Prognostic Factors for Survival of Patients with Hepatocellular Carcinoma in National Cancer Institute, Cairo University

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Abstract: Background: Hepatocellular carcinoma (HCC) is a major contributor to cancer incidence and mortality. HCC is a highly fatal disease and is the third leading cause of death from malignancy worldwide. The aim of the study was to determine long-term survival and prognostic factors predictive of the overall survival of HCC patients at the National Cancer Institute (NCI), Cairo University. Patients and methods: A prospective study was conducted on a cohort of 212 HCC patients attending to the medical oncology clinic at the National Cancer Institute (NCI) during the period from July,1, 2007 till August, 31,2008 and they were followed up by phone till November 7th, 2010. Results: The study revealed that 1-year, 2-year, 3-year survival rates of HCC patients were 26.9%, 9.4%, 5.0% respectively, and median overall survival was 6.3 months (95% CI 5.4-7.2). Multivariate analysis revealed that independent predictors of poor survival were pretreatment presence of extrahepatic metastasis and ascites, and not receiving radiofrequency ablation (RFA) as a treatment modality. Conclusion: The study concludes that most HCC patients at NCI presented at a late stage and their survival was poor. Preserved liver function, non-metastatic presentation of the hepatic tumor and receiving RFA as a treatment modality are associated with good survival of HCC patients.
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Key words: hepatocellular carcinoma, prognosis, survival, hepatitis C virus, smoking

1. Introduction

Hepatocellular carcinoma (HCC) is a major contributor to cancer incidence and mortality. It is a highly fatal disease and is the third leading cause of death from malignancy worldwide **[1].** The burden of HCC has been increasing in Egypt with a doubling in the incidence rate in the past 10 years **[2].** A population–based registry done in Gharbiah declared that over the three years 2000-2002 HCC was the most common type (accounting for 87.6%) of primary liver cancers **[3].** In the National Cancer Institute (NCI), Egypt, a hospital-based registry conducted by the Surgical Pathology Department reported that 70.5% of the histologically examined liver tumors during the period 2003-2004 were HCC **[4].**

The overall survival of the patients with HCC has not improved over the last 20 years, with the incidence rate almost equal to the death rate **[5].** Survival remains low in patients with HCC (median < 6-12 months), reflecting the currently high number of advanced tumors at diagnosis and the subsequent poor efficacy of treatment **[6].**

Factors that may affect prognosis of patients with HCC include: tumor stage at diagnosis (tumor size, number of nodules, vascular invasion, and presence of tumor capsule or metastasis), overall health of the patient, underlying liver disease severity and hepatic synthetic function e.g. ascites, encephalopathy and serum bilirubin, and efficacy of treatment **[5].**

To our knowledge, no reports on prognostic factors influencing long-term survival rates of HCC in a large series of patients have been published in Egypt to date. Thus, the purpose of this observational prospective study was to estimate the overall survival and to evaluate the influence of patient-related factors, tumor-related factors and treatment modalities on the survival of HCC patients at the NCI, Cairo University.

2. Patients and Methods

Patients:

A sample of 212 patients was consecutively recruited from the newly diagnosed HCC patients attending the medical oncology clinic at the NCI, Cairo University, during the period from July 2007 to August 2008. They were followed up every 3 months by phone interview to detect overall survival till November 2010. The sample size was estimated using *Sample Size Tables for Clinical Studies V 2.0,* with true hazard ratio (relative risk) of unexposed patients relative to exposed ones= 0.113, power=0.8 and α=0.05 to reject the null hypothesis that exposed and unexposed survival curves are equal.

Diagnostic criteria for hepatocellular carcinoma:

- Cytopathological criteria.

- Noninvasive criteria: (restricted to patients with cirrhosis) 1) Focal lesion ≤ 2 cm: Two imaging techniques with arterial hypervascularisation and venous washout, 2) Focal lesion > 2 cm: one imaging technique with arterial hypervascularisation and venous washout.

Techniques to be considered: contrast ultrasound, dynamic computed tomography and magnetic resonance imaging **[7]**.

Methods:

This was a prospective study using an interview questionnaire. A pilot study was conducted on 20 patients to assess the acceptability of the patients to participate in the study and to assess the questionnaire (clarity, time consumed and different responses) and it was modified accordingly. The questionnaire involved: 1) demographic data including residence (urban and rural), and occupational history with emphasis on exposure to agricultural pesticides, 2) Special habits (smoking, and alcohol drinking), 3)Past medical history of diabetes mellitus, and schistosomal infection and its parenteral therapy and 4) family history of cancer. Occupation was defined as the longest job that the patient ever had and was categorized into agricultural, industrial, and administrative. Definitions of the different categories were based on Soliman *et al.* **[8].** Cigarette ever-smokers are defined as those who smoked ≥100 cigarettes during their lifetime. Ex-smokers are those who quitted smoking at least one year before study enrollment **[9].**

Data Collection

The interview of each patient was started by explaining simply the objectives of the study, ensuring the confidentiality of the taken data and taking the patient's verbal consent. Recorded clinical data from patients' files were collected using a completion sheet. A follow up sheet was used for recording the patients' status every 3 months through phone interview.

Statistical Analysis

Data were analyzed using SAS (Statistical Analysis Package) version 8.2. Overall survival of the different prognostic factors was estimated using Kaplan and Meier procedure. Overall survival was measured from the first day of attending NCI to the date of death from HCC and its related diseases or the date of last contact with the patient. Comparisons between the survival distributions of different groups were performed by the Logrank test. To study the independent effects of each factor after controlling for all other covariates, factors which had a significance level less than 0.100 were entered into Stepwise Cox Proportional Hazards procedure. Due to the large number of cases with missing values of albumin & bilirubin, these measurements were excluded from the multivariate analysis. Probability (p-value) equal or less than 0.05 was considered significant.

3. Results

The mean age of the study group was 58.6±9.3 years (range 26-80 years), 79.7% were males, 62.7% were residents of rural areas, 35.8% had their longest occupation in the agricultural field, and 47.6% had history of exposure to agricultural pesticides. More than half (52.4%) of the studied patients were cigarette ever-smokers (31.6% current smokers and 20.8% ex-smokers), 31.1% were shisha ever- smokers (11.8%% current smokers and 19.3% ex-smokers), and only 14.6% ever alcohol drinkers (3.8% current drinkers and 10.8% ex-drinkers).

Nearly, half of the patients (50.5%) had history of schistosomal infection, 34.0% were diabetics and 87.6% of those investigated for viral hepatitis (n = 89) were found to have anti-HCV antibodies.

Examination of patients' background liver functions, tumor characteristics and treatment modalities revealed the following findings. Ascites was reported in 30.2% of patients at time of HCC diagnosis, 97.6% were cirrhotic, median values for baseline levels of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), and total bilirubin were above normal, and albumin was below normal indicating hepatic dysfunction. We also found that 52.4% of patients had single mass, largest diameter of the mass was ≥ 5 cm in 56.6% of patients, the right hepatic lobe was affected in 54.7% of patients, 17.9% of patients had extrahepatic metastasis at time of HCC diagnosis, and baseline level of Alpha-fetoprotein (AFP) was greater than 350 ng/mL in 47.6%. More than half (59.0%) of HCC patients received only supportive care or palliative treatment, 27.4% received transarterial chemoembolization (TACE), 6.1% were offered radiofrequency ablation (RFA), 5.3% received chemotherapy either intravenous or oral, and only 2.4% undergone surgical resection.

The median follow up period was 6.3 months (range 0.03-45.07). At the end of the study, 203 patients died (95.8%). One-year overall survival rate was 26.9%, 2-year rate was 9.4%, 3-year was 5.0% and median overall survival was 6.3 months (95% CI: 5.4-7.2) **(Table 1 and Figure 1).**

There was no statistically significant effect of age, sex, residence and occupation on overall survival **(Table 1).** Current shisha smokers had significantly lower median survival compared to never and ex-smokers (p = 0.025) **(Table 2).** While no significant association was found in relation to

exposure to agricultural pesticides, cigarette smoking status, drinking alcohol **(Table 2),** history of schistosomal infection and its parenteral therapy, diabetes mellitus, HCV infection **(Figure 2),** and family history of cancer **(Table 3).**

Table 1: Overall survival in relation to demographic characteristics

Factor	n	Overall survival (%)			Median Survival* (95% CI)	p-value
		1-Year	2-Year	3-Year		
All Cases	212	26.9	9.4	5.0	6.3(5.4-7.2)	
Age, years						
≤60	125	26.4	8.8	4.0	6.0(5.0-7.0)	0.511
>60	87	27.6	10.3	6.9	7.6 (5.7-9.5)	
Sex						
Male	169	24.9	7.7	3.4	6.3(5.4-7.3)	0.166
Female	43	34.9	16.3	11.6	6.1(1.3-11.0)	
Residence						
Urban	79	31.6	11.4	6.1	7.6(5.8-9.4)	0.243
Rural	133	24.1	8.3	4.2	6.0 (5.0-7.1)	
Occupation						
Agricultural	76	22.4	5.3	3.9	5.9(5.0-6.9)	
Industrial	50	26.0	6.0	0.0	7.2(5.2-9.2)	0.372
Administrative & Housewife	86	31.4	15.1	9.2	6.1(3.5-8.7)	

*Measured in months, CI: confidence interval

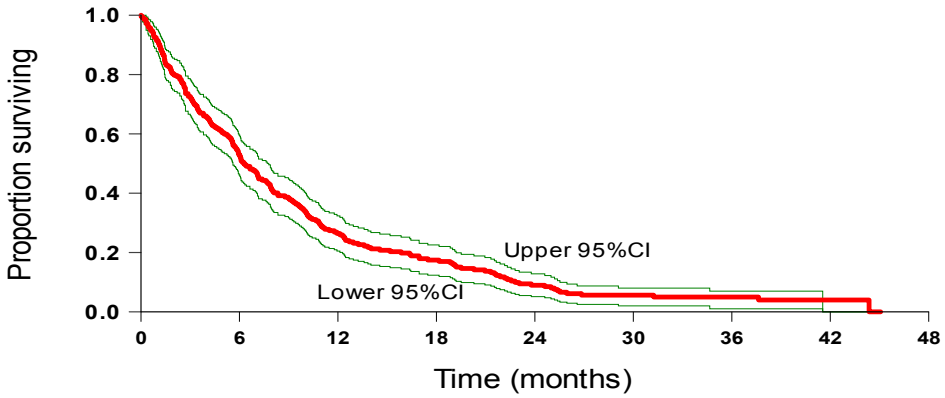

Figure 1: Overall survival of HCC patients with 95% CI

Table 2: Overall survival in relation to exposure to agricultural pesticides and special habits

Factor	n	Overall survival (%)			Median Survival* (95% CI)	p-value
		1-Year	2-Year	3-Year		
Exposure to agricultural pesticides						
No	103	28.2	11.7	6.4	6.8 (4.8-8.8)	0.692
Yes	101	27.7	7.9	4.0	6.3 (4.9-7.8)	
Cigarette smoking status						
Never smoker	98	30.6	13.3	6.8	5.8 (4.3-7.3)	0.297
Current smoker	67	17.9	3.0	0.0	6.8 (5.5-8.1)	
Ex-smoker	44	34.1	11.4	9.1	7.7 (5.6-9.7)	
Shisha smoking status						
Never smokers	142	23.9	9.2	4.9	6.1 (5.0-7.2)	**0.025**
Current smokers	25	20.0	0.0	0.0	4.2 (2.2-6.2)	
Ex-smokers	41	43.9	17.1	9.8	8.1 (2.9-13.2)	
Ever alcohol drinking						
No	173	28.9	11.0	5.5	6.5 (5.1-7.9)	0.273
Yes	31	22.6	6.5	3.2	6.2 (2.5-9.9)	

Some data were missing due to inability of some patients to remember their smoking history and exposure to pesticides and some refused to say their alcohol drinking status.
*Measured in months, CI: confidence interval

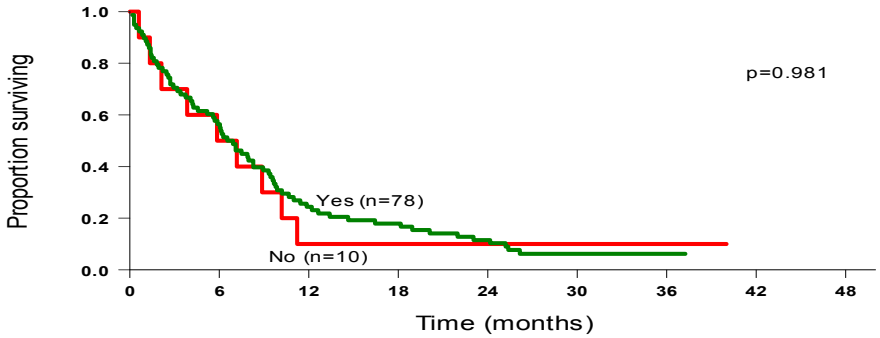

Figure 2: Overall survival of HCC patients according to HCV infection status

Table 3: Overall survival in relation to history of schistosomal infection and its parenteral therapy, Diabetes mellitus, HCV infection, and family history of cancer

Factor	n	Overall survival (%) 1-Year	2-Year	3-Year	Median Survival* (95% CI)	p-value
History of schistosomal infection						
No	62	29.0	11.3	9.7	6.1 (3.5-8.7)	0.867
Yes	107	32.7	11.2	4.7	7.1 (5.4-8.9)	
History of Parenteral anti-schistosomal therapy (PAT)						
No	81	28.4	11.1	8.6	6.8 (4.7-8.8)	0.488
Yes	71	36.6	14.1	5.6	8.6 (5.8-11.3)	
Diabetes mellitus						
No	138	25.4	8.0	4.1	6.1 (5.1-7.0)	0.479
Yes	72	30.6	12.5	6.9	7.2 (4.9-9.3)	
HCV infection						
No	10	20.0	10.0	10.0	6.8 (2.6-10.9)	0.981
Yes	78	25.6	11.5	6.2	6.8 (4.8-8.7)	
Family history of cancer						
No	152	26.3	10.5	5.8	6.1 (5.1-7.2)	0.841
Yes	53	30.2	5.7	—	7.1 (4.5-9.6)	

Some data were missing due to inability of some patients to remember their medical or family history of cancer
A dash (—) indicates that last patient was censored after 26.8 months
*Measured in months, CI: confidence interval

Patients who didn't have ascites at time of diagnosis of HCC (p = 0.001), those with higher albumin levels (>3.1 g/dL) (p = 0.036), those presented with tumor diameter of < 5 cm in its largest dimension (p = 0.001) and those with pretreatment AFP levels less than 350 ng/mL (p = 0.003), had longer median survival however **(Tables 4 and 5).**

Table 4: Overall survival in relation to background liver factors

Factor	n	Overall survival (%) 1-Year	2-Year	3-Year	Median Survival* (95% CI)	p-value
Ascites						
No	147	33.3	10.9	5.0	8.0 (6.2-9.7)	**0.001**
Yes	64	12.5	6.3	4.7	3.5 (2.4-4.6)	
Splenomegaly						
No	75	33.3	14.7	7.8	7.9 (6.1-9.8)	0.121
Yes	122	24.6	7.4	3.9	6.1 (5.0-7.2)	
ALT (IU/L)						
≤ 51	94	35.1	9.6	5.1	8.1 (6.1-10.1)	0.212
> 51	87	24.1	12.6	6.7	6.1 (4.6-7.6)	
AST (IU/L)						
≤ 70	92	33.7	10.9	6.0	8.6 (6.7-10.5)	0.147
> 70	89	25.8	11.2	5.6	6.0 (4.3-7.8)	

ALP (IU/L)						
≤ 228.5	76	35.5	13.2	—	9.0 (6.7-11.2)	0.223
> 228.5	76	25.0	9.2	6.6	6.1 (4.4-7.9)	
Albumin (g/dL)						
≤ 3.1	66	25.8	6.1	3.0	7.2 (5.2-9.2)	**0.036**
> 3.1	55	36.4	16.4	9.1	10.0 (8.5-11.6)	
Total Bilirubin (mg/dL)						
≤ 1.4	88	30.7	12.5	6.4	7.9 (5.9-9.9)	0.077
> 1.4	84	25.0	8.3	4.8	5.6 (3.9-7.1)	

For ALT, AST, ALP, Albumin & Bilirubin, the cut off was set as the median value
A dash (—) indicates that last patient was censored after 32.1 months
Some data were missing from patients' files
Abbreviations: ALT; Alanine Aminotransferase, AST; Aspartate Aminotransferase, ALP; Alkaline Phosphatase.
*Measured in months, CI: confidence interval

Table 5: Overall survival in relation to background tumor factors

Factor	n	Overall survival (%)			Median Survival* (95% CI)	p-value
		1-Year	2-Year	3-Year		
Number of masses						
Single	111	29.7	11.7	7.1	7.1 (5.6-8.7)	0.128
Multiple	100	24.0	7.0	3.0	5.9 (4.3-7.6)	
Hepatic lobe affected						
Right	116	33.6	10.3	6.7	7.2 (4.8-9.6)	0.066
Left	34	26.5	11.8	—	6.3 (4.8-7.9)	
Both	52	13.5	5.8	1.9	5.9 (4.1-7.8)	
Largest dimension of the mass						
<5 cm	43	39.5	20.9	16.3	8.1 (5.2-11.0)	**0.001**
5+ cm	120	26.7	5.0	0.8	6.0 (4.9-7.2)	
Pathological grade						
Grade I	21	42.9	19.0	14.3	11.2 (10.0-12.5)	0.491
Grade II	35	42.9	17.1	8.6	9.0 (6.5-11.5)	
Grade III	8	25.0	12.5	—	4.8 (0.0-9.8)	
AFP (ng/mL)						
< 350	97	36.1	14.4	7.7	8.6 (6.4-10.8)	**0.003**
≥ 350	90	18.9	4.4	1.1	5.6 (4.0-7.1)	
Presence of extrahepatic metastasis at time of diagnosis						
No	174	28.2	9.8	5.0	7.1 (5.8-8.4)	0.115
Yes	38	21.1	7.9	5.3	3.2 (0.1-6.3)	

For AFP a round figure 350 ng/mL was set as cut off value
A dash (—) indicates that last patient was censored after: 32.1 months for left hepatic lobe affected and 31.2 months for pathological grade III
Some data were missing from patients' files Abbreviation: AFP; Alpha-fetoprotein
*Measured in months, CI: confidence interval

Table 6: Overall survival in relation to type of treatment modality

Factor	n	Overall survival (%)			Median Survival* (95% CI)	p-value
		1-Year	2-Year	3-Year		
BSC						
No	24	16.7	0.0	0.0	5.8 (2.1-9.6)	0.071
Yes	188	28.2	10.6	5.6	6.3 (5.1-7.6)	
TACE						
No	154	24.0	9.1	5.8	5.3 (4.0-6.6)	**0.031**
Yes	58	34.5	10.3	3.4	9.5 (7.7-11.4)	
RFA						
No	199	23.6	6.5	3.0	6.1 (5.1-7.0)	**<0.001**
Yes	13	76.9	53.8	34.6	25.3 (13.0-37.6)	

Abbreviations: BSC; Best Supportive Care, TACE; Transarterial chemoembolization, RFA; Radiofrequency Ablation; *Measured in months, CI: confidence interval

Patients who received TACE had statistically significant longer median survival than those who didn't (p = 0.031). RFA had statistically significant effect on survival of HCC patients (p <0.001), while BSC had statistically insignificant effect on survival of HCC patients **(Table 6 and Figures 3- 4).**

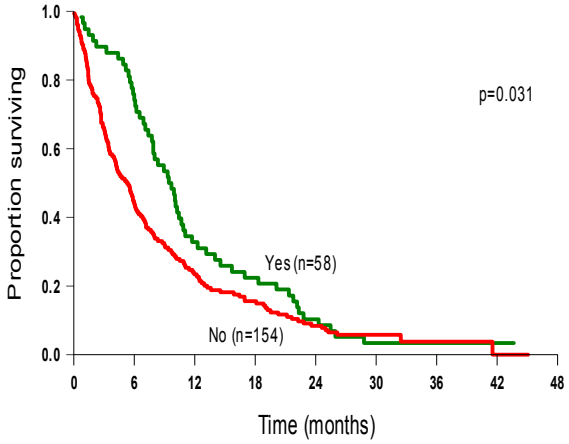

Figure 3: Overall survival of HCC patients in relation to TACE as treatment modality

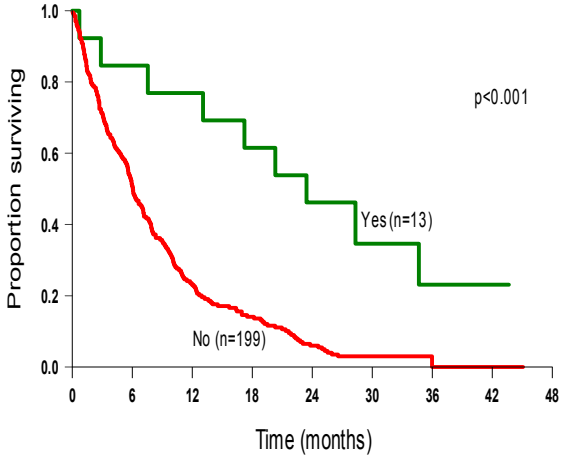

Figure 4: Overall survival of HCC patients in relation to RFA as treatment modality

Multivariate analysis was conducted to study the independent effects of each factor after controlling for other covariates. It revealed that patients who presented at the time of diagnosis with metastasis or ascites, or did not receive RFA were more likely to die from liver cancer (hazard ratio 1.53, 1.66 and 3.63 respectively) **(Table 7).**

Table 7: Cox Proportional Hazards model for overall survival and its relation to prognostic factors

Variable		B	SE	HR	HR 95% CI		p-value
					Lower	upper	
Pretreatment presence of extrahepatic metastasis	Yes	0.426	0.188	1.53	1.06	2.21	**0.023**
	No			Ref			
Ascites	Yes	0.505	0.157	1.66	1.22	2.26	**0.001**
	No			Ref			
RFA	No	1.288	0.349	3.63	1.83	7.19	**<0.001**
	Yes			Ref			

Abbreviations: B; Regression Coefficient, SE : standard error HR; Hazard Ratio

4. Discussion

One-year overall survival rate of HCC patients in the current series was 26.9%, 2-year rate was 9.4%, 3-year was 5.0% and median overall survival was 6.3 months (95% CI 5.4-7.2). A previous study at NCI reported a median survival of 4.0 months, but survival time was measured from the time of treatment **[10].**

Different rates were reported in other countries; 1-year, 2-year, and 3-year survival rates were 44.8%, 32.8%, and 17.6% respectively in a Lebanese study conducted **[11].** In Turkey, 1- and 2-year rates were 60.4% and 4.3% respectively **[12].** In USA, 1-year survival was reported between 47-63% and 2-year rates ranged from 29% to 39%, median survival was 16.4 to 22.3 months **[13-15]**. Different survival rates may be attributed to the difference in study population, or early detection of HCC, through surveillance programs applied in some countries e.g. USA, giving patients better chance for liver transplantation or surgical resection with better prognosis.

Age, sex, residence, and occupation were not significantly related to survival of HCC patients in the current series. This agrees with several studies **[12-14, 16-18].** However, other studies showed that females had significantly longer survival **[19-20]**, which may be explained by higher compliance with surveillance than a real biological difference.

In the current study, we found no significant association between cigarette smoking and survival in HCC cases. This finding was in agreement with many studies **[10, 14, 21-23],** but other studies found that cigarette smoking was significantly related to HCC mortality **[24-26].** However we found that shisha smoking was associated with shorter median survival. This may be attributed to lack of use of the

standardized definitions of cigarettes smoking behavior in the different study populations and absence of those definitions in relation to shisha smoking. This might hinder valid comparison across different studies in different counties. Also, Alcohol consumption was not found to be a significant predictor of survival in the current study which was in concordance with many studies **[17, 27].**

We also found that, past history of HCV infection, diabetes mellitus, schistosomal infection and its parenteral therapy were not related to survival of HCC cases. Results for HCV infection were consistent with those reported in USA **[13, 14].** However, reports from Korea **[28],** Taiwan **[29],** and Pakistan **[5]** showed that HCV infection was an independent predictor of poor survival. Different results in the current series may be due to having limited number of cases investigated for HCV.

Among background liver factors, only ascites was found to be significantly associated with shorter survival in univariate and multivariate analyses, while low albumin was significantly associated with shorter survival only in univariate analysis. It was excluded from multivariate analysis due to large number of missing cases (n = 91). Ascites and pretreatment albumin levels were showed to be independent predictors of poor survival in other studies, either by themselves **[18, 30-32]** or as a part of Child-Pugh score **[28, 33, 34].**

Results for ALP and total bilirubin were consistent with those reported by other studies **[5, 12, 13],** but total bilirubin was found to be an independent predictor of HCC survival either by itself **[11, 30, 32]** or as a part of Child-Pugh score **[28, 33, 34].** Different results may be attributed to excluding total bilirubin from multivariate analysis due to large number of cases with missing values. Although it can be argued that these parameters may simply reflect severe end-stage liver disease rather than tumor morbidity per se, this issue is not pertinent in clinical practice, as most patients will eventually die from progressive liver failure or complications of end-stage liver cirrhosis **[17].**

In the current study, among tumor factors, extrahepatic metastasis was found to be an independent predictor of poor prognosis, which is consistent to what was reported in a Korean study **[33].** Also HCC mass size < 5 cm was a significant predictor of longer survival similar to those reported by others **[30].**

The pathological grade of HCC was reported by a previous study to be significantly related to survival **[34].** This was inconsistent with that reported in the present work and can be explained by having a relatively small number of patients (n = 64) with known pathological grade. Some studies agree with the finding that pretreatment level of AFP is not significantly related to survival of HCC patients **[10, 13, 14],** while others reported it as an independent predictor of HCC survival **[12, 18, 28, 31– 34].**

Regarding treatment modalities, in the current study RFA was an independent predictor of longer survival, whereas other studies reported local ablation therapy, either RFA or PEI, as an insignificant determinant of overall survival **[31, 32].** The inconsistence between those studies and the current work may be due to not studying RFA per se. The current study also showed that TACE is an insignificant predictor of survival of HCC patients. The same conclusion was reached in a prospective study in Australia **[31].** In contrast, others reported that offering TACE was an independent predictor of longer survival **[5, 32].** Different results may be attributed to different study populations or stage specification.

In summary, the current study identified pretreatment presence of ascites and extrahepatic metastasis, and not receiving RFA as independent predictors of poor survival of HCC. The advanced stage at presentation, poor background liver function and the absence of a national liver transplantation program limit treatment options. Less than half (41.0%) of patients were considered suitable for specific treatment. The overall prognosis remains bleak. This total view of tragedy should direct us towards screening programs for early detection of HCC in high risk patients at a national level and searching for new approaches in management; this may change the clinical end points towards favorable ones. There is an urgent need to educate the public about the risks of hepatitis B and C. Urgent consideration needs to be given to the development of a sustainable national liver transplant program in our country.

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