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SOCIO-DEMOGRAPHIC FACTORS RELATED TO ADVANCED HEPATOCELLULAR CARCINOMA: A SINGLE CENTRE RETROSPECTIVE STUDY

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***Keywords**: Hepatocellular Carcinoma, cirrhosis, socioeconomic status.*

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Abstract

Aim: To evaluate the patients various socio-demographic and clinical factors related to advanced HCC at our HCC unit at Tanta university hospitals.

Methods: This study was performed at HCC center of Tanta university hospital by retrospective evaluation of the various socio-demographic data (age, gender, residence, socioeconomic condition and habits), clinical presentation, underlying risk factors (CHC, CHB and un-specified), child's classification and APRI scoring of liver fibrosis of all 690 HCC patients that were recorded at HCC database in the period from January 2014 to December 2015. All patients were divided to two groups: Group 1 that included 250 patients with early HCC, their ages with mean ± standard deviation (SD) equal 54.8 ± 12.795, with male to female ratio 155/95. Group 2: It included 440 patients with intermediate to advanced HCC, their ages with mean ± SD equal 57.05 ± 13.366, with male to female ratio 299/141. Diagnosis of HCC was based on 4-phases multi-detector computed tomography (MDCT) and/or dynamic contrast enhanced MRI.

Results: Our results revealed that, advanced HCC patients in group2 had significant higher age distribution, present significantly more in rural patients and present also significantly more in poor socioeconomic conditions than early HCC patients in group1 (P values 0.0309, 0.0455 and 0.0107 respectively). Advanced HCCs patients of group2 showed highly significance higher grade underlying liver fibrosis by APRI score and Child's classification B or C significantly more than early HCC patients of group1 (P values <0.0001 for both). Male gender, smoking, BMI and DM non-significantly linked to advanced HCC patients of group2 (P values 0.0309, 0.0628, 0.6168 and 0.0969). The clinical presentations of early HCC patients in group1 were asymptomatic incidentally discovered presentations significantly more than that of advanced HCC patients in group2 (P value < 0.0001). CHB and CHC were the most risk factors for both early and advanced HCCs (P value < 0.0033).

Conclusion: Advanced HCCs are significantly related to poor socioeconomic status especially in rural areas that may lead to delayed diagnosis until HCCs become more advanced and symptomatic, at the same time, advanced HCCs are related to high grade liver fibrosis and more advanced liver disease. From these conclusions we should recommend regular screening programs for early discovering of HCCs especially in rural areas with poor socioeconomic status especially for older patients with high grade liver fibrosis and Child's B or Child's C.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and its incidence is increasing in Asia and in the United States [1]. In Egypt, HCC was reported to account for about 4.7% of chronic liver disease (CLD) patients [2]. The epidemiology of HCC is characterized by marked demographic and geographic variations. Its

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development is linked to the occurrence of a chronic liver disease due to chronic infection of hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol consumption, and metabolic syndrome. The underlying liver parenchyma is rarely normal and shows various histological changes including inflammation and fibrosis leading to cirrhosis [3].

Potentially curative therapies are tumor resection, liver transplantation, and percutaneous interventions that can result in complete responses and improved survival in a high proportion of patients. In selected cases, transarterial interventions result in palliation with good response rates and improved survival. Drugs as well as conventional radiotherapy have no proven efficacy to date [4].

HCC has a poor prognosis if diagnosed at an advanced stage, with a 5-year survival rate of 0-10%. However, if it is treated in the early stages, the 5-year survival can be as high as 70%. HCC was identified at an earlier stage by screening, such that tumors were smaller and patients more likely to undergo potentially curative treatment and reduce mortality [5].

While curative interventions are effective in patients with limited disease (1–3 lesions, <5 cm in diameter) and compensated underlying liver disease (cirrhosis Child A), at the time of diagnosis, more than 80% of patients present with advanced HCC and advanced liver disease that restrict the therapeutic measures to best supportive care[6].

Reasons for delayed diagnosis of HCC should be evaluated to overcome this high percentage of advanced HCC. At this respect we tried to evaluate various patients' socio-demographic and clinical factors related to advance HCC at our HCC unit at Tanta university hospitals.

Patients and methods

This study was performed at HCC center of Tanta university hospital by retrospective evaluation of the various socio- demographic, clinical and laboratory data of all 690 HCC patients that were recorded at HCC database in the period from January 2014 to December 2015.

We divided all HCC patients according to Barcelona Clinic Liver Cancer (BCLC) staging system [7] to two groups:

- *Group 1*: It included 250 patients with early HCC, their ages with mean ± SD equal 54.8 ± 12.795, with male to female ratio 155/95.
- *Group 2*: It included 440 patients with intermediate to advanced HCC, their ages with mean ± SD equal 57.05 ± 13.366, with male to female ratio 299/141.

Various demographic data for all patients of both groups were evaluated including age, sex, residence, special habits and socioeconomic conditions, in addition to determination of body mass index (BMI), diabetes mellitus (DM), underlying risk factors as HCV and HBV. The underlying liver conditions were assessed by using both Child's Pugh classification and the non-invasive scoring of liver fibrosis that was done using the aspartate aminotransferase (AST) to platelet ratio index (APRI) scoring system using the following formula [(AST/upper limit normal of AST)/platelet count (10^9/l) × 100].[8]

Diagnosis of HCC was based on 4-phases multidetector computed tomography (MDCT) and/or dynamic contrast enhanced MRI [9].

Statistically analysis

Comparison between groups was performed using the Student's t‑test for continuous variables with normal distribution and the Chi‑square or fisher's exact tests for categorical variables. A $P < 0.05$ was considered statistically significant. For the statistical analysis, SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) was used.

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Results

Our results revealed that, advanced HCC patients in group2 had higher age distribution than that in early HCC patients in group1 with a significant difference (Mean ± SD was 57.05 ± 13.366 and 54.8 ± 12.795 respectively with p value 0.0309).

Our results showed also that, advanced HCC patients in group2 had male gender distribution more than that in group1 with early HCC however without a significant difference (male/female equal 299/141 and 155/95 respectively, with p value 0.1328).

As regards the patients' residence, we found that urban/rural patients were 120/130 for group1 and 176/264 for group2 with a significant difference (P value 0.0455).

Special habits were evaluated for all patients of both groups and we found, 129 (51.6%) patients with smoking habit in group1 comparable to 264 (60%) patients with smoking habit in group2 with a non-significant difference (P value 0.0628). one patient (0.4%) in group1 and 4 (0.9%) patients was found to be alcohol consumer.

The socio-economic status for all patients showed that 131 (52.4%) patients in group1 had poor socioeconomic status in comparison to 295 (67%) patients in group2 with a significant difference (P value 0.0107).

Our results showed that BMI of goroup1 was 28.160 ± 2.824 while that of group2 was 28.327 ± 3.125 without a significant difference (P value = 0.6168). At the same time, diabetic patients in group1 were 85 (34%) while in group2, patients with DM were 192 (43.6%) without significance (P value 0.0969).

Patients with group1 were being classified according to Child's-Pugh classification of liver condition and they were 226 (90.4%) for Child's A and 24 (9.6%) for Child's B, while group2 showed 144 (32.7%) for Child's A, 176 (40%) for Child's B and 120 (27.3%) for Child's C with a high significant difference (P value < 0.0001).

At the same time, liver fibrosis was scored non-invasively by APRI scoring system; in this regard the results of group1 showed 1.820 ± 0.2578 while that of group2 showed 2.056 ± 0.2878 with a high significant difference (P value < 0.0001).

The underlying causes of liver cirrhosis in group1 were chronic hepatitis C (CHC), chronic hepatitis B (CHB), co-infection (CHB+CHC) and unspecified causes in ratios [205 (82%), 20 (8%), 5 (2%) and 20 (8%) respectively] for group1, while that of group2 were [308 (70%), 66 (15%), 22 (5%)and 44 (10%) respectively] with a significant difference (P value 0.0033).

As regards the clinical presentation of HCCs in all patients, our results identified that, 222 (88.8%) early HCC patients in group1 and 198 (45%) advanced HCC patients in group2 were discovered incidentally during non-relevant evaluation of patients using abdominal ultrasound, while 28 (11.2%) HCC patients in group1 and 242 (55%) HCC patients in group2 were symptomatically discovered with a high significant difference (P value < 0.0001).

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All these results and values are illustrated in the following table.

Result table: Socio-demographic factors for all patients.

Parameter		Group1 (Early HCC) n=250	Group2 (Moderate to advanced HCC) n=440	P value
Age (yr)	**Mean ± SD**	54.8±12.795	57.05±13.366	***0.0309***
Sex	**Male**	155 (62%)	299 (68%)	***0.1328(ns)***
	Female	95 (38%)	141 (32%)	
Residence	**Urban**	120 (48%)	176 (40%)	***0.0455***
	Rural	130 (52%)	264 (60%)	
Special habits	**No habits**	120 (48%)	172 (39.1%)	***0.0628(ns)***
	Smoking	129 (51.6%)	264 (60%)	
	Alcohol	1 (0.4%)	4 (0.9%)	
Socio-economic status	**Poor**	131 (52.4%)	295 (67%)	***0.0107***
	Good	119 (47.6%)	145 (33%)	
BMI	**Mean ± SD**	28.160±2.824	28.327±3.125	***0.6168(ns)***
DM		85 (34%)	192 (43.6%)	***0.0969(ns)***
Risk factor	**CHC**	205 (82%)	308 (70%)	***0.0033***
	CHB	20 (8%)	66 (15%)	
	Coinfection(HBV+HCV)	5 (2%)	22 (5%)	
	Un-specified	20 (8%)	44 (10%)	
Child's classification	**A**	226 (90.4%)	144 (32.7%)	***< 0.0001***
	B	24 (9.6%)	176 (40%)	
	C	0	120 (27.3%)	
APRI score	**Mean ± SD**	1.820± 0.2578	2.056 ± 0.2878	***< 0.0001***
Clinical presentation	**Incidentally**	222 (88.8)	198 (45%)	***< 0.0001***
	Symptomatic	28 (11.2%)	242 (55%)	

Discussion

Despite the scientific advances and the implementation of measures for early HCC detection in patients at risk, patient survival has not yet significantly improved during the last three decades. This is in part due to the advanced stage of the HCC at the time of diagnosis, and in part due to the limited therapeutic options especially for these advanced stages of HCC [6].

Early screening of HCC is critical for discovering of less advanced HCCs applicable for curative modalities [6]. In this respect we tried to evaluate retrospectively the various socio-demographic, clinical and laboratory data of our recorded HCC patients in our HCC unit in trying to understand if there are a significant relation between these data and the vast majority of advanced HCC cases that were being discovered in our locality.

Firstly, our results showed that the male gender had advanced HCC more than that in female gender however it did not reach significance (P value 0.1328).

These results are similar to El-Zayadi AR et al who found that HCC is more prevalent in men than in women [10.11], which may be at least in part explained by differences in exposure to risk factors. However, sex hormones and other

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x-linked genetic factors may also be important [12]. It has been speculated that estrogens and androgens could modulate hepatocarcinogenesis and explain the higher incidence of HCC in men.[13]

As regards patient ages, our results revealed that, advanced HCC patients in group2 had higher age distribution than that in early HCC patients in group1 with a significant difference (Mean ± SD was 57.05 ± 13.366 and 54.8 ± 12.795 respectively with p value 0.0309).

This is consistent with Velazquez et al[2] who found that cirrhotic patients older than 54 years are at four times greater risk to develop HCC. This also is consistent with El-Zayadi AR et al, [10] where patients of the age group 40-59 years were at 3.7 times and of age group ≥60 years were at 11 times more risk to develop HCC. Generally, HCC affects predominantly middle-aged and elderly individuals and affects men more than women. However, the age of peak incidence differs substantially in various geographic regions. The age at diagnosis in patients with HCC is lower in hepatitis B-endemic areas, such as Korea, than in hepatitis C-endemic areas, such as Western countries[2,10]. This suggests that HCC screening should begin at a younger age in hepatitis B-endemic areas than in hepatitis C-endemic areas[2,10].

As regards the patients' residence and their socio-economic conditions, we found that rural patients with advanced HCCs in group2 were significantly more than rural patients with early HCCs in group1 (P value 0.0455). At the same time, we found that advanced HCCs presented in patients with poor socioeconomic status in group2 significantly more than early HCC patients with poor socioeconomic status in group1 (P value 0.0107). We may relate this finding to decreased awareness about HCC and its regular screening idea in rural areas combined with relative costly regular follow up of poor socioeconomic patients mostly present in rural areas.

However, previous Egyptian studies showed that, the awareness about HCC has been greatly improved, which subsequently led to better screening and earlier diagnosis of HCC. This is evidenced by increased rate of diagnosis of small lesions from 14.9% to 22.7% and decreased rate of diagnosis of large HCC lesions from 85.1% to 77.3%.[3,10]

So, we must encourage screening programs at rural areas by special teams and it must financially being covered.

As regards special habits, we found that advanced HCC presented more in smokers than in non smokers but without significance (P value 0.0628). Alcohol is highly restricted in our country so, it represented only in 1 (0.4%) patient in group1 and only in 4 (0.9%) patients in group2.

The relationship between cigarette smoking and HCC has been examined in many studies in both low and high rate areas with variable results which suggest that any effect of smoking on HCC is likely to be weak and limited to a subset of the general population[14]. Heavy alcohol intake for prolonged periods is a well established HCC risk factor. It is unclear whether risk of HCC is significantly altered in those with low or moderate alcohol intake. Most data point to that alcohol does not have a carcinogenic effect in itself; the increased risk is rather through the cirrhosis that prolonged alcohol intake can cause[15].

Body mass index (BMI) slightly related to advanced HCC but without significance (P value 0.6168). Similarly, diabetic patients were slightly more in group2 with advanced HCC but without significance (P value 0.0969). This is evidenced by many population-based cohort studies that found a 2–3 fold increased HCC risk in obese men and women compared to those with normal BMI[16,17]. Many studies reported that diabetes, particularly type2, has been proposed to be a risk factor for both chronic liver disease and HCC possibly through development of NAFLD and NASH[14].

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HBV and HCV infection are considered as the major risk factors that contribute to the development of HCC. This is evidenced by several studies that analyzed the risk factors of HCC in patients with CLD[18,19]. Previously, there was strong evidence that hepatitis B virus (HBV) was the major cause of HCC in Egypt, but more recently HCV has become the predominant factor associated with the more recent increased incidence of HCC. The prevalence of HCV in Egypt is much more increased [20]. The natural history of HCV infection and disease progression, however, are influenced by additional factors such as duration of infection, age at infection, sex, co-infection with HBV, the level of HCV viraemia and its genotype [21]. The role of HBV infection in pathogenesis of HCC differs from that of HCV infection; HBV-DNA genome integrates in hepatocellular chromosomes [22], while HCV exerts its effect, most probably, through production of cirrhosis with severe liver damage [23].The major part of the data shows that HCV plays an indirect role in hepatocarcinogenesis, and this may appear as a consequence of long-standing associated cirrhosis through the direct promotion of the chronic liver inflammation[24].

As regards the link between advanced HCC and Child's classification of liver condition, we found that patients with Child's B and Child's C were highly significantly more in group2 with advanced HCC than that in group1 with early HCC (P value <0.0001) . At the same time, liver fibrosis of all patients of both groups was scored non-invasively using APRI score system and we found that, APRI scoring of liver fibrosis of patients in group2 -with advanced HCC- was highly significantly higher than that in group1 with early HCC (P value <0.0001). APRI may be an important indicator for cirrhosis, the most important factor for the development of HCC in patients with chronic hepatitis as evidenced by many studies that suggest also that high APRI values were associated with HCC recurrence after RFA[25-27].

As regards the clinical presentation of HCC, we found that most patients of early HCCs were asymptomatic and incidentally discovered during the non-relevant examination of patients using abdominal ultrasound, while most of patients with advanced HCC were symptomatically discovered with a high significant value (P < 0.0001).

The growth of HCC is characteristically silent in nature, which may delay diagnosis for as long as 3 years from the time of development [28]. The clinical picture is variable, the patient may be asymptomatic, the tumor diagnosed accidentally, also the presentation may be florid and liver failure rapidly develops [29]. Active surveillance for HCC in high-risk populations has increased the frequency of diagnosis of HCC in asymptomatic patients.

From all these data, we can conclude that Advanced HCCs are significantly related to poor socioeconomic status especially in rural areas that may lead to delayed diagnosis until HCCs become more advanced and symptomatic, at the same time, advanced HCCs are related to high grade liver fibrosis and more advanced liver disease. From these conclusions we should recommend regular screening programs for early discovering of HCCs especially in rural areas with poor socioeconomic status especially for older patients with high grade liver fibrosis and Child's B or Child's C liver disease.

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