Characteristics of Hepatocellular Carcinoma in Egyptian Patients : A Single Center Pilot Study

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Background and study aim: Hepatocellular Carcinoma (HCC) is regarded as one of the most widespread leading causes of mortality annually . The most frequent risk factors for HCC are chronic viral hepatitis infection, which account for 80% of all HCC cases globally. This study aims to highlight epidemiological, clinical, laboratory and radiological characteristics of HCC in patients attending Tropical Medicine Department.

Patients and Methods: A Retrospective study was conducted on medical records of all patients attending Tropical Medicine Department to determine the socio demographic, laboratory, clinical and radiological characteristics of HCC.

Results: 715 patients with HCC were included in this study. The mean age of HCC onset was (59.76±8.14), 68% were males, 32 % were females, 39.7 % were diabetic , Two thirds of the patients were Child-Pugh A (67%), the remaining third were child B (28.2%) and child C (4.9%). 9.5% were jaundiced, 20% were ascitic, 74.8% had splenomegaly, 8.7% had malignant PVT while 0.4 % had Benign PVT, AFP was > 400 in 16.2 % of patients. 19.8 % had received HCV treatment, 67 % were active HCV.

Conclusion: Hepatocellular carcinoma is predominant in older- male patients with chronic hepatitis C not receiving treatment, and have diabetes mellitus.

INTRODUCTION

HCC is the most prevalent type of primary liver cancer, accounting for 75–85% of cases **[1].** HCC incidence has risen to the fifth and ninth most prevalent cancers in both men and women, respectively **[2].** HCC is regarded as a serious public health problem in Egypt, where it accounts for 33.63 % of all malignancies in men and 13.54% in women **[3].**

Egypt is undergoing an epidemiologic transition, like the same situation in many developing nations **[4].** With the high burden of HCV, rising urbanization, smoking rates, environmental exposures, age, and lifestyle changes, it is expected that HCC will continue to rise in the coming years **[5] .**

Viral hepatitis C, hepatitis B, alcoholic and non alcoholic fatty liver disease are the main risk factors for liver cancer in clinical practice **[6-8]**

Cirrhosis caused by HCV and HBV is the most prevalent risk factor for HCC globally **[9].** HBV is the most prevalent cause of HCC in Southeast Asia and sub-Saharan Africa **[10].**

In Egypt, the situation is completely different, with an overall prevalence about 14.7**%** HCV infected patients **[11]**

In addition to several genetic and epigenetic factors involved in complex molecular pathogenesis of liver cirrhosis and progression to HCC **[12-17]**.

PATIENTS AND METHODS

Study design: It is a retrospective study.

Study settings: This study was carried out in The Tropical Medicine Department, faculty of medicine, Mansoura University, Egypt in the period from November 2010 to October 2020.

Study patients: This study was carried out on patients with HCC who attended inpatient and outpatient clinics at the Tropical Medicine Department.

Sample size:

All patients with HCC and recorded data during the study period were listed (N = 715), this is estimated to be about **715** according to patients records

Inclusion Criteria:

All the patient of HCC were included:

All sociodemographic, clinical, laboratory and radiological data were obtained from the medical records.

Exclusion Criteria:

All hepatic tumors other than HCC.

Statistical analysis and data interpretation:

Data analysis was performed by SPSS software, version 28 (SPSS Inc., PASW statistics for windows version 18. Chicago: SPSS Inc.) Qualitative data were described using numbers and percent. Quantitative data were described using mean, standard deviation for normally distributed data after testing normality using Kolmogrov-Smirnov test. The Significance of the obtained results was judged at the (0.05) level.

RESULTS

This study included 715 patients with HCC, their mean age was (59.76±8.14), 68% of them were males, while 32% were females, 39.7% had diabetes mellitus, while 30.6% had systemic hypertension, 10.6 % were smokers. More than two thirds were from urban areas (68.3 %), and the majority of them were married (94.5 %). (**Table 1**)

Regarding clinical findings, we found that *more than half* of the patients were Child A (67%), Child B were (28.2%) and Child C were (4.9%).

Most of the patients were BCLC (A); (42.5%) 42.8% were BCLC (B), 6.6%, were BCLC (C); 6.4%, were BCLC (D) , and 1.7 % were BCLC (0);

As regarding clinical picture it was found that Jaundice, splenomegaly and ascites were present in 9.5%, 74.8% and 20% of patients respectively. (**Table 2**)

Regarding radiological results, 57.6% had single nodules, while 42.4% had multiple nodules, Moreover half of the patients had HCC nodules between 2-5 cm, 15.2% had HCC nodule < 2cm and 23.5% had HCC nodule > 5 cm.

Most of the lesions were in the right lobe (85.6%) and only 33.4 % were in left lobe. Extra hepatic metastasis with lymph node, organs and bone involvements were found in 3.1%, 1.1%, 0.8% of patients respectively.

8.7% had malignant PVT while 0.4 % had benign PVT

(Table 3)

Regarding laboratory data, level of hemoglobin was 12.05±1.89, platelet level was 104 (35 -278), the level of serum albumin was 3.44±0.61, bilirubin level was 1.2(0.9-12.3), creatinine level was 0.9(0.2-9), INR level was 1.2(0.6-1.8). AFP level was < 400 ng/dl in most patients of HCC , while only 16.2% had AFP > 400. 67.8% of patients who not receiving any HCV treatment , 12.4% had negative HCV virology, 19.8% had received antiviral treatment.

As regard treatment, 4.6% received interferon, 95 % received direct antiviral drugs. **(Table 4) .**

Table (1): The socio demographic data of studied patients (715).

Sociodemographic data	n=715	%
Age/years (Mean ± SD)	59.76±8.14	
Male	486	68.0
Female	229	32.0
DM	284	39.7
Hypertension	219	30.6
Smoking	76	10.6 %
Rural	227	31.7
Urban	488	68.3
Single	39	5.5
Married	676	94.5

SD = standard deviation, **DM** = diabetes mellitus ,

Table (2): Clinical data of studied patients.

	N = 715	%
Child score		
A5	276	38.6
A6	203	28.4
B7	98	13.7
B8	44	6.2
B9	59	8.3
C10	28	3.9
C11	5	0.7
C12	2	0.3
BCLC score		
0	12	1.7
A	304	42.5
B	306	42.8
C	47	6.6
D	46	6.4
Jaundice	68	9.5
Splenomegaly	435	74.8
Ascites	143	20.0

BCLC: Barcelona Clinic for Liver Cancer, **CTP:** Child Turcotte Pugh

Table (3): Radiological data of studied patients.

Radiological	n=715	Percentage %
Number of nodules		
Single	412	57.6
Multiple	303	42.4
Size of nodule /cm		
<2	109	15.2
2-2.9	191	26.7
3-5	247	34.5
>5	168	23.5
right lobe	612	85.6
Left lobe	239	33.4
lymph node infiltration	22	3.1
organ mets	8	1.1
bone mets	6	0.8
PVT malignant	62	8.7
PVT benign	3	0.4

PVT*:* portal vein thrombosis , mets : metastasis

Table (4): Laboratory data of studied patients.

HB (g/dl)	mean±SD		**12.05±1.89**
PLT (mcL)	med (min-max)		104(35 -278)
Albumin (g/dl)	mean±SD		3.44±0.61
Bilirubin (mg/dl)	med (min-max)		1.2(0.9-12.3)
INR	med (min-max)		1.2(0.6-1.8)
Creatinine (mg/dL)	med (min-max)		0.9(0.2-9)

A.F.P (0-10)	188	26.3
(11-20)	184	25.7
(21-30)	25	3.5
(31-40)	24	3.4
(41-50)	42	5.9
(51-100)	49	6.9
(101-400)	76	10.6
(>400)	116	16.2
Total	704	98.5

A.F.P: Alfa Feto Protein, **HB:** hemoglobin, **INR:** International Normalized Ratio, **PLT**: platelets , SD: Standard Deviation

Virology	N / (n=539)	%
Negative virology (HCV)	67	12.4
Cured HCV	107	19.8
Viable HCV	365	67.8
HBV	Zero	0.00

HB : Hepatitis B Virus, **HCV**: Hepatitis C Virus

DISCUSSION

One of the highest incidences of all hepatic malignancies is hepatocellular carcinoma **[18].** It often arises in cirrhotic livers with serious complications **[19].** Recent efforts have been made to change the reality of poor prognosis and short survival times **[20-22]**. Options for treatment mostly depend on the stage of the HCC tumor.

In this study, males were more predominantly exposed to HCC (68%) than females (32%) with a ratio about (2.1:1). This in accordance with previous results of Hossain et al. **[23];** Guyton et al. **[24]**; Yang et al. **[25]**; Huang et al. **[26]** Ganong et al. **[27];** Graevfore et al. **[28],** this can be explained by the delayed development of HCC in females and in some racial groups, which support the hypothesis of a protective effect of female sex hormones against HCC development.

In this work, incidence of HCC was increased in patients more than 50 years , this also reported by El-Serag et al. **[29**] who reported that older male patients had increased HCC incidence in cirrhotic individuals.

Other studies support our results such as; **Hossain et al. [23]** who found that patients between 41 and 50 years were the most commonly exposed to HCC**,** this can be explained by long standing chronic viral hepatitis all over years and accumulated risk factors with age such as ;liver cirrhosis

In accordance with results of **Hashem et al. [30]** who demonstrated increased HCC incidence among older HCV infected patients due to long standing established risk factors like HCV and liver cirrhosis.

Also, **Dohmen et al. [31]** reported that increased incidence may be linked to increased life expectancy, which increases the incidence of HCC development in older patients

In this work, there was high incidence of HCC among child A patients than child B & C.

The only possible explanation for these findings was the strict early screening program for detection of HCC in our tertiary center, which allows early detection of small lesions, unlike what is expected, advanced cirrhosis may not be linked to a high incidence of HCC

AFP (alfa feto protein) is a protein made in the liver of a developing baby and healthy adults should have very low levels of AFP.

AFP synthesis is suppressed in adults. Only during pregnancy, in specific tumours (such as HCC, gastric carcinoma, lung cancer, pancreatic cancer, and testicular carcinoma), and in non-tumor situations (such as chronic hepatitis and liver cirrhosis) are elevated AFP serum levels observed in the maternal serum. **[32]**

When the cut-off value is 20 ng/ml, serum AFP has a sensitivity of 41–65% (so it may be false negative) and a specificity of 80–94%.

However, AFP levels more than 400 g/L are typically regarded as diagnostic of HCC **[33]** A recent meta-analysis on the effectiveness of AFP in the diagnosis of HCC included seven studies and indicated a pooled sensitivity of 66% with a specificity of 86%**. [33, 34]**

At the time of tumour diagnosis, AFP appears to have prognostic value. Patients with HCC who have high AFP concentrations (400 ng/mL) have larger tumours, bilobar involvement, portal vein invasion, and a worse median survival rate**.[35]**

Patients with blood AFP levels greater than 1000 ng/ml have a higher frequency of vascular invasion (61% versus 32%). **[36]**

Our results demonstrated that 26.3% of patients with HCC had normal AFP level, 83.8% had AFP < 400 ng/dl and only 16.2 % had AFP more than 400 ng/dl.

These surprising results may be due to the fact that some types of HCC may not secrete AFP i.e.; fibrolamellar HCC **[37].**

Furthermore, in AFP-producing HCC, AFP can also be employed as a marker to identify tumour progression. If the pre-treatment increased AFP levels drop to and stay at normal levels during future follow-up measurements after the tumour has been treated, a full response is anticipated **[38].**

There was 26.3% had normal AFP level (below 10 ng/mL) which will be missed in diagnosis if we depended on AFP level only , so we finally reported that, no diagnostic AFP cut off level for HCC diagnosis, because patients with HCC may have normal titer of AFP, and diagnosis doesn't depends only on AFP alone but radiology is mandatory.

One of our interesting findings that, the majority of patients with HCC were not received any lines of treatment for HCV infection, while small portion of patients who received different modalities of therapy developed HCC, this may be due to the effect of HCV particles and liver cirrhosis induced by HCV infection and comorbidities: DM and Insulin Resistance **[39],** [**40], [41].**

Our results are supported by previous findings of**;** El-Zayadi et al. **[42];** Shi J et al. **[43].** These findings explained by that HCV is the major risk factor of HCC in cirrhotic patients.

In addition to that, treatment of HCV may be a protective factor against HCC development in accordance with Marrero et al. **[44];** Griffith et al. [**45]**; who demonstrated that successful DAA therapy is associated with a 71% reduction in HCC risk.

This can be explained by eliminated HCV particles by DAA treatment which activate CD8+ T cells to respond to the HCV also induces a T-cell mediated response and increased immune surveillance to the virus-induced aggressive HCC tumor and also due to decreased liver fibrosis after HCV treatment.

In our study, there were (39.7%) diabetic patients with HCC, this can be explained by; One possible mechanism of carcinogenesis

suggested that patients with non insulin dependent diabetes mellitus are characterized by insulin resistance, compensatory hyper-insulinemia and increased growth factor production **[46]**.

It is believed that hyperinsulinemia and hyperglycemia directly stimulate hepatic stellate cells, leading to activation of connective tissue growth factor and subsequent accumulation of extracellular matrix **[47]**. Although insulin can directly induce tumour growth, many of its mitogenic and antiapoptotic effects are operating through the (Insulin like growth factor)IGFI system, in particular breast and prostate cancers, have been documented.**[48].**

With regard to incidence of HCC in diabetic patients**,** widespread unhealthy dietary habits associated with a sedentary lifestyle have made NAFLD the most frequent chronic liver disease worldwide, with a global prevalence of ~25%. Although NAFLD is mainly considered a benign disease, it can progress to severe liver fibrosis

and hepatocellular carcinoma (HCC), with the latter found in non-cirrhotic livers in about 40% of cases.

CONCLUSION

Hepatocellular carcinoma is predominant in older male patients with chronic hepatitis C who are not receiving any modalities of treatment and have diabetes mellitus.

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Conflict of interest: None

Ethical consideration:

Prior to the study's execution, the Ethical Committee of Mansoura University's Faculty of Medicine gave its approval (IRB no. MS. 21.02.1386).

HIGHLIGHTS

- Hepatocellular Carcinoma is one of the most widespread leading causes of mortality.
- The most frequent risk factors for HCC are chronic HBV and HCV infection, which account for 80% of all HCC cases globally.

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