Pan Arab Journal of Oncology

Original Article

Comparison between cirrhotic HCC patients versus non-cirrhotic HCC patients

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Received 3 Dec 2016
Accepted 21 Feb 2017
Revised version
Available online 12 Mar 2017

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Keywords:
Hepatocellular carcinoma,
Cirrhosis,
Liver,
Yemen,
Survival

ABSTRACT

Objectives: Hepatocellular carcinoma (HCC) usually occurs in patients with cirrhosis, but can also develop in noncirrhotic livers. In the present study we compared patients and tumor characteristics and outcomes in HCC patients with and without underlying cirrhosis.
Methods: Patients with HCC diagnosed in the period January 2010 – December 2014 in the National Oncology Centre, Sana'a, Yemen were evaluated. Patients were categorized according to the presence of cirrhosis on the basis of histology or combined radiological and laboratory features.
Results: In total, 43.8% of the 486 HCC patients had no underlying cirrhosis. Non-cirrhotic HCC patients were less likely to have hepatitis C virus or Hepatitis B virus than did cirrhotic HCC patients. HCCs in noncirrhotic livers were more often unifocal (58.2 vs. 36.1%) and tumor size was larger (11 vs. 10 cm) (p=0.011). Overall survival was significantly better than in cirrhotic. In multivariate and Cox regression analyses, thrombocytopenia and portal vein thrombosis were independent predictors for lower mortality.
Conclusion: Liver cirrhosis was found in only half of the studied HCC patients. HCC patients with liver cirrhosis were more likely to have multiple tumor and more advanced stage at presentation as well as significantly worse overall survival when compared to non-cirrhotic HCC patients.

INTRODUCTION

Primary liver cancer is the sixth most common cancer in the world and the second cause of cancer-related death [1]. Hepatocellular carcinoma (HCC) represents more than 90% of all primary liver cancers and typically occurs in patients with underlying cirrhosis. Nevertheless, HCC can also develop in noncirrhotic livers. On the basis of previous studies, the proportion of HCC in the absence of cirrhosis varied widely (from 2 to 54%) between various geographical regions [2–7].

The incidence rate of HCC varies widely from 52.1 per 100.000 populations in China to 5.1 per 100.000 populations in Northern Europe, depending on the geographical location and the exposure to viral aetiology.[8]In the Middle East, HCC is reported to account for about 4.7% – 7.3% of patients with chronic liver disease.[9]

The global age distribution of HCC varies by incidence, gender and, possibly, also by etiology. The major, well-established risk factors for HCC are chronic infection with Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV), dietary exposure to aflatoxin B_1 contaminated foodstuffs and alcoholic cirrhosis. Overall, it is estimated that HBV and HCV infections are causally associated with over 80% of HCC worldwide.[10]

In Yemen, HCC is among the most common gastrointestinal tumors, representing 38.66% of all gastrointestinal malignancy.[11] Both HBV and HCV were considered risk factors for HCC occurrence with a greater role for HBV among Yemeni patients.[12]

The severity of the underlying liver disease has a great impact on treatment decisions and prognosis in HCC patients: presence of cirrhosis and resulting impaired liver function may limit surgical and nonsurgical options. In contrast, absence of cirrhosis could favor use of surgical treatment with curative intent [6, 13, 14].

METHODS

All patients with an HCC diagnosis in the period January 2010–December 2014 in the National Oncology Centre, Sana'a, Yemen were evaluated. Diagnosis of HCC was based on AASLD 2005 and 2011 guideline criteria [15, 16]. Collected data were obtained from medical records. Patients were categorized according to the presence or absence of cirrhosis. Patients were included in the 'no cirrhosis' group on the basis of the following criteria as essentially proposed by El-Serag et al. [17]: (A) histology without cirrhosis in biopsy within 1 year of HCC diagnosis combination with absence of radiological features of cirrhosis, or (B) (in absence of liver histology) all two of the following criteria: (1) two of the following three laboratory tests within normal range: (a) albumin greater than 35g/l, (b) platelet counts greater than 200×109/l, (c) international normalized ratio less than 1.1, and (2) absence of radiological features of cirrhosis. Patients who had histology demonstrating cirrhosis or (in absence of histology) clear radiological features of cirrhosis and/or did not fulfill the above mentioned criteria for the 'no cirrhosis' group were included in the 'cirrhosis' group.

This study was approved by the Ethical Committee of Faculty of Medicine -Alexandria University and the National Oncology Centre Sana'a Yemen. A written consent was obtained from each patient. Confidentiality of records were considered and patients' names were coded.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics (version 20.0; IBM Corp., Armonk, New York, USA). Independent samples t-test was used for the comparison of 2 means. Univariate and multivariate logistic regression analyses were performed to evaluate patient characteristics (i.e. sex, age, and etiology of underlying liver disease) associated with risk of HCC. Survival time was calculated from date of diagnosis to date of death or end of follow-up (latest: end of study 30 October 2015). The Kaplan–Meier survival curves and logrank tests were used to compare survival rates between the cirrhotic and noncirrhotic patients in the total group. Possible predictors for overall mortality were tested using univariate and multivariate Cox proportional hazard regression. A two-sided P-value of less than 0.05 was considered statistically significant.

RESULTS

This is a retrospective study that included 486 HCC patients who presented to the National Oncology Centre, Sana'a –Yemen during the period from January 2010 to December 2014.

A total number of 694 patients were registered as HCC patients during this period; however 208 patients were excluded from the study due to unavailability of adequate documentation to fulfill the criteria of HCC diagnosis.

Liver Cirrhosis

Liver cirrhosis was identified in 263 patients (54.1%). The C-P score A was found in 116 patients out of 263 HCC patients with cirrhotic liver (44.1%). Hundred patients (38%) had Stage C by BCLC staging system, and only seven patients (2.7%) had BCLC Stage A.

Regarding viral markers, in cirrhotic HCC patients HCV antibody testing was positive in 45.2% compared to 5.6% of non-cirrhotic patients. Forty percent of cirrhotic HCC patients had positive HBsAg test, compared to 4.7% in non-cirrhotic patients and the difference was statistically significant. Smoking was more common among cirrhotic HCC patients, while khat consumption was more common among non-cirrhotic patients and the difference was statistically significant. (Table 1)

Clinical and laboratory manifestations of liver decompensation and poor ECOG PS were more common among cirrhotic HCC patients at presentation. The difference was statistically significant. The mean serum AFP value was significantly higher in cirrhotic HCC patients versus non-cirrhotic patients (631.8±389.9 versus 518.5±419.8 respectively). (Table 2-3)

The incidence of multiple hepatic tumor, PV thrombosis and portal hypertension were more common among cirrhotic HCC patients than non-cirrhotic. The difference was statistically significant. Cirrhotic HCC patients had statistically significant more advanced TNM stage at presentation. (Table 4)

Table 1. Socio-demographic characteristics of cirrhotic versus non-cirrhotic HCC patients

Item	Cirrhotic (n=263)		Non-cirrhotic (n=213)		*P*
	No	%	No	%	
Sex					
Male	181	68.8	148	69.5	0.876
Female	82	31.2	65	30.5	
Age (years) Mean ±SD	62.5±11.1		63.9±11.8		t (p)= 1.330 (0.184)
Risk factors					
HBsAg	106	40.3	10	4.7	<0.001*
HCV Ab	119	45.2	12	5.6	<0.001*
Khat chewing	209	79.5	169	79.3	0.973
Shamma	57	21.7	63	29.6	0.048*
Smoking	142	54.0	87	40.8	0.004*
Alcohol	2	0.8	4	1.9	FEp=0.415
Rural residence	218	82.9	175	82.2	0.835
Farmers	177	67.3	127	59.6	0.083
Diabetes mellitus	37	14.1	35	16.4	0.474

*: Statistically significant at $p \leq 0.05$
FE: Fisher Exact for Chi square test for comparing between group I and II
t, p: t and p values for Student t-test for comparing between the two groups

Table 2. Clinical characteristics of cirrhotic versus non-cirrhotic HCC patients

Item	Cirrhotic (n=263)		Non-cirrhotic (n=213)		*p*
	No	%	No	%	
Abdominal pain	255	97.0	208	97.7	0.644
Abdominal mass	225	85.6	173	81.2	0.204
Bleeding	14	5.3	1	.5	0.003
Jaundice	103	39.2	47	22.1	<0.001*
Cachexia	73	27.8	24	11.3	<0.001*
Ascites	125	47.5	34	16.0	<0.001*
Splenomegaly	128	48.7	28	13.1	<0.001*
Hepatomegaly	188	71.5	177	83.1	0.003*
Metastasis	53	20.2	35	16.4	0.299
Performance status:					
ECOG 0-1	81	30.8	92	43.2	t=11.043* p = 0.027*
ECOG 2-4	182	69.2	121	56.8	

p values for Chi square test for comparing between the two groups
t, p: t and p values for Student t-test for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

Table 3. Laboratory findings in cirrhotic versus non-cirrhotic HCC patients

Item	Cirrhotic (n=263)	Non-cirrhotic (n=213)	T-test	
	Mean ± SD	Mean ± SD	T	*p*
Hemoglobin concentration (g/dl)	11.7±1.4	12.3±1.1	5.107*	<0.001*
Total white blood cells (x10^9/L)	7.19±2.25	7.58±2.75	1.702	0.089
Platelets count (x10^9/L)	287.4±113.1	331.0±105.1	4.316*	<0.001*
Total bilirubin (mg/dl)	2.02±3.05	1.19±1.32	3.700*	0.0002*
Albumin concentration (g/dl)	3.3±0.5	3.6±0.4	7.106*	<0.001*
INR	1.32±0.36	1.01±0.13	5.269*	<0.001*
Alfa fetoprotein (ng/ml)	631.8±389.9	518.5±419.8	3.046*	0.0025*

Table 4: Radiological findings and TNM staging in cirrhotic versus non-cirrhotic HCC patients

Item	Cirrhotic (n=263)		Non-cirrhotic (n=213)		*p*
	No	%	No	%	
- Site of tumor:					
Right lobe	122	46.4	94	44.1	
Left lobe	36	13.7	41	19.2	0.257
Bilobar	105	39.9	78	36.6	
- Number of masses:					
Single lesion	95	36.1	124	58.2	<0.001*
Multiple lesions	168	63.9	89	41.8	
- Size of the biggest mass (cm)	8.2±2.1		8.7±2.2		t (p)= 2.528* (0.011*)
- Portal vein thrombosis	47	17.9	21	9.9	0.013*
- Hepatic vein thrombosis	9	3.4	15	7.0	0.073
- Portal hypertension	35	13.3	6	2.8	<0.001*
-TNM staging					
I-II	105	39.9	97	45.5	0.005*
III-IV	158	60.1	116	54.5	

Regarding histopathological tumor features, classical HCC was found in 93.1% and 83.8% of cirrhotic and non-cirrhotic HCC patients respectively. The difference was statistically significant.

Therapeutic Modalities

Regarding, therapeutic modality, 61.9% of the studied patients received supportive treatment alone, while 26.9% of patients received chemotherapy in the form of doxorubicin (22.8%); capecitabin (3.9%) and gemcitabine (0.2%). Sorafenib was given to only 12 patients (2.5%). Surgical resection was performed in ten patients (2.1%), and only one patient had liver transplantation. Three patients (0.6%) had TACE.

Median Survival

The median survival was 7.92 and 13.8 months in cirrhotic and non-cirrhotic HCC patients respectively and the difference was statistically significant (p= 0.033); Figure (1)

Prognostic Factors

Presence of PV thrombosis or thrombocytopenia (platelet count below 150000/mm^3) was associated with worse OS (Table 5)

Table 5. Cox regression for the determining the independent factors affecting mortality

Item	B	SE	p	OR
Khat Chewing	1.111	0.805	0.167	3.037
ECOG	0.650	0.700	0.353	1.916
PLAT	1.599	0.339	<0.001*	4.946
PVT	1.098	0.307	<0.001*	2.999
Smoking	0.492	0.325	0.130	1.636
HCV result	0.249	0.324	0.442	1.283

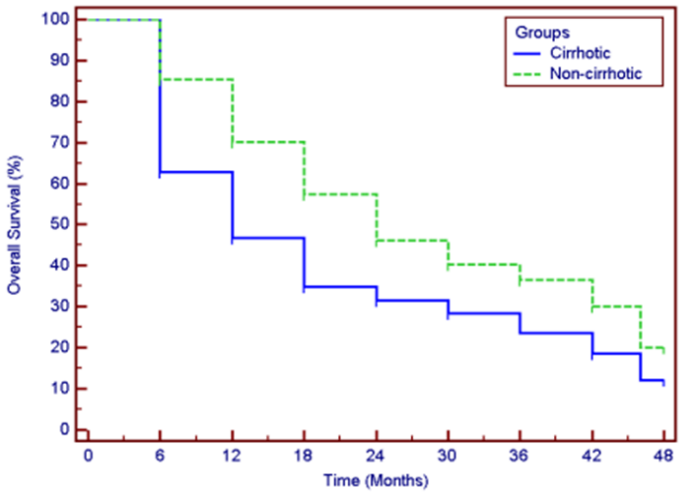

Fig. 1. Kaplan-Meier curves for over all survive in both cirrhosis and non-cirrhosis HCC patients all over the period of follow up

DISCUSSION

Worldwide, HCC is one of the most common malignancies associated with poor prognosis. The magnitude of the problem of HCC in Yemenis has not been explored yet. There has been a remarkable increase of the proportion of HCC among Yemenis population.

The present study was carried out to study the different clinicopathologic features and treatment of HCC cases in the period between 2010 and 2014.

In the present study, patients with cirrhosis HCC (n=263) were categorized according to BCLC system to stages A, B, C and D. Most of the patients presented in late stages; 38% had stage C and 31.5% had stage D while 27.8% had stage B and 2.7% had stage A. This might be explained first by poor liver functions of patients at presentation. Second, most of the patients presented by late tumor stage and with poor performance status.

In the current study, 353 of patients had pathologic diagnosis of HCC. The classic histopathological type was identified in 98.6% of cases, whereas only 1.4% of cases were of the fibrolamellar type. This agrees with the WHO classification of tumors of the liver that reported that fibrolamellar HCC accounted for only 0.5–9% of primary liver cancers.[18]

With regarding to treatment, management tools of HCC were variable in the present work. Most of the studied patients (62%) were treated with supportive measures. Although, 37.2% of the patients had solitary liver lesion, regional therapies were applied only in very limited number of patients. Only, 2.1% of studied patients had surgical resection of the tumor, 0.6% had TACE and 0.2% underwent liver transplantation. This also might be explained by limited resources and low experience for applying such curative regional therapies. Systemic chemotherapy was given in 26.9% of studied patients. Sorafenib was given in only 2.5% of patients; reflecting lack of reimbursement for Sorafenib by Government. Assessment of outcomes of any given treatment was not feasible in the present study due to variability of applied treatment modalities, lack of adequate documentation of patients' progress and lack of long term follow up data. Additionally, some of patients were referred to other facilities for treatment leading to loss of the patients' follow-up.

In the current study, cirrhotic was identified radiologically in 54.1% of the studied patients, while 43.8% of cases were non-cirrhotic HCC. Statistical analysis was carried out to compare cirrhotic versus non-cirrhotic HCC patients.

Shamma chewing was more common among non-cirrhotic HCC patients, while cigarette smoking was more prevalent among cirrhotic HCC patients. The difference was statistically significant. HBV testing was positive in 40% of HCC patients with liver cirrhosis, compared to only 4.7% of HCC patients without cirrhosis (p=0.0001). HCV infection was present in 45% of cirrhotic HCC patients compared to only 5.6% of non-cirrhotic HCC patients (p=0.0001). This reflects the need for research to identify significant unknown risk factors for development of HCC in Yemeni population other than hepatitis. Dietary exposure to aflatoxin B1 (AFB1) may play an important etiological role. Aflatoxins are difuranocoumarin derivatives of Aspergillus flavus and Aspergillus parasiticus. These fungi contaminate crops, particularly maize, ground nuts and fermented soybeans, in tropical and sub-tropical countries with warm, humid climates. Contamination occurs both during growth of the crops and as a result of their improper storage. Sub-Saharan Africa and the Asia-Pacific region have high levels of exposure to the fungal toxin. AFB1 is the aflatoxin most often found in contaminated human foodstuffs and is the most potent hepatocarcinogen.

Manifestations of liver impairment were significantly more common among cirrhotic HCC patients. Serum AFP values were significantly higher in cirrhotic HCC patients than in non-cirrhotic patients.

HCC patients with cirrhotic liver were more likely to have multiple hepatic tumors and advanced TNM stage at presentation, while non-cirrhotic patients were more likely to have single hepatic lesion and larger mass sizes. Additionally, PV thrombosis and portal hypertension were more common among patients with liver cirrhosis. These findings were statistically significant. This agrees with the results of the study by Van Meer et al. that reported HCCs in non-cirrhotic livers were more often unifocal (67 vs. 48%), but tumor size was significantly larger (8 vs 4 cm).[19]

HCC patients with liver cirrhosis had significantly worse OS when compared to non-cirrhotic HCC patients. The median survival was 7.92 and 13.8 months in cirrhotic and non-cirrhotic HCC patients respectively (p=0.033). This is comparable with data by Gaddikeri et al. study that reported non-cirrhotic patients with HCC have better OS and disease-free survival than cirrhotic patients with HCC.[20]

Regarding prognostic factors, neither age nor sex had significant impact on the OS of the studied patients, this is similar to results from a Japanese study, which reported no significant correlation between age and sex in relation to median survival.[21] On the other hand, ECOG PS scale of 2 or more was associated with significantly worse survival in the present study, this agrees with the results of the study by Nishikawa et al. that reported poorer PS was an independent predictor linked to OS.[22]

Patients' social habit like smoking and Khat chewing had negative impact on OS (p=0.001). This may highlight the impact of Khat as a hepatocarcinogen; partly due to the fact that pesticides are heavily used within Khat farms. Also, this may suggest that Khat may induce a degree of liver cell damage. Further research is needed to address these issues.

In the present work, presence of HCV infection had no significant impact on survival. This is in disagreement with a Japanese study conducted by Masafumi Ikeda et al. that stated that positivity of anti-HCV Abs was a good prognostic factor and was strongly associated with favorable tumor-related factors, such as smaller tumor size and tumor number.[23] This variation maybe explained by lack of effective antiviral treatment, paucity of follow-up date as well as limited use of definitive therapies for HCC in the present study. Furthermore, marked cirrhosis and impairment of liver functions that accompanied HBV and HCV infections that might affect patients' survival and led to limitation of treatment options in the studied patients.

In the current work, serum AFP level had no significant impact on survival which was consistent with a study done by A. Martins et al. concluded that level of AFP was not of predictors for survival in HCC.[24]

Thrombocytopenia had a significantly adverse effect on survival. Patients with PV thrombosis had significantly lower OS rates. This was consistent with the South Korean study by Choi Y et al. that reported PV thrombosis was independent prognostic factors for OS.[25]

HCC is a common malignancy among Yemeni population and half of the HCC patients present with liver cirrhosis. Approximately half of the studied patients had neither HBV nor HCV infection, this suggest that other etiologic factors are contributing to the emergence of HCC in Yemeni population.

Because of the high incidence, inadequate treatment and graver prognosis of HCC, prevention of the tumor is an urgent priority. Incorporation of a full program of HBV vaccination into an Expanded Program of Immunization in Yemen can prevent thousands of deaths from cirrhosis and HCC. Attempts at prevention of HCV and HBV infection should include encouraging the avoidance of the high-risk behaviors of illicit drug injection and unsafe sexual activity as well as careful screening of donated blood for the presence of these viruses.

Despite recent advances in treating patients with chronic hepatitis, the high cost of the anti-viral agents remains an impediment in low-income countries. National efforts should focus on acquiring adequate expertise and equipment for applying surgical and loco-regional therapies in patients presenting with early HCC.

National Cancer registry in Yemen, besides its role in patients' care and compiling databases, has the mission furthermore to implement cancer screening program and adequate data Registry.

CONCLUSION

Hepatocellular carcinoma is a grave disease with a dismal outcome and short OS.

More than half of the studied patients had developed HCC in cirrhotic liver, while 43 % were non-cirrhotic HCC. Half of the patients had seropositive testing for either HC Ab or HBs Ag.

Most of the patients are presented in late stages where only palliative therapies could be applied.

Thrombocytopenia and PV thrombosis are significant prognostic factors for poor survival.

HCC patients with liver cirrhosis had significantly worse OS when compared to non-cirrhotic HCC patients.

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