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Research Article

Risk Factors and Survival of Early Versus Late Recurrences of Hepatocellular Carcinoma after Hepatectomy

Chen-Guo Ker[1]*, Jen-Lung Chen[1], Yaw-Sen Chen[1], Kun-Chou Hsieh[1], Hui-Ming Lee[1], Chung-Yen Chen[1], Jian-Han Chen[1] and Chao-Ming Hung[2]

[1]*Department of General Surgery, E-Da Hospital, I-Shou University, Kaohsiung, Taiwan*

[2]*Department of General Surgery, E-Da Cancer Hospital, I-Shou University, Kaohsiung, Taiwan*

***Corresponding author:** Chen-Guo Ker, MD, M.Ph.D, FACS, Professor, Department of General Surgery, E-Da Hospital, I-Shou University, Yan-Cho District, Kaohsiung 824, Taiwan.

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Abstract

Aim: Despite the treatments applied, the hepatocellular carcinoma (HCC) patients still show a high frequency of tumor recurrence. This study aimed to investigate the risk factors and overall survival rate (OS) of the patients with early or late recurrence after hepatectomy.

Patients and Methods: Totally, 527 HCC patients were enrolled and received hepatectomy from 2012 to 2019. The basic profiles and clinical features were analyzed for the risk factors of the early and late recurrence after hepatectomy.

Results: Pre-operative variables were identified significantly including monocyte, systemic inflammatory response index and albumin-to-alkaline phosphatase ratio (AAR) for the subgroup with recurrent time within 6 months, albumin-bilirubin score and AAR for the subgroups within 1 year and 2 years, and platelet for more than 2 years. Alfa-fetoprotein acted as a significant predicted risk factor for recurrent time more than 2 years (p=0.048). The over-all survival (OS) rates for recurrence (+) patients were 93.0%, 69.0%, and 53.0%, and recurrence (-) were 91.9%, 77.5%, and 73.5% for 1, 3, and 5 years respectively (P<0.001). However, their OS of 5-year were 18.0%, 20.5% and 63.1% and 83.1% (P<0.001) for the recurrent time within 6 months, 1 year, 2 years and more than 2 years respectively. Thus, it was pertinent to prove that earlier recurrent time will result in a poor survival rate.

Conclusion: The identification of specific clinical laboratory and histopathology findings may reflex the risk of recurrence and could guide the decision-making for pre-/post-hepatectomy to lengthen the time to recurrence. The concepts of risk factors based on the time of recurrence in the HCC therapeutic landscape is obligatory, and could optimize patient outcome where possible.

Keywords: Hepatocellular carcinoma, Recurrence, Diagnosis, Risk of recurrence, Survival rate

Introduction

Hepatocellular carcinoma (HCC) is a common disease and has been leading cause of death in man and the third in women for decades in Taiwan [1]. Its long-term prognosis after resection is still unsatisfactory despite improvements in treatment for HCC, because HCC patients have a high frequency of recurrence in most patients and reflex a life-threatening status [2]. Generally, the 5-year

recurrence rates after surgical resection and/or radiofrequency ablation can be as high as 70–80%, depending on the patient's disease stage, tumor pathology, and treatment strategy [3,4]. Thus, a better understanding of risk factors, time to recurrence, and long-term prognosis after hepatectomy, may help surgeons to make a surgical decision-making before or during recurrence.

Currently, a standardized definition of the early and late recurrence of HCC after hepatectomy has not yet been established. However, several studies have used different cutoff points for distinguishing early vs. late recurrence after hepatectomy for liver cancers, depending on study design, and statistical modeling. There were 6[5], 8[6,7], 11[8], 12[2,9], 17[10] and 24 months [10-13] used as a model for the cut-off time of recurrence reported from previous studies. Nevertheless, the term of ultra-early or very early recurrence were used specific for the recurrent time within 6 months with several features among these patients [5,14]. The overall survival (OS) rates of the HCC patients were strongly influenced by the time of the recurrences [11,15]. In case of early recurrence, poor prognosis could be expected and could indicate the needs for closer surveillance and further postoperative adjuvant therapies after treatment [14]. The emerging predictors include pre-operative laboratory findings, tumor burdens, and histopathological patterns. The risk factors of recurrence can be classified as tumor- or patient-related. Among the tumor-related factors, vascular invasion, tumor size, and number of lesions have shown a long-established predictive capacity [16]. Understanding patient-related predictors of recurrence and optimal management of cancer etiologic factors and metabolic comorbidities, is important to achieve better outcomes [17,18].

In the present study, we aim to identify the attributable risk factors and OS stratified by their different time of recurrence after hepatectomy in patients with HCC. Therefore, a retrospective study was conducted to investigate the risk factors possibly contributing to different times to recurrence among primary HCC patients who underwent hepatectomy.

Patients and Method

Study design

All patients were retrospectively collected from the cancer registry information system database of E-Da hospital. The criteria included the adult patients receiving hepatectomy as a curative treatment and with a pathological diagnosis of HCC. Patients treated from 2012 to 2019. Subsequently, they were sub-grouped based on the time of recurrence. Postoperative follow-up consisted of periodic blood tests and monitoring of AFP and liver function test. Echographic examination of the remnant liver was performed every 3-4 months after hepatectomy and whole abdominal CT was performed if recurrence HCC was suspected. The tumor recurrent time was set at within 6 months, 1 year, 2 years, and longer than 2 years during post-operative follow-up. The inclusion criteria were as follows: (a) patients with imaging and a pathological diagnosis of HCC, (b) patients treated with surgical liver resection, (c) adults age ≥18-year-old. The exclusion criteria included as follws: (a) patient with severe systemic diseases, and (b) those who were deceased from non-HCC factors within 2 months postoperatively. Two endpoints of this study were the time of intrahepatic recurrence and OS, which were measured from the date of hepatectomy. This study was approved by the Institutional Review Board and Ethical Committee of E-Da Hospital (Code no. EDAHS 110012).

Profiles of the Pre-Operative Patient Variates

Basic profiles of patients were included their age, gender, history of alcohol, diabetics (DM), BMI, hepatitis B/C, TMN stage, Child-Pugh classification, Barcelona Clinic Liver Cancer (BCLA) stage, and tumor burden etc. (Table 1). Pre-operative laboratory profiles included WBC count(103/μL) and their classification of neutrophil, monocyte, and lymphocyte, as well as platelet(103/μL). Chemistry serum study included Hemoblobin A1c (HbA1c, %), International Normalized Ratio for prothrombin time (INR), Indocyanine green test (ICG %), alfa-fetoprotein (AFP, ng/mL), bilirubin (mg/dL), glutamic oxaloacetic transaminase (GOT,μL)/glutamic pyruvate transaminase (GPT,μL) ratio, alkaline phosphatase (Alk-p,μL) and albumin (Alb, g/dL). Combination inflammatory and nutritional indices were assessed, namely, the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII) [19], systemic inflammatory response index (SIRI) [20], albumin-bilirubin score (ALBI) [21], and albumin-to-alkaline phosphatase ratio (AAR) [22] as shown in the Table 2. The operative and pathological findings used as variates were listed in the Table 3. All variables were stratified and selected for evaluation if their values were significant for establishing a nomogram for prediction of recurrent probability.

Statistical Analysis

Statistical analysis was performed using SPSS (Version 25.0, IBM) and R statistical software (Version 3.3.3, *https://www.r-project.org*. RStudio 2023.12.0+369 for windows). Multiple variates were initially selected to determine the most relevant features. Variables not meeting the consistency threshold, or showing no statistical differences ($P > 0.05$) were removed based on Student's t-test. With regard to the process preconditions, univariate analysis was first performed to compare the clinical variables using the chi-square test and Wald test score to categorize the variables and independent Student t-test for continuous variables where appropriate. Moreover, a logistic regression model analysis for hazard ratio, and receiver operating characteristic curves for sensitivity and specificity were utilized. Nomogram construction was performed and established using multivariate analysis of patients. The included variables were selected using a stepwise multiple logistic regression analysis. Survival curves were constructed and compared using the Kaplan-Meier survival method. The OS rates set at 1-, 3-, and 5-year were assessed for

surgical outcomes. The calibration probability was assessed using calibration curves and considered to have predictive power and P < 0.05 was considered statistically significant.

Results

Demographic of Clinical Profiles and Cohort of Their Recurrent Times

The clinical characteristics of 527 HCC patients totally, 409(77.6%) in male and 118(22.6%) in female, were sub-grouped by their recurrent times; <6-month, < 1-year, <2-year, and ≧2-year. The cumulative recurrent rates within 6 months, 1year, 2 years and ≧2 years were 8.3%, 17.1%, 25.8% and 15.0% respectively. Significant pre-operative variables were identified first, including BCLC stage, Child-Pugh classification, serum bilirubin, Alk-p, and AFP in the subgroups of recurrence within 6 months and 1 year as shown in Table 1.

Table 1: Baseline characteristics of HCC patients based on the tumor recurrent times after hepatectomy.

Variable n (%)	Total N=527 M±SD	Recurrent time							
		<6-month n=44 (8.3%)	P	<1-year n=90 (17.1%)	P	<2-year n=136 (25.8%)	P	≧2-year n=79 (15%)	P
Age(years)	61.0±10.8	61.7±9.2	0.67	62.1±10.6	0.277	61.9±10.3	0.247	60.5±10.9	0.864
<65	322(61.1)	26(59.1)	0.775	51(56.7)	0.343	81(59.6)	0.669	52(65.8)	0.392
≧65	205(38.9)	18(40.9)		39(43.3)		55(40.4)		27(34.2)	
Sex									
Male	409(77.6)	36(81.8)	0.484	69(76.7)	0.814	104(76.5)	0.712	65(82.3)	0.305
Female	118(22.4)	8(18.2)		21(23.3)		32(23.5)		14(17.7)	
BMI	24.9±3.8	24.6±3.4	0.55	24.6±3.6	0.461	24.7±3.7	0.602	25.2±4.0	0.469
<27	380(73.1)	32(74.4)	0.836	64(73.6)	0.911	99(75.0)	0.564	57(73.1)	0.885
≧27	140(26.9)	11(25.6)		23(26.4)		33(25.0)		21(26.9)	
DM(+)	138(26.2)	11(25.0)	0.852	22(24.4)	0.68	31(22.8)	0.296	20(25.3)	0.647
Alcohol									
0	349(67.6)	29(69.0)	0.838	57(64.8)	0.529	84(63.6)	0.255	54(69.2)	0.962
01-Feb	167(32.4)	13(31.0)		31(35.2)		48(36.4)		24(30.8)	
ECOG									
0-1	519(99.0)	41(100)	0.513	85(97.7)	0.158	131(98.5)	0.45	79(100)	1
02-Apr	5(1.0)	0(0)		2(2.3)		2(1.5)		0(0)	
BCLC									
0-1	304(57.7)	20(45.5)	0.017	43(47.8)	0.014	72(52.9)	0.073	53(67.1)	0.09
02-Mar	223(42.3)	24(54.5)		47(52.2)		44(47.1)		26(32.9)	
Child-Pugh									
A	509(98.5)	41(95.3)	0.085	84(95.5)	0.012	127(96.9)	0.106	78(98.7)	1
B	8(1.5)	2(4.7)		4(4.5)		4(3.1)		1(1.3)	
Hepatitis									
Non	104(19.7)	11(25.0)	0.721	15(16.7)	0.565	22(16.2)	0.47	14(17.7)	0.678
B	257(48.8)	22(50.0)		42(46.7)		65(47.8)		40(50.6)	
C	151(28.7)	10(22.7)		31(34.4)		44(32.4)		24(30.4)	
B&C	15(2.8)	1(2.3)		2(2.2)		5(3.7)		1(1.3)	
AST(IU/I)	57.1±70.7	57.7±41.9	0.952	58.6±39.3	0.822	56.4±43.4	0.895	54.9±32.9	0.757
ALT(IU/I)	53.7±75.8	48.4±43.6	0.634	51.2±41.8	0.734	49.5±41.9	0.456	58.9±40.9	0.656
Albumin	4.14±0.36	4.10±0.37	0.487	4.04±0.44	0.004	4.09±0.40	0.075	4.19±0.33	0.366
<4.0	126(24.8)	9(21.4)	0.602	27(30.7)	0.157	41(30.6)	0.068	17(21.8)	0.836
≧4.0	383(75.2)	33(78.6)		61(69.3)		93(69.4)		61(78.2)	
Bilirubin,T	0.89±0.37	0.94±0.40	0.457	0.91±0.40	0.624	0.90±0.39	0.708	0.92±0.34	0.451

<1.0	349(67.5)	25(59.5)	0.249	59(67.0)	0.92	91(67.9)	0.907	53(67.9)	0.514
≧1.0	168(32.5)	17(40.5)		29(33.0)		43(32.1)		25(32.1)	
									0.902
INR	1.24±1.79	1.07±0.24	0.507	1.05±0.20	0.262	1.38±2.19	0.282	1.18±1.17	0.932
Alk-P	334.5±269.2	464.5±340.9	0.008	397.0±323.0	0.05	365.1±275.6	0.214	313.8±162.4	0.724
ICG_{15}	12.22±9.15	14.04±12.9	0.173	13.24±10.58	0.248	12.59±9.69	0.579	13.53±8.49	0.108
<20	451(87.4)	35(81.4)	0.215	73(82.0)	0.093	113(84.3)	0.213	69(87.3)	0.722
≧20	65(12.6)	8(18.6)		16(18.0)		21(15.7)		10(12.7)	
AFP(ng/ml)	8628.7±	16397.9±	0.218	10371.3±	0.676	7074.8±	0.627	684.3±	0.077
	43231.7	51141.2		37682.5		30926.9		2173.9	
<200	362(71.1)	25(58.1)	0.05	55(61.8)	0.033	91(67.4)	0.267	59(77.6)	0.258
≧200	147(28.9)	18(41.9)		34(38.2)		44(32.6)		17(22.4)	

Systemic Immune Inflammation and Nutrition Index of HCC Patients

Laboratory systemic immune inflammation and nutrition indexes formatted for the HCC patients were also stratified by their mean values (Table 2). Significant preoperative variables were identified including monocyte, SIRI and AAR for the subgroup with recurrent time less than 6 months, ALBI and AAR for the less than subgroups of within 1 year and 2 years, and platelet for more than 2 years as illustrated in Table 2.

Table 2: Systemic immune inflammation and nutrition index-related factors according to the recurrent time after hepatectomy.

Variable	Total N=527 (M±SD)	Recurrent time							
		<6-month n=44	P	<1-year n=90	P	<2-year n=136	P	≧2-year n=79	P
WBC	6.6±2.5	7.0±2.2	0.268	6.6±2.3	0.855	6.4±2.2	0.293	6.2±1.8	0.118
Neutrophil	64.3±13.8	63.3±11.5	0.73	64.7±12.3	0.831	63.0±12.9	0.389	64.4±12.8	0.86
Monocyte	6.7±2.3	7.7±2.5	0.032	7.0±2.4	0.27	6.9±2.3	0.299	6.5±2.1	0.877
Lymphocyte	25.7±12.0	25.2±11.6	0.852	24.9±11.1	0.643	26.8±11.6	0.393	25.6±11.4	0.844
Platelet	194.7±78.5	207.9±82.3	0.247	195.4±90.7	0.931	192.8±85.8	0.738	179.8.±56.4	0.039
Index,									
1.NLR	4.22±6.83	3.95±3.84	0.839	3.92±3.45	0.747	3.50±3.11	0.331	3.73±3.63	0.567
<4.22	156(74.6)	17(73.9)	0.932	30(71.4)	0.592	44(73.3)	0.783	20(74.1)	0.884
≧4.22	53(25.4)	6(26.1)		12(28.6)		16(26.7)		7(25.9)	
2.MLR	0.48±1.28	0.53±0.48	0.852	0.46±0.42	0.932	0.40±0.38	0.672	0.27±0.13	0.603
<0.48	94(80.3)	11(68.8)	0.209	19(70.4)	0.137	28(77.8)	0.642	9(90.0)	0.679
≧0.48	23(19.7)	5(31.3)		8(29.6)		8(22.2)		1(10.0)	
3.PLR	173.4±268.5	156.3±126.8	0.748	156.1±109.1	0.642	146.9±101.2	0.368	162.1±189.1	0.687
<173.4	156(74.3)	17(73.9)	0.965	30(71.4)	0.636	43(71.7)	0.583	22(81.5)	0.413
≧173.4	54(25.7)	6(26.1)		12(28.6)		17(28.3)		5(18.5)	
4.SII	841.0±1173.1	816.1±972.5	0.914	808.2±867.6	0.84	724.6±792.6	0.364	682.7±788.9	0.365
<841.0	149(71.3)	16(69.6)	0.846	28(66.7)	0.459	42(70.0)	0.793	21(77.8)	0.446
≧841.0	60(28.7)	7(30.4)		14(33.3)		18(30.0)		6(22.2)	
5.SIRI	5.2±14.8	4.9±4.4	0.938	3.8±3.6	0.504	3.4±3.4	0.29	3.4±3.4	0.432
<5.2	160(77.7)	13(59.1)	0.027	30(73.2)	0.44	45(76.3)	0.76	20(76.9)	0.859
≧5.2	46(22.3)	9(40.9)		11(26.8)		14(23.7)		6(23.1)	
6.ALBI	-2.69±0.61	-2.64±0.66	0.577	-2.64±0.56	0.381	-2.69±0.49	0.888	-2.79±0.28	0.109
<-2.69	320(62.9)	23(56.1)	0.349	44(50.6)	0.009	74(55.6)	0.045	50(65.8)	0.94

≧-2.69	189(37.1)	18(43.9)		43(49.4)		59(44.4)		26(34.2)	
7.AAR	0.52±1.39	1.38±3.56	0.001	1.07±2.78	0.001	0.87±2.29	0.006	0.35±0.71	0.571
<0.52	275(73.7)	15(55.6)	0.026	38(64.4)	0.076	57(63.3)	0.01	45(78.9)	0.7
≧0.52	98(26.3)	12(44.4)		21(35.6)		33(36.7)		12(21.1)	

Note*: *Seven indexes were stratified by their mean values of HCC patients.

Operation and Pathological Related Risk Factors of Tumor Recurrent Time

Operation and pathological tumor burden of the HCC patients after hepatectomy were stratified by their findings (Table 3). The early recurrent risk factor was tumor size for recurrence less than 6 months, 1 year and 2 years. The existences of satellite nodules were significant among all subgroups. Tumor size, satellite nodule, cellular differentiation, and microvascular invasion also showed significant roles in recurrence (Table 3).

Table 3: Operation and pathological related risk factors of tumor recurrent time.

Variable	Total N=527 n(%)	Recurrent time							
		<6-month n=44	P	<1-year n=90	P	<2-year n=136	P	≧2-year n=79	P
Tumor location									
1. segment 1	7(1.3)	1(2.3)	0.481	2(2.2)	0.51	4(2.9)	0.161	1(1.3)	0.947
2. left (S2+3)	102(19.4)	5(11.4)		13(14.4)		22(16.2)		16(20.3)	
3. right (S4-8)	410(77.9)	37(84.1)		74(82.2)		109(80.1)		61(77.2)	
4. 2.&3.	7(1.3)	1(2.3)		1(1.1)		1(0.7)		1(1.3)	
Op. method									
Open	410(77.8)	38(86.4)	0.153	78(86.7)	0.026	113(83.1)	0.085	62(78.5)	0.557
Laparoscopic	117(22.2)	6(13.6)		12(13.3)		23(16.9)		17(21.5)	
Tumor extension									
non	489(92.8)	41(93.2)	0.945	84(93.3)	0.878	129(94.9)	0.596	76(96.2)	0.473
capsule	11(2.1)	1(2.3)		1(1.1)		1(0.7)		1(1.3)	
extrahepatic	4(0.8)	0(0)		1(1.1)		1(0.7)		0(0)	
ruptured n	23(4.4)	2(4.5)		4(4.4)		5(3.7)		2(2.5)	
Blood loss, ml	319.3±504.8	312.5±320.8	0.925	278.2±282.3	0.396	284.9±306.4	0.355	251.8±281.7	0.159
<999	494(93.9)	43(97.7)	0.347	88(97.8)	0.226	131(96.3)	0.35	75(96.2)	0.29
1000-1999	22(4.2)	0(0)		1(1.1)		4(2.9)		3(3.8)	
≧2000	10(1.9)	1(2.3)		1(1.1)		1(0.7)		0(0)	
Blood transfusion									
non	474(89.9)	41(93.2)	0.456	82(91.1)	0.686	123(90.4)	0.823	75(94.9)	0.09
yes	53(10.1)	3(6.8)		8(8.9)		13(9.6)		4(5.1)	
Tumor size	52.4±36.1	67.6±44.5	0.003	61.9±40.5	0.006	57.1±38.3	0.077	30.3±3.4	0.24
≦20mm)	62(11.8)	2(4.5)	0.188	4(4.4)	0.047	8(5.9)	0.047	11(13.9)	0.272
21-50mm	275(52.2)	22(50.0)		48(53.3)		76(55.9)		46(58.2)	
≧51mm	190(36.1)	20(45.5)		38(42.2)		52(38.2)		22(27.8)	
Tumor number	1.06±0.40	1.14±0.35	0.157	1.04±0.39	0.782	1.04±0.39	0.535	1.04±0.37	0.561
1	457(90.7)	38(86.4)	0.303	76(89.4)	0.661	118(91.5)	0.718	68(90.7)	0.93
≧	47(9.3)	6(13.6)		9(10.6)		11(8.5)		7(9.3)	
Satellite nodule									
non	450(85.4)	29(65.9)	<0.001	63(70.0)	<0.001	103(75.7)	<0.001	70(88.6)	<0.001
yes)	77(14.6)	15(34.1)		27(30.0)		33(24.3)		9(11.4)	

Distal margin	8.52±9.00	7.32±7.96	0.37	7.12±6.88	0.125	7.92±8.24	0.384	10.16±12.48	0.132
<10mm	379(77.0)	34(82.9)	0.349	68(84.0)	0.105	102(81.0)	0.225	57(76.0)	0.943
≧11mm	113(23.0)	7(17.1)		13(16.0)		24(19.0)		18(24.0)	
Safety margin									
yes	507(96.2)	42(95.5)	0.786	87(96.7)	0.801	133(97.8)	0.26	79(100)	0.03
not safe	20(3.8)	2(4.5)		3(3.3)		3(2.2)		0(0)	
Differentiation									
well	40(8.2)	0(0)	0.039	1(1.2)	0.007	3(2.3)	0.008	10(14.3)	0.066
moderated	421(85.9)	38(88.4)		76(88.4)		115(89.1)		59(84.3)	
poor	29(5.9)	5(11.6)		9(10.5)		11(8.5)		1(1.4)	
MVI*									
non	367(70.2)	20(45.5)	<0.001	49(54.4)	<0.001	79(58.1)	<0.001	70(88.6)	0.001
yes	156(29.8)	24(54.5)		41(45.6)		57(41.9)		9(11.4)	
MVI score*									
0	364(69.6)	21(47.7)	0.004	50(55.6)	0.006	80(58.8)	0.004	69(87.3)	0.007
1	112(21.4)	16(36.4)		29(32.2)		42(30.9)		7(8.9)	
2	47(9.0)	7(15.9)		11(12.2)		14(10.3)		3(3.8)	
Ishak score	3.2±2.1	3.1±2.2	0.784	3.2±2.2	0.939	3.3±2.2	0.497	3.4±2.3	0.181
0	62(12.6)	5(12.5)	0.946	14(16.9)	0.42	17(13.4)	0.804	10(13.7)	0.078
01-May	330(66.9)	26(65.0)		52(62.7)		82(64.6)		42(57.5)	
6	101(20.5)	9(22.5)		17(20.5)		28(22.0)		21(28.8)	

Note*: *MVI; microvascular invasion, MVI score; 0=MVI (-), 1=microscopically, and 2=macroscopically.

Predictive Risk of Factors of Recurrent Times of HCC Patients After Hepatectomy

The odds ratio (OR) of risk factors for recurrent time after hepatectomy was obtained via univariate and multiple logistic regression analysis based on stratification of the variables. All significant variables were used for multiple logistic regression analysis. Significant predicted risk variables were listed according to the subgrouping by recurrent time mainly including AFP and AAR (Table 4). Only AFP acted as a main predicted risk factor for recurrent time loner than 2 years (p=0.048). Variables resulting in statistically significant difference were then studied by Cox regression analysis; univariate and then multivariate based on the forward stepwise Cox regression. The results were represented in hazard ratio (HR) with 95% confidence interval (CI).

Table 4: Predictive risk of factors of recurrent time of HCC patients after hepatectomy via univariate and multivariate logistic regression analysis.

Variable	Univariate		Multivariate	
	HR (95%, CI)	P value	HR (95%, CI)	P value
1. Recurrence (total)				
AAR	1.252 (1.134, 1.383)	<0.001	1.252 (1.072, 1.461)	0.004
AFP	1.000 (1.000, 1.000)	0.358	1.000 (1.000, 1.000)	0.956
Tumor number	0.961 (0.684, 1.351)	0.819	0.097 (0.016, 0.581)	0.011
Monocyte	1.075 (0.983, 1.176)	0.114	1.323 (1.029, 1.700)	0.029
2. Recurrence< 6-month				
AAR	1.265 (1.122, 1.426)	<0.001	1.420 (1.106, 1.823)	0.006
Hepatitis				
Non (Ref.)	1		1	
B	0.811 (0.393, 1.673)	0.571	9.056 (0.829, 98.941)	0.071
C	0.619 (0.263, 1.458)	0.273	0.363 (0.011, 12.193)	0.572

BC	0.632 (0.082, 4.894)	0.66	-	
MLR	1.025 (0.748, 1.403)	0.879	10.636 (1.120, 101.013)	0.04
3. Recurrence < 1-year				
AAR	1.252 (1.134, 1.383)	<0.001	1.339 (1.119, 1.746)	0.003
AFP	1.000 (1.000, 1.000)	0.358	1.000 (1.000, 1.000)	0.028
Hepatitis				
Non (reference.)	1		1	
B	1.170 (0.801, 1.709)	0.416	24.319 (1.905, 310.488)	0.014
C	1.324 (0.884, 1.984)	0.173	1.701 (0.152, 19.040)	0.667
BC	0.956 (0.403, 2.271)	0.92	-	
Ishak score				
0 (Ref.)	1		1	
1-5	0.854 (0.533, 1.367)	0.51	0.018 (0.001, 0.267)	0.004
6	0.720 (0.517, 1.002)	0.052	0.111 (0.013, 0.935)	0.043
4. Recurrence< 2-year				
AAR	1.252 (1.134, 1.383)	<0.001	1.237 (1.065, 1.437)	0.005
AFP	1.000 (1.000, 1.000)	0.358	1.000 (1.000, 1.000)	0.016
5. Recurrence≧2-year				
AFP	1.073 (1.001, 1.150)	0.048		

Calibration Plot Model and Nomogram for Prediction of Recurrence

The calibration plot model diagram was constructed using the significant predictive risk variables of patients totally including the MVI score, blood lost, AFP, platelet, monocyte, AAR, and Alk-p totally to predict OR of recurrent time before hepatectomy (Table 5 and Figure 1). A nomogram was constructed from six valuables to predict the risk of overall recurrence in HCC patients. To use this nomogram, the scores for each variable were obtained after logarithmic transformation on the corresponding axis. A line drawn from the total points' axis to the risk and determine the probability of recurrent risk with a C-index score was 0.721 as in the Figure 2. Total maximal score from the nomogram was 110 points. Increasing risk scores in the nomogram will increase the prediction probability of recurrence and dismal OS rates.

Table 5: Risk variables for overall survival rate after hepatectomy.

Variables	Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value
Vascular inv score				
0 (Ref.)	1		1	
1+2	2.101 (1.450, 3.044)	<0.001	1.763 (0.829, 3.749)	0.141
Blood loss	1.000 (1.000, 1.000)	<0.001	1.001 (0.999, 1.001)	0.645
Platelet	1.001 (0.999, 1.003)	0.446	1.001 (0.997, 1.004)	0.669
Monocyte	1.028 (0.939, 1.124)	0.555	1.099 (0.909, 1.328)	0.328
AAR	1.273 (1.164, 1.392)	<0.001	1.269 (1.114, 1.445)	<0.001
Alk-P	1.000 (1.000, 1.001)	0.032	1.002 (1.000, 1.003)	0.035

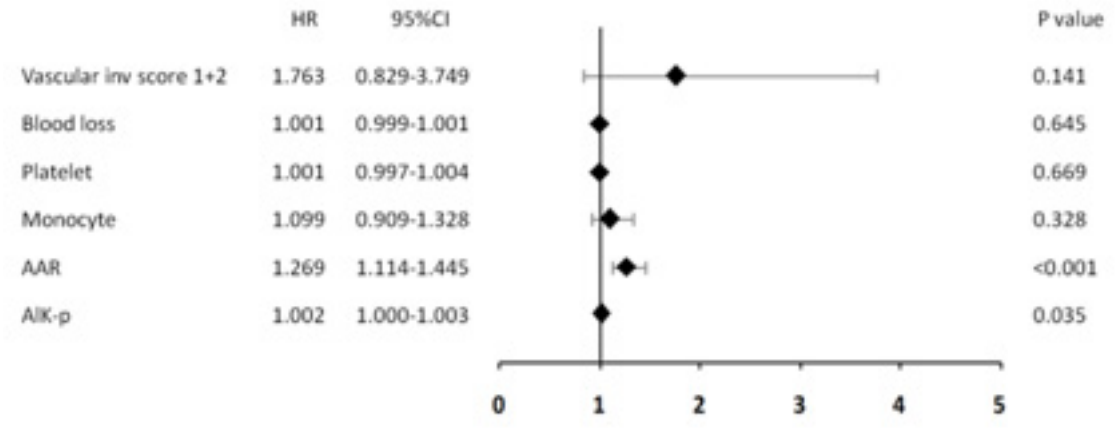


Figure 1: Forest plot illustration of hazard ratio of independent risk factors of recurrence after hepatectomy.

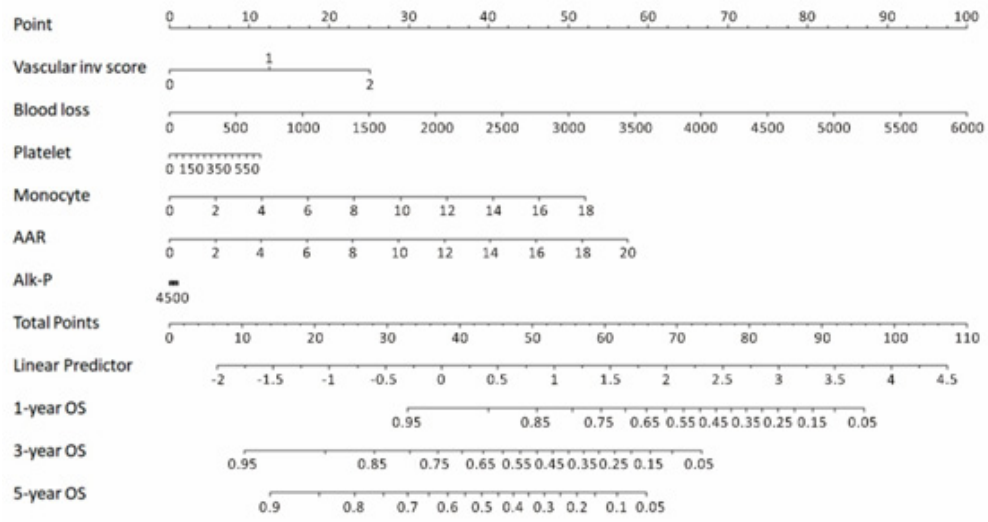


Figure 2: Significant independent risk factors of the survival if tumor recurrence is presented in a nomogram for HCC patients after hepatectomy. Total number of points for six variables for the prediction was 110 (C-index=0.721).

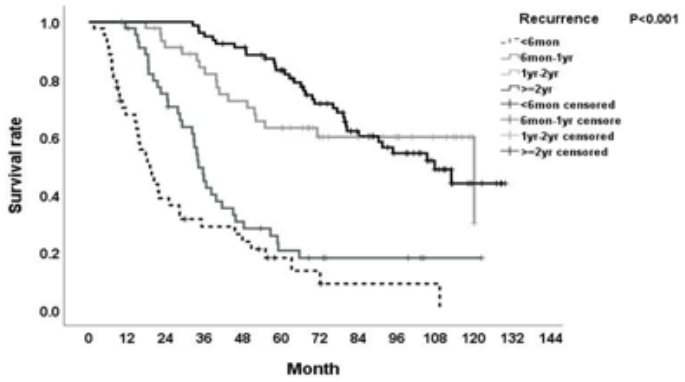
Tumor Recurrence and Overall Survival Rates After Hepatectomy

The survival rate was estimated using the Kaplan-Meier method, while the difference between the different recurrence groups was evaluated using the log-rank test. The OS totally after hepatectomy were 92.4%, 73.6%, and 63.6%, for 1, 3, and 5 years respectively. In the recurrence cohort, the OS rates of recurrence (+) patients were 93.0%, 69.0%, and 53.0%, and of recurrence (-) were 91.9%, 77.5%, and 73.5% totally respectively (P<0.001). However, their OS of 5-year were 18.0%, 20.5% and 63.1% and 83.1% (P<0.001) for the recurrent time within 6 months, 1 year, 2 years and longer than 2 years respectively as shown in the Figure 3. Thus, it was pertinent to prove that earlier recurrence will result in a poor survival rate.

Discussion

Recurrence after hepatectomy is typically classified into early and late recurrences based on the time of tumor recurrence after hepatectomy for HCC patients [2]. These classifications are used because they can reflect different underlying mechanisms and influence prognosis and treatment strategies. However, there is no standardized definition for early or late time of recurrence of HCC after treatment. Most studies have used different cutoff points for distinguishing time of recurrence after treatment, depending on study design and statistical method. The study of *Wei, et al.* [7], they suggested a cut-off time point of 8 months, which was defined as the optimal threshold based on sensitivity analyses relative to post-recurrence survival for early (37.2%) versus late recurrence (62.8%). A co-operative study of China and Korea revealed that

recurrence was observed in 42/149 (28.2%) patients within 1 year as a cut-off time [2]. In a large series of 1,247 patients treated by resection or local ablation, and recurrence within 2 years was 1,247(13.7%) reported by *Goh, et al.* in Korea [13]. Among these studies, the cut-off time for early recurrence after hepatectomy was within 2 years in majority because the recurrent patients were clustered in the second year after treatment and enrolling a sufficient number of cases for clinical study. In the recent years, the recurrent rate ranged from 13.7% to 44.3% for within 2 years [13,15,23,24], and 6.7% to 38.5% for within 1-year recurrent rates [2,25,26]. The overall recurrence rate was 23.7% within 1 year, 64.5% within 3 years, and 76.1% within 5 years as reported by Kumata [27]. In another study, the recurrence rate within 3 years was 51.34% after radical hepatectomy among 224 patients [28]. Post-operation recurrence rate was 29.2% (52/178) within 6 months, suggesting that multifocal HCC is an important risk factor associated with very early recurrence of advanced HCC after hepatectomy reported by *Lu, et al.* [29]. The National Taiwan University Hospital reported 653 (38.4%) of 1,701 patients who developed late recurrence at more than 2 years [15]. In our current series, the patients developed recurrent tumors found within 6 months, 1year, and 2 years were 8.3%, 17.1%, and 25.8% respectively, but more than 2 years was 15.0% among all patients. In case of late recurrence, better prognosis could be expected and suggested the needs for closer surveillance and further post-operative adjuvant therapies, especially for early recurrences [30].



Recurrence	Survival rate (%)			P value
	1-year	3-year	5-year	
<6 mon	67.8	28.8	18	<0.001
6 mon-1 year	97.8	44.6	20.5	
1-2 years	100	84.2	63.1	
≧2 years	100	94.9	83.2	

Figure 3: The Kaplan-Meier curves for overall survival rates based on their recurrent times of HCC patients after hepatectomy.

Usually, patients with HCC have a high-risk of multi-centric (MC) tumor occurrence due to either a risk carcinogenic background in the diseased liver or another high risk of intrahepatic metastasis (IM) [31]. HCC recurrences with IM or MC patterns are significantly different in their developmental pattern and clinical outcome [32,33]. An early recurrence, mainly determined by the aggressiveness of the primary tumor, is characterized by a larger tumor, higher rates of MC and intrahepatic spread, higher probability of vascular invasion and higher levels of AFP, as an IM pattern [34,35]. Conversely, late recurrence is generally related to etiology, cirrhosis and risk factors for hepatocarcinogenesis, and not arisen from the primary tumor, but through a MC pattern [27,32,36]. *Kumada, et al.* assessed the occurrence rate of IM and MC patterns based on the type of recurrence with a result; the IM group (n=29, 50.9%) and the MO group (n=28, 49.1%) after initial treatment for small HCC [27]. The genetic analysis has shown that 60–80% of recurrent tumors are originated from the primary HCC lesion as an IM pattern [37,38]. In fact, differentiation between IM and MC in HCC patients at the time of initial treatment is difficult, but important in understanding the development and biological behavior of the HCC. The complete removal of the initial lesion in patients with HCC does not provide a permanent cure because of the presence of MC [32]. Hence, the therapeutic management should not be based only on the time point of recurrence, but also on the tumor characteristics and aggressiveness. Therefore, postoperative early detection of recurrence may be necessary to decide the treatment strategy for obtaining a good outcome where possible [31,39].

A comprehensive understanding of the risk factors for early recurrence after liver resection in HCC patients can help surgeons to evaluate a surgical decision-making for these patients. The recurrent risk variables could be classified and formatted from the laboratory, radiological, operative, and pathological findings. It's well known that inflammation is involved in the process of liver carcinogenesis, tumor growth and metastasis through various molecular path ways [40]. Therefore, several inflammation-based scores or indices including NLR, platelet/lymphocyte ratio, or aspartate aminotransferase/platelet ratio index are proposed to serve as prognostic predictors of HCC patients after treatments [41,42]. The weight of each risk factors were variable based on the time to recurrence. In case of an ultra-early recurrence (within 6 months) after hepatectomy, it was often associated with vascular invasion and R1 resection due to occult micro-metastasis [14]. However, in the early recurrence within 2 years after hepatectomy is often associated with micro-metastasis, poor differentiation, or multi-nodularity [14]. On the other hand, late recurrence, may suggest multiple occurrence or de novo tumor formation, especially in HCC with underlying liver cirrhosis, or less aggressive tumor behavior [14,27]. *Wang, et al.* reported 39 cases (11.7%) of ultra-early recurrence within 6 months and revealed tumor morphology, age, AFP, GGT, ALP, PT, and satellite nodules identified as independent prognostic factors for ultra-early recurrence among 332 patients with early solitary HCC after hepatectomy [5]. In our current series, the ultra-early recurrence within 6 months was associated with AAR, AFP, Tumor number and monocyte. A multivariate analysis showed that a tumor diameter >5 cm, the absence of a tumor capsule and the presence of microvascular invasion were correlated with early recurrence (< 2 years), whereas liver cirrhosis and AFP >400 μg/l were independent risk factors for late recurrence (>2 years) [43]. Comparison of the clinical baseline characteristics of recurrence within 3 years revealed significant intergroup differences in BCLC staging, MVI, serum AFP, and GOT levels in the HCC patients after hepatectomy [28]. Thus, multiple recurrent factors could be found from the previous studies due to the different enrolled patients, treatment methods, and study models. HCC recurrence is related to the complexity of factors at the primary treatment, such as tumor burden, AFP levels, and pathological features [30,44,45]. Although hepatectomy is the most effective treatment for HCC, early recurrence within 1 year is usually considered a critical determinant for a poor prognosis [9,11,14].

The differentiation between early and late recurrence is significant not only in terms of the therapeutic decision but also in terms of prognosis and OS. The 5-year OS is significantly lower in patients with recurrence and varies from 36.8 to 41.0%, 4.5 to 58.5%, and 25.7 to 94.0% at <1 year, <2 years, and > 2 years according to the previous studies listed in the Table 6. In our current study, the 5-year OS were 18.0%, 20.5% and 63.1% and 83.2% (P<0.001) for the recurrent time < 6 months, 1 year, 2 years and ≧2 years respectively. *Wang X, et al.* reported that the OS of patients with ultra-early recurrence (<6 months) (mean 30.96 months, 95% CI 22.18–39.73 months) was significantly lower than that of patients without ultra-early recurrence (mean 80.11 months, 95% CI 76.18–84.04 months, P<0.001) among HCC patients treated with hepatectomy [5]. In our current cohort study, the 5-year OS rates were 53.0% and 73.5% for recurrent and non-recurrent group respectively. (P<0.001). Therefore, it was suggested that earlier recurrence will result in a poor survival rate.

The differentiation of early and late recurrence may have implications on strategies in adjuvant therapy to prevent recurrence. To date, no adjuvant therapies have been conclusively proven to prevent recurrence through the mechanism of inhibition of tumor cell proliferation, invasion, or angiogenesis [52]. Moreover, the treatment of a recurrent HCC is generally more complex than the treatment of the primary lesion due to the changes in tumor burden and remained functional liver conditions. Patients at high risk of early recurrence are candidates for close surveillance after resection and potentially adjuvant therapy, which has not yet been standardized due to variability in results usually [53,54]. With regard to anatomic or non-anatomic resection, most surgeons attempt to perform anatomic liver resection in order to get a better results, but the merit or un-merit of surgical results were not solid about the time to recurrence or OS from the previous studies [55-57]. Moreover, pre-operative transcatheter arterial chemo-embolization (TACE) has been used as a neo-adjuvant therapy to improve long-term survival by preventing cancer cell dissemination and intrahepatic recurrence [58,59]. However, several reports, including the randomized controlled trials, failed to demonstrate an improvement in survival rate with the administration of TACE preoperative [60,61]. *Amisaki, et al.* reported that preoperative TACE seemed to worsen the long-term outcomes of the patients who underwent surgical resection for the treatment of resectable HCC. Therefore, preoperative TACE should not be considered as a standard therapy in patients with resectable HCC [62]. Theoretically, TACE would indeed help for treating small satellite nodules and destroying microscopic tumor foci, thus facilitating the achievement of an adequate resection for a better prognosis. Furthermore, *Gao, et al.* also believe it is prudent to recommend preoperative TACE only in certain types of HCC, namely, multinodular and infiltrative types of HCC [61].

Conclusion

In conclusion, the clinical management of HCC is still a challenging and requires evaluation of multiple risk factors with a significant impact on prognosis. The identification of specific clinical, laboratory and histopathological characteristics that may predict the risk of recurrence early could guide the decision for pre-/post-operative treatment after surgery to prolong the time to recurrence and OS. The cut-off of time to recurrence remains arbitrary and has not universally accepted. Moreover, the time of recurrence should be always be considered before selecting the appropriate therapy, as a more aggressive treatment is needed in cases of early recurrent

HCC. Generally, a multidisciplinary therapeutic approach according to tumor and patient characteristics is mandatory to achieve better OS rates. Furthermore, the concepts of risk factors for the time of recurrence in the HCC therapeutic landscape is obligatory, and could optimize patient surgical outcomes.

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Confliction of Interest

Not applicable.

Statement

This study was approved by the Institutional Review Board and Ethical Committee of E-Da Hospital (Code no. EDAHS 110012).

Contribution of Authors

Conceptualization: Ker CG, Chen JL, Hung CM.

Methodology and analysis: Ker CG.

Resources: Chen JL, Chen YS, Hsieh KC, Chen JH, Lee HM, Chen CY, Hung CM

Drafting and editing: Ker CG, Chen JL

Supervision: Ker CG, Chen YS.

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