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PREVALENCE OF METABOLIC DYSFUNCTION- ASSOCIATED FATTY LIVER DISEASE IN EGYPTIAN PATIENTS WITH HEPATOCELLULAR CARCINOMA

By

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Abstract

Hepatocellular carcinoma is the third common cause of mortality worldwide with major changes of the prevalence of different etiologies. Nowadays we found more conflicting data about metabolic dysfunction -associated fatty liver disease (MAFLD) and its effect on a major spectrum of liver diseases as an increasing cause of hepatocellular carcinoma worldwide.

The study was to assessed prevalence of MAFLD as a single causes of HCC among HCC patients presented to the Hepatoma specialized outpatient clinic and to evalute effect on tumor burden and survival as compared to HCV infection patients related HCC.

Twenty nine patients with MAFLD related HCC were included in group A while 58 patients with HCV related HCC were enrolled as group B .In group (A) ; the mean age was 58.86 (±8.47) years, this group included 20 male patients (68.97%) and 9 female patients (31.03%). While in group (B); the mean age was 60/05(± 6.83) years, with 45 males (77.59%) and 13 females (22.41%) without significant difference between both as to age (P=0.482) or sexes (P=0.383). In the MAFLD related HCC group there were 19 /29 patients (65.5%) had Diabetes mellitus, 15 patients (51.7%) had hypertension and 9 patients (31%) were on antidyslipidimic drugs. The mean Body mass index (BMI) was 29kg/m^2 (±SD 2.81) Also, comparison between groups regarding tumor burden and characteristics of HCC, Child Pugh score, or Barcelona clinic liver cancer (BCLC) showed no significant statistical difference between both groups except for lymph node metastases which was higher in patients with HCV related HCC.

One year survival rate was higher in MAFLD group (72.4%) than of that in HCV related HCC group (58.6%) however, no significant statistical difference between both groups p=0.184.

Keywords: Metabolic (dysfunction) associated fatty liver disease, cirrhosis, Hepatocellular carcinoma.

Introduction

Hepatocellular carcinoma (HCC) is globally the sixth most common cause of cancer and third most frequent cause of mortality worldwide (Bray ***et al,*** 2018). Globally, MAFLD becomes the most common cause of liver disease. Its impact includes a wide spectrum of liver diseases ranging from steatosis to metabolic steatohepatitis to MAFLD -related cirrhosis and hepatocellular carcinoma (Pinyol *et al,* 2021).

MAFLD is different in a significant way from previous diagnostic criteria (Valenti and Pelusi, 2020). The two most important and significant differences between them are, MAFLD diagnosis does not exclude patients with alcohol intake, or other chronic liver diseases and the presence of metabolic disease is mandatory to diagnose of MAFLD (Fouad *et al,* 2020). MAFLD is characterized by lipid accumulation in liver which can progress to inflammation and substantial liver injury (Pinyol *et al,* 2021). It progresses to the steatohepatitis which is a major risk factor for developing cirrhosis and HCC but HCC can also arise in absence of cirrhosis (Marengo *et al,* 2016). HCC incidence in patients with MAFLD related cirrhosis is lower than in hepatitis C (HCV) or hepatitis B (HBV) related cirrhosis (Sagnelli *et al,* 2019). The incidence varied globally from 6% to 35%, being (20%-30%) in Western countries and (10%-20%) in Eastern ones (Wang *et al,* 2020). While in Middle East

and North Africa countries, the average rates for MAFLD incidence and related deaths were 8.9% and 8.6%, respectively, and the incidence of MAFLD increased between 2009 and 2019 by >25% (Golabi *et al,* 2021).

Many risk factors were associated with MAFLD like age and sex, with systemic metabolic dysregulation the main cause for development and progression (Pinyol *et al,* 2021). MAFLD can be considered within the spectrum of metabolic syndrome and its associated abnormalities including abnormal high body mass index (BMI), insulin resistance, type 2 diabetes mellitus, elevated systolic blood pressure and dyslipidaemia, its increasing prevalence induced HCC reflects the increase in the incidence of obesity and metabolic syndrome (Huang *et al,* 2021).

This study aimed to determine MAFLD prevalence as a single leading cause of HCC among HCC patients presented to the Hepatoma group and to assess its effect on tumor burden as well as survival of the patients in comparison with HCV related HCC.

Patients and Methods

This is a single-center retrospective comparative cross sectional study assessed prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) in patients with HCC at the Hepatoma specialized outpatient clinic at Tropical Medicine Department, between January 2015 and December 2020.

They were 2448 cases, 2125 were HCC cases due to different etiologies, from them all patients meeting new MAFLD criteria (Eslam *et al,* 2020) as HCC only cause of were 29 patients (1.36%) that included and named GA, compared to a double number of randomly selected HCC (58) patients due to HCV named GB.

Data were retrieved from the file system of the included patients. HCC was diagnosed based on American Association for the Study of Liver Diseases criteria (Bruix and Sherman, 2011) clinical, radiological and/or histological criteria

Inclusion Criteria: in GA All patients with excluded other causes of HCC and meeting the new MAFLD criteria presented at Hepatoma specialized outpatient Clinic at Tropical Medicine Department at Ain Shams University Hospitals from January 2015 to December 2020 with age's of18 to70 years. Exclusion Criteria was other HCC causes (HCV, HBV, autoimmune hepatitis, budd-chiari syndrome, Wilson disease, hemochromatosis …etc.), incomplete file.

Inclusion criteria: in GB HCC patients on top of HCV related liver cirrhosis. Exclusion criteria were patients younger than 18 years old or above age of 70 years, Other HCC causes, Hepatic steatosis, Obesity, Hypertension, Diabetes mellitus, or Dyslipidemia

Assessment at presentation included personal history and baseline demographics data, metabolic syndrome as body mass index (BMI), type 2 diabetes mellitus, hyperlipidemia, antidyslipidimic drugs and hypertension.

Laboratory investigations were complete blood count, serum creatinine, serum bilirubin, serum albumin, prothrombin time, alanine aminotransferase, aspartate aminotransferase and alphafetoprotein. Also, MAFLD related HCC group were recorded such as HBA1C, serum triglycerides, serum cholesterol, low and high density lipoproteins. Decompensation degree (Child–Pugh stage) and MELD scores were calculated.

Radiological investigations for HCC including (ultrasonography, Doppler, Triphasic abdominal CT scan to confirm HCC by presence of arterial enhancement of focal lesion followed by washout in porto-venous and delayed phases**,** Magnetic resonance imaging abdomen with diffusion for inconclusive or atypical cases (Ghanaati *et al,* 2012).

Tumor characteristics included, Barcelona Clinic Liver Cancer (BCLC) staging, number and site of hepatic focal lesions, size of largest lesion at diagnosis and total sizes of all HFLs. Also data included if there was vascular invasion by HCC, lymph nodes metastases or distant metastases.

Patients were followed from time of HCC diagnosis to either date of death or last follow-up and then analyzed one year survival rate for all enrolled patients.

Statistical analysis: Data were coded, tabulated and analyzed by Statistical package for Social Science (SPSS 23). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. Mean (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data. Student T test parametric numerical data, and Mann Whitney test for non-parametric numerical data. Chi-Square and Fisher's exact tests evaluated between two qualitative variables, Kaplan-Meier survival analyzed distribution of time-to-event variables. P >0.05: non-significant (NS), & P< 0.05: Significant (S).

Ethics approval and consent: The study was approved by the Ethics Committee of Faculty of Medicine, Ain Shams University (assurance no. FWA00017585). Data were obtained from patients' files with preservation of rights and privacy of patients' data.

Results

MAFLD as single HCC cause was 1.36% of HCC patients (2125). In GA mean age were (58.86±8.47) years, who were 20 males (68.97%) and 9 females (31.03%). While in GB mean age was 60/05±6.83) years, who were 45 males (77.59%) and 13 females (22.41%), without significant difference between ages (P=0.482) or sexes (P=0.383).

In GA regarding risk factors of MAFLD was 19/29 patients (65.5%) had DM, 15 patients (51.7%) had HTN and 9 patients (31%) were on anti-dyslipidimic drugs.

Mean BMI of 29 (±SD 2.81) and median level of 29(27.5-29.9), 2 patients (6.9%) had normal BMI, 20 patients (69%) were overweight, 6 patients (20.7%) were obese and one patient (3.4%) had morbid obesity.

As to MAFLD investigations, HBA1C showed mean level of 7.23% (SD±1.29) and median level of 7.3% (IQR 6-8.2). Lipid profile showed that mean level of triglycerides was 134.14 mg dl, 18 (62.1%) of patients had normal TGs mean level, but 11 patients (37.95%) had abnormal TGs mean level. Seven patients (24.1%) had abnormal mean level of serum cholesterol, seven had abnormal LDL mean level and 14 had abnormal HDL mean level.

There was no significance between both groups as to MELD score in GA had a mean 10.34±4.91 level and in GB had 10.34±4.91. Child score of patients, in GA mean was 6.48 ± 2.26; 22 patients (75.86%) in Child class A, a patient (3.45%) in class B and 6 patients (20.69%) in class C. In GB mean child score was 6.71 ± 2.19, with 40 patients (68.97%) in class A, 8 patients (13.79%) in class B and 10 patients (17.24%) in class C. Difference between both groups as to Child score and class was insignificant (P=0.658 & 0.324 respectively). As to BCLC staging system, patients in GA were BCLC B (34.48%), but in GB (29.32%) were BCLC B and (27.59%) were BCLC D without significant difference (p= 0.952).

Radiological data showed significant difference only in abdominal lymphadenopathy. Median HFL largest size in GA was 55 mm (IQR 30-80), GB was 40.5mm (IQR 30-60) with significant differences (p=0.076), median of HFLs total size in GA was 72 mm (IQR 35-110) and in GB was 65mm (IQR 50-80) without significant difference (p=0.508)

In GA 3/29 patients (10.34%) had abdominal lymphadenopathy, 2 radiological criteria benign lymphadenopathy and malignancy, but in GB 9 showed abdominal lymphadenopathy, with radiological criteria of malignant lymphadenopathy with significant difference (P=0.045). In GA seven with malignant PVT and in GB 14 with malignant PVT without significant difference (p=0.914).

In GA 22 patients without distant metastasis, 6 (20.69%) had malignant portal vein invasion and one (3.45%) had both features. In GB 40 patients (68.97%) had no metastasis, 4 (6.9%) had LN metastasis, 9 (15.52%) had malignant portal vein invasion, 4 (6.9%)

developed LN metastasis with PV invasion and 1 (1.72%) had LN, lung and PV metastasis with insignificant difference (p=0.649). Patients' survival for one year after HCC diagnosis showed higher MAFLD (72.4%) compared to HCV related HCC (58.6%), without significant difference (p=0.184). Details were given in tables (1, 2, 3, 4 & 5).

Table 1: Demographic data of groups (N=87)

Variations	GA (N=29)	GB (N=58)	Test of significant	
	No. (%)	No. (%)	P value	Sig.
Age in years	58.86 ± 8.47	60.05 ± 6.83	0.482(T)	NS
Female	9 (31.03%)	13 (22.41%)	0.383(C)	NS
Male	20 (68.97%)	45 (77.59%)		

(T) Student t-test of significance, (C) Chi-Square test of significance.

Table 2: Risk factors and laboratory investigations of MAFLD group (N=29)

MAFLD group (N= 29)		N/ Mean	% / SD	Median (IQR)	Range
DM	No	10	34.5%		
	Yes	19	65.5%		
HTN	No	14	48.3%		
	Yes	15	51.7%		
Antidyslipidimic drugs	No	20	69.0%		
	Yes	9	31.0%		
BMI value		29.0	2.81	29(27.5- 29.9)	(23.9-35.9)
BMI($kg/m^{2)}$	Normal (18.5-24.9)	2	6.9%		
	Over weight (25-29.9)	20	69.0%		
	Obese (30 - 34.9)	6	20.7%		
	Morbid obesity (>35)	1	3.4%		
HbA1C		7.23	1.29	7.3(6-8.2)	(5-9.5)
Triglycerides (mg/dl)		134.14	38.54	133 (103-166)	(60-220)
Triglycerides	Normal	18	62.1%		
	Abnormal	11	37.9%		
Serum cholesterol(mg/dl)		168.10	46.78	170 (137-195)	(82-267)
Serum cholesterol	Normal	22	75.9%		
	Abnormal	7	24.1%		
LDL(mg/dl)		89.38	17.80	90 (80-99)	(49-132)
LDL	Normal	22	75.9%		
	Abnormal	7	24.1%		
HDL(mg/dl)		38.97	4.75	39 (35-42)	(31-49)
HDL	Normal	15	51.7%		
	Abnormal	14	48.3%		

Table 3: Comparison of MELD, Child score and BCLC in 2 groups (N=87)

Variations		GA (N=29)	GA (N=29)	Test of significant	
		No. (%)	No. (%)	P value	Sig.
MELD Value		10.34 ± 4.91	11.02 ± 4.75	0.540(T)	NS
MELD score	<= 9	17 (58.62%)	34 (58.62%)	1.00(F)	NS
	10 -19	10 (34.48%)	19 (32.76%)		
	20 – 29	2 (6.9%)	5 (8.62%)		
Child score		6.48 ± 2.26	6.71 ± 2.19	0.658(T)	NS
Child class	A	22 (75.86%)	40 (68.97%)	0.324(C)	NS
	B	1 (3.45%)	8 (13.79%)		
	C	6 (20.69%)	10 (17.24%)		
BCLC	A1	3 (10.34%)	6 (10.34%)	0.952(F)	NS
	A2	5 (17.24%)	11 (18.97%)		
	A4	2 (6.9%)	2 (3.45%)		
	B	10 (34.48%)	17 (29.31%)		
	C	3 (10.34%)	6 (10.34%)		
	D	6 (20.69%)	16 (27.59%)		

(F) Fisher's Exact test of significance, (M) Mann-Whitney test of significance,

Table 4: Comparison of radiological findings between Median (IQR) in both groups

Variations		GA (N=29)	GA (N=29)	Test of significant	
		No. (%)	No. (%)	P value	Sig.
Liver parenchyma	Coarse	28 (96.55%)	55 (94.83%)	1.00(F)	NS
	Heterogenous	1 (3.45%)	3 (5.17%)		
Number of HFLs	One	14 (48.28%)	25 (43.1%)	0.933(C)	NS
	Two	6 (20.69%)	11 (18.97%)		
	Three	4 (13.79%)	9 (15.52%)		
	Multiple	5 (17.24%)	13 (22.41%)		
Site	Right lobe	20 (68.97%)	25 (43.1%)	0.056(C)	NS
	Left lobe	5 (17.24%)	13 (22.41%)		
	Both lobes	4 (13.79%)	20 (34.48%)		
largest size(mm)		55 (30 - 80)	40.5 (30-60)	0.076(M)	NS
Total Size of HFLs (mm)		72 (35 - 110)	65 (50-80)	0.508(M)	NS
Lymphadenopathy	No	26 (89.66%)	49 (84.48%)	0.743(F)	NS
	Yes	3 (10.34%)	9 (15.52%)		
Lymphadenopathy	Benign	2 (66.67%)	0 (0%)	0.045(F)	S
	Malignant	1 (33.33%)	9 (100%)		
PV patency	No	22 (75.86%)	44 (75.86%)	0.914(F)	NS
	Main	2 (6.9%)	6 (10.34%)		
	Right PVT	1 (3.45%)	3 (5.17%)		
	Left PVT	1 (3.45%)	2 (3.45%)		
	Segmental PVT	1 (3.45%)	1 (1.72%)		
	Right and Left	1 (3.45%)	0 (0%)		
	Main, Right and Left	1 (3.45%)	1 (1.72%)		
	Main and Right	0 (0%)	1 (1.72%)		
Ascites	No	22 (75.86%)	42 (72.41%)	1.00	NS
	Mild	4 (13.79%)	8 (13.79%)		
	Moderate	3 (10.34%)	7 (12.07%)		
	Severe	0 (0%)	1 (1.72%)		
Size of Spleen	No	6 (20.69%)	23 (39.66%)	0.111	NS
	Mild	10 (34.48%)	20 (34.48%)		
	Moderate	7 (24.14%)	12 (20.69%)		
	Marked	5 (17.24%)	3 (5.17%)		
	Splenectomy	1 (3.45%)	0 (0%)		
Extrahepatic spread	No	22 (75.86%)	40 (68.97%)		
	LN	0 (0%)	4 (6.9%)	0.649	NS
	PV	6 (20.69%)	9 (15.52%)		
	LN and PV	1 (3.45%)	4 (6.9%)		
	LN, PV and pulmonary	0 (0%)	1 (1.72%)		

Table 5: Comparison of one year survival between groups

	Time by months	Cumulative proportion surviving at time	Survivals Number	Log rank (P value)	
MAFLD	3	100.0%	29	0.184	NS
	6	75.9%	22		
	9	72.4%	21		
	12	72.4%	21		
HCV	3	89.7%	52		
	6	70.7%	41		
	9	60.3%	35		
	12	58.6%	34		

Discussion

MAFLD becomes the most common cause of liver disease, ranging from steatosis to metabolic steatohepatitis to MAFLD-related cirrhosis and HCC (Pinyol *et al,* 2021). There were controversial studies on tumor behavior and aggressiveness of HCC, some studies revealed MAFLD related HCCs were diagnosed at early or mediate stage (Pinyol *et al,*2021) ,while other studies concluded that MAFLD related HCC were detected at advanced stage with more aggressive pattern and vascular invasion (Ahn *et al.*2020).

In the present study, mean age was 58.86 (±8.47) years in MAFLD related HCC and 60/05 (± 6.83) years in HCV related HCC,

with male predominance, but without significant difference. This agreed with Piscaglia added that with HCV patients had worse liver function as compared to MAFLD patients, particularly Child-Pugh class A was in 366 (68.1%) HCV versus 107 (82.3%) MAFLD, while (2.3%) of MAFLD were child C and (3.7%) of HCV were child C. This may be explained by larger number of MAFLD patients in their study that were 145 patients and 611 patients with HCV compared to the present studied patients. Xie *et al*. (2022) on 135 MAFLD related HCC found (23%) of patients had T2 DM (34.1%) pre-diabetes, (81.5%) had obesity and (54.8%) had hypertension, Also, patients (61.4%) with dyslipidemia, (45.9%) had hypertriglyceridemia & (47.4%) had low HDL. Nguyen *et al.* (2022) reported that 63.9% of MAFLD related HCC patients had HTN, (78%) had T2DM and (31%) had hyperlipidemia.

In the present study, the MELD score of GA had a mean level of 10.34 ± 4.91, and GB had a mean level of 10.34±4.91, without significant difference. Myers *et al.* (2021) reported the mean MELD was 10 (8–14) of MAFLD related HCC as well as mean score of MELD was 9. Chen *et al.* (2022) found mean MELD score of MAFLD related HCC was 9.2 (7.5, 12.3).

In the current study, majority of MAFLD related HCC patients were child class A (75.68%), (3.45%) class B and (20.69%) class C which was much worse than in HCV related HCC ones (68.97%) were class A, (13.79%) class B and (17.24%) class C. Difference between both Child score and Child class wasn't significant (P=0.658 & 0.324 respectively). The present Child score disagreed with Nguyen *et al.* (2022), who found that 47.2% of MAFLD related HCC were in class A, 33.3% were in class B, none in class C and 19.5% without cirrhotic liver. Ahn *et al.* (2020) on 56 patients with NAFLD related HCC reported that 39 (69.6%), 16 (28.6%) and 1 (1.8%) were child class A, B & C respectively.

In the present study, most GA patients were BCLC B (34.48%), in GB (29.32%) were BCLC B and (27.59%) were BCLC D with no significant statistical difference between both groups. This may be explained by late detection of HCC in MAFLD group due to lack of regular surveillance in risky patients for MAFLD. This agreed to Chen *et al.* 2020) where 32.3 % of MAFLD related HCC patients were of the within BCLC B.

This disagreed with Nguyen *et al*. (2022) whose most MAFLD related HCC patients (52.8%) were BCLC C, while other compared (non MAFLD related HCC group) had 55.2 % patients with BCLC C but patients with BCLC D were lower than that found in our study. This disagreed with Piscaglia *et al*. (2016)they reported lower number of patients with BCLC D (2.1%) in MAFLD patients and (4.9%)in HCV patients.

In the current study there was statistical difference between both groups regarding AFP, median of AFP of MAFLD related HCC was (7.2ng/ml) but higher in HCV related HCC (129.2ng/ml) with p=0.001.This could be explained by existence of higher percentage of vascular invasion and distant metastases in HCV related HCC patients than in MAFLD related HCC patients. This differed from Pais *et al*. (2017) described in their study in which the median of AFP of MAFLD related HCC was 27ng/ml, also lower than the that concluded by a study of Ahn *et al*.(2020) which was (182 ng/ml) in MAFLD. Paradoxically, mean level of AFP described by Myers *et al*. (2021) was 9.5 (4-463)ng/ml inMAFLD related HCC group. Piscaglia *et al.* (2016) agreed with the present results they found that median AFP was 7.13 (range 1.5-83110.2) in MAFLD and 20.4 (1-267912) in HCV group with statistical significant difference between both groups p=0.001

In the present study, radiological data reflected tumor aggressiveness of HCC, MAFLD related HCCs were less aggressive. This disagreed with Ahn *et al.* (2020), who on 56 patients with MAFLD related HCC and 566 with HCC due to HBV and ALD

found that MAFLD-related HCCs had a larger tumor diameter (6.2 ±3.4 cm) more often had an infiltrative pattern (26.8%), macrovascular invasion (30.4%), extra-hepatic metastases (30.4%) and lymph node metastases (10.7%).

In the current study, there was no statistical difference between both as to HFLs number, or site or size. MAFLD patients had higher largest size percentage of HCC than in HCV patients. This agreed with Piscaglia *et al.* (2016) who didn't find significant difference between MAFLD and HCV as to tumor size, as mean largest HFL size was 3.2cm in MAFLD and 3.4 cm in HCV. Also, Pais *et al.* (2017) who studied 39 patients with MAFLD related HCC found that the HFLs mean diameter was (87±55mm) and non MAFLD-HCC showed mean diameter of (62±43mm). But, the present study disagreed with Chen *et al.* (2020) reported that maximum tumor size was 40 mm (2.3-7.6) in MAFLD related HCC patients.

In the present study, extra-hepatic and vascular spread of HCC, HCV related HCC patients experienced more vascular invasion and distant metastases than MAFLD ones. Paradoxically, Piscaglia *et al.* (2016) found 15.4% of MAFLD related HCCs were infiltrative which was more than found in HCV related HCCs (4%). They concluded that 9.3% had extrahepatic spread and 17.5% had macrovascular invasion in MAFLD, while HCV patients showed 17.2% and 14.7% of extrahepatic metastases and vascular invasion respectively. Pais *et al.* (2017) reported that 44% of MAFLD patients and 43% of non MAFLD had malignant vascular invasion. This agreed with Singh*et al.* (2022), they found no difference in alfafeto-protein, BCLC stage, tumor size, lesions number, and CTP score between MAFLD-HCC and HCV-HCC, But disagreed in extra-hepatic spread as was significantly less common in MAFLD-HCC than in HCV-HCC (21%) vs. (48.5%) with p=0.01.

In the present study, higher rate of 1 year MAFLD related HCC survival (72.4%) than HCV related HCC (58.2%) without significant difference p=0.184. This can be due to less aggressive phenotype of MAFLD related HCC, more preserved liver function, early diagnosis which enable more curative therapy than others. Piscaglia *et al*. (2016) showed that 1year survival rate was 76.4% in MAFLD related HCC and 84.2% in HCV related HCC. But, Ahn *et al.* (2020) reported that 54% of MAFLD related HCC survived for a year, as non-MAFLD related HCC (57%) without significance (P=0.135). The MAFLD-related HCC patients were older and detected at an advanced tumor stage due to late diagnosis were older age, irregular tumor surveillance, more advanced tumor and BCLC staging, vascular invasion (30%), infiltrative pattern (26.8%) and extrahepatic metastases (30.4%). Nguyen *et al.* (2022) reported that MAFLD related HCC had similar survival to HCC with other under lying liver diseases, despite MAFLD related HCC patients were older and comorbidities, larger tumor burden and advanced BCLC stage (D). This may be due to aggressive MAFLD tumor of related HCC and reduced capacity for sequential therapies.

Conclusion

Tumor aggressiveness and survival rates among aforementioned can be attributed to late diagnosis in patients or a later referral of MAFLD-HCC patients to the study centers with a more advanced tumor stage rather than to more aggressive tumor biology.

The natural history and progression were quite similar to HCV related HCC. There was strong association between metabolic syndrome as a MAFLD risk factor for development and the prevalence of HCC.

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Authors' contribution: Shaker and Barakat designed and supervised the study, Zaky and Arafat analyzed and interpreted the data, Farid wrote the manuscript, Montasser revised the manuscript for important intellectual content. All authors approved the final form.

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