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Original Article

A model integrated fibrinogen and D-dimer for prediction of hepatocellular carcinoma recurrence following liver transplantation: a multicentre study

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Abstract: Background: We aimed to investigate whether D-dimer and fibrinogen levels could predict prognosis of patients with hepatocellular carcinoma (HCC) following liver transplantation. Methods: From January 2015 to January 2020, we conducted a study on patients with hepatitis B-related liver cancer. Two hundred seventy (270) liver transplant recipients were recruited. Considering D-dimer and plasma fibrinogen levels, a model was established to predict liver cancer recurrence following liver transplantation. Subsequent verification was performed on a validation cohort of 295 recipients from two other hospitals. Results: Elevated D-dimer and plasma fibrinogen levels demonstrated independent correlation between overall survival and tumour-free survival among patients with HCC who underwent liver transplantation. Those who had preoperative fibrinogen ≥2.27 g/L had significantly reduced overall survival and tumour-free survival than those who had preoperative fibrinogen <2.27 g/L, in the discovery cohort. Recipients with increased risk had preoperative plasma D-dimer ≥2400 μg/L. The model was: Y= logit (P) =0.91* fibrinogen concentration +0.967* D-dimer +0.585* alpha-fetoprotein +1.623* Milan criteria +0.68* microvascular invasion -3.159. At a cut-off score of -1.524, the validation cohort had area under curve values of 0.764 and 0.828 respectively; analysis of this data optimised predictive performance for overall and tumour-free survival. Conclusions: For patients who have undergone liver transplantation for HCC, preoperative D-dimer and fibrinogen levels independently predicted key outcomes such as overall survival and tumour-free survival.

Keywords: Hepatocellular carcinoma, liver transplantation, D-dimer, fibrinogen, predictive model

Introduction

Hepatocellular carcinoma (HCC) is the second leading cancer responsible for numerous deaths [1, 2]. For these cancer patients at late stage, liver transplantation (LT) is a relatively ideal treatment modality to greatly enhance and improve chances of survival. For those patients who have undergone LT, the probability of HCC recurrence is 20% [3]. Clinical characteristics such as the tumour size and number, histopathologic grading, microvascular invasion and immunosuppression are risk factors that independently influence tumour recurrence and patients' survival [4-7]. Additionally, several serum biomarkers, including alpha-fetoprotein (AFP) [8-10], des-gamma-carboxy prothrombin [11], glycosylated AFP (L3 fraction) [10], C-reactive protein [12, 13], microRNAs [14], fibrinogen [15, 16], and neutrophil-to-lymphocyte ratio [17], have been found to predict tumour recurrence risk following LT. In humans, important coagulation factors, including D-dimer as well as fibrinogen, are involved. Relevant predictors of poor prognosis for malignancy were D-dimer as well as fibrinogen, based

on analysis of relevant data from cases of HCC, ovarian tumours, lung cancer and pancreatic cancer. Following entry of procoagulant substances into the blood due to cellular infiltration and destruction by tumour cells, fibrinolysis and coagulation are in turn activated, which increase plasma D-dimers and fibrinogen.

Not many studies on the outcome of HCC among LT patients based on the increase of preoperative D-dimer and fibrinogen levels have been reported. To enhance post-transplantation surveillance and monitor therapeutic effects of LT, new predictive biomarkers and models with high specificity and sensitivity for HCC recurrence are needed. In this study, the prognostic value of such relevant data was analysed in depth, including preoperative coagulation parameters such as D-dimer and plasma fibrinogen levels. There are not many studies that have been performed on prediction analysis involving this area. Some studies have reported the role of D-dimer or fibrinogen in predicting tumour recurrence in liver transplantation of HCC, but as far as we know, no previous studies have reported the predictive prognostic value of D-dimer combined with fibrinogen level in HCC recurrence after LT. Here, we constructed an innovative model including both D-dimer and fibrinogen to predict the HCC recurrence after LT.

Methods

Patients

The patients were recruited from the First Affiliated Hospital, Zhejiang University School of medicine. The patients had hepatitis B virus (HBV)-related HCC and underwent LT. A total of 270 patients were recruited, and the period of study was from January 2015 to January 2020. The indications for LT were determined based on Hangzhou criteria: (1) the total diameter of the tumour was greater than 8 cm, which included case grades I or II, and the preoperative alpha fetoprotein content was less than or equal to 400 in ng/mL, (2) the total diameter of the tumour was equal to or less than 8 cm [18, 19]. Multivariate analysis was performed which considered patients' body mass index (BMI), gender, age, diabetic status, hypertension, model for end stage liver disease score, Child-Turcotte-Pugh classification and other characteristics. Laboratory findings included fibrinogen concentration, D-dimer and AFP, one week before LT, were also considered. Upon developing the model, the tumour number, size, TNM stage, degree of portal vein invasion, Barcelona Clinic Liver Cancer (BCLC) stage, cold ischemia time, degree of microvascular invasion (MVI), histopathological grade and other related information were collected and inputted. Data regarding whether patients underwent radiofrequency ablation, embolization (TACE), hepatic arterial chemotherapy before LT were also collected.

The patients studied were recruited between January 2015 and January 2020, totalling 295 cases, and were treated at two independent centres (149 underwent LT at the Affiliated Hospital from Qingdao University and 146 underwent LT at Shulan Hospital). Other relevant demographic and clinical data were also collected.

Patients without HCC cirrhosis, those who underwent LT because of concomitant hepatocellular cholangiocarcinoma, those who died in the perioperative period because of surgical complications, and those with other diseases were not included. In addition, 52 of the recipients, as well as 68 validation cohort patients, were also not included because of incomplete clinical and follow-up data.

Follow-up and surveillance

Follow up commenced after transplantation, and their data after discharge were accordingly collected. The procedure was started with a frequency of one in January and followed up with six in June. Not only that, these patients need to come back to the outpatient clinic every month for AFP test, liver function test and other various biochemical tests. After completion of LT, abdominal magnetic resonance or CT imaging, and chest computed tomography (CT) were done every 3 months for 2 years, with follow-up examinations at a semi-annual frequency. During the workup, if a tumour within the liver was found to have adverse signs, such as those characteristic of either metastasis or recurrence, it was considered recurrence. If, when imaging diagnosis is made, there is a certain level of examination difficulty that cannot be precisely resolved, then tissue diagnosis informed the evaluation. The follow-up ended on 31st August 2020.

Table 1. Patient demographics and clinical characteristics in discovery and validation cohort

	Discovery Cohort (n=270)			Validation Cohort (n=295)		
	Non-recurrence	Recurrence	P	Non-recurrence	Recurrence	P
Recipient characteristic						
Male (%)	169 (89.4%)	75 (92.6%)	0.418	197 (88.3%)	67 (93.1%)	0.257
Age (yr)	53.1±0.67	53.1±1.05	0.998	52.65±0.6	50.81±1.25	0.059
BMI ≥25 (%)	55 (29.1%)	16 (19.8%)	0.110	81 (36.3%)	22 (30.6%)	0.372
Liver cirrhosis	184 (97.4%)	77 (95.1%)	0.336	208 (39.3%)	66 (91.7%)	0.645
TACE before LT (%)	94 (49.7%)	58 (71.6%)	0.001	30 (13.5%)	7 (9.7%)	0.406
RFA before LT (%)	33 (17.5%)	17 (21.0%)	0.494	20 (9%)	2 (2.8%)	0.082
Fibrinogen ≥2.27 g/L (%)	54 (28.6%)	48 (59.3%)	<0.001	120 (53.8%)	51 (70.8%)	0.011
D-dimer ≥2400 ug/L (%)	41 (21.7%)	37 (45.7%)	<0.001	12 (5.4%)	18 (25%)	<0.001
Hypertension (%)	40 (21.2%)	12 (14.8%)	0.225	32 (14.3%)	9 (12.5%)	0.693
Diabetes (%)	26 (13.8%)	9 (11.1%)	0.553	34 (15.2%)	7 (9.7%)	0.239
Tumor diameter >3 cm (%)	93 (49.2%)	61 (75.3%)	<0.001	110 (49.3%)	55 (76.4%)	<0.001
Tumor number >3 (%)	33 (17.5%)	36 (44.4%)	<0.001	21 (9.4%)	29 (40.3%)	<0.001
TMN stage (I/II/III/IV/V/VI)	81/61/40/0/3/4	9/24/43/0/2/3	<0.001	124/25/47/17/9/1	24/6/15/10/16/1	<0.001
BCLC stage (A/B/C)	117/50/19	19/36/26	<0.001	148/53/22	22/29/21	<0.001
AFP (ng/ml)	2124.0±653.2	7612.4±2129.5	0.002	2321.7±636.9	15190±8495.9	<0.001
CEA (ug/L)	3.06±0.26	3.24±0.51	0.754	4.11±0.51	3.12±0.37	0.124
HBV-DNA	$1.5*10^{e6}$±$7.4*10^{e5}$	$1.0*10^{e6}$±$2.9*10^{e5}$	0.703	$6.1*10^{e5}$±$1.3*10^{e5}$	$5.8*10^{e5}$±$8.4*10^{e4}$	0.843
Beyond Milan criteria (%)	79 (41.8%)	71 (87.7%)	<0.001	112 (50.2%)	51 (70.8%)	0.002
Portal vein invasion (%)	19 (10.1%)	27 (33.3%)	<0.001	20 (9.0%)	21 (29.2%)	<0.001
MVI (%)	31 (16.4%)	42 (51.9%)	<0.001	45 (20.3%)	39 (54.2%)	<0.001
Histopathologic grading (I/II/III/IV)	33/77/41/38	7/29/21/24	0.111	23/126/73/1	5/25/36/6	<0.001
Beyond Hangzhou criteria (%)	40 (21.2%)	49 (60.5%)	<0.001	104 (46.6%)	38 (52.8%)	0.365
Cold ischemia time (h)	8.97±0.22	9.46±0.32	0.21	6.59±0.14	7.67±0.31	0.081
MELD score	11.82±0.40	11.46±0.57	0.613	15.74±0.82	17.67±1.39	0.223
Child score	7.12±0.15	6.84±0.19	0.272	8.84±0.133	9.49±0.227	0.334
Donor characteristic						
Donor age (yr)	43.69±1.08	41.85±1.48	0.338	47.47±12.79	47.67±1.52	0.789
Donor male (%)	158 (83.6%)	64 (79%)	0.366	189 (84.8%)	61 (84.7%)	0.995
DBD/DCD/DBCD	52/116/21	19/47/15	0.247	23/189/11	5/62/5	0.586
Donor BMI ≥25 (%)	44 (23.3%)	13 (16%)	0.182	50 (22.4%)	10 (13.9%)	0.118
Cause of death						
Trauma	109	44	0.611	122	41	0.740
CVA	80	37		101	31	

BMI: Body mass index; TACE: Transhepatic arterial chemotherapy and embolization; RFA: Radio frequency ablation; TMN stage: Tumor node metastasis stage; BCLC stage: Barcelona clinic liver cancer stage; AFP: α-fetoprotein; CEA: carcinoembryonic antigen; HBV: hepatitis B virus; MELD score: Model for end-stage liver disease; MVI: Microvascular invasion; DBD: Donation after circulatory death; DCD: Donation after brain death; DBCD: Donation after circulatory and brain death; CVA: cerebralvascular accident.

Statistical analysis

Statistical calculations during the course of the study were preformed using SPSS version 23.0 (IBM, Armonk, NY), a statistical package for the social sciences commonly used for comparison. Data from the two groups were evaluated using Fisher's exact test or chi square test, which was used for categorical variables such as whether the patient underwent radiofrequency ablation before it or hepatic arterial chemotherapy, etc., gender, tumour size, hypertension, tumour number, diabetic status, MVI, BCLC stage and TMN stage. Based on the normality possessed by the distribution of continuous variables according to the Mann-Whitney U test or Student's t-test such as donor and recipient age, AFP level, MELD score, Child-Turcotte-Pugh score and cold ischemia time. Overall survival (OS) was defined as referring to the time period between the last date of follow-up from when a patient has undergone Lt. Tumour-free survival (TFS) was defined as the time period between LT until after tumour recurrence. For the computational analysis of the relationship between D-dimer, fibrinogen levels and OS, TF in LT patients, the Kaplan Meier

Table 2. The correlation between the tumour factors and the levels of pre-operative plasma fibrinogen

	Discovery Cohort (n=270)			Validation Cohort (n=295)		
	Fibrinogen <2.27 g/L	Fibrinogen ≥2.27 g/L	P	Fibrinogen <2.27 g/L	Fibrinogen ≥2.27 g/L	P
Tumor diameter >3 cm (%)	86 (51.2%)	68 (66.7%)	0.013	59 (47.6%)	106 (62%)	0.014
Tumor number >3 (%)	30 (17.9%)	39 (38.2%)	<0.001	14 (11.3%)	36 (21.1%)	0.027
TMN stage (I/II/III/IV/V/VI)	71/53/37/3/2	15/32/46/2/5	<0.001	70/14/25/6/8/1	78/17/37/21/17/1	0.154
BCLC stage (A/B/C)	105/41/17	31/41/27	<0.001	80/32/12	90/50/31	0.06
AFP (ng/ml)	2668.8±795.1	5585.2±1647.9	0.003	1214.4±428.8	8542.9±3669.5	0.004
Beyond Milan criteria (%)	72 (42.9%)	78 (76.5%)	<0.001	83 (66.9%)	80 (46.8%)	0.001
Portal vein invasion (%)	18 (10.8%)	28 (28%)	<0.001	9 (7.3%)	32 (18.8%)	0.005
MVI (%)	34 (20.2%)	39 (38.2%)	0.001	22 (17.7%)	62 (36.5%)	<0.001
Histopathologic grading (I/II/III/IV)	29/68/36/35	11/38/26/27	0.348	10/79/31/4	18/72/78/3	0.001
Beyond Hangzhou criteria (%)	37 (22%)	52 (51%)	<0.001	74 (59.7%)	68 (39.8%)	0.001
Cause of recipient death						
CVA	2	2		1	0	
Liver graft dysfunction	2	1	0.096	/	/	0.046
Tumor recurrence	24	28		14	27	
MODS	7	5		1	10	

TMN stage: Tumor node metastasis stage; BCLC stage: Barcelona clinic liver cancer stage; AFP: α-fetoprotein; MVI: Microvascular invasion; CVA: cerebralvascular accident; MODS: multiple organ dysfunction syndrome.

method was used, in the comparison phase, with the log rank test. In the case of risk factors, with the Cox regression analysis. In the stepwise multivariable regression model, a variable selected for univariate analysis was entered [20]. To analyse the high and low levels of the predictive ability of the models, the corresponding accurate assessment can be made by the area under the receiver operating characteristic curve (AUROC). For comparison of AUROC, Medcalc (MedCalc software, Ostend, Belgium) was used. Two tailed tests were undertaken with a *P* value cut-off point of 0.05, for inclusion in the analytical data.

The data for the content of this study were obtained from the Chinese liver transplant registry, and the work was carried out through the review and approval of relevant departments. This study was approved by the Ethics Committee of The First Affiliated Hospital of Zhejiang University on the basis of the Regulations on Human Organ Transplant and national legal requirements and the ethics statement number is 2018 quick review of scientific research No. 768. This study complies with the guidelines of China's Ethical Committee and the Helsinki Declaration. All donors and recipients gave informed consent before transplantation. No donor organs were obtained from executed prisoners. For all organ transplant parties, they were informed of this study ante mortem, and permission was acquired, in compliance with regulatory requirements.

Results

Table 1 for demographic data. **Tables 2** and **3**, for association data of D dimers, plasma fibrinogen levels and tumour factors. All participants were HBV related HCC patients with follow-up times averaging 732 418 days. In the discovery cohort, the 5-year OS rate parameter values were 65% and the TFS parameter values were 62%. In the validation cohort, the 5-year OS rate parameter values were 75% and the TFS rate parameter values were 65%.

Discovery cohort

HCC patients undergoing LT, among whom those with lower preoperative fibrinogen concentration levels, had significantly longer OS and TFS than those with lower fibrinogen concentrations (concentration values <2.27 g/L vs. ≥2.27 g/L; TFS 1627±60 vs. 1064±101 days, P<0.01; **Figure 1A**; OS 1617±60 vs. 1360±91 days, P=0.025; **Figure 1B**). In prognostic contrast, patients with higher D-dimer levels were inferior to those with lower D-dimer levels (Concentration <2400 μg/L vs. ≥2400 μg/L; TFS 1573±66 vs. 1043±108 days, P< 0.001; **Figure 2A**; OS 1649±61 vs. 1228±101 days, P<0.001; **Figure 2B**).

Table 3. The correlation between the tumour factors and the levels of pre-operative plasma D-dimer

	Discovery Cohort (n=270)			Validation Cohort (n=295)		
	D-dimer <2400 ug/L	D-dimer ≥2400 ug/L	P	D-dimer <2400 ug/L	D-dimer ≥2400 ug/L	P
Tumor diameter >3 cm (%)	101 (52.6%)	53 (67.9%)	0.021	146 (55.1%)	19 (63.3%)	0.389
Tumor number >3 (%)	43 (22.4%)	26 (33.3%)	0.062	45 (17%)	5 (16.7%)	0.965
TMN stage (I/II/III/IV/V/VI)	67/72/44/0/4/4	19/13/39/0/1/3	<0.001	128/30/57/24/24/2	20/1/5/3/1/0	0.538
BCLC stage (A/B/C)	103/61/22	33/21/22	0.003	156/73/36	14/9/7	0.285
AFP (ng/ml)	2348.7±767.8	7270.4±1969.3	<0.001	5449.3±2369.2	5578.7±2492.2	0.928
Beyond Milan criteria (%)	99 (51.6%)	51 (65.4%)	0.038	146 (55.1%)	17 (56.7%)	0.870
Portal vein invasion (%)	23 (12%)	23 (30.7%)	<0.001	34 (12.9%)	7 (23.3%)	0.117
MVI (%)	39 (20.3%)	34 (43.6%)	<0.001	76 (28.8%)	8 (26.7%)	0.807
Histopathologic grading (I/II/III/IV)	30/85/44/33	10/21/18/29	0.003	25/142/92/6	3/9/17/1	0.087
Beyond Hangzhou criteria (%)	45 (23.4%)	44 (56.4%)	<0.001	126 (47.5%)	16 (53.3%)	0.548
Cause of recipient death						
CVA	3	1		1	0	
Liver graft dysfunction	2	1	0.001	/	/	0.462
Tumor recurrence	26	26		34	7	
MODS	6	6		10	1	

TMN stage: Tumor node metastasis stage; BCLC stage: Barcelona clinic liver cancer stage; AFP: α-fetoprotein; MVI: Microvascular invasion; CVA: cerebralvascular accident; MODS: multiple organ dysfunction syndrome.

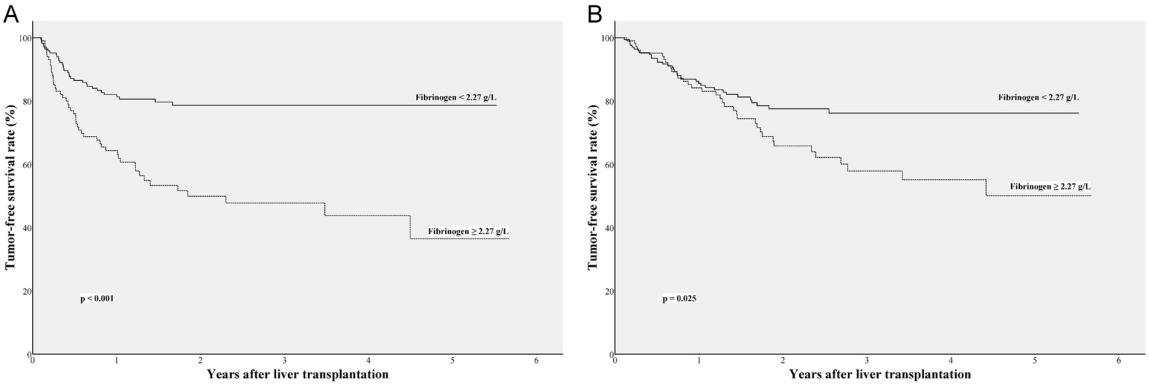

Figure 1. Overall survival time and tumour-free survival time of the recipients (at different fibrinogen concentrations) based on the discovery cohort. A: At lower concentrations, the TFS was significantly prolonged (<2.27 g/L) than patients with higher fibrinogen (≥2.27 g/L) concentration. B: At lower concentrations, OS was significantly prolonged (<2.27 g/L) than patients with higher fibrinogen concentration (≥2.27 g/L).

Poor TFS was associated with higher plasma fibrinogen concentrations, higher D-dimer levels, pre-operative TACE, greater tumour size and number, TNM stage, BCLC stage, AFP level, Milan criteria, Hangzhou criteria, portal vein invasion, and MVI. These associations were all determined by univariate analysis (**Table 1**). Further, we constructed a mathematical model to predict recurrence risk. Based on 95% CIs, it is known that Milan criteria, MVI, AFP level ≥50 ng/mL, and D-dimer (≥2400 μg/L) and elevated fibrinogen (≥2.27 g/L) levels were related with HCC recurrence (**Figure 3**). The HCC recurrence model was expressed as: Y= logit (P) =0.91* fibrinogen concentration (fibrinogen concentration ≥2.27 g/L, score 1) +0.585* AFP (AFP ≥50 ng/mL, score 1) +0.967* D-dimer (D-dimer ≥2400 ug/L, score 1) +1.623* Milan criteria +0.68* MVI-3.159. HCC recurrence in the discovery cohort with a predicted AUROC parameter value of 0.828 (**Figure 4A**). Taking the -1.524 cut-off, the resulting model specificity was 0.656, showing a sensitivity of 0.877. Recipients with the resulting score <-1.524 had significantly higher TFS and OS than those of recipients with scores ≥-1.524 in the discovery cohort (TFS 1844±45 vs. 980±86 days, P<0.001; OS 1796±52 vs. 1255±78 days, P<

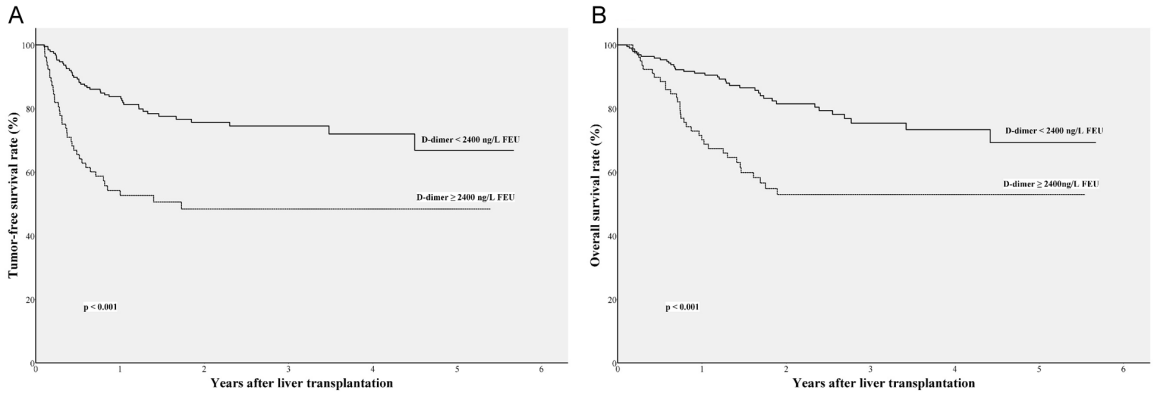

Figure 2. Receptors (different D-dimer concentrations), their overall survival time, and tumour free survival time. A: D-dimer concentration (<2400 ug/L) versus (≥2400 ug/L), the TFS of the former was significantly longer than that of the latter. B: D-dimer concentration (<2400 ug/L) versus (≥2400 ug/L), OS was significantly longer in the former than in the latter.

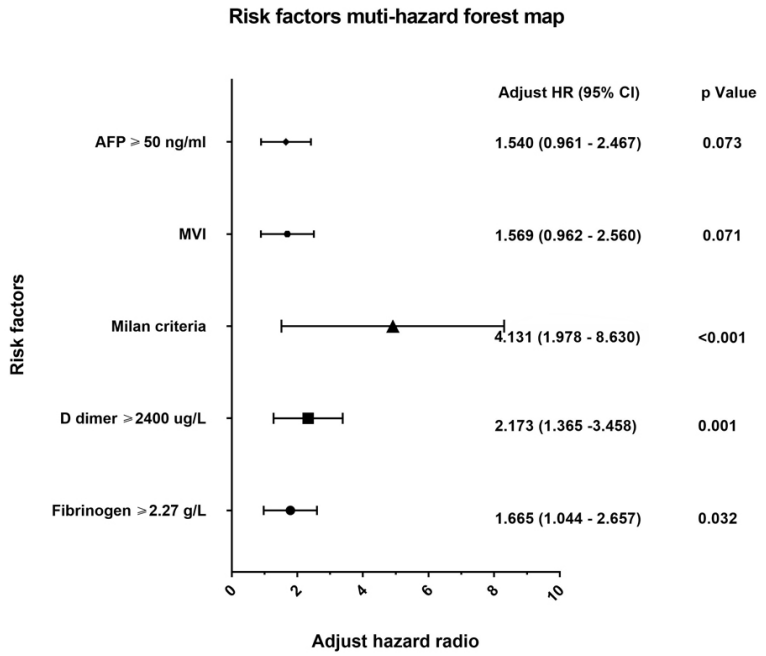

Figure 3. Risk factor Cox regression analysis forest plot in the discovery cohort. Milan criteria, MVI, AFP ≥50 ng/mL, elevated D-Dimer (≥2400 ug/L) and fibrinogen (≥2.27 g/L) levels, and HCC recurrence had relatively high associations.

0.001; **Figure 5**). For the prediction of recurrence within 1 and 3 years, a nomogram was completed (**Figure 6**).

Validation cohort

We used an independent cohort to validate the predictive model. The differential comparison of OS and TFS was significant between those with scores <-1.524 and ≥-1.524 (OS 1579±52 vs. 1368±70 days, P<0.001; TFS 1865±46 vs. 1226±77 days, P<0.001; **Figure 7**). The AUROC of the Cox proportional hazards model for predicting HCC recurrence in the validation cohort was 0.764 (**Figure 4B**).

Discussion

After LT, the main independent risk factors for HCC recurrence include D-dimer as well as preoperative plasma fibrinogen levels, with corresponding increases exerting a large effect on TFS as well as OS after LT. Such studies can be used to initially screen for HCC recurrence after LT with more economically and more effectively. D-dimer and fibrinogen tests are easily available in routine medical practice, offer effective prognostic information, and are an alternative for expensive predictive tests such as tissue biopsies. Based on multivariate analysis, it was found that the inclusion of AFP level, increased D-dimer and plasma fibrinogen content, Milan criteria, MVI and other risk factors in the combined Cox risk model was able to enhance the predictive effect of the model generated. Moreover, we tested the prediction accuracy of the model using a validation cohort from two LT centres and found that the current

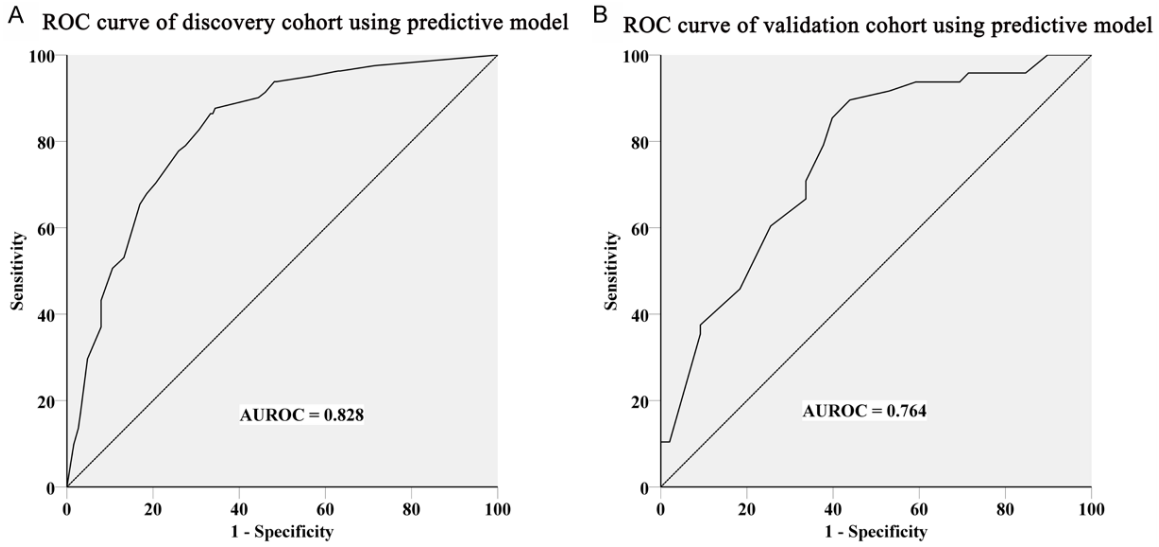

Figure 4. ROC curve prediction of the integrated model for HCC recurrence (validation cohort and discovery cohort). A: ROC curve (discovery cohort). HCC recurred after liver transplantation and the procedure validated good discrimination (AUROC 0.828). B: ROC curve (validation cohort). HCC recurred after liver transplantation and the procedure validated good discrimination (AUROC 0.764).

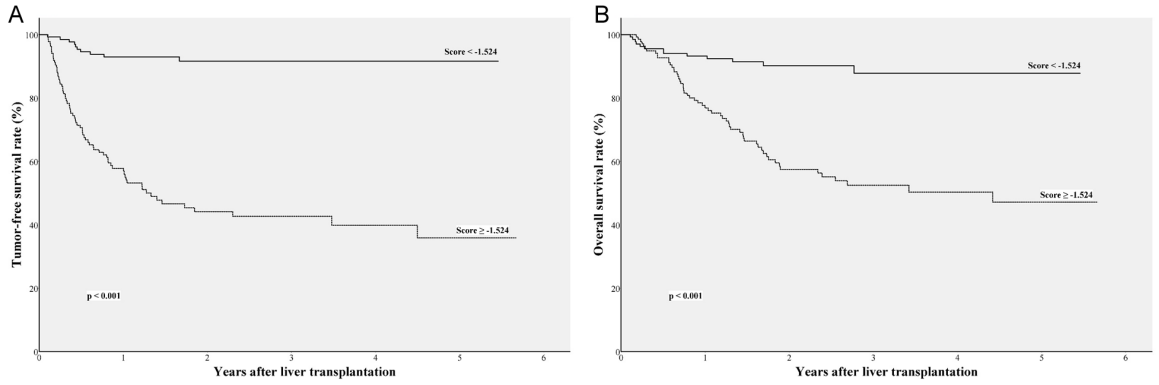

Figure 5. At -1.524 cut-off, the recipients in the discovery cohort were divided into TF and OS. A: TFS was significantly longer in the former than in the latter (score <-1.524 and score ≥-1.524). B: OS was significantly longer in the former than in the latter (score <-1.524 and score ≥-1.524).

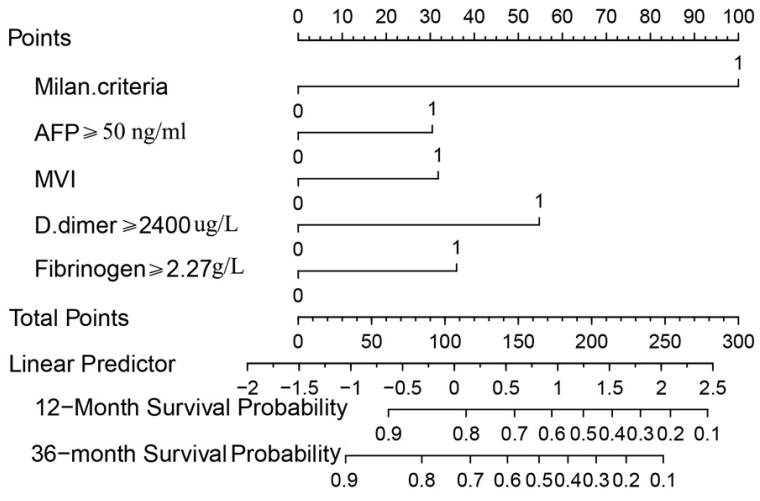

Figure 6. HCC recurrence after liver transplantation. Nomograms were taken for prediction. AFP: alpha fetoprotein; MVI: microvascular invasion.

predictive model may be utilized in guiding post-transplantation surveillance and clinical practice.

It is clear that hyperfibrinogenaemia is a predictor of worse outcome and outcome as analysed by various solid malignancies [21, 22]. In the physi-

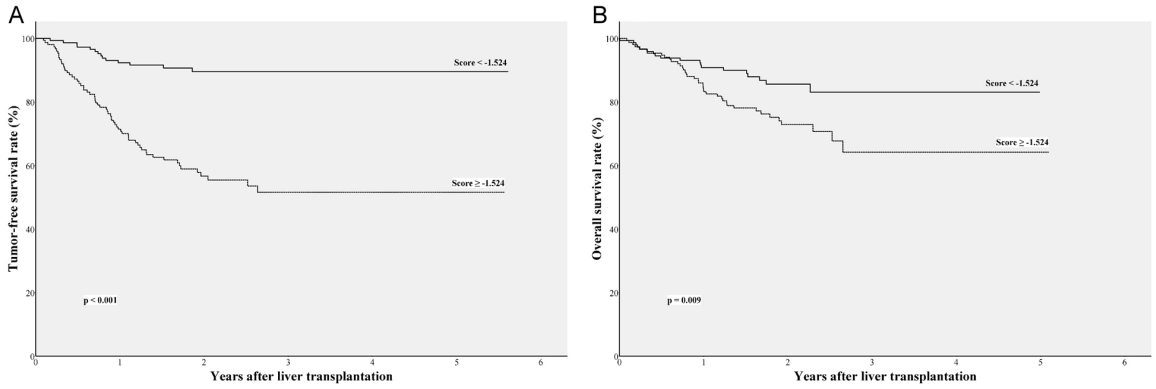

Figure 7. At the -1.524 cut-off, the recipients (validation cohort) were partitioned into TF and OS. A: In the validation cohort, the TFS of the former was significantly longer than that of the latter (score <-1.524 and score ≥-1.524). B: in the validation cohort, the 5-year OS of the former was significantly longer than that of the latter (score <-1.524 and score ≥-1.524).

ological structure of the liver, fibrinogen has a very important role as its receptor, including intercellular adhesion molecule-1, are expressed in some tumour cells [23]. The activated form of fibrin, which is able to contribute considerably to metastatic spread [24]. During the process of fibrinolysis, the D-dimer content rises constantly because it is the degradation product polymer. It is more widely used in medical fields, and studies have found that its increased level is associated with shorter cancer survival, recurrence, as well as metastasis [25]. Venous thromboembolism is fatal for cancer patients, and an increased D-dimer level indicates whether embolism should be clinically anticipated. D-dimer and fibrinogen levels are readily available, and they can be used as practical and economical prognostic indicators in clinical practice that can be applied to many medical units. That is, transplant specialists who study detection of abnormalities as part of research have better scientific, more economical, as well as more effective approaches. D-dimer and fibrinogen levels can be used for LT recipient stratification to improve survival outcomes, inform personalized medicine and prevent recurrence. We analysed the relationship between liver cirrhosis and fibrinogen and D-dimer because most of recipients have liver cirrhosis. Some research showed fibrinogen and D-dimer will elevate in liver cirrhosis patients because the activation of fibrinolysis according to the severity of liver dysfunction [26]. But there is no significant difference in fibrinogen and D-dimer between recipients with or without liver cirrhosis in the present study (Supplementary Table 1).

In this study, a prediction model for HCC recurrence after LT was established, and the efficacy of the prediction model was investigated. However, its application in practice to various scenarios of liver disease aetiology also needs validation and analysis to increase its accuracy and scientific validity. This study was retrospective and the results should be validated in a prospective clinical trial.

This study, however, found out that preoperative stage, elevated D-dimer and plasma fibrinogen levels, were independent risk factors for HCC recurrence after LT, and poor prognosis in HCC recipients. We also constructed a pre-transplantation model to predict post-transplantation HCC recurrence based on our multicentre experience of LT for HCC. This model may provide scientific guidance for post-transplant monitoring, which should be followed by practice and validation tests with a larger sample size, and be prospectively analysed to verify the predictive effect of abnormal coagulation parameters on HCC recurrence after LT.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Association between recipient liver cirrhosis and fibrinogen and D-dimer in discovery and validation cohort

	Recipient of Discovery Cohort (n=270)			Recipient of Validation Cohort (n=295)		
	Non-liver cirrhosis	Liver cirrhosis	P	Non-liver cirrhosis	Liver cirrhosis	P
D-dimer <2400 ug/L	6	3	0.765	17	248	0.163
D-dimer ≥2400 ug/L	186	75		4	26	
Fibrinogen <2.27 g/L	4	5	0.263	6	118	0.195
Fibrinogen ≥2.27 g/L	164	97		15	156	