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Epidemiology of Hepatocellular Carcinoma in Fayoum Governorate-Egypt

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Abstract

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and the burden is expected to increase in coming years. HCC has become the second most prevalent cancer among men in Egypt. This study aimed to estimate the prevalence; identify the risk factors and detect clinical features of HCC in Fayoum governorate. The study was a descriptive cross-sectional study with a convenient sample conducted at Tropical & Hepatology Medicine Department in Fayoum University Teaching Hospital. An interview structured questionnaire was used; thorough clinical examination with biochemical and serological investigation. The majority of cases came from rural area, farmers constituted 39.3% of cases. More than 90% of cases suffering from hepatic cirrhosis and more than half of cases having Bilhariziasis. Hepatitis C was the main aetiology 79.8%, followed by hepatitis B 15.4%.

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Most of focal lesions were in right lobe 57.1% and in the form of single lesion 57.1%. AFP was found to be a weak diagnostic predictor with low sensitivity. HCC was multifactorial pathogenesis with many risk factors (cirrhosis, HCV and schistosomiasis). HBV infection has a declining role in hepatocarcinogenesis. Proper surveillance program is needed for early detection and diagnosis of HCC.

Keywords: Hepatocellular carcinoma; epidemiology; HCV; Fayoum.

1. Introduction

Hepatocellular carcinoma (HCC) is one of the common primary malignant tumours of the liver; represents approximately 85-90% worldwide [1]. It is the fifth most common cancer worldwide and the third cause of cancer mortality [2]. HCC is one of the few cancers with well-defined major risk factors. The most frequent underlying factors are chronic viral hepatitis and cirrhosis, alcohol abuse, and/or non-alcoholic steato-hepatitis (NASH) [3].The Eastern and South-Asia, Middle and Western Africa are considered to be of high incidence rate. Most of the burden is in developing countries; where almost 85% of the cases occur particularly in men. As well as low rates are estimated in developed regions, with the exception of Southern Europe where the incidence in men (10.5 per 100,000) is significantly higher than in other developed regions. There were an estimated 694 000 deaths from liver cancer in 2008 (477 000 in men, 217 000 in women) [4] . As in many developing countries, Egypt is undergoing an epidemiologic transition with increasing urbanization, smoking rates, environmental exposures, and aging. Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide, with rising rates of HCC [5]. It is the second most common cancer in men and the 6th most common cancers in women. In Egypt the incidence of HCC in the past 10 years has been doubled [6]. It is estimated that the prevalence of HCC will increase in Egypt, reaching its peak by the year 2018 [7]. The heavy burden of HCC parallels high rates of HCV and its complications while hepatitis B virus (HBV) rates have declined after the introduction of the vaccine in 1992 [8&9&10&11] .Egypt has a significant prevalence of HBV, HCV, bilharzial infection and smoking, which may allow us to identify a high-risk group of patients with HCC among those with chronic liver disease and cirrhosis [12]. HCC prevalence is high in Nile Delta area, more common in males, rural residents and farmers especially in HCV patients [13].

Hospital-based studies from Egypt have reported an overall increase in the relative frequency of all liver-related cancers, from approximately 4% in 1993 to 7.3% in 2003. Another studies documented the increasing importance of HCV infection in the aetiology of liver cancer, estimated to account for 40–50% of cases, and the declining influence of HBV and HBV/HCV infection 25% and 15%, respectively [14&15].

This study aimed to estimate the prevalence; identify the risk factors and detect clinical features of HCC in Fayoum governorate.

2. Materials and Methods

The study was a descriptive cross-sectional study conducted over a period of one year at Tropical & Hepatology Medicine Department in Fayoum University Teaching Hospital. The sample was a convenient sample based on the time allocated for the practical phase with a number of 84 HCC patients included in the study (56) males and

(28) females referred from: general public hospitals of (Fayoum- Senors- Tamia – Abshawi – Itsa - yossef El Sedik) after an orientation meeting with the staff of the Tropical Medicine in each hospital to explain the aim of the study and inclusion and exclusion criteria of the patients and method of referral to the Fayoum University Teaching Hospital. All HCC cases have been diagnosed by American Association for the study of liver diseases (AASLD) diagnostic criteria [16] with inclusion criteria of: Histopathological evidence of hepatocellular carcinoma. Non- invasive criteria (restricted to cirrhotic patients):

A. **Radiological criteria:** Two coincident imaging techniques (Ultrasonography, Spiral CT, MRI, angiography) and focal lesion > 2 cm with arterial hyper-vascularization.

B. **Combined criteria :** One imaging technique with AFP: Focal lesion > 2 cm with arterial hyper-vascularization. AFP levels > 400 ng/ml.

Exclusion criteria: Focal lesions other than primary HCC (cholangiocarcinoma, hemangioma, hepatoblastoma, metastatic focal lesions…etc).

Study Tools:

1. **An interview structured questionnaire** was prepared and designed to ensure that all the interviewed patients will be able to understand the questions. Pre-coded close ended questions were chosen, so that information obtained can be easily computed. The questionnaire investigated the following data: Socio-demographic characteristics (age, sex, residence, occupation with a special consideration of being a farmer). Current medical history: Diabetes Mellitus, hypertension, or both. Special habits: smoking, alcohol intake, drug addiction especially (Hashish). History suggestive of schistosomiasis. History of present illness: with special emphasis on jaundice, abdominal pain, ascites, encephalopathy, hematemesis or melena, bleeding tendency, general manifestations as (fever and weight loss and fatigue) and GIT symptoms as (heart burn, dyspepsia and nausea).
2. **Thorough clinical examination** for detection of the general manifestations of systemic diseases & peripheral signs of liver cell failure with special emphasis on pallor, jaundice, lymphadenopathy and lower limb edema, cachexia, spider nevi, palmer erythema, clubbing, flapping tremors, and gynecomastia.
3. **Abdominal Examination**: To detect: Abdominal tenderness, Abdominal mass, Liver (size, surface, consistency and tenderness), Spleen, if enlarged or not and Presence of ascites.
4. **Laboratory Investigations included:** Complete blood count, Liver biochemical profile (AST, ALT, Alkaline phosphatase, T.bilirubin, T.proteins & S.albumin), Prothrombin time, concentration & INR, Kidney function tests (B.urea and S.creatinine), Viral markers (HBsAg and anti-HCV), Alpha fetoprotein and Bilharzia indirect haemagglutinition test.
5. **Modified Child's score**: Evaluation of the severity of liver cirrhosis was assessed in each patient with the Modified Child score. This system relies on clinical and laboratory evaluation including ascites, grade of encephalopathy, serum albumin, bilirubin and prothrombin time **(table I).**

Table 1: Modified Child score

Points	**1**	**2**	**3**
Serum bilirubin(mg/dl)	Below 2.0	2.0-3.0	Over 3.0
Serum albumin(g/dl)	Over 3.5	2.8-3.5	Under 2.8
Prothrombin time (seconds prolonged)	1-3	4-6	Over 6
Ascites	none	Easily controlled	Poorly controlled
Encephalopathy (grade)	none	G 1-2	G 3-4
Total numerical score 5-6=Child A, 7-9=Child B, 10-15=Child C			

6. Barcelona Clínic Liver Cancer (**BCLC) classification:** detection of HCC staging according to (BCLC) classification. According to **EASL- EORTC (2012)** guidelines which endorse the (BCLC) classification for several reasons as it includes prognostic variables related to tumour status, liver function and health performance status along with treatment dependant variables obtained from cohort studies and randomized trials. It has been externally validated in different clinical settings.

3. Data entry and statistical analysis

Data was collected, coded and analyzed using SPSS (Statistical Package for Social sciences) software (Version 18) on Windows 7, and a simple descriptive analysis in the form of percentage distribution, means and S.D. (Standard Deviation) was executed. Categorical data was analyzed by computing percentages, and consequent differences were tested statistically by applying chi square tests for comparisons between groups;, and a P-value of <0.05 was considered statistically significant.

4. Results

This study focused primarily on group of patients (84) who had hepatic focal lesion presented to Tropical & Hepatology Medicine Department in Fayoum University Teaching Hospital. The study aimed at answering the questions what was the risk factors predisposes to HCC.

The age of the patients ranged from 24 to 83 years with the mean age of 62.73±10.59 years old. The socio-demographic characteristics of the study are represented as the following: two third of patients are males 66.7% and the remaining are females 33.3% in a ratio of 2:1. One third of the patients are inhabitants at Atsa district 32.1% (rural areas); and 22.6% at Fayoum district (rural-urban areas). In addition, farmer's occupation constituted 39.3% of patients and housewives constituted 33.3%. Regarding some special habits as smoking cigarette or taking opium and drinking alcohol more than half of the patients 58.3% did not smoke or drink alcohol or opium; 38.1% of the patients were cigarette smoker and 2.4% were opium users; while alcohol consumption was the lowest habit of only 1.2% of patients. As regards history of chronic diseases; Diabetes affection of patients was 14.3%; while Hypertension affection was 11.9% of patients. As well as, patients suffering from both Diabetes and Hypertension were only 6%.

Table 2: Serologic Tests (Hepatitis Markers) of the Patients

Hepatitis markers	**N**	**%**
Hepatitis C	67	**79.8**
Hepatitis B	13	15.4
Hepatitis B&C	3	3.5
None B nor C	1	1.1
Total	84	100.0

Table (1): showed that 79.8% of the patients were hepatitis C positive (HCV Ab, ELISA), 15.4% were hepatitis B positive (HBs Ag), and 3.5% were combined B&C positivity leaving only 1.1% negative for both HCV and HBV.

Bilhariziasis was prevalent in 52.4% of our patients detected through previous receiving anti-schistisomal therapy or positive anti-schistosomal antibody > 160. More than half 56.7% of HCV patients were positive for bilhariziasis. The prevalence of cirrhosis among HCC cases was 95.2% compared to 4.76% developed the malignancy on top of a non cirrhotic liver. Triphasic CT revealed multicentre mass >7cm without the typical imaging appearance. Histopathological examination showed hepatocellular carcinoma of fibrolamellar type.

Table 3: Clinical presentation (symptoms & signs) of HCC patients

Symptoms	**Yes**	
	N=84	**%**
Abdominal pain	60	71.4
Gastrointestinal symptoms	45	53.6
General manifestations	30	35.7
Accidently discovered	24	28.6
Yellowish discoloration	20	23.8
Abdominal swelling	9	10.7
Signs	**N**	**%**
Splenomegaly	61	72.6
Hepatomegaly	46	54.8
Ascites	40	47.6
Lower limb oedema	31	36.9
Shrunken Liver	28	33.3
Abdominal mass	15	17.9

The clinical features of the patients demonstrated that abdominal pain was the commonest symptom 71.4%; then gastrointestinal manifestations (as dyspepsia, heart burn and nausea) was 53.6%.

This is followed by general manifestations 35.7% as (generalized fatigue, bone aches and loss of weight). The rest came with other manifestations as abdominal swelling and yellowish discoloration of skin. Splenomegaly was detected in two third of the patients 72.6%. Half of the patients were suffering from enlarged liver and ascites that constituted 54.8% and 47.6% of the patients respectively. Also lower limb edema and shrunken liver were present in one third of the patients, while 17.9% had abdominal mass as shown in Table (2).

Table 4: The severity of liver cirrhosis among HCC cases

Child Classification	**N=76**	**%**
Class A	3o	37.37
Class B	37	**46.25**
Class C	13	15.5
AFP	**N**	**%**
Less than 10ng/ml	13	15.5
+10-100ng/ml	39	46.4
+100-200ng/ml	13	15.5
Above 200ng/ml	19	**22.6**
Total	84	100.0

Table (3): revealed that according to Child Classification of HCC 46.25% of cases were classified as class B, 37.37% as class A while 15.5% were of class C. AFP was diagnostic (> 200ng/ml) in 19 patient 22.6% while 46.4% of patients had AFP level between (10- 100) .

Table (4): described the malignant focal hepatic lesions; as concerned with the number, site and size of the lesion. More than half 57.1 % of the lesion was single and in the right lobe which is the predominantly affected lobe. As regards size of the lesion 32.1% was more than 3 cm up to 5 cm. 27.4% was more than 7 cm.

Table (5): described the malignant focal hepatic lesions of HCC patients; 64.2 % of the lesion was in the right lobe. Size of the lesion was 34.3% more than 3 cm up to 5 cm. 26.9% was more than 7 cm.

There was 12% of cases were metastatic mainly lung metastases 7.1% and 2 cases 2.4% had both lung and lymph nodes metastases while 88% had no metastases.

According to BCLC score 11.9% of our patient were classified as early stage, 27.4% were of intermediate stage, 29.8% were at advanced stage while 31% were end stage HCC.

Table 5: Descriptive analysis of HCC focal hepatic lesion (FHL) by Ultrasonography

Numbers of Lesions	**N**	**%**
Single	48	**57.1**
2-3	21	25.0
More than 3	15	17.9
Site of the Lesions	**N**	**%**
Right Lobe	48	**57.1**
Left Lobe	17	20.2
Both	19	22.6
Size of Lesion	**N**	**%**
Less than 3 cm	13	15.5
+3-5 cm	27	**32.1**
+ 5-7 cm	21	25.0
More than 7 cm	23	27.4

Table 6: Relation between HCV infection and site and size of the tumor

Hepatitis C	**N= 67**	**%**
Site of Lesion		
Right Lobe	43	64.2
Left Lobe	12	17.9
Both	12	17.9
Size of Lesion		
< or = 3 cm	10	14.9
>3-5 cm	23	34.3
> 5-7 cm	16	23.9
More than 7 cm	18	26.9

5. Discussion

HCC is one of the few cancers with well-defined major risk factors**.** The most frequent underlying factors are chronic viral hepatitis and cirrhosis**.** Interaction between schistosomiasis and hepatitis due to viral infection in chronic liver disease has been also reported [14].

In the current study, HCC was presented in males more than females with ratio 2: 1. This was in agreement with

Reference [17] who reported that males have higher liver cancer rates than females, with male: female ratios averaging between 2:1 and 4:1. Several factors may explain that males are more likely to be infected with HBV and HCV, in addition to cigarettes smoker, and alcohol consumer Testosterone rate has been shown to correlate with HCC indicating a probable role for the sex hormones in the development of HCC [18].

We found that 77.3% of HCC patients were coming from rural areas and 39.4% used to work as farmer. This is in agreement with [19] who reported high incidence of HCC in rural areas due to exposure to organophophorus and carbamate pesticides and environmental carcinogens such as aflatoxin are additive risk factors to current HCV and HBV infection. Also, the high incidence of non municipal water supply may carry certain pollutants or metals that are still undetermined as risk factors (such as arsenic).

Although alcoholism is a well identified risk factor for HCC and has a well recognized interaction with HBV and HCV, but this role was not clear in our study. This may be due to different socioeconomic and religious status that forbidden alcohol intake [20].

In this study we found that liver cirrhosis was present in 95.2% of HCC case. This was in agreement with [18] who stated that 70%-90% of hepatocellular carcinomas develop in patients with macronodular cirrhosis. Also this result agrees with [21] results as 96% and 83% of the patients respectively develop HCC on top of liver cirrhosis respectively.

Chronic HCV infection, as a cause of cirrhosis, accounted for 79.8% of our patients reflecting the close relationship between HCV and HCC. The presence of cirrhosis and chronic hepatic inflammation with associated oxidative stress and accompanying potential for cellular DNA damage are important contributing causes to HCV-associated HCC [22]. However, there is a direct role for HCV in cancer promotion. The incidence of HCC appears to be greater in HCV-associated cirrhosis 7-13% over 5 years [23] than in cirrhosis resulting from autoimmune hepatitis [24].

While patients with HBsAg positive were 15.4% of our study, as HBV infection is declining due to the administration of vaccination. This agrees with [25] who reported that according to a meta-analysis regarding viral hepatitis prevalence in Egypt, HBV and HCV were found among 25.9% and 78.5% of HCC cases. This is also in agreement with [15] who noticed a significant decline of HBV infection in HCC patients from 38.6% to 20.5% in their study for HCC in Egypt over a decade, and attributed that partially to successful control measures of blood transfusion introduced in the mid-seventies and partially to the presence of undiagnosed cases of mutant HBV infection.

In our study, 52.4% of our patients had positive anti-schistosomal Ab and 57.8% of patients had Co infection of HCV /schistosomiasis. The high seroprevalence of HCV with schistosomiasis confirmed by the results of [15] as the presence of schistosomal infection modify the course of hepatitis C genotype for co-infection and may leading to complications, such as portal hypertension at an earlier stage with accelerated progression to hepatitis C-associated fibrosis and thus quicker progression to HCC, than those patients who do not have disease burden.

The clinical features of HCC patients in our study were similar to patients with cirrhosis as 71.4% had right

hypochondrial pain, which are in agreement with [26] stated that pain is the most frequent symptom. Also [27] reported that in many patients, HCC is asymptomatic and then diagnosed in an advanced stage. That is why, for cirrhotic patients, surveillance is strongly recommended to detect early HCC patients for proper curative treatment.

In the present study, 57.1 % of total patients with HCC, had single focal hepatic lesion (FHL) by Ultrasonography. Alpha fetoprotein (AFP) has been widely used as a serologic marker for the diagnosis of HCC in patients with chronic liver disease [28], however AFP concentrations are not specific for HCC because increased concentrations also occur in normal pregnancy, in certain benign liver diseases, and in some non-HCC malignancies such as nonseminomatous germ cell tumors, [29]. In the current study, 22.6% of patients with HCC had serum AFP values over 200 ng/ml which has been used as a cut off level in diagnosing HCC; no correlation was found between level of AFP and the size of tumors. This could be explained by the fact that tumor differentiation appears to be more important than tumor size in determining the level of AFP produced by HCC. This issue concerning the number of focal lesions per liver (according to BCLC scoring system) is important in planning different management modalities for cases with HCC.

6. Conclusions

Our study concluded that HCC was a multi-factorial disease with many risk factors as (cirrhosis, HCV and schistosomiasis). HBV infection has a declining role in hepatocarcinogenesis. Occupational exposure (farmers) to chemicals such as pesticides increased risk of HCC development.

Screening and diagnosis of HCC don`t depend on single diagnostic modality yields diagnostic accuracy consistently. Therefore, screening with AFP, ultrasonography, and CT provide the best hope for early diagnosis.

7. Recommendations

This study recommended that compulsory HBV vaccination of newborns and vaccination of all risk groups is mandatory. Careful handling of blood and blood products, safe medical procedures and discarding contaminated syringes after their usage for prevention of HCV.

Strict governmental laws to control manufacturing and consumption of pesticides with safety stored of grains to prevent aflatoxin contamination. Regular screening of cirrhotic patients by tumour markers and imaging modalities is highly recommended for early detection of HCC

8. Ethics

This study was reviewed and approved by the Fayoum University-Faculty of Medicine (Research Ethical Committee). The official approval was obtained from the general director of hospital and the manager of the outpatient clinic and the head of the Tropical Medicine department.

9. Consent to participate

The study was performed after explaining its objectives and confidentiality was expressed to the participants.

Written consent was taken from the participants as an agreement to join the study before clinical examination and laboratory investigation. All participants had the right not participate in the study.

10. Declaration

The authors declare that this manuscript did not previously publish or considered for publication in any other journal. The authors do not hold any stocks or shares, fees, funding or salary from any organization that may in any way gain or lose financially from the publication of this manuscript, either now or in the future.

List of Abbreviations:

- HCC: Hepatocellular carcinoma
- HCV: Hepatitis C virus
- HBV: Hepatitis B virus
- NASH: Non-alcoholic steato-hepatitis
- AASLD: American Association for the study of liver diseases
- BCLC: Barcelona Clinic Liver Cancer
- EASL: European Association for the Study of the Liver
- EORTC: European Organization for Research and Treatment of Cancer
- AFP: Alpha fetoprotein
- SPSS: Statistical Package for Social Sciences
- SD: Standard Deviation

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