IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 18, Issue 2 Ser. 11 (February. 2019), PP 43-53
www.iosrjournals.org

Prognostic Factors and Outcomes after Liver Resection for Hepatocellular Carcinoma in Non-Cirrhotic, Non-Fibrotic Liver

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Abstract
Background: *Hepatocellular carcinoma (HCC) is a major health burden and its incidence is increasing globally.Numerous publications have addressed the prognostic factors and long-term survival after liver resection for HCC, but most of these studies have included patients with and without cirrhosis. The aim of the present study is to identify predictive factors and survival outcome after liver resection for non-cirrhotic HCC.*
Methods: *This is a retrospective analysis of prospectively collected data between January 2011 and December 2015.Of the 76 patients who had liver resections for HCC, 30 patients had no underlying parenchymal liver disease (no cirrhosis or fibrosis) and these 30 patients were included in the study.*
Results: *Out of 30 patients, 25 patients (83%) underwent major hepatectomy whereas only 5 patients (17%) underwent minor hepatectomy. The overall 1-, 2-, 3- year survival rates were 86.7%, 66.7% and 63.3% respectively.In the univariate analysis, high-grade tumor, prothrombin time and serum bilirubin level were significant predictors of poor long-term survival. In the multivariate analysis, only high-grade tumor was identified as independent prognostic factor for overall survival. The overall 1-, 2-, 3- year disease-free survivals were 66.6%, 53.3% and 50% respectively. In the univariate analysis, need for blood transfusion, post-operative liver failure, wound infection, sepsis, high-grade tumor, vascular invasion, prothrombin time, serum bilirubin, post-operative length of stay significantly affected the disease-free survival. The multivariate analysis identified high-grade tumors, vascular invasion, and sepsis as independent prognostic factors for disease free survival after liver resection for non-cirrhotic HCC patients.*
Conclusion: *Vascular invasion, tumor differentiation and sepsis are identified as poor prognostic factors after liver resection in patients with non-cirrhotic HCC. The presence of these poor prognostic factors in non-cirrhotic HCC patients necessitates a stringent follow-up to detect and treat recurrence.*
Keywords: *Hepatocellular carcinoma, Non-cirrhotic liver, Prognostic factor, Overall survival.*

Date of Submission: 04-02-2019 Date of acceptance: 21-02-2019

I. Introduction

Hepatocellular carcinoma (HCC) is a major health burden and its incidence is increasing globally [1]. HCC ranks the 6th most common cancer worldwide with more than 1 million new cases diagnosed every year [1,2].Regardless of etiology, more than 80% of HCC occur in patients with cirrhosis worldwide [3].However, in India, more than 40% of HCC occurs in non-cirrhotic liver.

The presence or absence of underlying liver disease is important because the clinical presentation, treatment approaches and prognosis differs depending upon whether HCC develops in cirrhotic or non- cirrhotic liver [4].In patients with HCC in cirrhotic liver, tumors are more likely to be detected early as part of routine

screening and hence are treated by more minor intervention or by liver transplantation.In contrast, patients with HCC in non-cirrhotic liver present at later stage with large tumors and are usually treated by major liver resection due to high rate of recurrence in transplanted liver [5,6,7].Moreover, transplantation for HCC in non-cirrhotic liver has no additional benefit of improving the patient's long-term liver function. Therefore, in order to improve the surgical outcomes in these patients, it is of paramount importance to identify the prognostic factors for survival and the risk factors for intra- hepatic tumor recurrences after curative resection for HCC in non- cirrhotic liver [8].

Numerous publications have addressed the prognostic factors and long-term survival after liver resection for HCC, but most of these studies have included patients with and without cirrhosis [9-13].The prognostic factors for survival or the risk factors for tumor recurrence in patients undergoing liver resection for HCC in non-cirrhotic liver is not well documented [14].Data analyzing the outcomes of liver resection for HCC in patients with non-cirrhotic liver is also limited [4].

The aim of the present study is to identify predictive factors and survival outcome after liver resection for non-cirrhotic HCC. We also evaluated the peri-operative and short-term outcomes after liver resection for HCC in non-cirrhotic liver.

II. Methodology

This is a retrospective analysis of prospectively collected data between January 2011 and December 2015. All consecutive patients with histologically proven HCC in non-cirrhotic, non-fibrotic liver undergoing liver resection were included in the study. Patients undergoing liver resection with palliative intent were excluded from the study. Patients with histological proven HCC in cirrhotic or fibrotic background and patient who refuses to give informed consent were also excluded from the study. During this period, 76 patients with HCC underwent liver resection in the Institute of Surgical gastroenterology and liver transplantation at Government Stanley Medical College and Hospital, Chennai, Tamilnadu, India. Of the 76 patients, 30 patients had no underlying parenchymal liver disease (no cirrhosis or fibrosis) and were included in the study

Routine pre-operative evaluation include recording of detailed demographic profile, history of presenting symptoms, physical examination and routine laboratory investigations were recorded. Serum alpha-fetoprotein and upper gastro-intestinal endoscopy were done in all patients. Pre-operative investigations performed to assess the extent of disease included Chest X-ray, abdominal ultrasonography, contrast enhanced computerized tomography (CECT) and/or MRI abdomen in all patients and CECT thorax in selected patients. Liver function status was assessed by the Child-Pugh grading. Patient performance status was determined according to the Eastern Co-operative Oncology Group (ECOG). Prior to surgery, all patients were discussed in a multidisciplinary meeting in order to ensure an optimal management strategy. Staging laparoscopy was done immediately before surgery in all patients.

The operation was performed through a Maakuchi's incision or bilateral subcostal incision with an upward midline extension (Mercedez-Benz incision). Intra-operative ultrasound was done in all cases to detect any additional tumor and relationship of tumor to vasculo-biliary structures. Selective vascular inflow and outflow control was obtained followed by parenchymal transection under low central venous pressure (CVP) anaesthesia, using a combination of kellyclasia, harmonic, ultrasonic dissector and water jet. Intra-operative parameters like type of liver resection, duration of surgery, blood loss, number of blood transfusion and intra-operative complications were recorded.

All patients were monitored in the intensive care unit during the initial post-operative period. Liver function test with prothrombin time and INR were routinely done in 1^{st}, 3^{rd} and 5^{th} post-operative days to detect post- operative liver insufficiency. All post-operative complications were recorded. A standard histo-pathological assessment of tumoral and non-tumoral tissue was performed.

All patients were followed up in the outpatient department, every month during the first 3 months, then every 3 months for initial 2 years and every 6months thereafter. The diagnosis of recurrence was based on clinical, laboratory (elevated serum AFP level) and radiological (abdominal ultrasound/CT, chest X-ray) findings. The number and pattern of recurrence (intrahepatic, extra-hepatic or both) were also recorded. Patients with isolated and resectable intra-hepatic recurrence underwent re-resection. All others were treated with TACE, systemic therapy or best supportive care.

III. Statistical analysis

All clinico-pathological and follow-up data were prospectively collected and entered with regular update of any tumor recurrence for each patient after each follow-up. Categorical variables were expressed as percentages and compared using chi-square test or Fisher exact test. Continuous variables were expressed as mean ± SD and compared using the student-t test. Survival and recurrence were expressed as median ± SEM. Patient survival and recurrence were calculated using the Kaplan- Meier test and compared using the log-rank

test. Clinico-pathological variables found to bear prognostic significance in univariate analysis were entered into Cox multivariate proportional hazard model to determine which of these factors possessed independent predictive value. p-value< 0.05 was considered statistically significant and analysis was carried out using the Statistical Package for the Social Sciences (SPSS 18.0; SPSS, Inc., Chicago, IL, USA)

IV. Results

Demographics and Predisposing factors

The mean age (table 1) at presentation was 48.23 years (range: 13-77). The gender distribution shows that there were 19 males (63%) and 11 females (37%) with male: female ratio of 1.7: 1. The potential risk factors for the development of HCC were present in 18 patients (60%). Four patients (13%) presented with current or past hepatitis B viral infection and no patient were positive for anti- HCV antibody. Tobacco and alcohol consumption were found in 9 patients (30%). Diabetes mellitus was observed in 8 patients (26.7%) and overweight in 3 patients (10%). In contrast, 12 patients (40%) did not reveal any underlying risk factor for the development of HCC.

Presentation

Abdominal pain was the most common presentation in the non- cirrhotic HCC patients, which was noted in all 30 patients (100%), followed by anorexia and weight loss (93%), abdominal mass (23%), fever (13%) and jaundice (6%). Hepatomegaly was observed in 17 patients (57%) and none of the patients had ascites. Three patients had undergone pre-operative biopsy and none of the patient received any type of pre-operative treatment. Serum alpha-fetoprotein level (table-2) was normal in 20 patients (67%) and elevated above 1000ng/ml in only 2 patients (6%). The mean AFP level was 6.8 ng/ml ± 5922.9 (range: 0.3-32476).

Surgical outcome

Out of 30 patients (Table-3), 25 patients (83%) underwent major hepatectomy whereas only 5 patients (17%) underwent minor hepatectomy. The most common procedure performed was right hepatectomy(40%), followed by left hepatectomy (20%), extended right hepatectomy (17%), bi-segmentectomy (6.7%) and extended left hepatectomy, central hepatectomy, left lateral segmentectomy in 1 patient (3.3%) each. Non-anatomical resection was done in 2 patients (6.7%). Three patients (10%) underwent enbloc resection of adjacent organ (diaphragm) involvement to achieve R0 resection. The mean post-operative length of stay was 16.7 ± 7.0 days. (range: 9-35 days). In-hospital mortality was noted in 1 patient (3.4%) due to post-operative liver failure (Table-4).

Overall, the post-operative complications (Table-5) occurred in 15 patients. The most common post-operative complication was intra-abdominal collection and wound infection noted in 6 patients (20%) each, followed by sepsis (16.7%), Post-operative liver failure and chest infection in 4 patients (13.4%) each. Bile leak was noted in 3 patients (10%) and renal failure in 1 patient (3.4%).

The mean size of tumor on histo-pathological examination was 13.2 ± 5.22 cm (range: 5-25cm). The majority of patients (76.7%) had solitary tumor (Table-6). Tumor encapsulation was noted in 19 patients (63.3%) with capsular invasion of tumor observed in 5 patients (26.3%). Histological differentiation of tumor was grade I in 13 patients (43.3%), grade II in 8 patients (26.7%) and grade III in 9 patients (30%). Microvascular invasion was observed in 15 patients (50%) but none of the patient had macrovascular invasion. The resected margin was found negative for tumor cells in 22 patients (73.3%). The surrounding non-tumor liver showed steatotic changes in 4 patients (13.3%).

Recurrence

In the whole study population, tumor recurrence was identified in 14 patients (46.6%) within the follow-up period(Table- 7). Of these 14 patients, 5 patients (35.7%) had isolated intra-hepatic recurrence, 3 patients (21.4%) had isolated extra-hepatic recurrence and 6 patients (42.8) had both intra-hepatic and extra-hepatic recurrence. Of the 5 patients with isolated intra-hepatic recurrence, 2 patients underwent re-resection, 2 patients received systemic chemotherapy and 1 patient was managed with supportive care. Two patients with isolated extra-hepatic recurrence and 2 patients with both intra and extra-hepatic recurrence were treated with systemic chemotherapy. The remaining 1 patient with isolated extra-hepatic recurrence and 4 patients with multiple recurrences were managed symptomatically.

Overall survival

At the time of analysis, there had been 11 deaths (36.7%) with 19 survivors (63.3%). The overall 1-, 2-, 3- year survival rates for the entire study group are 86.7%, 66.7% and 63.3% respectively. At the end of 1, 2, 3 year, there were 26, 20, 19 alive patients respectively. In the univariate analysis, high grade tumor ($p = 0.007$), prothrombin time($p = 0.046$) and serum bilirubin level ($p = 0.034$) were significant predictors of poor long term

survival (Table-8). In the multivariate analysis (Chart-1), only high-grade tumor (p = 0.039) was identified as independent prognostic factor for overall survival after liver resection for HCC in non-cirrhotic patients (Table-9).

Disease-free survival

Excluding the post-operative death within 30 days, the overall 1-, 2-, 3- year disease-free survival rates after curative liver resection for HCC in non-cirrhotic patients were 66.6%, 53.3% and 50% respectively. In the univariate analysis, need for blood transfusion (p = 0.012), post-operative liver failure (p = 0.023), wound infection (p = 0.021), sepsis (p = 0.001), high-grade tumor(p = 0.001), vascular invasion (0.0001), prothrombin time (p = 0.041), serum bilirubin (p = 0.012), post-operative length of stay (p = 0.010) significantly affected the disease-free survival (Table-8). The multivariate analysis (Chart 2-4)identified high-grade tumors (p = 0.039), vascular invasion (p = 0.002), and sepsis (p = 0.011) as independent prognostic factors for disease free survival after liver resection for non-cirrhotic HCC patients (Table-10).

V. Discussion

Although most HCC arise in the cirrhotic liver, approximately 10-40% of cases develop in non-cirrhotic, non-fibrotic liver [5].In our study, we found that HCC in non-cirrhotic liver represented nearly 39% of our resections performed for HCC, thus making it an important clinical entity. Many studies have analyzed the outcomes after liver resection for HCC, however only few studies have focused solely on outcomes after liver resection for HCC in non-cirrhotic, non-fibrotic liver. The mean age of HCC in non-cirrhotic patients in our study was 48.3 years, similar to that reported by Bismuth et al[6] and Chang et al [16], which is about 10 years younger than in cirrhotic patients with HCC. As in previous other reports [17-19],there was a lower male preponderance in our study with male: female ratio of 1.7: 1, compared to 4- 8:1 in cirrhotic patients.

The etiological factors for the development of HCC in non- cirrhotic liver are not well documented [20].The well-known fact that HBV infection has direct carcinogenic potential was supported by a small proportion (13%) of patients with HBV infection in our study. Although there are few reports [17,21,22]of HCV infection in non- cirrhotic HCC, there were no such patients in our study. Only 30% of our patients are associated with alcohol intake, which is concordant with the hypothesis that alcohol has carcinogenic potential. In accordance with previous studies [16,21,22] the prevalence of three main risk factors for HCC (HBV, HCV and alcohol) are low in our study, when compared to cirrhotic patients with HCC. There were significant proportion of patients with diabetes mellitus (27%) and obesity (10%) in the present study. This finding appears to be relevant because many recent reports suggest that diabetes and obesity are major risk factors for HCC in non-cirrhotic liver. However, in 40% of patients, the etiology was unknown. Such a high proportion of non-cirrhotic HCC patients without any identifiable etiological factor suggest the possibility of another hitherto unknown factor or pathogenic pathway for non-cirrhotic HCC, which requires further study.

Due to the absence of underlying liver disease in non-cirrhotic patients, HCC is often diagnosed when it has reached a size that produces symptoms [23].The mean tumor size in our study was 13.2 cm, which is more than most reported series (<10 cm). This may possibly be due to delay in diagnosis, referral bias or tolerance and neglect of non-specific symptoms by our patients. All the patients in our study presented with pain support the view that most of our patients seek attention only when tumor has grown sufficient size to produce mass-related symptoms. Several studies [24]have proposed that AFP production depends on the tumor size or differentiation. In contrast, the AFP level was normal in 67% of our patients despite the mean tumor size of 13.2cm and also normal in 30% of patients with poorly differentiated tumors. Moreover, a study by Madanagopalanet al [25]has shown the prevalence of AFP in HCC was about 51%. Like most other studies [4,14,18], none of the peri- operative parameters were found to be significantly associated with outcome after liver resection of non-cirrhotic HCC in the present study.

The post-operative morbidity rate in our study (50%) was higher than most reported series (19%-39%). The high post-operative morbidity in the present study possibly suggests the inevitable consequence of the major resections (83%) performed for large tumors (mean size: 13.2cm) in non-cirrhotic patients. The most common complication in our study was intra-abdominal collection and wound infection followed by sepsis and post-operative liver failure. Sepsis was found to be an independent prognostic factor for disease-free survival in our study. The reason behind this finding is not clear. However, what is clear is that improved survival does not stem from the differences in recurrence.

Similar to Poon et al [9]and Shrager et al [15], the positive surgical margin in our study was less (26.7%) in comparison with previous studies. However, the multi-nodularity, tumor capsule formation, tumor differentiation and vascular invasion were similar to most other reported series [4,14,18,21]. The important negative prognostic factors predicting survival in the literature are large tumor size, vascular invasion, positive surgical margin, multi-nodularity, tumor differentiation [4,14,18,21]. In the present study, tumor differentiation was found to be independent predictor for both poor survival and earlier recurrence whereas vascular invasion

was significant negative prognostic factor for early recurrence.

In our study, the overall survival rate of non- cirrhotic HCC was 86.7%, 66.7% and 63.3% at 1-, 2- and 3-years after curative resection respectively, comparable with the results of other studies [4,14,18,21]. It is important to note that such high survival rate and cure are achieved only rarely with non-surgical treatment for non- cirrhotic HCC and even with newer innovative approaches, and long-term survival is observed only exceptionally [26].This highlights the pivotal role of liver resection in non-cirrhotic patients with HCC and should be aimed for in all resectable tumors. The disease-free survival after liver resection for non-cirrhotic HCC ranges between 31-56% and 24-61% at 3- and 5-year respectively in the literature [4,14,18,21]. The recurrence rate in our study was 50% and the intrahepatic, extra-hepatic and both intra & extra-hepatic recurrences were 38%, 21%, and 43% respectively, which is in accordance with previous studies. The hypothesis that most early recurrences result from metastatic spread rather than de novo origin [27]was supported by the finding that more than 85% recurrences were detected within first year. This data highlights the necessity of strict surveillance in the first 2 years to identify early recurrence after liver resection in non-cirrhotic HCC and thereby perform potentially benefitting surgical re-resection.

Among the different predictive factors in different studies, the most constant independent predictor for poor survival and early recurrence are large tumor size, vascular invasion, positive surgical margin, multi-nodularity, tumor differentiation. In the present study, the only independent predictive factor for poor survival after liver resection non-cirrhotic HCC in both univariate and multivariate analysis was high tumor grade. Similarly, the independent predictive factors for early recurrence in both univariate and multivariate analysis were high tumor grade, vascular invasion, and sepsis. Since vascular infiltration was associated with large tumor size, high grade and multifocality in this study, a combination of tumor size, grade and number of tumor may be regarded as surrogate marker of vascular infiltration.

The limitations of this study are its retrospective nature and small size of the study population. However this study lays foundation for future long-term studies and larger prospective study

VI. Conclusion

To conclude, we noticed a lower male preponderance and lower prevalence of main risk factors (HBV, HCV, Alcohol) in patients with non-cirrhotic HCC. In spite of delayed presentation and large tumor size, major resection can be performed safely in non-cirrhotic HCC patients. Vascular invasion, tumor differentiation and sepsis are identified as poor prognostic factors after liver resection in patients with non-cirrhotic HCC. The presence of these poor prognostic factors in non-cirrhotic HCC patients necessitates a stringent follow-up to detect and treat recurrence. However, a larger study may be required to confirm this hypothesis.

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Table 1: Clinical characteristics of 30 patients with HCC in non-cirrhotic liver studied.

Variables	n	%
Age		
<50 years	13	43
>50 years	17	57
Sex		
Male	19	63
Female	11	37
Risk factor		
1. Hepatitis B virus infection	4	13
2. Hepatitis C virus infection	0	0
3. Chronic alcohol intake	9	30
4. Tobacco smoking	9	30
5. Diabetes mellitus	8	26.7
6. Obesity	3	10
7. Unknown	12	40
Symptoms		
1. Abdominal pain	30	100
2. Weight loss and anorexia	28	93
3. Abdominal mass	7	23
4. Fever	4	13
5. Jaundice	2	6
6. Hepatomegaly	17	57
ECOG performance status		
0	26	87
1	3	10
2	1	3
Pre-operative biopsy		
Present	3	10
Absent	27	90

ECOG: Eastern Co-operative Oncology Group.

Table 2: Pre-operative laboratory data in 30 patients with HCC in non-cirrhotic liver studied.

Laboratory parameter (unit)	Normal range	Mean ± Standard deviation (range)
Hemoglobin (gm/dl)	14-18	10.73 ± 1.6 (8.5-14)
Total leucocyte count (cells/cu.mm)	4000-11000	8346.3 ± 2428 (2200-15000)
NLR		2.77 ± 1.58 (1.09-7.33)
ESR (mm/hr)	0-20	41.6 ± 26.49 (8-120)
Platelet (cells/cu.mm)	1.5 -4	3.71 ± 1.80 (1.42-7)
Prothrombin Index		97.36 ± 5.66 (77.77-100)
INR		1.04 ± 0.09 (1-1.4)
Sugar (mg/dl)	<160	120.93 ± 48.85 (67-268)
Urea (mg/dl)	10-50	21.67 ± 7.70 (13-50)
Creatinine (mg/dl)	0.6-1.1	0.80 ± 0.24 (0.4-1.54)
Bilirubin (mg/dl)	0-1	1.12 ± 0.83 (0.25-3.6)
AST (U/L)	0-40	84.6 ± 91.45 (21-498)
ALT (U/L)	0-37	47.66 ± 35.70 (8-173)
GGT (U/L)	0-45	98.93 ± 196.27 (10-1050)
SAP U/L)	0-290	261.87 ± 123.56 (85-617)
Albumin (g/dl)	3.8-4.4	3.42 ± 0.55 (2.5-4.9)
AFP (ng/ml)	<20	6.8 ± 5922.9 (0.3-32476)

NLR: Neutrophil-leucocyte ratio, ESR: Erythrocte Sedimentation rate, INR: Internationalized normalized ratio, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutaryltransferase, SAP: serum alkaline phosphatase, AFP: Alpha feto-protein.

Table 3: Type and extent of liver resection in 30 patients with HCC in non-cirrhotic liver studied.

Surgical procedures	n	%
Major Hepatectomy (n=25)		
1. Right Hepatectomy	12	40
2. Left Hepatectomy	6	20
3. Extended Right Hepatectomy	5	16.7
4. Extended Left Hepatectomy	1	3.3
5. Central hepatectomy	1	3.3
Minor Hepatectomy: (n=5)		
1. Left lateral segmentectomy	1	3.3
2. Bisegmentectomy	2	6.7
3. Non-anatomical resection	2	6.7

Table 4: Perioperative factors in 30 patients with HCC in non-cirrhotic liver studied.

Peri-operative factors	Mean ± Standard deviation or n (%)
Operative time (hours)	2.45 ± 0.59
Blood loss (ml)	216.5 ± 119.32
Need for blood transfusion	2 (6.7%)
Mean post-operative stay (days)	16.7 ± 7.0
Morbidity	15 (50%)
Mortality	1 (3.4%)

Table 5: Overall postoperative complications occurred in 15 of 30 patients with HCC in non-cirrhotic liver studied.

Post-operative complications	n	%	Death (3.4%)
Intra-abdominal collection	6	20	
Post-operative liver failure	4	13.4	1
Renal failure	1	3.4	
Chest infection	4	13.4	
Wound infection	8	26.7	
Bile leak	3	10	
Sepsis	5	16.7	

Table 6: Histo-pathologic characteristics of tumor and surrounding parenchyma in 30 patients with HCC in non-cirrhotic liver studied.

	n	%
Size		
<6cm	5	16.7
>6cm	25	83.3
Number of tumor		
Solitary	23	76.7
Multiple	7	23.3
Encapsulation		
Present	19	63.3
Absent	11	36.7
Differentiation		
I	13	43.3
II	8	26.7
III	9	30.0
Microvascular invasion		
Present	15	50.0
Absent	15	50.0
Macrovascular invasion		
Present	0	0.0
Absent	30	100
Capsular invasion		
Present	5	26.3
Absent	14	73.7
Margin		
Positive	8	26.7
Negative	22	73.3
Steatosis		
Present	4	13.3
Absent	26	86.7
pTNM-(AJCC-7th edition)		

I	6	21
II	14	45
III	9	29
IV	1	5
Okuda stage		
I	9	30
II	20	67
III	1	3

pTNM: pathologic tumor-node-metastasis

Table 7: Pattern of recurrence and its management in 14 of 30 patients with HCC in non-cirrhotic liver studied.

Pattern of recurrence (n=14)	n	%
Isolated Intra-hepatic recurrence		
Unifocal	3	21.4
Multifocal	2	14.2
Isolated Extra-hepatic recurrence		
Lung	2	14.2
Bone	1	7.1
Both Intra-hepatic and Extra-hepatic		
Unifocal intra-hepatic + Extrahepatic	2	14.2
Multifocal intra-hepatic + Extrahepatic	4	28.6
Management of recurrence		
Intra-hepatic alone		
1. Re-resection	2	
2. Systemic chemotherapy	2	
3. Best supportive care	1	
Extra-hepatic alone		
1. Systemic chemotherapy	2	
2. Best supportive care	1	
Both Intra-hepatic and Extra-hepatic		
1. Systemic chemotherapy	2	
2. Best supportive care	4	

Table 8: Clinico-pathological and operative prognostic factors for overall and disease-free survival in 30 non-cirrhotic HC patients (Univariate Analysis)

	OVERALL SURVIVAL			**DISEASE-FREE SURVIVAL**		
Characteristics	**n**	**%**	**p-value**	**n**	**%**	**p-value**
Age (years)			0.458			0.625
<60	11	18 ± 2.6		14	22 ± 1.9	
>60	19	29 ± 2.23		16	33 ± 2.21	
Gender			0.223			0.097
Male	12	11 ± 2.5		11	19 ± 2.7	
Female	18	28 ± 2.75		19	26 ± 3.9	
HBs antigen			0.792			0.511
Negative	4	25 ± 4.6		3	13 ± 7.1	
Positive	26	33 ± 1.9		27	27 ± 3.8	
Alcohol intake			0.091			0.351
No	4	31 ± 3.9		7	16 ± 4.6	
Yes	26	39 ± 4.1		23	21 ± 2.9	
AFP			0.191			0.055
<20	9	39 ± 2.3		17	26 ± 4.59	
>20	21	27 ± 1.9		13	30 ± 2.77	
Bilirubin			**0.034**			**0.012**
<1.5	3	23 ± 7.3		3	18 ± 6.53	
>1.5	27	11 ± 1.8		27	29 ± 2.32	
Prothrombin time			**0.046**			**0.041**
<15	26	25 ± 1.7		28	27 ± 2.32	
>15	4	13 ± 1.9		2	11 ± 0.51	
Albumin			0.061			0.241
<3	5	16 ± 4.9		3	12 ± 0.82	
>3	25	46 ± 2.7		27	29 ± 2.31	
Size			0.576			0.061
<6	11	17 ± 2.8		14	18 ± 7.51	
>6	19	26 ± 1.7		16	31 ± 1.92	
Number			0.061			0.180
Solitary	26	15 ± 6.5		25	18 ± 6.6	
Multiple	4	21 ± 2.4		5	29 ± 2.33	
Capsule			0.106			0.210
Present	11	25 ± 1.7		14	23 ± 6.1 27 ±	

Absent	19	33 ± 1.9		16	3.21	
Grade			**0.007**			**0.001**
High	21	32 ± 1.8		21	30 ± 1.99	
Low	9	25 ± 4.4		9	12 ± 0.71	
Vascular invasion			0.07			**0.0001**
Present	12	13 ± 1.7		15	20 ± 5.45	
Absent	18	21 ± 6.4		15	32 ± 1.79	
Capsular invasion			0.07			0.266
Present Absent	12	13 ± 1.7		3	11 ± 0.61	
	18	21 ± 6.4		27	30 ± 7.1	
Steatosis			0.576			0.082
Present	4	15 ± 1.9		3	20 ± 2.19	
Absent	26	18 ± 2.6		27	29 ± 2.2	
Major resection			0.069			0.351
Yes	17	29 ± 1.92		20	31 ± 6.7	
No	13	21 ± 0.60		10	22 ± 7.1	
Blood transfusion			0.199			**0.012`**
Yes	2	18 ± 0.09		2	11 ± 0.50	
No	28	31 ± 2.4		28	27 ± 2.31	
Post-op stay			0.659			**0.010**
<15	19	36 ± 3.1		17	28 ± 1.712	
>15	11	23 ± 2.2		13	11 ± 0.07	
Wound infection			0.346			**0.021**
Present	6	11 ± 0.50		8	18 ± 2.90	
Absent	24	31 ± 1.91		22	28 ± 2.21	
Sepsis			0.062			**0.001**
Present	6	19 ± 2.96		5	12 ± 2.19	
Absent	24	33 ± 1.71		25	29 ± 2.33	
Post-op liver failure			0.792			**0.023**
Present	3	15 ± 4.6		4	12 ± 0.43	
Absent	27	23 ± 0.792		26	29 ± 2.08	

Table 9: Significant prognostic factors for overall survival by multivariate analysis in 30 patients with non-cirrhotic HCC

Variables	Hazard ratio	95% CI	p-value	Model prediction
High grade tumors	**0.820**	**(0.694-0.698)**	**0.019***	
Bilirubin	1.846	(0.893-3.816)	0.098	
Prothrombin time	0 .488	(0.117-2.044)	0.327	46.27

95% CI: 95% confidence interval, p <0.05 = statistically significant

Table10: Significant prognostic factors for disease-free survival by multivariate analysis in 30 patients with non-cirrhotic HCC

Variables	Hazard ratio	95% CI	p-value	Model prediction
High grade tumors	**0.092**	**(0.015-0.590)**	**0.039***	
Sepsis	**0.091**	**(0.015-0.574)**	**0.011 ***	
Vascular invasion	**0.073**	**(0.014-0.389)**	**0.002 ***	
Bilirubin	2.289	(0.129-40.550)	0.572	
Prothrombin time	0 253	(0.033-1.935)	0.185	
Blood transfusion	0.134	(0.006-2.774)	0.194	
Hospital stay	0.981	(0.818-1.176)	0.883	
Wound infection	0.283	(0.016-5.136)	0.393	55.70
Post-op liver failure	0.498	(0.671-2.116)		

95% CI: 95% confidence interval, p <0.05 = statistically significant

Chart-1: Overall survival of non-cirrhotic patients treated for HCC according to tumor differentiation

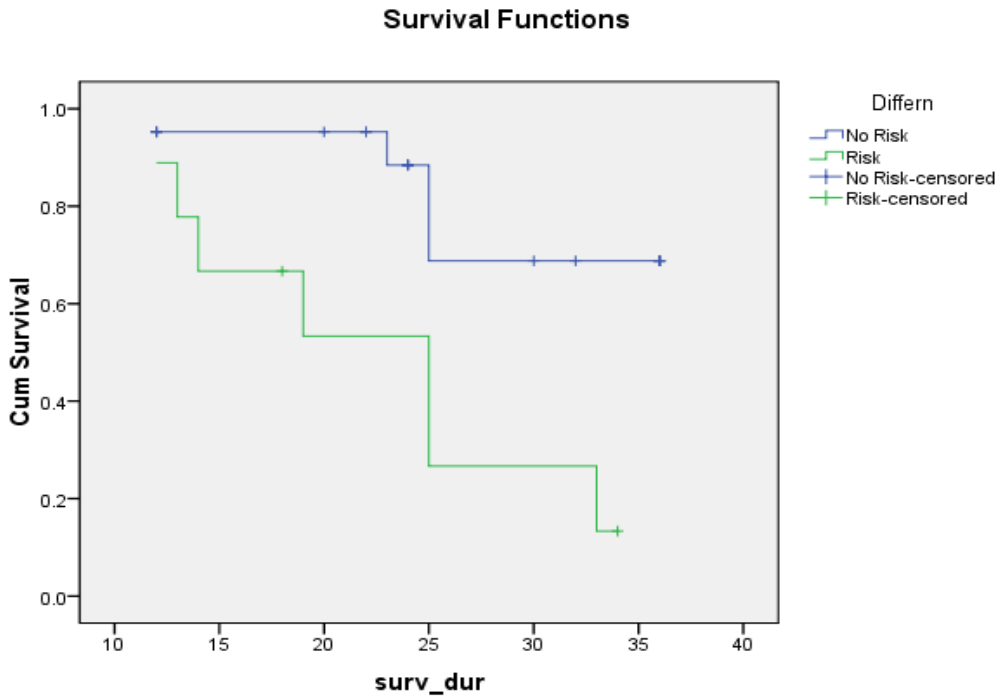


Chart-2: Disease-free survival of non-cirrhotic patients treated for HCC according to tumor differentiation

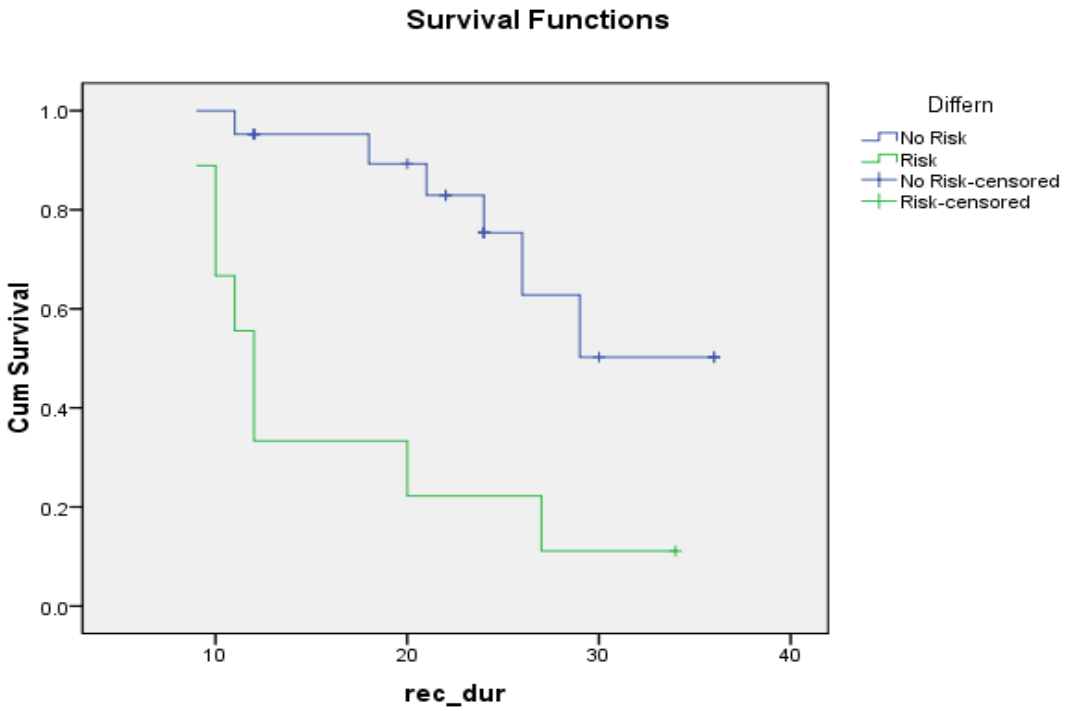


Chart-3: Disease-free survival of non-cirrhotic patients treated for HCC according to sepsis

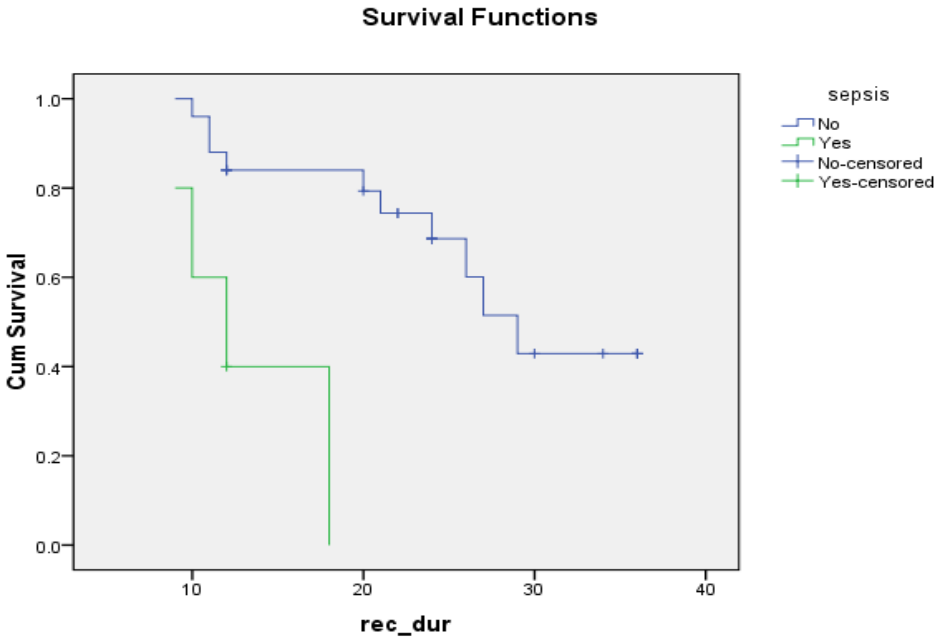
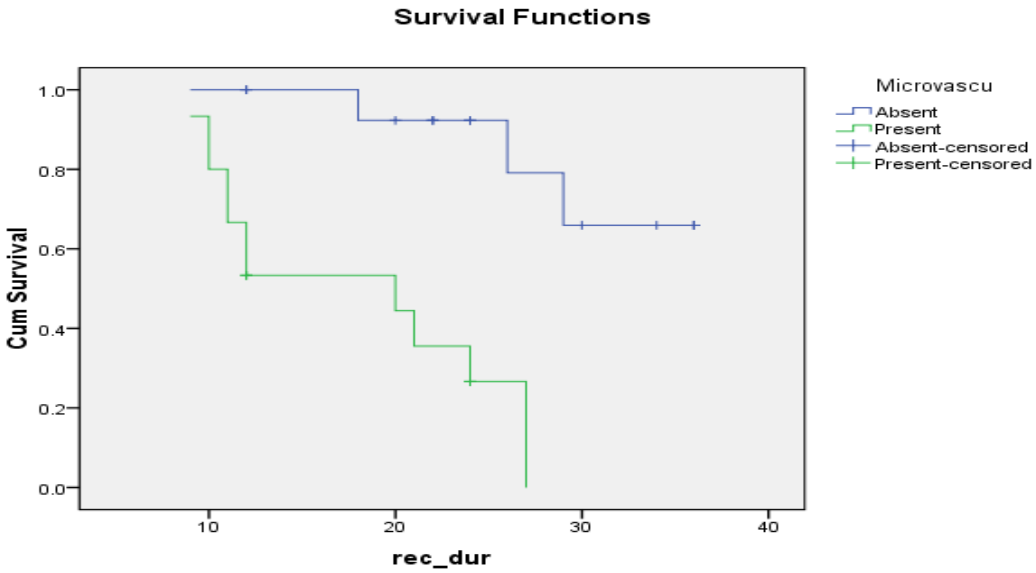


Chart-4: Disease-free survival of non-cirrhotic patients treated for HCC according to Microvascular invasion



Satish Devakumar Murugesan" Prognostic Factors and Outcomes after Liver Resection for Hepatocellular Carcinoma in Non-Cirrhotic, Non-Fibrotic Liver." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 18, no. 2, 2019, pp 43-53.