0.81(0.29-2.21)	0.43(0.13-1.41)		
Prothrombin time (INR) ≥ 1.3	0.69(0.16-2.98)	1.63(0.50-5.32)		
Albumin < 3.0 mg/dL	1.69(0.52-5.51)	0.90(0.24-3.46)		
Child-Pugh score B (vs A)	1.39(0.45-4.30)	0.75(0.20-2.72)		
CSPH	2.97(1.48-5.96)	2.32(1.15-4.70)	2.03(0.88-4.67)	1.63(0.71-3.75)
Renal impairment (>1.5mg/dL)	1.19(0.43-3.29)	0.84(0.28-2.51)		
FIB-4 index > 3.25	2.15(1.22-3.79)	1.86(1.06-3.25)	1.40(0.67-2.90)	1.13(0.56-2.30)
Diabetes	1.37(0.74-2.54)	1.38(0.75-2.54)		
ALBI grade 2 or 3 (vs 1)	1.29(0.63-2.61)	1.17(0.59-2.34)		
Tumor characteristics				
Size ≥ 3 cm	0.84(0.48-1.47)	0.80(0.46-1.39)		
Multinodularity	3.71(1.84-7.49)	2.25(1.09-4.66)	3.66(1.72-7.80)	2.50(1.14-5.50)
AFP ≥ 20 ng/mL	2.33(1.31-4.14)	1.64(0.92-2.91)	2.06(1.12-3.81)	1.40(0.75-2.58)
BCLC stage A (vs 0)	1.55(0.79-3.05)	1.32(0.68-2.53)		
Histopathological findings				
Edmonson grade III & IV	0.96(0.36-2.56)	2.04(0.88-4.72)		
Ishak fibrosis score 4-6	0.94(0.50-1.74)	0.98(0.53-1.81)		
Viral factors				
HBV	1.61(0.70-3.68)	4.75(1.53-14.8)	1.88(0.77-4.63)	5.11(1.59-16.4)
HCV	2.63(1.11-6.21)	8.90(2.81-28.2)	2.44(0.93-6.41)	8.07(2.41-27.0)
HBV and HCV	2.09(0.44-9.96)	2.87(0.39-21.3)	1.13(0.19-6.58)	1.91(0.24-15.5)
Treatment modality				
RFA-TACE (vs Surgery)	1.32(0.72-2.30)	1.59(0.91-2.78)		

aHR: adjusted hazard ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; CSPH: clinically significant portal hypertension; ALBI: albumin-bilirubin; AFP: alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona-Clınic Liver Cancer staging

system; RFA-TACE: Radiofrequency ablation with or without transcatheter arterial chemoembolization.

Table 3 Predictors for overall survival after primary curative treatment by using Cox regression model

Variables	Univariate model	#Multivariate model		
		Model I Time-invariant without recurrence	Model II Time-invariant with recurrence	Model III Time-varying with recurrence
	HR(95%CI)	aHR(95%CI)	aHR(95%CI)	aHR(95%CI)
Time-dependent variables				
Recurrence type				
No	1.00			1.00
Early recurrence(≤1yr)	9.44(4.98-17.9)			6.62(3.79-11.6)
Late recurrence(>1yr)	6.46(3.17-13.2)			3.75(1.99-7.08)
Time-independent variables				
Recurrence type				
No	1.00		1.00	
Early(≤1yr)	4.51(2.42-8.39)		3.09(2.03-4.71)	
Late(>1yr)	1.73(0.91-3.28)			
Host-related factors				
Age > 65 years	1.64(1.09-2.48)		1.43(0.92-2.21)	1.55(1.01-2.36)
Male	1.23(0.81-1.86)			
AST >80 IU/L	1.30(0.80-2.11)			
ALT >80 IU/L	0.99(0.60-1.63)			
Total bilirubin ≥1.5 (mg/dL)	1.93(1.00-3.72)			
Prothrombin time (INR) ≥ 1.3	1.86(0.86-4.04)			
Albumin ≤ 3.0 mg/dL	2.38(1.20-4.75))			
Child-Pugh score B (vs A)	1.63(0.75-3.53)			
CSPH	2.31(1.50-3.56)	1.53(0.93-2.52)	1.71(1.04-2.82)	1.97(1.26-3.08)
Renal impairment (>1.5mg/dL)	2.04(0.98-4.22)	1.93(0.92-4.02)	1.89(0.90-3.97)	
Diabetes	1.23(0.79-1.90)			
ALBI grade 2 or 3 (vs 1)	1.91(1.02-3.59)			
FIB-4 index >3.25	2.50(1.63-3.84)	2.02(1.23-3.31)	1.83(1.12-3.01)	
Tumor characteristics				
Size ≥ 3 cm	1.02(0.67-1.54)			
Multinodularity	1.18(0.75-1.84)			
AFP ≥ 20 ng/mL	1.20(0.79-1.81)			

BCLC stage A (vs 0)	1.94(1.03-3.65)	1.88(1.00-3.55)		
Histopathological findings				
Edmonson grade III & IV	1.35(0.76-2.40)			
Ishak fibrosis score 4-6	1.24(0.79-1.96)			
Viral factors				
HBV	5.23(2.86-9.57)			
HCV	5.36(2.96-9.70)			
HBV and HCV	10.3(3.77-28.1)			
Treatment modality				
RFA-TACE (vs. Surgery)	1.25(0.82-1.91)			
Model selection				
-2 log likelihood ratio		871.9	847.7	834.5
AIC		879.9	857.7	842.5

aHR: adjusted hazard ratio; ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; CSPH: clinically significant portal hypertension; ALBI: albumin-bilirubin; AFP: alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona-Clınic Liver Cancer staging system; RFA: radiofrequency ablation; AIC; Akaike information criterion.

[#]Multivariate analyses were performed by the Cox proportional model with forward selection, with P<0.15 indicating inclusion and removal for variable selection. Model 1: Variables without recurrence. Model 2: recurrence as time-invariant variables. Model 3: recurrence as time varying variables.

Figure legends

Figure 1. Comparison of survival curves of the patients with early stage HCC who underwent RFA-TACE or SR. (A) Cumulative OS curves of patients who underwent RFA-TACE and patients who underwent SR. (B) Cumulative DFS curves of patients who underwent RFA-TACE and patients who underwent SR. (C) The cumulative OS curves of patients who underwent RFA-TACE and patients who underwent SR after propensity score matching. (D) The cumulative DFS curves of patients who underwent RFA-TACE and patients who underwent SR after propensity score matching.

Figure 2. Cumulative risk for mortality in early HCC patients after primary curative treatment with low, intermediate, and high predicted scores in our cohort, scores of <1, 1 to 2, and >2 indicate low, intermediate, and high risk, respectively.

Figure 3. Adjusted RFA-TACE to SR ratios of hazard ratios and their 95% confidence intervals (horizontal lines) for the association of various liver reserve and tumor factors and long-term outcomes of HCC. (A) Subgroup analysis for disease free survival. (B) Subgroup analysis for overall survival. All estimated results were based on Cox proportional hazard regression with adjustment for age, gender, tumor size, tumor number, portal hypertension, albumin level and etiologies of hepatitis.

Figure 1.

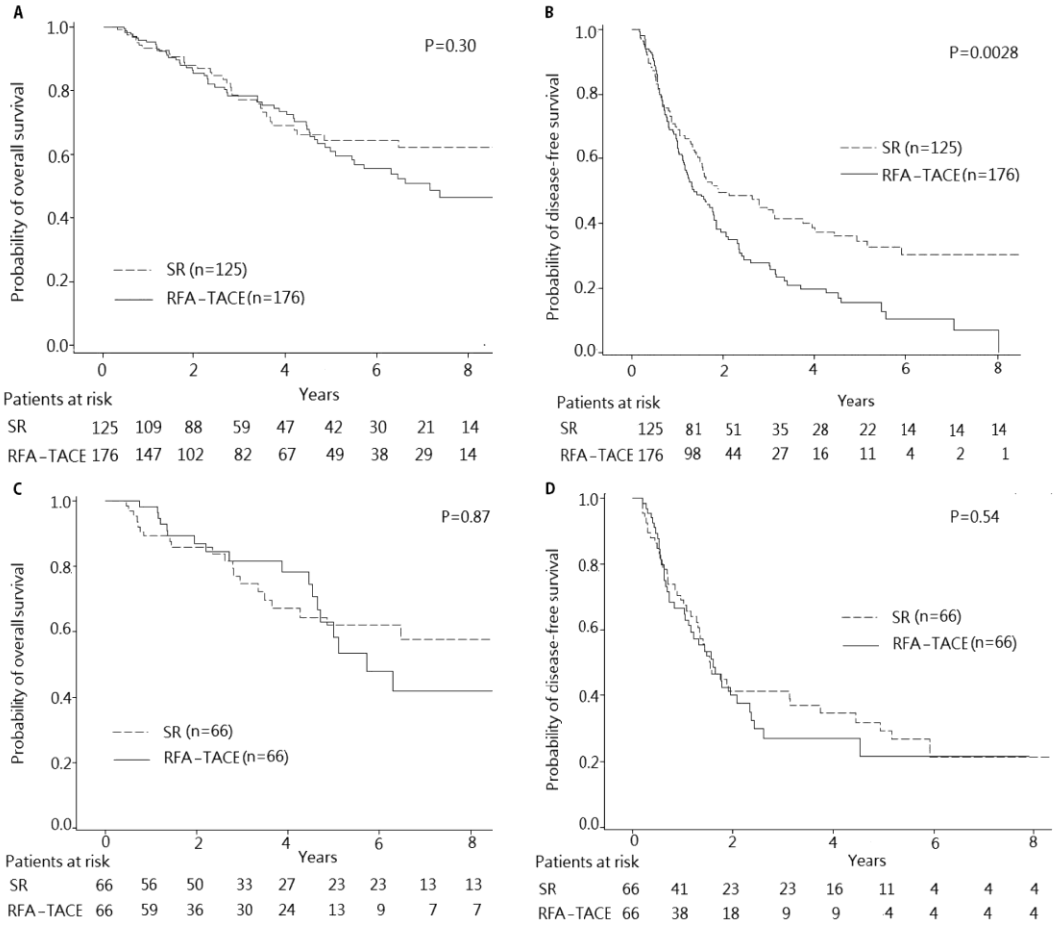

A
P=0.30
Probability of overall survival
SR (n=125)
RFA-TACE (n=176)
Patients at risk
SR 125 109 88 59 47 42 30 21 14
RFA-TACE 176 147 102 82 67 49 38 29 14
Years
B
P=0.0028
Probability of disease-free survival
SR (n=125)
RFA-TACE (n=176)
Patients at risk
SR 125 81 51 35 28 22 14 14 14
RFA-TACE 176 98 44 27 16 11 4 2 1
Years
C
P=0.87
Probability of overall survival
SR (n=66)
RFA-TACE (n=66)
Patients at risk
SR 66 56 50 33 27 23 23 13 13
RFA-TACE 66 59 36 30 24 13 9 7 7
Years
D
P=0.54
Probability of disease-free survival
SR (n=66)
RFA-TACE (n=66)
Patients at risk
SR 66 41 23 23 16 11 4 4 4
RFA-TACE 66 38 18 9 9 4 4 4 4
Years

Figure 2.

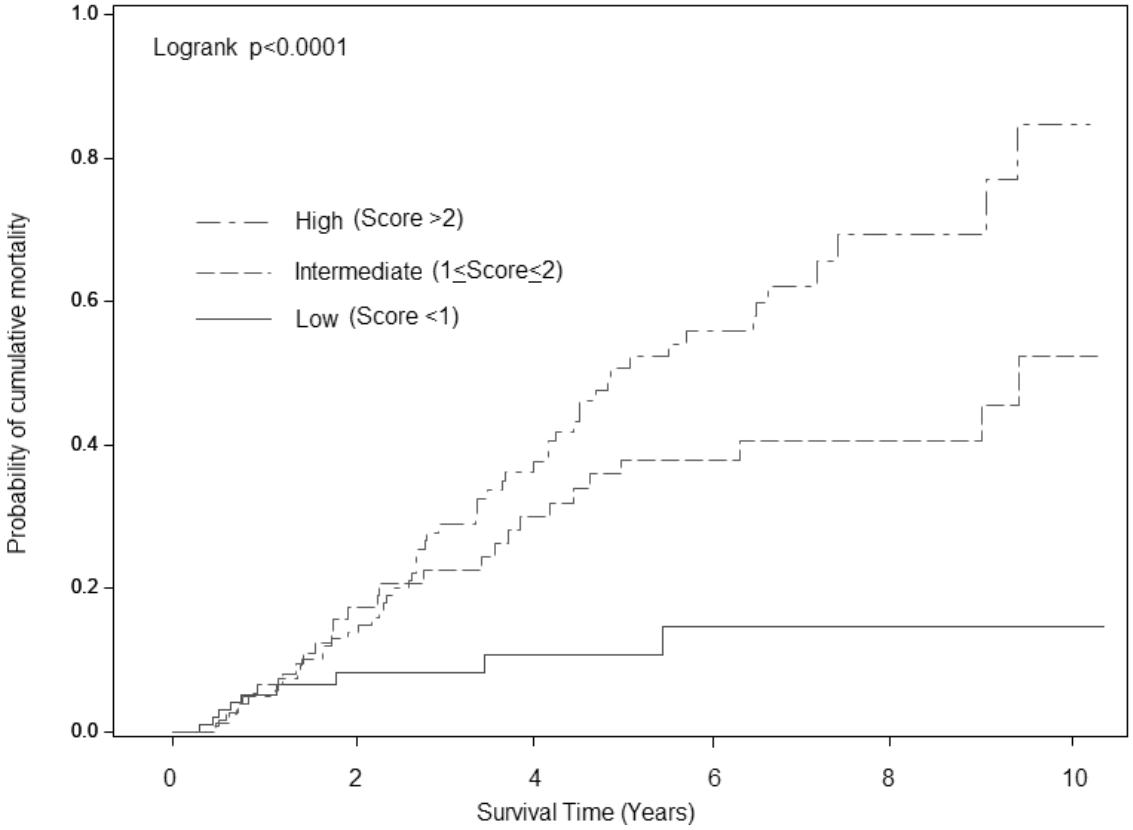
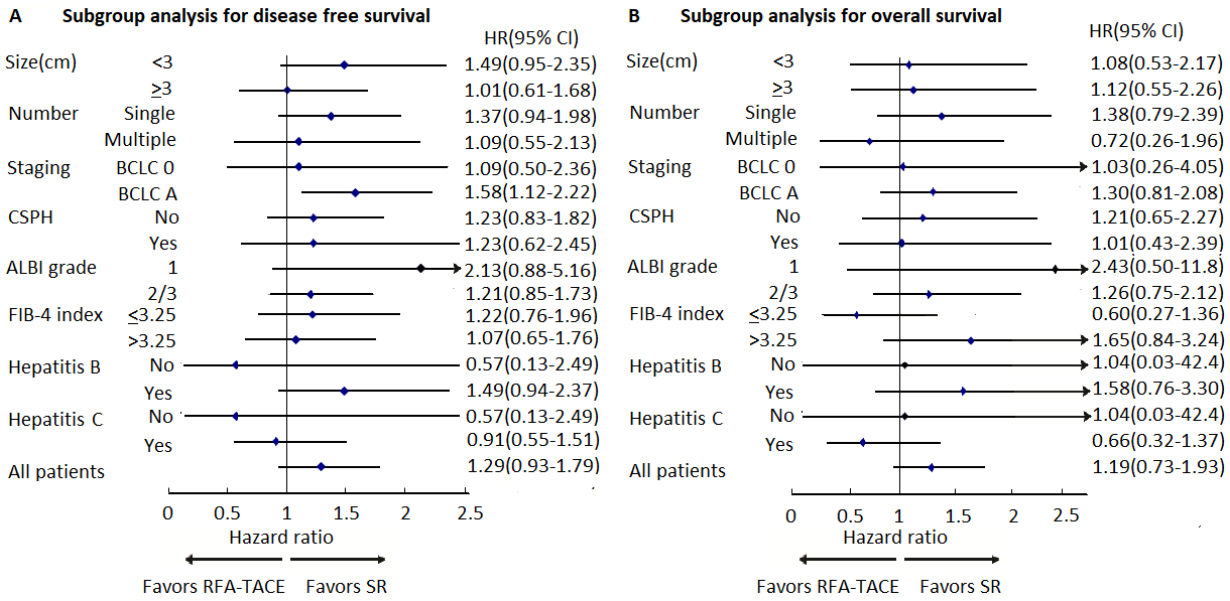

Logrank p<0.0001
High (Score >2)
Intermediate (1≤Score≤2)
Low (Score <1)
Probability of cumulative mortality
1.0
0.8
0.6
0.4
0.2
0.0
0
2
4
6
8
10
Survival Time (Years)

Figure 3.


A Subgroup analysis for disease free survival
HR(95% CI)
Size(cm) <3 1.49(0.95-2.35)
≥3 1.01(0.61-1.68)
Number Single 1.37(0.94-1.98)
Multiple 1.09(0.55-2.13)
Staging BCLC 0 1.09(0.50-2.36)
BCLC A 1.58(1.12-2.22)
CSPH No 1.23(0.83-1.82)
Yes 1.23(0.62-2.45)
ALBI grade 1 2.13(0.88-5.16)
2/3 1.21(0.85-1.73)
FIB-4 index ≤3.25 1.22(0.76-1.96)
>3.25 1.07(0.65-1.76)
Hepatitis B No 0.57(0.13-2.49)
Yes 1.49(0.94-2.37)
Hepatitis C No 0.57(0.13-2.49)
Yes 0.91(0.55-1.51)
All patients 1.29(0.93-1.79)
0 0.5 1 1.5 2 2.5
Hazard ratio
Favors RFA-TACE Favors SR
B Subgroup analysis for overall survival
HR(95% CI)
Size(cm) <3 1.08(0.53-2.17)
≥3 1.12(0.55-2.26)
Number Single 1.38(0.79-2.39)
Multiple 0.72(0.26-1.96)
Staging BCLC 0 1.03(0.26-4.05)
BCLC A 1.30(0.81-2.08)
CSPH No 1.21(0.65-2.27)
Yes 1.01(0.43-2.39)
ALBI grade 1 2.43(0.50-11.8)
2/3 1.26(0.75-2.12)
FIB-4 index ≤3.25 0.60(0.27-1.36)
>3.25 1.65(0.84-3.24)
Hepatitis B No 1.04(0.03-42.4)
Yes 1.58(0.76-3.30)
Hepatitis C No 1.04(0.03-42.4)
Yes 0.66(0.32-1.37)
All patients 1.19(0.73-1.93)
0 0.5 1 1.5 2 2.5
Hazard ratio
Favors RFA-TACE Favors SR

Declaration

Abbreviations

HCC: hepatocellular carcinoma; SR: surgical resection; RFA: percutaneous radiofrequency ablation; TACE: transcatheter arterial chemoembolization; RFA-TACE: percutaneous radiofrequency ablation with or without transcatheter arterial chemoembolization; OS: overall survival; DFS: disease-free survival; CSPH: clinically significant portal hypertension; BCLC: Barcelona Clinic Liver Cancer staging system; EASL: European Association for the Study of the Liver; AASLD: American Association for the Study of Liver Diseases; ROC: receiver operating characteristic; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALBI: albumin-bilirubin; AFP: Alpha-fetoprotein; INR: international normalized ratio; HBV: hepatitis B virus; HCV: hepatitis C virus; aHR: adjusted hazard ratio; AIC: Akaike information criterion

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Authors' contributions

Kuo MJ and Chen CL designed the study and drafted the article; Kuo MJ and Mo LR were responsible for the collection of parameters and interpretation of the

results; Kuo MJ and Chen CL made critical revisions to the article for important intellectual content; all authors approved the final version of the article.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of the Medical Research Committee of Show Chwan Memorial Hospital (IRB no. 1000701). The written informed consent was obtained from all subjects prior to participating in this study. All methods were also performed in accordance with the principles stated in the Declaration of Helsinki.

Consent for Publication

Not applicable

Competing interests

Ming-Jeng Kuo, Lein-Ray Mo, Chi-Ling Chen declare that they have no conflict of interest.

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References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015, 65(2):87-108.
2. Daniele B, Bencivenga, A.,Megna, A. S.,Tinessa, V. Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology 2004, 127(5 Suppl 1):S108-112.
3. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004, 130(7):417-422.
4. Chan AWH, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, Tada T, Chong CCN, Xiang BD, Li LQ, et al. Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018, 69(6):1284-1293.
5. Xu XL, Liu XD, Liang M, Luo BM. Radiofrequency Ablation versus Hepatic Resection for Small Hepatocellular Carcinoma: Systematic Review of Randomized Controlled Trials with Meta-Analysis and Trial Sequential Analysis. Radiology 2018, 287(2):461-472.
6. Toyoda H, Lai PB, O'Beirne J, Chong CC, Berhane S, Reeves H, Manas D, Fox RP, Yeo W, Mo F, et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. Br J Cancer 2016, 114(7):744-750.
7. Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S.

Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology 2008, 47(1):82-89.

8. Li Q, Wang J, Juzi JT, Sun Y, Zheng H, Cui Y, Li H, Hao X. Clonality analysis for multicentric origin and intrahepatic metastasis in recurrent and primary hepatocellular carcinoma. J Gastrointest Surg 2008, 12(9):1540-1547.
9. Gao Q, Wang XY, Zhou J, Fan J. Multiple carcinogenesis contributes to the heterogeneity of HCC. Nat Rev Gastroenterol Hepatol 2015, 12(1):13.
10. Chan EE, Chow PK. A review of prognostic scores after liver resection in hepatocellular carcinoma: the MSKCC, SLICER and SSCLIP scores. Jpn J Clin Oncol 2017, 47(4):287-293.
11. Sun HC, Xie L, Yang XR, Li W, Yu J, Zhu XD, Xia Y, Zhang T, Xu Y, Hu B, et al. Shanghai Score: A Prognostic and Adjuvant Treatment-evaluating System Constructed for Chinese Patients with Hepatocellular Carcinoma after Curative Resection. Chinese medical journal 2017, 130(22):2650-2660.
12. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012, 56(4):908-943.
13. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011, 53(3):1020-1022.
14. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, Kawasaki S. Surgery for small liver cancers. Semin Surg Oncol 1993, 9(4):298-304.
15. Kudo M. Radiofrequency ablation for hepatocellular carcinoma: updated review

in 2010. Oncology 2010, 78 Suppl 1:113-124.

16. Ni JY, Liu SS, Xu LF, Sun HL, Chen YT. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. World J Gastroenterol 2013, 19(24):3872-3882.

17. Peng ZW, Chen MS. Transcatheter arterial chemoembolization combined with radiofrequency ablation for the treatment of hepatocellular carcinoma. Oncology 2013, 84 Suppl 1:40-43.

18. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010, 116(23):5452-5460.

19. Yamakado K, Nakatsuka A, Takaki H, Yokoi H, Usui M, Sakurai H, Isaji S, Shiraki K, Fuke H, Uemoto S, et al. Early-stage hepatocellular carcinoma: radiofrequency ablation combined with chemoembolization versus hepatectomy. Radiology 2008, 247(1):260-266.

20. Takuma Y, Takabatake H, Morimoto Y, Toshikuni N, Kayahara T, Makino Y, Yamamoto H. Comparison of combined transcatheter arterial chemoembolization and radiofrequency ablation with surgical resection by using propensity score matching in patients with hepatocellular carcinoma within Milan criteria. Radiology 2013, 269(3):927-937.

21. Liu H, Wang ZG, Fu SY, Li AJ, Pan ZY, Zhou WP, Lau WY, Wu MC. Randomized clinical trial of chemoembolization plus radiofrequency ablation

versus partial hepatectomy for hepatocellular carcinoma within the Milan criteria. Br J Surg 2016, 103(4):348-356.

22. Yi PS, Huang M, Zhang M, Xu L, Xu MQ. Comparison of Transarterial Chemoembolization Combined with Radiofrequency Ablation Therapy versus Surgical Resection for Early Hepatocellular Carcinoma. Am Surg 2018, 84(2):282-288.

23. Shi M, Zhang CQ, Zhang YQ, Liang XM, Li JQ. Micrometastases of solitary hepatocellular carcinoma and appropriate resection margin. World journal of surgery 2004, 28(4):376-381.

24. Zhang X, Li J, Shen F. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. Journal of gastroenterology and hepatology 2018, 33(2):347-354.

25. Wu JC, Huang YH, Chau GY, Su CW, Lai CR, Lee PC, Huo TI, Sheen IJ, Lee SD, Lui WY. Risk factors for early and late recurrence in hepatitis B-related hepatocellular carcinoma. J Hepatol 2009, 51(5):890-897.

26. Hoshida Y. Risk of recurrence in hepatitis B-related hepatocellular carcinoma: impact of viral load in late recurrence. J Hepatol 2009, 51(5):842-844.

27. Hoshida Y, Villanueva A, Kobayashi M, Peix J, Chiang DY, Camargo A, Gupta S, Moore J, Wrobel MJ, Lerner J, et al. Gene expression in fixed tissues and outcome in hepatocellular carcinoma. N Engl J Med 2008, 359(19):1995-2004.

28. Wu CY, Chen YJ, Ho HJ, Hsu YC, Kuo KN, Wu MS, Lin JT. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. JAMA 2012, 308(18):1906-1914.

29. Hsu YC, Ho HJ, Wu MS, Lin JT, Wu CY. Postoperative peg-interferon plus ribavirin is associated with reduced recurrence of hepatitis C virus-related hepatocellular carcinoma. Hepatology 2013, 58(1):150-157.

30. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007, 133(2):481-488.

31. Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology 2015, 61(2):526-536.

32. Grgurevic I, Bozin T, Madir A. Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards? Clin Exp Hepatol 2017, 3(4):181-186.

33. Su CW, Yang YY, Lin HC. Impact of etiological treatment on prognosis. Hepatol Int 2018, 12(Suppl 1):56-67.

34. Eguchi S, Kanematsu T, Arii S, Okazaki M, Okita K, Omata M, Ikai I, Kudo M, Kojiro M, Makuuchi M, et al. Comparison of the outcomes between an anatomical subsegmentectomy and a non-anatomical minor hepatectomy for single hepatocellular carcinomas based on a Japanese nationwide survey. Surgery 2008, 143(4):469-475.

35. Shi C, Zhao Q, Liao B, Dong Z, Wang C, Yang J, Shen W. Anatomic resection and wide resection margin play an important role in hepatectomy for hepatocellular carcinoma with peritumoural micrometastasis. ANZ J Surg 2019,

89(11):E482-e486.

36. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatology international 2017, 11(4):317-370.

37. Chong CC, Chan AW, Wong J, Chu CM, Chan SL, Lee KF, Yu SC, To KF, Johnson P, Lai PB. Albumin-bilirubin grade predicts the outcomes of liver resection versus radiofrequency ablation for very early/early stage of hepatocellular carcinoma. Surgeon 2017.

38. Kubo S, Takemura S, Sakata C, Urata Y, Uenishi T. Adjuvant therapy after curative resection for hepatocellular carcinoma associated with hepatitis virus. Liver Cancer 2013, 2(1):40-46.

Figures

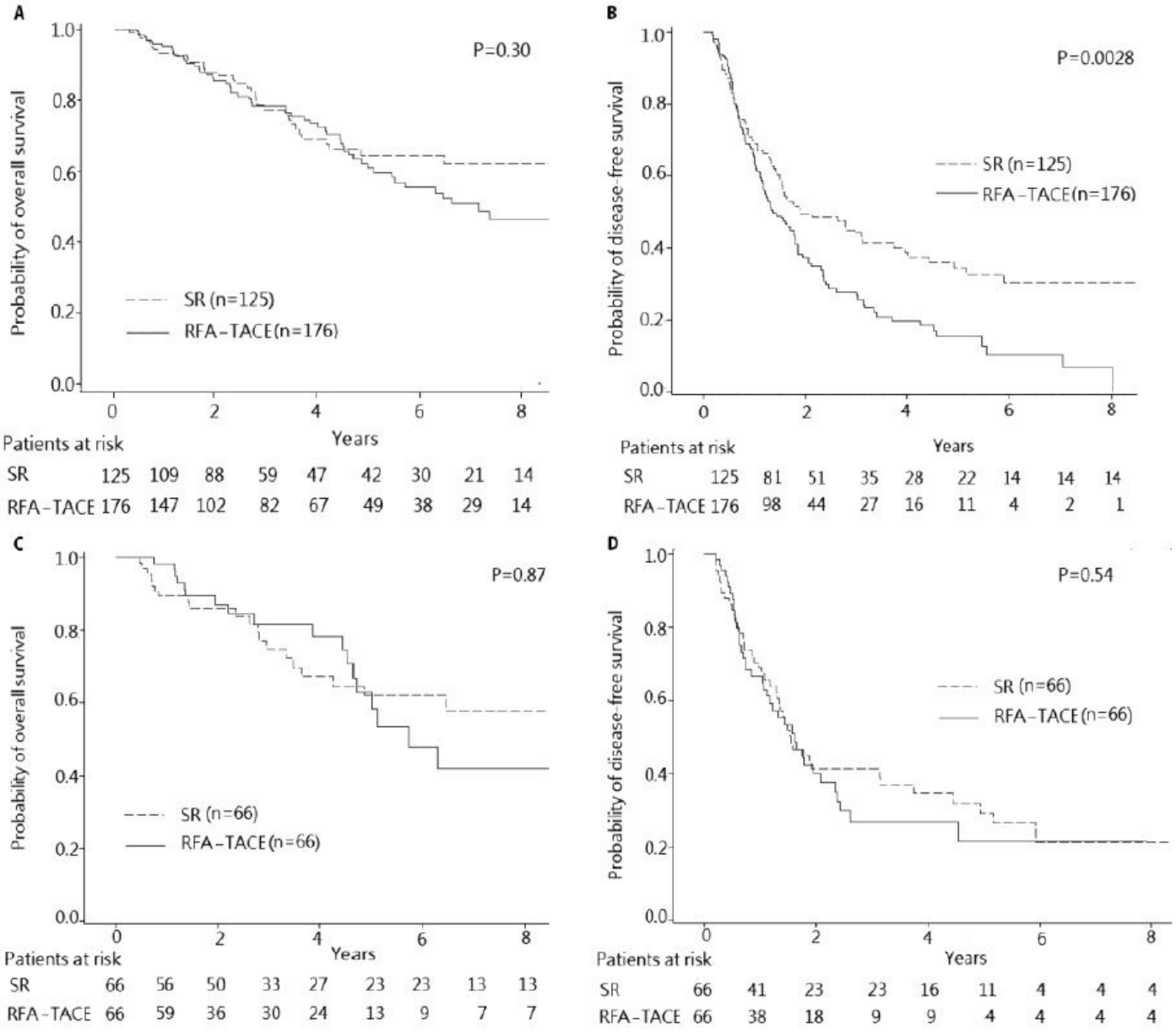

Figure 1

Comparison of survival curves of the patients with early stage HCC who underwent RFA TACE or SR. (A) Cumulative OS curve s of patients who underwent RFA TACE and patients who underwent SR. (B) Cumulative DFS curves of patients who underwent RFA TACE and patients who underwent SR. (C) The cumulative OS curves of patients who underwent RFA TACE and patients who underwent SR after propensity score matching . (D) The cumulative DFS curves of patients who underwent RFA TACE and patients who underwent SR after propensity score matching.

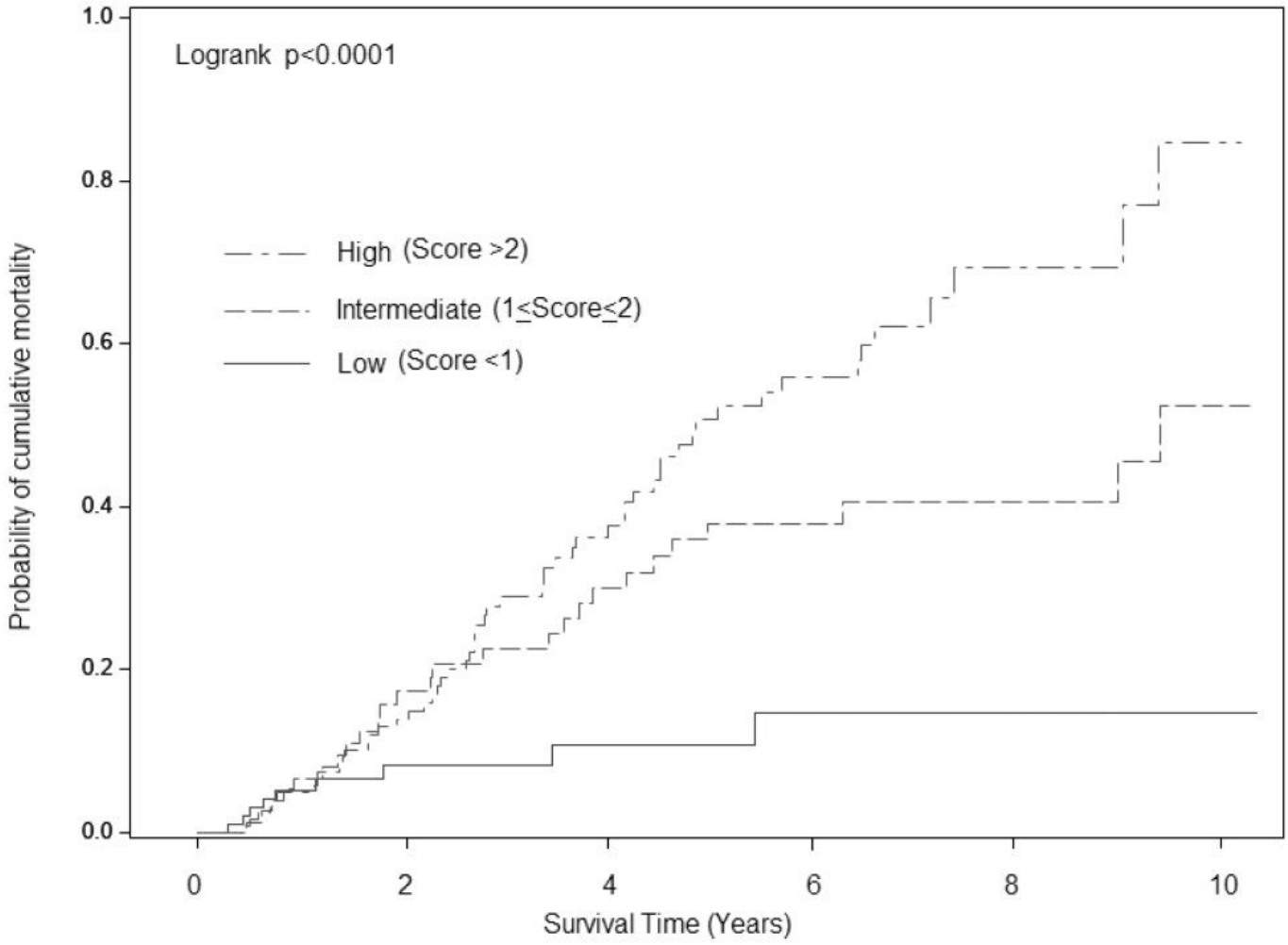

Figure 2

Cumulative risk for mortality in early HCC patients after primary curative treatment with low, intermediate, an d high predicted scores in our cohort, scores of <1, 1 to 2, and >2 indicate low, intermediate, and high risk, respectively.

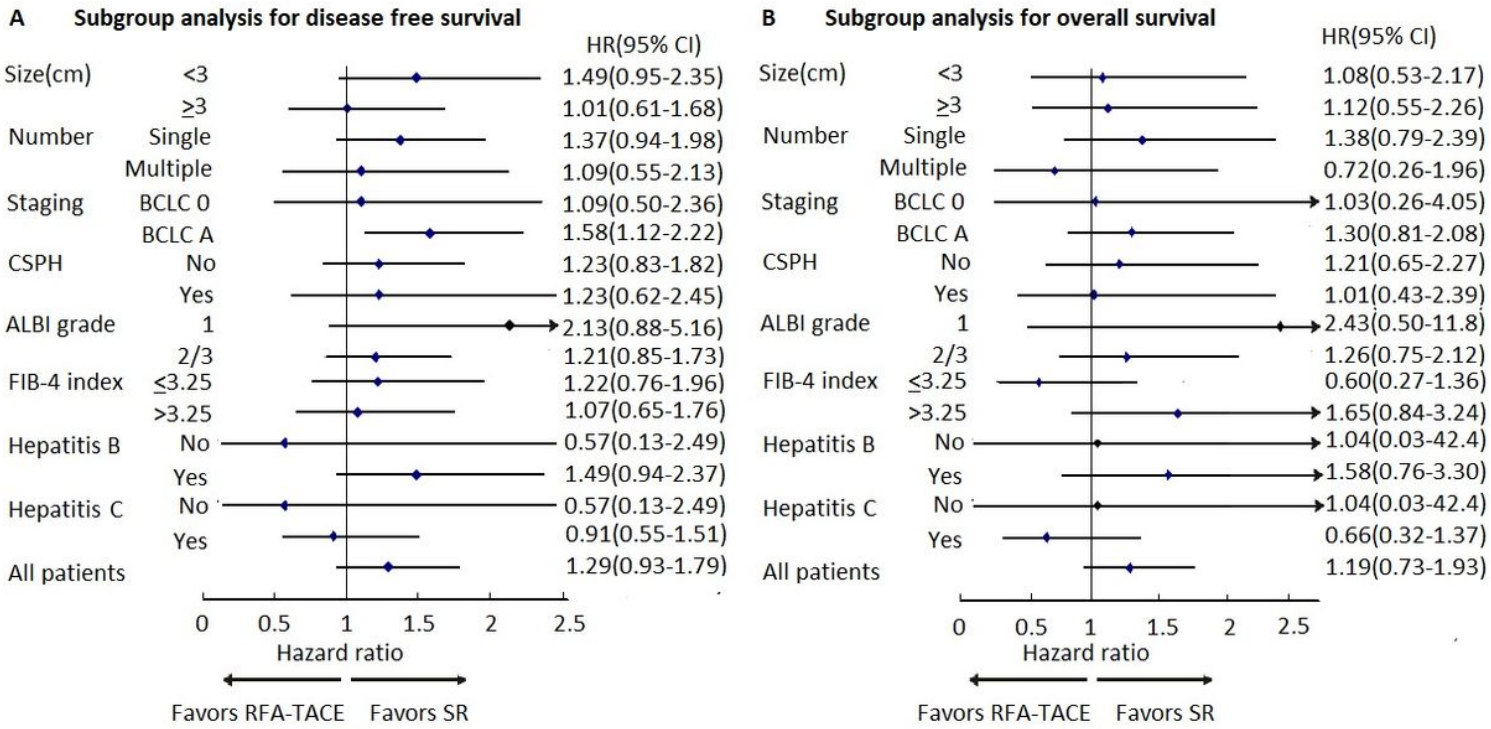

Figure 3

Adjusted RFA TACE to SR ratios of hazard ratios and their 95% confidence intervals (horizontal lines) for the association of various liver reserve and tumor factors and long term outcomes of HCC. (A) Subgroup analysis for disease free survival. (B) Subgroup analysis for overall survival. All estimated results were based on Cox proportional hazard regression with adjustment for age, gender, tumor size, tumor number, portal hypertension, albumin level and etiologies of hepatitis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supportinginformation.pdf