Hepatocellular Carcinoma (HCC): Epidemiology, Risk Factors, and Survival

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Abstract

Background: HCC is an aggressive tumour with unpredictable outcome. It is fourth most common cause of cancers in India. However, information on HCC is inadequate in India.Therefore purpose of study is to determine overall survival for patients diagnosed with hepatocellular carcinoma (HCC) and association between various predictive factors and survival.

Results: The median overall survival (OS) was 5 months ranging from 0-13 months. Majority of patients were in advance stage (III/IV). All patient died by 13 months. None of the possible predictive factors were found to be significantly associated with survival (P > 0.05) by univariate analysis. However age < 59 yrs, male gender, KPS ≤ 60, AFP ≥ 400, cirrhosis, multifocality, tumour size > 10 cm, advance stage (IIIB/IV), child pugh score B/C, CLIP score ≥ 4 and raised bilirubin level had poorer survival compared to other predictive factors. Median survival was better in patient treated with TACE followed by sorafenib + palliative care group (9 month) then sorafenib + palliative care and palliative care alone group (5 and 4 months respectively). Although results were not statistically significant (p: 0.133). Amongst all possible variables, highest hazard was found with multifocal lesion (2.0577) and results were statistically significantly (p 0.0451, 95 % confidence interval : 0.9225 to 4.5900) as compared to unifocal lesion with median survival period of 7 vs 9.5 months by Kaplan-Meier survival curve analysis using log rank test.

Conclusion: Multifocality was independent predicator for poor survival in HCC. Further clinical studies are necessary to improve the outcomes of patients with high risk features.

Background

HCC ranks fifth amongst all cancer worldwide, and the fourth in the list to cause of cancer-related death. (1, 2) The age-adjusted incidence rate of HCC in India for men ranges from 0.7 to 7.5 and for women 0.2 to 2.2 per 100,000 population per year. (3) The usual age of presentation ranges from 40 to 70 years. HCC is male predominant cancer with a male: female ratio of 4:1.

Major risk factors for hepatocellular carcinoma include infection with HBV or HCV and alcoholic liver disease. Less common causes include hereditary hemochromatosis, alpha1-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease. The distribution of these risk factors among patients with hepatocellular carcinoma is highly variable, depending on geographic region and race or ethnic group. (4)

The existence of the chronic liver disease, especially cirrhosis, represents a potential risk for the development of HCC. Cirrhosis, mainly caused by hepatitis B virus (HBV) and hepatitis C virus (HCV), constitutes a major risk factor for HCC, with a 5-year cumulative incidence ranging from 15–20%. (5) India lies in the intermediate endemic zone of HBV infection with hepatitis B surface antigen (HBsAg)

carrier frequency of 2–4% in the community. (6) HBV infection is the leading cause of chronic liver disease in India and is responsible for 35–60% of chronic liver disease and 60–80% of HCC. (7)

At early stages, curative treatment strategies, such as surgical therapies (resection and liver transplantation) and locoregional procedures (radiofrequency ablation) can be considered. However, a disease that is diagnosed at an advanced stage or with progression after locoregional therapy has a poor prognosis. Treatment options are limited (Surgical resection, Transarterial chemoembolization (TACE), Chemotherapy, Targeted therapy/ Sorafenib, Liver transplantation) and are often inefficient.(8) With most solid tumors, the estimation of life expectancy is related to tumor stage at diagnosis, and staging is directly linked to treatment indication. By contrast, in patients with hepatocellular carcinoma (HCC), the prediction of prognosis is more complex.

In India, information on HCC concerning clinical profile, risk factors, and outcome of therapy and survival of HCC patients is inadequate. Such information may be important to formulate guidelines for early detection and treatment of HCC. Therefore, the study aims to determine risk factors, clinical outcomes and their impact on survival.

Methods

After approval by an institutional ethics committee (Decision Date: June 28, 2018; Certificate Reference Number: AIIMS/IEC/2018/586), 59 patients of HCC presenting to the radiotherapy out-patient department of a tertiary care center, from April 2015 to April 2018 were retrospectively enrolled in the study.

Inclusion criteria:

1. All patients that are registered in the hospital's electronic database.
2. Either Histologically proven cases of hepatocellular carcinoma or Radiological (Multiphasic CT or MRI) findings suggestive of hepatocellular carcinoma with raised AFP levels > 400 ng/ml
3. Hepatocellular carcinoma with or without distant metastasis

Exclusion criteria:

1. Histology other than Hepatocellular carcinoma
2. Patients not having an electronic record

All eligible patients fulfilling inclusion and exclusion criteria were approached and data (including demographic profile, radiological/ imaging, serum markers, lab studies) was collected retrospectively from the case records of AIIMS, Hospital information system, and any additional information required was collected telephonically. Variables recorded were Age, Gender, Karnofsky performance score (KPS), history of Addiction (alcohol), Viral markers (HBsAg / HCV), Alfa-fetoprotein (AFP) levels, based on imaging: features of Cirrhosis, Portal vein thrombosis, Unifocal/ multifocal, Tumour size, Tumour stage (AJCC 8th). Also, the disease was classified based on Child Pugh and CLIP scoring system. Also, any form of therapy undergone by the patient was recorded.

Out of 68 patients enrolled in the study, 9 patients were excluded from the study due to inadequate data.

The data were analyzed to determine survival from the time of initial diagnosis and the association between risk factors.

4. Statistical Analysis

Data were entered in an Excel sheet to prepare the master sheet and transported to statistical software for calculations. Linear variables were summarized as mean and standard deviations while nominal/categorical variables were expressed as proportions (%).

Unpaired T-test and one-way ANOVA test were used for comparison of linear variables whereas Chi-square test and Fisher Exact test were used for Univariate analysis of nominal/categorical variables to find out associated factors for survival period.

Kaplan-Meier survival curve analysis was done for suspected risk factors for the survival period and hazards ratios with 95% confidence interval were calculated. The survival period was compared by using the Log Rank test.

'p' Value < 0.05 was taken as significant.

Medcalc 16.4 version software was used for all statistical calculations.

Results

A total of 59 patients were retrospectively analyzed. In the current study mean age was 59.63 ± 10.88 years ranging from 29–80 years and KPS was ≤ 60 in 17 patients (28.81 %). Study showed male predominance, 86.44 % (n = 51) were male and 13.56 % (n = 8) were female. Out of 59 patients, 24 patients were alcoholic (40.68 %) and 23 patients were HbsAg reactive (38.98 %).

In the present study, 48 patients (81.36 %) were FNAC (fine needle aspiration cytology) / biopsy proven and 11 patients (18.64 %) were diagnosed on basis of imaging and AFP levels.

Serum AFP levels were ≥ 400 ng/mL in 44 patients (79.66 %). Twenty six patients (44.07 %) were grouped as Child-Pugh class B, while 17 (28.81 %) and 16 (27.12 %) patients were grouped in Child Pugh Class A and C respectively. 42 patients (71.19 %) had multifocal lesions, 27 patients (45.76 %) had tumour size > 10 cm, 15 (25.42 %) and 18 (30.51 %) patients (25.42 %) had accompanying cirrhotic liver and portal vein thrombosis respectively. Also 45.76 % (n = 27) of patients had bilirubin levels > 3mg/dL while prothrombin time was prolonged by < 4, 4–6 and > 6 seconds in 72.88 % (n = 43), 20.34 % (n = 12) and 6.78 % (n = 4) of patients respectively.

The majority of the patients were classified as TNM stage IV (62.71 %) and 69.48 % (n = 41) of patients had a CLIP score ≥ 3.

In current study most of the patients, 84.75 % (n = 50) received sorafenib + palliative care, while 6.78 % (n = 6) patient received TACE followed by sorafenib + palliative care and 8.47 % (n = 5) was eligible for only palliative care (Table 1).

Table 1
Patients Characteristic

Age	**No.**	**%**
< 59	26	44.07
≥ 59	33	55.93
Gender		
Female	8	13.56
Male	51	86.44
Alcoholic		
No	35	59.32
Yes	24	40.68
HCV/ HBSAG		
Non-reactive	36	61.02
Reactive	23	38.98
AFP(ng/mL)		
< 400	12	20.34
≥ 400	47	79.66
Cirrhosis		
Absent	44	74.58
Present	15	25.42
Portal Vein Thrombosis		
Absent	41	69.49
Present	18	30.51
Multifocal		
No	17	28.81
Yes	42	71.19
Stage		
III A	7	11.86
III B	15	25.42
IV A	28	47.46

Age	No.	%
IV B	9	15.25
CLIP Score		
1	9	15.25
2	9	15.25
3	15	25.42
4	11	18.64
5	10	16.95
6	5	8.47
Child Pugh Score		
A	17	28.81
B	26	44.07
C	16	27.12
Prothrombin Time		
1	43	72.88
2	12	20.34
3	4	6.78
Bilirubin		
1	27	45.76
2	5	8.47
3	27	45.76
KPS	**No.**	**%**
≤ 60	17	28.81
> 60	42	71.19
Tumour Size		
≤ 10	32	54.24
> 10	27	45.76
Histology		
HCC	48	81.36

Age	No.	%
On Imaging + AFP	11	18.64
Treatment		
Palliative Care Only	5	8.47
Sorafanib + Palliative Care	50	84.75
TACE –-> Sorafenib + Palliative Care	4	6.78

5.1 Overall Survival And Association with Various Risk Factors

In present study ,the mean overall survival (OS) was 5.2 ± 3.17 months (median survival: 5 months) ranging from 0–13 months.

Table 2 shows a comparison of the survival period concerning possible determinants such as age, gender, KPS, Alcohol addiction, Viral Status (HbsAg/ HCV), AFP levels, cirrhosis, portal vein thrombosis, multifocality, tumor size, tumor stage, child-pugh score, CLIP score, bilirubin levels, prothrombin time and treatment modality and it was observed that none of the possible determinants were significantly associated with survival period ($P < 0.05$)

Table 2

Comparison of survival period with respect to suspected associated/predictive factors

Age	N	Mean	SD	Median	Minimum	Maximum	'P' Value
< 59	26	4.92	3.21	5	0	13	0.552*
≥ 59	33	5.42	3.17	5	0	12	
Gender							
Male	51	5.04	2.95	5	0	12	0.320*
Female	8	6.25	4.46	5.5	0	13	
Alcoholic							
No	35	5.00	3.46	5	0	13	0.557*
Yes	24	5.50	2.75	5	1	12	
HCV/ HBSAG							
Non-reactive	36	4.81	3.16	5	0	12	0.231*
Reactive	23	5.83	3.16	5	1	13	
AFP(ng/mL)							
< 20	1	6.00		6	6	6	0.337#
20–399	11	6.00	2.72	6	0	10	
≥ 400	47	5.00	3.30	5	0	13	
Cirrhosis							
Absent	44	5.41	3.15	5	0	13	0.398*
Present	15	4.60	3.27	4	1	12	
Portal Vein Thrombosis							
Absent	41	5.29	3.16	5	0	13	0.747*
Present	18	5.00	3.29	5	0	12	
Multifocal							
No	17	5.71	3.65	5	1	13	0.444*
Yes	42	5.00	2.98	5	0	12	
Stage							
III A	7	6.29	2.06	7	3	9	0.546#

Age	N	Mean	SD	Median	Minimum	Maximum	'P' Value
III B	15	4.40	2.80	4	1	12	
IV A	28	5.50	3.39	6	0	13	
IV B	9	4.78	3.80	5	0	12	
CLIP Score							
1	9	6.44	3.17	5	3	13	0.683#
2	9	5.22	2.39	6	1	8	
3	15	5.67	3.79	5	0	12	
4	11	4.18	2.56	5	1	8	
5	10	4.60	3.53	4.5	0	12	
6	5	5.00	3.39	5	1	10	
Child Pugh Score							
A	17	6.59	3.47	6	1	13	0.090#
B	26	4.46	2.72	5	0	10	
C	16	4.94	3.26	5	1	12	
Bilirubin							
1	27	5.74	3.36	5	0	13	0.480#
2	5	4.40	2.88	5	1	8	
3	27	4.82	3.05	5	0	12	
KPS							
≤ 60	17	4.24	2.63	4	0	9	0.137
> 60	42	5.60	3.31	5	0	13	
Histology							
HCC	48	5.29	3.17	5	0	13	0.662
On Imaging + AFP	11	4.82	3.31	5	0	12	
Tumour Size							
≤ 10	32	5.56	2.91	5	1	13	0.352
> 10	27	4.78	3.47	4	0	12	

Age	N	Mean	SD	Median	Minimum	Maximum	'P' Value
Treatment							
Palliative Care Only	5	4.60	2.61	4	1	8	0.133
Sorafanib + Palliative Care	50	5.02	3.10	5	0	13	
TACE + Sorafenib + Palliative Care	4	8.25	3.86	9	3	12	

*Unpaired 't' test #One way AnoVa

However, the mean survival period was more in the age group ≥ 59 years, female gender, KPS > 60 and AFP < 400 levels. Also, patients with the unifocal lesion, tumor size ≤ 10 cm, non-cirrhotic liver status, absence of portal vein thrombosis, and lesser bilirubin levels were associated with a longer survival period.

Patients with stage IIIA had high survival as similar to a patient with Child pugh score A and clip score 1 and 2. In current study, it was observed that patient receiving TACE followed by sorafenib + palliative care (median survival: 9 months) had longer survival compared to patients receiving only palliative care (median survival: 4 months)

Univariate analysis using chi-square test and Fisher exact test was done to find out associated factors for survival period, to compare the probability of survival for 6 months period according to various possible risk factors. None of the variables were found to be significantly associated with 6 months of survival (P > 0.05). However age ≥ 59 years, female gender, KPS > 60, AFP < 400, non-cirrhotic, tumor size ≤ 10 cm, stage III A, child-pugh score A, CLIP score ≤ 3, bilirubin levels < 2 had higher survival.

Table 3 shows the median survival and hazard ratio between various associated factors using Kaplan-Meier survival curve analysis. In the present study < 59 years has 1.0933 times more hazard as compared to age ≥ 59 years with a median survival period of 7 and 7.5 months respectively. Similarly KPS ≤ 60, male gender, alcoholic, HbsAg reactive and presence of portal vein thrombosis has 1.8792, 1.8267, 1.2647, 0.8182 and 1.2749 times more hazard as compared to KPS > 60, female gender, non-alcoholic, HbsAg non-reactive and absence of portal vein thrombosis with a median survival period of 6.5 vs 8 months, 7 vs 9.5 months, 7 vs 8 months, 7 vs 7.5 months, 6.5 vs 8 months respectively. However, this difference was not found statistically significant. Similarly, the highest hazard was found with a multifocal lesion (2.0577) and it was significantly higher than unifocal lesion (95 % confidence interval: 0.9225-4.5900, p 0.0451) with a median survival period of 7 vs 9.5 months (Fig. 1).

Table 3
Kaplan-Meier survival curve analysis of suspected associated/predictive factors

Factor	Median survival	Hazard ratio	95% CI	'p' value*
Focal				
Unifocal	9.5	2.0577	0.9225 to 4.5900	0.0451
Multifocal	7			

*Log Rank Test

Median survival was better in a patient treated with TACE followed by sorafenib + palliative care (10 months) then in Sorafenib + palliative care and palliative care alone group, median survival was 7 months respectively. Although the results were not statistically significant (p = 0.5524) by Kaplan meier survival curve analysis. (Fig. 2)

Discussion

Hepatocellular carcinoma (HCC), is aggressive tumor with higher morbidity and mortality compared to other cancers and is usually diagnosed in advance stage.(8) Most of the burden lies in developing countries.(9)

This study focuses on patient characteristics, tumor characteristics, risk factors and outcomes in HCC patients from India as data in view of clinical profile and outcomes are limited in India sceniora.

In present study mean age was 59.63 ± 10.88 years ranging from 29–80 years with male predominance (male to female ratio: 6.4: 1) which was similar to Salem S et al study, 59.9 ± 11.0 years ranging from 28–85 years and male to female ratio 5.7:1.(9)

Alcohol addiction and HbsAg reactivity was seen in 40.68 % and 38.98 % patients respectively. HBV and HCV are the most important precursors for HCC development on a global scale, together accounting for over 80% of liver cancer cases worldwide.(10) HBV infection is the leading cause of chronic liver disease in India and is responsible for 35–60% of chronic liver disease and 60–80% of HCC.(7) Earlier studies from India suggest that the odds ratio of HbsAg positivity among HCC patients is one of the highest in the world.(11) About 15 million people are infected by HCV and the population prevalence of anti-HCV antibodies is about 1%.(12) Thus, there is a large pool of people who are at risk of developing chronic liver disease and, therefore, HCC. In the current study, no patient was HCV reactive.

Also, the younger age of HCC patients with HBV infection can be explained by 2 facts. First, the HBV carrier pool in India usually reaches a plateau by the age of 5 years. (13, 14) In the general population, it is estimated that about 75% of carriers would have acquired infection by horizontal spread during early

childhood and about 25% by vertical transmission.(15) Second, HBV is a more potent oncogenic stimulus and can cause HCC without cirrhosis.(16)

In our study majority of the patient had AFP ≥ 400 (79.66 %) which was contradictory to Greten et al. study in which AFP ≥ 400 was observed in 41%.(17)

In a study by Salem S et al. (9) larger bulk of patients presented with multifocality (53.8 %) and cirrhotic liver (82.3 %), which was in comparison was contradictory to the present study, multifocality and cirrhosis were seen in 71.19 % and 25.42%, respectively. Cirrhosis is one of the cause that increases risk for HCC at various levels. Cirrhosis due to viral hepatitis are at higher risk of developing HCC than non-viral-induced cirrhosis. The portal vein thrombosis was observed in 30.51 % of patients in the present study which was similar to the study by Zhu Q et al. (36 %).(18)

The median tumor size 10 cm ranging from 6–22 cm while a study by Salem S et al. found the median tumor diameter was 6.0 cm (range 1.5–15.0 cm).(9)

In the present study documentation of diagnosis was dominantly achieved by biopsy/ FNAC then radiological and laboratory test/AFP (81.36% vs 18.64 %) which was similar to Salem S et al. study (63% vs 19%).(9) While it was mainly by radiological and laboratory tests in the Italian study.(19) However, there is a dramatic shift to radiological and laboratory tests for the diagnosis of HCC nowadays. Also an elevated AFP level in conjunction with imaging results showing the presence of growing liver mass has been shown to have a high positive predictive value for HCC in 2 retrospective analyses (20, 21) involving the small number of patients.

The majority of patients in the current study are in the advance stage (III/ IV), child pugh score B and C, CLIP score ≥ 3 which was similar to Salem S et al. (9) (TNM and Child Pugh Score) and Cabibbo et al. (19) study (Barcelona Clinic Liver Cancer (BCLC), Child Pugh Score, Cancer of the Liver Italian Program scores.), athought these study used different staging system.

6.1 Overall Survival

The median overall survival (OS) in current study was 5 month which was comparable to overall survival reported by Salem S et al.(9), Kim et al,(22) Pawarode et al,(23) Yeung et al,(24) and Schoniger et al.(25) (Table 4). All patients died by 13 months. However, the Italian group (19) reported a higher median OS (6.8 months) and 12 month OS rate (32%), and Llovet et al.(26) reported a higher 12 month and 24 month OS rate (54% and 40% respectively). The better survival could be related to the better prognosis of their patients as two-thirds of Llovet et al’s patients had Child-Pugh Class A. (26)

Table 4
Various Studies and Median Overall Survival

STUDY (YEAR)	MEDIAN OVERALL SURVIVAL
Kim et al (1989)	2 Months
Pawarode et al (1998)	2.2 Months
Yeung et al (2005)	3 Months
Schoniger et al (2001)	8 Months
Salem S et al (2015)	2.3 Months
Current Study	5 Months

6.2 Association Between Possible Risk Factors and Survival

In the current study, various possible risk factors such as age, gender, KPS, Alcohol addiction, Viral Status (HbsAg/ HCV), AFP levels, cirrhosis, portal vein thrombosis, multifocality, tumor size, tumor stage, child pugh score, CLIP score, bilirubin levels, prothrombin time and treatment modality were compared with survival period and it was observed that none of the factors were significantly associated with survival period ($P < 0.05$). Also, no of the variables showed significant associated with 6 months survival ($P > 0.05$) by univariate analysis using the chi-square test and fisher exact test. However age < 59 yrs, male gender, KPS ≤ 60, AFP ≥ 400, cirrhosis, multifocality, tumour size > 10 cm, advance stage (IIIB/IV), child pugh score B/C, CLIP score ≥ 4 and raised bilirubin level had poorer survival compared to other associated factors.

Also patients receiving TACE followed by sorafenib + Palliative care had better survival then patients for palliative care alone with median overall survival, 9 months and 4 months, respectively, p: 0.133. Ohki T et al. found that median overall survival time (861 vs. 467 days, $P = 0.01$) from the time of non-responsiveness to TACE were significantly longer with TACE followed by sorafenib within 14 days than TACE alone.(27)

Kaplan-Meier survival curve analysis was done using log-rank test for possible risk factors for survival period and hazards ratios with 95% confidence interval and it was observed that of all risk factors highest hazard was found with a multifocal lesion (2.0577) and results were significantly higher than unifocal lesion (95 % confidence interval: 0.9225 to 4.5900, p 0.0451) with median survival period of 7 vs 9.5 months. Similarly, it was observed in the present study that age < 59 years, KPS ≤ 60, male gender, alcoholic, HbsAg reactive, presence of portal vein thrombosis had 1.0933, 1.8792, 1.8267, 1.2647, 0.8182, and 1.2749 times more hazard as compared to age ≥ 59 years, KPS > 60, female gender, non-alcoholic, HbsAg non-reactive and absence of portal vein thrombosis with a median survival period of 7 vs 7.5 months, 6.5 vs 8 months, 7 vs 9.5 months, 7 vs 8 months, 7 vs 7.5 months, 6.5 vs 8 months respectively. However this difference was not found statistically significant. In current study we also observed that non

cirrhotic patients had 0.7550 times more hazards than cirrhotic patients with a median survival of 7 vs 9 months (p = 0.5284).

A study in contradictory to present study, found that HCC risk increased with age: adjusted HR was 1.97 (95% CI, 0.99–3.87) for 40–49 years; adjusted HR was 3.00 (95% CI, 1.55–5.81) for 50–59 years; and adjusted HR was 4.02 (95% CI, 2.03–7.94) for more than 60 years vs less than 40 years. (28) Presence of cirrhosis increased risk of developing HCC in patients than without cirrhosis (adjusted HR = 3.69; 95% CI, 2.82–4.83). However, even among non-cirrhotic patients with high levels of alanine aminotransferase—regardless of race, the annual incidence of HCC was more than 0.2% for patients older than 40 years. (28)

The present results were also not consistent with the finding of a study by Greten et al.(17) They observed that the presence of portal vein thrombosis, advanced liver cirrhosis (Child–Pugh score B or C), and CLIP score of > 2 were Independent negative prognostic parameters for survival (P < 0.05). Overall median survival was 11 months. (17)

A study by Rosellini et al.(29) concluded that absence of therapy, Child-Pugh's Class C, alfa-fetoprotein greater than 400 ng/ml, presence of symptoms, severe ascites, tumor involving both lobes and multifocality were variables associated with significantly decreased survival on univariate analysis. While Multiple regression analysis (Cox model) revealed that the mixed internal echo pattern of hepatocellular carcinoma and the presence of moderate or severe ascites were independent predictors of the high risk of death. The median survival from the time of diagnosis was 12 months.

Tumor size > 2 cm, multifocality, non-anatomic resection and vascular invasion were associated with worse prognosis (hazard ratio [HR] = 1.56, 1.34, 1.44, and 2.03, respectively P < 0.05) in study by Zhu Q et al. (18)

Paul et al. (30) observed that vascular invasion, Okuda staging, and therapy were independent factors associated with survival. Treated patients had better median survival compared to untreated ones (16 months vs. 7 months, p < 0.05) which was similar to the present study (9 months vs 4 months respectively) although results were not statistically significant (p: 0.133). The above study also concluded that Serum AFP is not a very sensitive marker for diagnosis or surveillance.

Male gender, advanced Child-Pugh class, ascites, and distant metastases were associated with poor survival (P< 0.05). While, in multivariate analysis; the presence of ascites and Child-Pugh class were independent predictors of poor survival as concluded by Salem et al.(9)

Child-Pugh class, serum alpha-fetoprotein, tumor size, portal vein thrombosis, and TNM stage were found to be independent prognostic factors for survival among HCC patients in a study by Lee S et al.(8), with median overall survival of 10.8 months.

The poor outcome in present study could be related to the late presentation as most patients present with stage III or IV and poor liver functional reserve. Late presentation could be related to decreased awareness among patients and possibly primary health care physicians. This could be due to the fact that

symptoms and signs of HCC could be attributed to the long-lasting underlying cirrhosis. Late presentation could also be related to the absence of adequate nationwide HCC screening programs. Other factors like pesticides may play a role in hepatocarcinogenesis (alfatoxins) and consequently HCCs in rural inhabitants. Also none of the patients was offered surgical resection due to the advanced stage of diseases in the present study.

In the present study, major constraints observed were retrospective study type, limited sample size, and no records focusing on assessment of molecular biology and tumor characteristic.

Also, no liver transplantation services were available at our center and also limited services with long waiting periods in India make availability difficult. Liver transplantation for hepatocellular carcinoma has the potential to eliminate both the tumor as well as the underlying cirrhosis and is the ideal treatment for HCC in cirrhotic liver as well as massive HCC in non-cirrhotic liver. Limitations in organ availability, necessitate the stringent selection of patients who would likely to derive the most benefit. Selection criteria have considered tumor size, number, volume as well as biological features. Cadaveric liver transplantation is limited by a shortage of donors and prolonged waiting periods. Additionally, the procedure is very expensive and, with no health insurance facilities available and severe economic constraints, it is virtually out of reach for the majority of the patients in India.(30) However, Living donor liver transplantation has expanded donor options and has the advantage of a lower waiting period and not impacting the non-HCC waiting list.

The inability to demonstrate a relationship between various possible risk factors (except multifocality) and OS on Kaplan-Meier survival curve analysis in the current study may be due to differences in study design, study population, definition, and criteria used in the study and underpowered sample size.

Conclusion

Hepatocellular carcinoma is an aggressive disease with poor outcomes. HCC rapidly progresses with its aggressive biological behavior and is usually diagnosed at an advanced stage. In the present study, the median overall survival was 5 months ranging from 0–13 months. All patients died by 13 months. Kaplan-Meier survival curve analysis concluded that of all risk factors highest hazard was found with a multifocal lesion (2.0577) and results were significantly higher than unifocal lesion (p 0.0451, 95 % confidence interval: 0.9225 to 4.5900) with a median survival period of 7 vs 9.5 months. Median survival was better in a patient treated with TACE followed by sorafenib + palliative care group then sorafenib + palliative care and palliative care alone group. Although results were not statistically significant (p: 0.133).

As most treatment modalities are less effective, much effort should be put into the field of prevention and screening programs. Further clinical studies are necessary to improve the outcomes of patients with high-risk features.

Abbreviations

HCC Hepatocellular carcinoma

HBV hepatitis B virus

HCV hepatitis C virus

TACE Transarterial chemoembolization

AFP Alfa-fetoprotein

HBsAg hepatitis B surface antigen

BCLC Barcelona Clinic Liver Cancer

Declarations

Ethics approval and consent to participate - This study has been approved by the All India Institute of Medical Sciences, Jodhpur, Rajasthan, India , Institutional Ethical Committee (IEC). (Decision Date: June 28, 2018; Certificate Reference Number: AIIMS/IEC/2018/586).

Consent for publication – Not Applicable

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Authors' contributions –

[1]**SS** - Conception and design of this study, acquisition of data, Data Analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing original draft, analysis and interpretation of data, Drafting and approval the manuscript.

[1]**PP** - Revising the manuscript critically for important intellectual content, approval the manuscript

[1]**SN** - Writing original draft, Interpretation of data, revising the manuscript critically for important intellectual content, approval the manuscript, Project administration

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[3]**AA** - Revising the manuscript critically for important intellectual content, approval the manuscript

All authors have read and approved the manuscript.
Acknowledgments – Not Applicable

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2001) Estimating the world cancer burden: Globocan 2000. Int J Cancer 94: 153–156.
2. Bosch FX, Ribes J, Diaz M, Cleries R (2004) Primary liver cancer: worldwide incidence and trends. Gastroenterology 127: S5–S16
3. International Agency for Research on Cancer (IARC–WHO) http:// Ci5.iarc.fr (Access number 9).
4. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-76.
5. Bruix J, Sherman M, Llovet JM, et al: EASL panel of experts on HCC. Clinical management of hepatocellular carcinoma: conclusions of the Barcelona 2000 EASL conference. European Association for the Study of Liver. J Hepatol 2001;35:421–430.
6. Acharya SK, Madan K, Datta Gupta S, Panga SK: Viral hepatitis in India. Natl Med J India 2006;19:203–217.
7. Yoshizawa H: Hepatocellular carcinoma associated with hepatitis C virus infection in Japan: projection to other countries in the foreseeable future. Oncology 2002;62(suppl 1):8–17.
8. Lee S, Shin H, Kim H, Lee S, Lee H, Hyun K et al. Analysis of prognostic factors and 5-year survival rate in patients with hepatocellular carcinoma: a single-center experience. The Korean Journal of Hepatology. 2012;18(1):48.
9. Salem S, Zeeneldin A, Darwish A, El-Gammal M, Hussein M, Saadeldin M. Untreated hepatocellular carcinoma in Egypt: outcome and prognostic factors. Journal of Hepatocellular Carcinoma. 2015:3.
10. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. Semin Liver Dis. 1999;19(3):271–285.
11. Kumar M, Kumar R, Hissar S, Saraswat M, Sharma B, Sakhuja P et al. Risk factors analysis for hepatocellular carcinoma in patients with and without cirrhosis: A case control study of 213 hepatocellular carcinoma patients from India. J Gastroenterol Hepatol. 2007;22(7):1104-1111.
12. Chowdhury A, Santra A, Chaudhuri S, et al: Hepatitis C virus infection in the general population: a community-based study in West Bengal, India. Hepatology 2003; 3 7: 802–809.
13. Tandon BN, Irshad M, Raju M, Mathur GP, Rao MN: Prevalence of HbsAg and antiHBC in children and strategy suggested for immunization in India. Indian J Med Res 1991;93:337–339.

14. Sobeslavsky O: Prevalence of markers of hepatitis B virus infection in various countries: a WHO collaborative study. Bull WHO 1980;58:621–628.
15. Aggarwal R, Naik SR: Prevention of hepatitis B infection: the appropriate strategy for India. Natl Med J India 1994;7:216–220.
16. International Agency for Research on Cancer: Monographs on the Evolution of Carcinogenic Risks to Humans: Hepatitis Viruses, vol 59. Geneva, World Health Organisation,1994.
17. Greten T, Papendorf F, Bleck J, Kirchhoff T, Wohlberedt T, Kubicka S et al. Survival rate in patients with hepatocellular carcinoma: a retrospective analysis of 389 patients. British Journal of Cancer. 2005;92(10):1862-1868.
18. Zhu Q, Yuan B, Qiao G, Yan J, Li Y, Duan R et al. Prognostic factors for survival after hepatic resection of early hepatocellular carcinoma in HBV-related cirrhotic patients. Clinics and Research in Hepatology and Gastroenterology. 2016;40(4):418-427.
19. Cabibbo G, Maida M, Genco C, et al. Natural history of untreatable hepatocellular carcinoma: A retrospective cohort study. World J 2012;4(9):256–261.
20. Torzilli G, Minagawa M, Takayama T, Inoue K, Hui A, Kubota K et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. Hepatology. 1999;30(4):889-893.
21. Levy I, Greig PD, Gallinger S, Langer B, Sherman M. Resection of Hepatocellular Carcinoma Without Preoperative Tumor Biopsy. Annals of Surgery. 2001;234(2):206-209.
22. Kim UB, Doo CJ, Baek SH, et al. Natural history and prognostic factors of primary hepatocellular carcinoma: study of 70 untreated patients. Korean J Intern Med. 1989;4(2):136–141.
23. Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. Am J Clin Oncol. 1998; 21(4):386–391.
24. Yeung YP, Lo CM, Liu CL, Wong BC, Fan ST, Wong J. Natural history of untreated nonsurgical hepatocellular carcinoma. Am J Gastroenterol. 2005;100(9):1995–2004.
25. Schoniger-Hekele M. Hepatocellular carcinoma in Central Europe: prognostic features and survival. Gut. 2001;48(1):103-109.
26. Llovet JM, Bustamante J, Castells A, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999;29(1):62–67.
27. Ohki T, Sato K, Yamagami M, Ito D, Yamada T, Kawanishi K et al. Erratum to: Efficacy of Transcatheter Arterial Chemoembolization Followed by Sorafenib for Intermediate/Advanced Hepatocellular Carcinoma in Patients in Japan: A Retrospective Analysis. Clinical Drug Investigation. 2016;36(1):93-96.
28. Mittal S, Kramer J, Omino R, Chayanupatkul M, Richardson P, El-Serag H et al. Role of Age and Race in the Risk of Hepatocellular Carcinoma in Veterans With Hepatitis B Virus Infection. Clinical Gastroenterology and Hepatology. 2018;16(2):252-259.

29. Rosellini SR, Arienti V, Nanni O, Ugenti F, Tassinari M, et al. Hepatocellular carcinoma. Prognostic factors and survival analysis in 135 Italian patients. J Hepatol. 1992 Sep;16(1-2):66-72.
30. Paul SB, Chalamalasetty B, Vishnubatla S, et al. Clinical Profile, Etiology and Therapeutic Outcome in 324 Hepatocellular Carcinoma Patients at a Tertiary Care Center in India. Oncology. 2009;77:162-171.

Figures

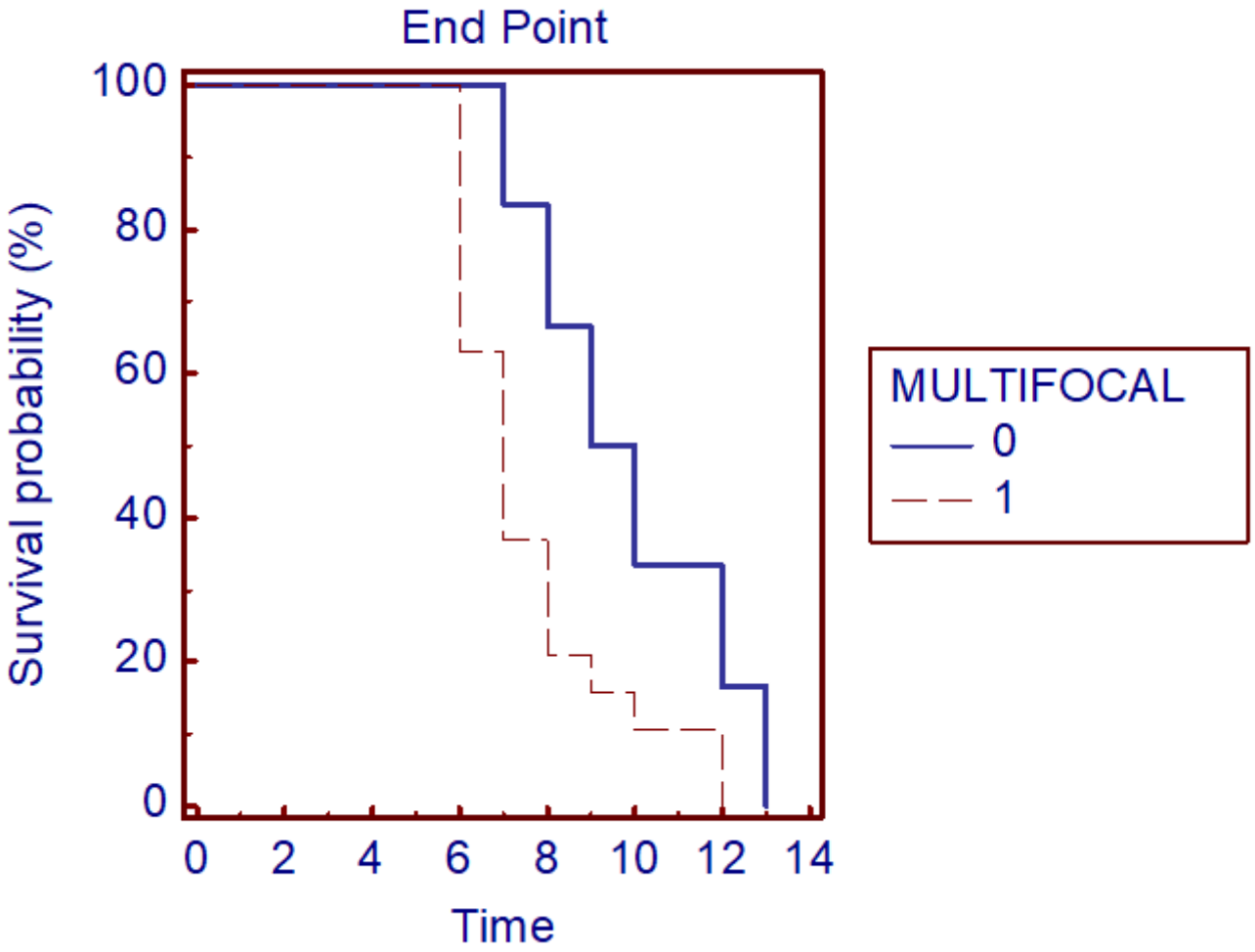

Figure 1

Kaplan Meir Survival Curve Analysis for Multifocality

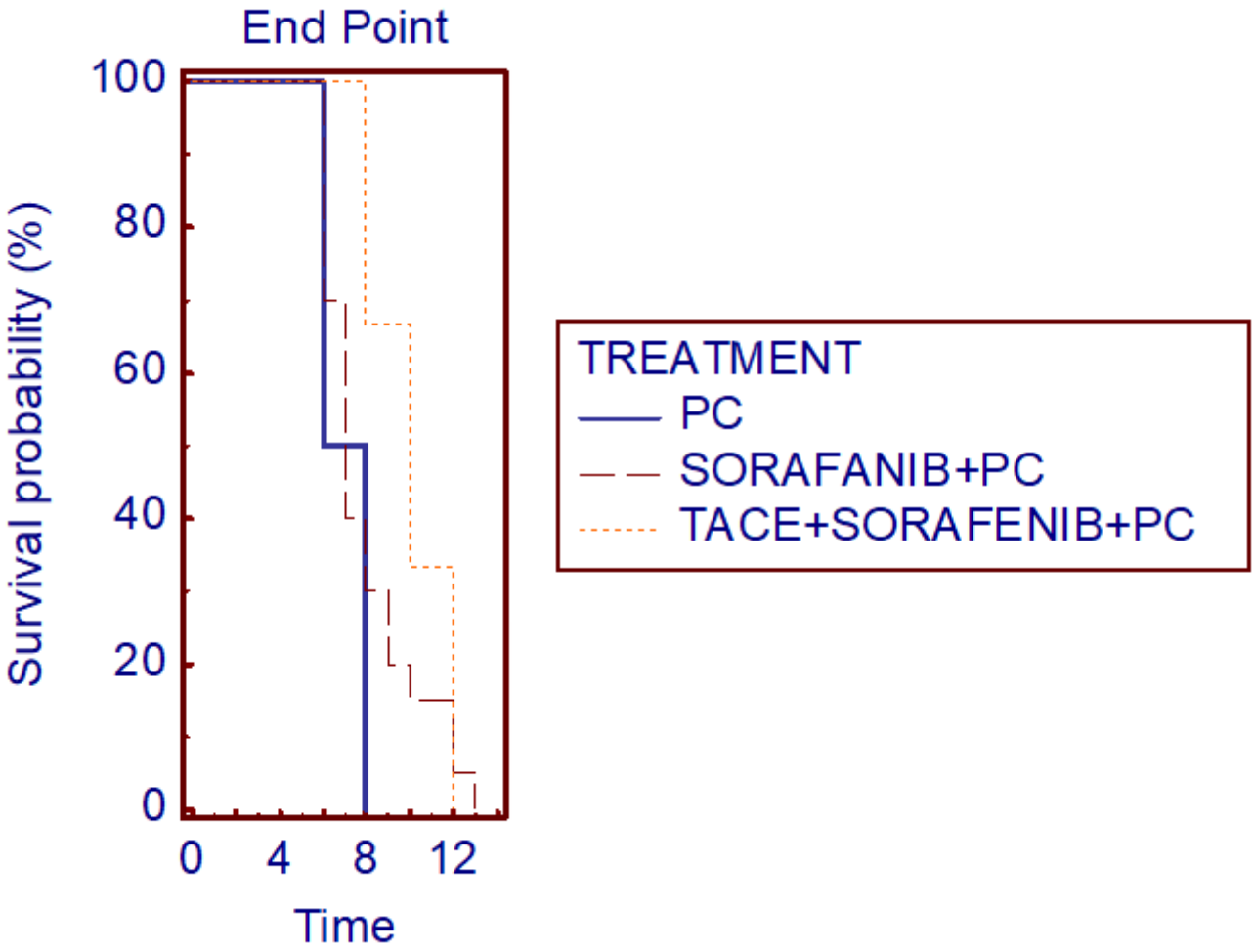

Figure 2

Kaplan Meir Survival Curve Analysis for various treatment methods