Predictors of early recurrence of hepatocellular carcinoma after hepatic resection in a single Egyptian institute: A retrospective study

Original Article

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ABSTRACT

Introduction: Liver resection for hepatocellular carcinoma (HCC) can have a recurrence rate of up to 50%. This study aims to define potential factors that can have a role in recurrence of the tumor by defining very early recurrence (VER) in the first 6 months after surgery.

Patients and Methods: This retrospective study was conducted on patients who underwent liver resection for HCC in the surgery department at Tanta University over 6 years between 2016 and 2022.

Collection of the preoperative, operative and postoperative data of 131 patients that met our criteria including laboratory, radiology and histopathology was done and postoperative complications, recurrence, and overall survival were reported. Analysis of the data available was done to figure out any correlation between these variants and both recurrence (including VER) and survival.

Results: There was a significant relation between preoperative alpha-fetoprotein (AFP) and recurrence. Elevation of liver enzymes [alanine transaminase (AST), aspartate aminotransferase (ALT)] was an incident that was recorded after surgery and there was a significant relation between the maximal elevation of AST, ALT, and recurrence. For VER maximum tumor diameter and preoperative AFP were significantly related to VER and also postoperative maximum AST had been shown to have a significant relation with recurrence. Of 131 patients, 92 patients are still alive at the last date of follow-up and 39 patients are deceased. Age of the patients (mean 68.1±11 SD) and maximum tumor diameter were found be significant factor in relation with mortality.

Conclusion: Within multiple preoperative and operative risk factors beside the criteria of the tumor, our study defined maximum tumor diameter, moderate to poor differentiation of the tumor, Milan criteria, preopertive AFP, postoperative AST, ALT as significant risk factors for recurrence.

Key Words: Hepatocellular carcinoma, hepatic resection, recurrence, survival.

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INTRODUCTION

Liver resection besides liver transplant is well known to be the only curative treatment for hepatocellular carcinoma (HCC). Patients who are presented with potentially resectable tumors can have recurrence rates up to 50% even after short intervals because of the occult vascular micrometastasis[1].

The available literature did not define a standard cut-off period to define the early recurrence but most of them reported it ranging from 6 months to 2 years after liver resection[2]. The American Joint Committee on Cancer's (AJCC)[3] and the Barcelona Clinic Liver Cancer's (BCLC) staging systems[4] are commonly applied in HCC patients. The BCLC which is well known organized routinely updated staging system recommended liver resection for stages 0 and A (depending on tumor size and liver and patient's condition), but not for stages B and C. In all these staging systems the tumor size invariably affects the prognosis but even with huge sized tumors proper selection, adequate techniques, and standardized care can provide favorable patients survival[5].

As these staging systems consider transplant as a cornerstone modality of treatment and because of the scarcity of donor organs in many countries (including Egypt), surgical resection remains the mainstay of curative treatment options is why every potential risk factor for recurrence (especially early recurrence) after resection should be incorporated into surgical decision-making processes among clinicians and patients[2]. In addition,

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postoperative recurrence surveillance by imaging for high-risk patients for early recurrence should be at shortened intervals[6].

Aim

The aim of this study is to set and figure out the possible predictors of early recurrence of HCC based on the assessment of the preoperative, clinical, imaging and laboratory variants and also operative factors and histopathological criteria of the tumor.

Primary outcome: prediction of prognosis and recurrence-free survival and overall survival.

Secondary outcome: better selection of potential candidates of resection.

PATIENTS AND METHODS:

This retrospective study was conducted on about 140 patients who underwent liver resection for HCC in the Surgery department at Tanta University over 6 years between 2016 and 2022 after obtaining ethical committee approval.

There was adequate supervision to maintain the privacy of the patients and confidentiality.

There was no conflict of interest nor conflict with religion, law or society standards.

Inclusion criteria

All patients had liver resection for HCC.

Exclusion criteria

Patients had previous liver resection and recurrent disease.

Patients had malignant portal vein thrombosis, distant metastasis, or local nodal metastasis.

Data collection and statistical analysis

Data of recurrence risk factors of were regarded as follows:

(a) Patient related factors including sex, age, American Society of Anesthesiologists (ASA) score.

(b) Liver clinicolaboratory related factors including the presence of cirrhosis, Child–Pugh classification together with preoperative alpha-fetoprotein (AFP) level, liver function tests, and liver enzyme results.

(c) Tumor histopathological factors including tumor number, multifocality, maximum tumor size or the size of viable tumor if already received locoregional therapies, bilobar disease, tumor encapsulation, satellite lesions, macroscopic or microscopic vascular invasion as well as tumor degree of differentiation (tumor grading).

(d) Previous treatment related factors as previous receiving of locoregional therapies like transarterial chemoembolization (TACE), radiofrequency ablation, or ethanol injection along with Surgery-related factors including intraoperative blood loss, intraoperative blood transfusion, type of resection (anatomical or nonanatomical), and extent of hepatectomy (major or minor), where resection of three or more Couinaud segments was regarded as major hepatectomy, while resection of fewer than three Couinaud segments was regarded as minor hepatectomy.

All data at admission and After discharge are collected, and follow-up data such as serum AFP level, ultrasonography or contrast-enhanced computed tomography (CT) scan or magnetic resonance imaging (MRI) of the chest and abdomen after 3 and then once every 3 months for the next year after surgery, then surveillance every 6-monthly interval for the next 4 years for evaluation of possible recurrence. Tumor recurrence was defined as the appearance of intrahepatic nodules or extrahepatic metastasis. Recurrence free interval and period of survival until last follow-up or death are determined.

Statistical analysis

Data were collected and fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using numbers and percent. The Shapiro–Wilk test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median, and interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The used tests were 1 - χ^2 test For categorical variables, to compare between different groups. 2 - Fisher's Exact or Monte Carlo correction Correction for χ^2 when more than 20% of the cells have expected count less than 5. 3 - Student t test for normally distributed quantitative variables, to compare between two studied groups, 4 - Mann–Whitney test for abnormally distributed quantitative variables, to compare between two studied groups.

RESULTS:

This study is a retrospective analysis of the pre, operative, and postoperative data of 140 patients that were operated on for HCC resection in Tanta University hospitals between 2016 and 2022, we excluded nine

patients either due to lost follow-up or noncurative surgery, so we had 131 patients for the study 46 (35.1%) of them had recurrence of the tumor in the follow-up period. The age of the patients was between 22 and 91 with mean age 64.9±12 SD, most of the patients were ASA 3 (98 patients), 15 patients were alcohol consumers and 89 patients had hepatitis C virus (HCV) infection before. 19 patients received targeted therapy (TACE or radiofrequency ablation or ethanol injection before). 66 (50.4%) patients underwent nonanatomical resection for single lesion, while 20 patients underwent major resection (right or left heptectomy), four patients had vascular invasion that did not affect their resectability. The mean operative time was 267.0±100.3 and intraoperative transfusion was needed in 31 patients, all these variants had no significant relation with the recurrence of the tumor and these data are illustrated in (Table 1).

123 patients were classified as Child A (93.9) and eight patients were Child B (6.1%), the pre-operative laboratory investigations was investigated including Albumin level (mean 3.98±0.49), Creatinine level (mean 0.95±0.36 SD), INR (mean 1.09±0.30 SD), platelet count (202±97.5 SD), and in both recurrent and non recurrent groups there was no significant relation with recurrence. AFP also was investigated before surgery and the mean was 1650.2±9350 SD, in the recurrence group the mean was 3005.7±13669.2 SD and in the nonrecurrence group the mean was 916.6±5800.7, so there was significant relation between preoperative AFP and recurrence (*P value* was 0.05). Analysis of the histopathological examination of the tissues resected revealed that 73 patients had moderately differentiated tumors and 41 had well differentiated tumor and 11 patients had poor differentiated tumor, the rest had mixed differentiation. The resection margin was free in 125 patients and the size of the tumor was within Milan criteria in 76 (58%) patients 21 of them had recurrence and this had a significant relation (*P value* 0.035) these data are illustrated in (Table 2).

The postoperative complications were also recorded and their relations with possible recurrence was investigated, the complications included bile leakage in six (4.6%) patients, postoperative ascites in 12 (9.2%) patients, bleeding in two (1.5%) patients, and surgical site infection in 17 (13%) patients and these complictions had no significant relation with recurrence. Elevation of liver enzymes (AST, ALT) was an incident that was recorded after surgery and there was significant relation between the maximal elevation of AST, ALT and occurrence of recurrence (*P value* were 0.003, 0.03, respectively). Follow-up of patients revealed that 92 (70.2%) patients are still alive, 28 patients did not survive due to recurrence of the tumor and metastasis and 11 patients died due to other causes including cardiac problems, bleeding varices and stroke, these data are illustrated in (Table 2).

Table 1: Comparison between the two studied groups according to different parameters

	Total sample (*N*=131) [*n* (%)]	No-Recurrence (*N*=85) [*n* (%)]	Recurrence (*n*=46)	Test of significance	*P*
Age at operation					
Mean±SD.	64.9±12.5	64.9±12.6	64.9±12.5	t=0.025	0.980
Median (Min–max)	65 (22–91)	65 (22–91)	65.5 (27–87)		
ASA					
1	1 (0.8)	1 (1.2)	0	χ^2=1.780	^{MC}=0.678
2	10 (7.6)	7 (8.2)	3 (6.5)		
3	98 (74.8)	65 (76.5)	33 (71.7)		
4	22 (16.8)	12 (14.1)	10 (21.7)		
HCV antibody	89 (67.9)	65 (49.6)	24 (18.4)	χ^2=1.471	0.225
Alcohol use	15 (11.5)	9 (10.6)	6 (13.0)	χ^2=0.177	0.674
Previous Tx for Target lesion	19 (14.5)	15 (17.6)	4 (8.7)	χ^2=1.929	0.165
Operative procedure #1					
Non-Anatomical one lesion	66 (50.4)	44 (51.8)	22 (47.8)		
Nonanatomical Multi lesion	5 (3.8)	4 (4.7)	1 (2.2)		
Segentectomy	20 (15.3)	12 (14.1)	8 (17.4)	χ^2=2.082	^{MC}P=0.868
Bisegmentectomy	20 (15.3)	14 (16.5)	6 (13.0)		
Left hepatectomy	5 (3.8)	3 (3.5)	2 (4.3)		
Right hepatectomy	15 (11.5)	8 (9.4)	7 (15.2)		
Major vascular invasion	4 (3.1)	3 (3.5)	1 (2.2)	χ^2=0.185	^{FE}P=1.000

Operative time (min)					
Mean±SD	267.0±100.3	259.8±104.7	280.4±91.3	U=1732.50	0.282
Median (Min–max)	270 (10–547)	255 (10–540)	270 (120–547)		
Intra-operative Transfusion	31 (23.7)	19 (22.4)	12 (26.1)	χ^2=0.230	0.631

χ^2, Chi square test; FE, fisher exact; MC, Monte Carlo; SD, standard deviation; t, Student t test; U, Mann–Whitney test.
P: P value for comparing between the two studied groups.

Table 2: Comparison between the two studied groups according to different parameters

	Total Sample (*N*=131) [*n* (%)]	No-Recurrence (*N*=85) [n (%)]	Recurrence (*N*=46) [*n* (%)]	Test of significance	*P*
Tumor diff					
Well	41 (31.3)	28 (32.9)	13 (28.3)	χ^2=5.471	^{MC}P=0.210
Moderate	73 (55.7)	49 (57.6)	24 (52.2)	U=1501.50*	0.028*
Poorly	11 (8.4	5 (5.9)	6 (13.0)		
Mod main with poor	4 (3.1)	1 (1.2)	3 (6.5)	χ^2=3.272	0.070
Well main with moderate	2 (1.5)	2 (2.4)	0	χ^2=9.104*	0.003*
Resection margin					
R0	125 (95.4)	78 (91.8)	45 (97.8)	χ^2=0.939	^{FE}P=0.665
R1	6 (4.6)	5 (5.9)	1 (2.2)		
Milan Criteria	76 (58)	55 (72.3)	21 (27.7)	χ^2=4.449*	0.035*
Albumin level					
Mean±SD.	3.98±0.49	4.03±0.51	3.89±0.46	t=1.617	0.108
Median (min–max)	4 (2.6–4.9)	4.1 (2.6–4.9)	3.9 (2.7–4.7)		
Creatinine					
Mean±SD.	0.95±0.36	0.95±0.39	0.94±0.31	U=1941.00	0.946
Median (min–max)	0.86 (0.49–3.18)	0.9 (0.5–3.2)	0.9 (0.6–1.9)		
INR					
Mean±SD	1.09±0.30	1.11±0.36	1.05±0.12	U=1753.50	0.286
Median (min–max)	1 (0.9–3.5)	1.0 (0.9–3.5)	1.0 (0.9–1.4)		
PLT ($\times 10^3$)					
Mean±SD	202±97.5	202.9±106	200.3±80.6	U=1844.00	0.592
Median (min–max)	187 (31–541)	184 (31–541)	187.5 (53–410)		
AFP					
Mean±SD	1650.2±9350	916.6±5800.7	3005.7±13669.2	U=1559.50	0.05
Median (min–max)	10.7 (0.8–89504)	10.7 (1–53000)	13.7 (0.8–89504)		
CTP (Child–Pugh classification)					
A	123 (93.9)	81 (95.3)	42 (91.3)	χ^2=0.829	^{FE}P=0.450
B	8 (6.1)	4 (4.7)	4 (8.7)		
C	0	0	0		
Bile Leakage	6 (4.6)	5 (5.9)	1 (2.2)	χ^2=0.939	^{FE}P=0.665
Postoperative ascites	12 (9.2)	8 (9.4)	4 (8.7)	χ^2=0.018	^{FE}P=1.000
Postoperative bleeding	2 (1.5)	2 (2.4)	0	χ^2=1.099	^{FE}P=0.541
SSI	17 (13)	12 (14.1)	5 (10.9)	χ^2=0.279	0.597
AST postoperative max					
Mean±SD	336.1±294.4	287.6±242.5	425.8±357.7	U=1348.50*	0.003*
Median (min–max)	236 (22–2126)	22 (22–1306)	332.5 (74–2126)		

ALT postoperative max					
Mean±SD	280.2±279.9	241.5±201.4	351.7±377.5	U=1506.00*	0.030*
Median (min–max)	211 (25–2487)	197 (25–1056)	258.5 (63–2487)		
Status					
Alive	92 (70.2)	65 (76.5)	27 (58.7)	χ^2=15.070*	0.001*
Death	28 (21.4)	10 (11.8)	18 (39.1)		
Death other cause	11 (8.4)	10 (11.8)	1 (2.2)		

χ^2, Chi square test; FE, Fisher Exact; SD, standard deviation; t, Student t-test; U, Mann–Whitney test.
P: P value for comparing between the two studied groups.
*: Statistically significant at *P* less than or equal to 0.05.

From 131 patients had liver resection for HCC, 20 (15.2%) patients had recurrence of the tumor in the first 6 months after surgery, we classified them as a separate group as very early recurrence (VER), we investigated the factors that might had a role in this incidence including the preoperative and operative procedures and criteria of the tumor in the histopathological examination and postoperative investigations, we found that extent of resection, major vascular invasion, intraoperative blood transfusion, tumor differentiation, presence of capsulated tumor and capsular or microvascular invasion and resection free margin , all these variants had no significant relation with VER, while maximum tumor diameter as large as (mean 8.73±5.55 SD) had a strong significant relation with VER (*P value* was 0.006). Another significant factor was pre-operative AFP, mean AFP (4677.5±19970.8 SD) was significantly related with VER (*P value* 0.019) and also postoperative maximum AST (reaching 477.8±477.7) had been shown to had a significant relation with recurrence (*P value* was 0.02). These data are illustrated in (Table 3).

Table 3: Comparison between no-recurrence and recurrence first 6 months according to different parameters

	No-Recurrence (*N*=85) [*n* (%)]	Recurrence first 6 months (VER) (*N*=20) [*n* (%)]	Test of significance	*P*
Operative procedure #1				
Nonanatomical one lesion	44 (51.8)	9 (45.0)		
Multi lesion	4 (4.7)	1 (5.0)		
Segentectomy	12 (14.1)	3 (15.0)	χ^2=3.930	MC*P*=0.521
Bisegmentectomy	14 (16.5)	2 (10.0)		
Left hepatectomy	3 (3.5)	0		
Right hepatectomy	8 (9.4)	5 (25.0)		
Major vascular invasion	3 (3.5)	1 (5.0)	χ^2=0.096	FE*P*=0.576
Intra-operative Transfusion	19 (22.4)	4 (20.0)	χ^2=0.052	FE*P*=1.000
Tumor diff				
Well	28 (32.9)	8 (40.0)		
Moderate	49 (57.6)	8 (40.0)		
Poorly	5 (5.9)	2 (10.0)	χ^2=5.849	MC*P*=0.168
Well main with poor	0	0		
Mod main with poor	1 (1.2)	2 (10.0)		
Well main with moderate	2 (2.4)	0		
Maximum tumor diameter				
Mean±SD	5.31±3.59	8.73±5.55	U=516.00*	0.006*
Median (min–max)	4.5 (0.7–19)	7.5 (1.2–20.5)		
Capsule formation	35 (41.2)	4 (20.0)	χ^2=3.110	0.078
Capsule infiltration	10 (11.8)	6 (30.0)	χ^2=4.168	FE*P*=0.076
Vascular invasion	16 (18.8)	8 (40.0)	χ^2=4.118	FE*P*=0.072
Resection margin				
R0	78 (91.8)	18 (90.0)	χ^2=0.064	FE*P*=0.680

R1	5 (5.9)	2 (10.0)		
AFP				
Mean±SD	916.6±5800.7	4677.5±19970.8	U=562.50*	0.019*
Median (min–max)	10.7 (1–53000)	21.7 (2.2–89504)		
CTP				
A	81 (95.3)	18 (90.0)	χ^2=0.842	FE*P*=0.321
B	4 (4.7)	2 (10.0)		
C	0	0		
AST postoperative max				
Mean±SD	287.6±242.5	477.8±477.7	U=564.0*	0.020*
Median (min–max)	22 (22–1306)	332.5 (74–2126)		
ALT postoperative max				
Mean±SD	241.5±201.4	397.7±524.9	U=638.00	0.084
Median (min–max)	197 (25–1056)	257.5 (66–2487)		

χ^2, Chi square test; FE, Fisher Exact; SD, standard deviation; t, Student t-test; U, Mann–Whitney test.
P: P value for comparing between the two studied groups.
*: Statistically significant at *P* less than or equal to 0.05.

From 131 patients, 92 patients are still alive at the last date of follow-up and 39 patients are deceased, different variants were investigated for relation with mortality and the following variants had been shown to be significant in the mortality group, age (mean 68.1±11 SD) (*P value 0.05*) and maximum tumor diameter (mean 6.83±3.99) was found also to be significant factor (*P value 0.034*). These data are illustrated in (Table 4).

Table 4: Comparison between the two studied groups (mortality) according to different parameters

	Total Sample (*N*=131) [*n* (%)]	Alive (*N*=92) [*n* (%)]	Died (*N*=39) [*n* (%)]	Test of Significance	*P*
Age at operation					
Mean±SD.	64.9±12.5	63.5±12.9	68.1±11	t=1.956	0.05
Median (min–max)	65 (22–91)	64 (22–91)	69 (44–88)		
ASA					
1	1 (0.8)	1 (1.1)	0	χ^2=5.316	MC*P*=0.117
2	10 (7.6)	8 (8.7)	2 (5.1)		
3	98 (74.8)	72 (78.3)	26 (66.7)		
4	22 (16.8)	11 (12.0)	11 (28.2)		
Major vascular invasion	4 (3.1)	2 (2.2)	2 (5.1)	χ^2= 0.808	FE*P*=0.582
Curative	107 (81.7)	77 (83.7)	30 (76.9)	χ^2= 0.840	0.360
Maximum Tumor Diameter					
Mean±SD	6.01±4.19	5.66±4.25	6.83±3.99	U=1373.00*	0.034*
Median (min–max)	5 (0.7–20.5)	4.25 (0.7–20.5)	6 (1.4–16.5)		
Resection margin					
R0	122 (93.1)	87 (94.6)	35 (89.7)	χ^2=0.995	FE*P*=0.450
R1	9 (6.9)	5 (5.4)	4 (10.3)		
Mean±SD.	1650.2±9350	2145.7±11068.9	481.4±1916.3	U=1777.00	0.932
Median (min–max)	10.7 (0.8–89504)	10.7 (0.8–89504)	10.7 (2.2–11678.9)		
CTP					
A	123 (93.9)	87 (94.6)	36 (92.3)	χ^2=0.243	FE*P*=0.695
B	8 (6.1)	5 (5.4)	3 (7.7)		
Bile Leakage	6 (4.6)	2 (2.2)	4 (10.3)	χ^2= 4.094	FE*P*=0.064

Postoperative Ascites	12 (9.2)	7 (7.6)	5 (12.8)	χ^2= 0.894	^{FE}P=0.340
Postoperative Bleeding	2 (1.5)	2 (2.2)	0	χ^2=0.861	^{FE}P=1.000
SSI	17 (13)	13 (14.1)	4 (10.3)	χ^2= 0.364	0.546
AST Postoperative max					
Mean±SD	336.1±294.4	335.8±319.8	336.9±227.4	U=1625.00	0.395
Median (min–max)	236 (22–2126)	232.5 (22–2126)	257 (74–1107)		
ALT Postoperative Max					
Mean±SD	280.2±279.9	282.1±301.8	275.7±223.3	U=1794.00	1.000
Median (min–max)	211 (25–2487)	211 (25–2487)	213 (48–1056)		

χ^2, Chi square test; FE, Fisher Exact; MC, Monte Carlo; SD, Standard deviation; t, Student t-test; U, Mann–Whitney test.
P: P value for comparing between the two studied groups.

The survival of the patients was demonstrated in (Table 5). Among 92 (70.22%) patients survived in the follow-up period, 65 (70.7%) patients were in the non recurrence group, 27 (29.3%) were in the recurrence group and 14 of them showed recurrence in the first 6 months after surgery. There was significant relation between recurrence and mortality (unexpectedly after first 6 months not in the first 6 months after surgery) (*P value was 0.012*).

Table 5: Relation between recurrence and mortality in total sample (n=131)

	Overall survival (*N*=92) [*n* (%)]	Mortality (*N*=39) [*n* (%)]	χ^2	*P*
Recurrence				
No-Recurrence	65 (70.7)	20 (51.3)	4.510*	0.034*
Recurrence first 6 month	14 (15.2)	6 (15.4	0.001	0.981
After 6 month	13 (14.1)	13 (33.3)	6.349*	0.012*

χ^2: Chi square test.
P: P value for Relation between mortality and Recurrence.
*: Statistically significant at *P* less than or equal to 0.05.

DISCUSSION

Hepatic resection for patients with HCC is the only chance for potential cure in patients who are not candidates for liver transplantation. Close follow-up after liver resection is a must because of the risk of recurrence of the tumor that is invariably affect the survival[7]. identifying the patients who are at high risk of early recurrence is very important for prediction of prognosis and for better selection before surgery and surveillance of the postoperative factors that might be risky for recurrence is important also for assessment of the need of adjuvant therapy[2].

In the available literature there is always variation in the definition of the cut-off between early and late recurrence of HCC after liver resection. A large study on 1501 patients by Xing and colleagues showed the optimal cut-off time to differentiate between early and late recurrence to be 8 months[2], while another large-scale study defined the recurrence in the first 6 months after surgery as VER regarding this group as a separate entity[8]. In our study we identified the preoperative, operative and postoperative factors that can be identified as independent risk factors for recurrence in 131 patients underwent hepatic resection for HCC in Tanta university hospitals between 2016 and 2022, we identified recurrence in the first 6 months after surgery as VER that is needed to be investigated separately, so the identification of this subgroup of patients would allow clinical trials to be conducted on these selected patients for adjuvant or neoadjuvant therapies. Yamamoto *et al*. Study on 252 patients established the optimal cutoff value of 17 months based on postoperative survival (OS) to stratify patients into early and late recurrence but the bias was inevitable since OS is inevitably better in the late recurrence cohort as these patients already have a better recurrence free survival[9].

Although there is no doubt that surgeon experience and qualified high volume center should have a role in the outcome of surgery[10], but our study focused mainly on the factors that might played a role on the recurrence as primary outcome , including pre-operative factors as age, ASA score, prior HCV infection , alcohol use, preoperative laboratory investigations including AFP, Child–Pugh classification and previous target regional therapy, operative factors including the extent of resection, operative time, blood transfusion, and major vascular invasion, pathological features as tumor differentiation, clear resection margin, microvascular invasion , maximum tumor diameter and inclusion into Milan criteria and presence of capsule and its infiltration and postoperative factors including complications and elevation of liver enzymes. Other

studies targeting predicting recurrence in HCC patients always included most of these variants into different models of statistical analysis and score systems also some recent studies applied a deep learning model of the pathological criteria and correlated it with the clinical data[11,12], and other studies applied a pre and post-operative web based nomograms including multiple clinical and pathological features and found to be helpful for prediction of early recurrence according to their multi-institutional study[2].

In our study, 20 (15.3%) patients out of 131 had major resection , the extent of resection had no significant relation with recurrence or OS, this was not the case in Shimada and colleagues study on 481 HCC patients, they found that a wider surgical margin and anatomical resection were statistically significant factors on the univariate analysis[13], they claimed that extended resection or segmentectomy might be recommended for younger patients even with solitary hepatic nodule because such patients have a chance of long-term survival and minimizing microscopic residual tumors or occult metastases, we think that this variation between the two studies may be because of the different sample sizes, while in a multi institutional study by Xing H *et al*., major resection was strongly related with recurrence as from 432 patient with major resection, 331 of them had recurrence (*P value* < *0.001*).

For the pathological criteria in our study, maximum tumor diameter (mean 8.73±5.55) was a strong independent significant factor for VER (*P value* was *0.006*), tumor differentiation (moderate to poor) and tumors outside Milan criteria were significant factors for recurrence, this was consistent with many studies in addition to other factors as satellite nodules, microvascular invasion (14, 15, 16). Surprisingly unclear resection margin was not consistent with recurrence significantly in our study and also in other studies[2,13].

In our study, preoperative AFP was a significant risk factor for recurrence and also for VER (*P value 0.05, 0.019*, respectively) and also postoperative maximum AST (*P value 0.003, 0.02*). preoperative laboratory investigations was important in multiple studies especially to evaluate pre-operative liver dysfunction , in Shimada and colleagues study ALBI grade (Albumin-Bilirubin) rather than Child-Pugh grade was a significant factor to predict recurrence in their preoperative model[13], preoperative AFP was important factor for prediction of recurrence in many studies[14–18], while to our knowledge our study is the only one to set elevation of postoperative AST, ALT as a risk factor that might have a role for prediction recurrence and VER.

Numerous studies to date have reported cumulative 5-year survival rates of ~40–50%, based largely on relatively short-term follow-up[19,20] and unfortunately there are no many studies that had longer follow-up periods like the Nagasu *et al*. study[21]. In our study the survival was (70.22%), we claim this difference was because of a shorter follow-up period in some patients and a smaller sample size that may contain less aggressive criteria of the tumor.

Our study was conducted in a single center in Egypt which is an important spot for the study of the disease due to the previous prevelance of HCV, a similar study was performed in another Egyptian center (Mansoura university) and focused in HCV cirrhotic patients exclusively , in 208 patients had liver resection from 2002 to 2011, recurrence occurred in 88 (42.3%) patients, in 55 (62.5%) patients recurrence was in the first year. Based on the univariate analysis; significant variables predicting tumor recurrence were AFP, blood transfusion, microvascular invasion, lack of capsule, multi-focality, cut margin, tumour grade, and staging, and in multivariate analysis, the main predicting factors were blood transfusion, cut margin, tumor capsule, and microvascular invasion[22].

According to the available studies, one of the most important Limitations of this study is that it is a single institution with short term follow-up (not exceeding 5 years), and the number of cases is not helpful to develop a scoring system or to be correlated with the available models and nomograms, but it can be useful for evaluation of the features of the disease in a specific population in Egyptian area that have specific criteria as the prevalence of HCV related cirrhosis. Also, we need to extend the follow-up period for better prediction of prognosis.

CONCLUSION

There are multiple preoperative and operative risk factors besides the criteria of the tumor that can be used for the prediction of the prognosis of hepatic resection for HCC regarding both recurrence and survival, these criteria can be indulged in multiple score systems and models to be validated and correlated with the available studies, our study defined maximum tumor diameter, moderate to poor differentiation of the tumor, Milan criteria, preopertive AFP, postoperative AST, ALT as significant risk factors for recurrence. Although currently there is still no universally accepted adjuvant therapy to prevent HCC recurrence, but the identification of a subgroup of the patients who are at risk of early or very early recurrence would allow clinical trials to be conducted on these selected patients for adjuvant or neoadjuvant therapies.

CONFLICT OF INTEREST

There are no conflicts of interest.

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