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Fibrosis Index and FIB4 in Prediction of HCC in Chronic Hepatitis C Patients

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Abstract: ***Introduction: In Egypt, HCC is now the first cause of cancer related mortality. This is attributed to the heavy burden of chronic HCV (CHC) infection. The increased risk to development of HCC in chronic HCV patients is largely restricted to cirrhotic patients and those with advanced fibrosis. Both FIB-4and fibrosis index (FI) are considered non-invasive tools for evaluation of hepatic fibrosis, using simple variables. Aim of the Work: This work aims to examine the utility of FIB4 score and FI score in predicting the risk of HCC development in chronic HCV Egyptian patients. Patients and Method: This study included 111 adult patients (100 males, 11 females) with chronic HCV and untreated HCC (group A) and 222 adult patients (128 males, 94 females) with chronic HCV without HCC (group B). FIB4 was estimated as follows: [Age x AST] / [Platelets x (ALT) $^{1/2}$]. FI was estimated as follows: 8.28-[(0.01xPlatelets (10^9/L) – (1.08* (10*serum albumin (gm/L)]. Results: FI and FIB4scores reported statistically significant high values in group A. The values of FIB4 were 7.15 ± 5.78 in group A compared to 3.42 ± 3.14 in group B (P ≤0.000). The values of FI score was 3.57 ± 1.07 in group A compared to2.43 ± 1.08 in group B (P≤0.000). The Stratified Specific LR for presence of HCC according to the score of FIB4 was (0.07, 1.22 and 2.43) in subjects with score (< 2, 2 – 4 and ≥ 4) respectively. The SSLR concerning HCC presence according to FI score was (0.22, 1.02 and 5.05) in subjects with score (< 2, 2 - 4 and ≥4) respectively. Conclusion: Both FI andFIB4 scores could be useful tools to predict the risk of development of HCC in Egyptian subjects with chronic HCV. Nevertheless, FI was superior to FIB4 in this aspect. FI ≥ 4 is 5.05 times more likely to occur in chronic HCV patients with HCC than those without. So, patients with chronic HCV with FI ≥ 4 must be subjected for meticulous follow-up.***

Keywords: HCC, FIB4, FI, HCV

1. Introduction

In Egypt, hepatocellular carcinoma (HCC) is a national health problem. It is now the first cause of cancer related mortality (1). This is mainly attributed to the heavy burden (14.7%) of chronic HCV infection, which leads to liver cirrhosis in approximately 20% of patients within 20 years of infection. Annually, 1-4% of patients with cirrhosis develop HCC (2). The diagnosis of HCC at early stages allows the application of curative therapies like surgery and thermal ablation. This can be achieved through the application of a surveillance program to high risk populations. The increased risk to HCC development in CHC patients is largely restricted to cirrhotic patients and those with advanced fibrosis (3). Both FIB-4and fibrosis index (FI) are considered non-invasive tools for evaluation of the stage hepatic fibrosis, using simple variables such as Age, AST, ALT, platelet count and serum albumin (4, 5).

2. Aim of Work

This work aims to examine the utility of FIB4 score and FI score in predicting the risk of development of HCC in Egyptian patients with chronic HCV.

3. Patients and Methods

This study was conducted in Specialized Medical Hospital, Mansoura University in the period from January 2014to December 2015. It included 111 adult patients (100 males, 11 females) with chronic HCV with untreated HCC (group A) and 222 adult patients (128 males, 94 females) with chronic HCV without HCC (group B). Chronic HCV was diagnosed using ELISA to detect HCV antibodies and confirmed by quantitative PCR forHCV. HCC was diagnosed according to the criteria of EASL in non-invasive diagnosis of HCC (6) i. e. hepatic focal lesion characterized by enhancement in the arterial phase followed by washout in the portal phase and the delayed phase using contrast enhanced abdominal CT ± MRI. Routine work up was done for all subjects including liver and renal biochemical tests. In all patients assessment of liver fibrosis was done using FIB4 score and Fibrosis index (FI) score. FIB4 was computed as follows :[(age in years) × AST (U/L)]/[platelets (10^9/L) × ALT (U/L) $^{1/2}$] (4). FI was computed as follows: 8.28 - [(0.01 x Plat. (10^9/L) - [1.08 * (10 * serum alb. (g/L))]] (5). Prediction of HCC by FIB4 score and FI was computed using ROC curve. Also, the stratum specific likelihood ratio (SSLR) was calculated as the proportion of diseased subjects with a test result in a given range (group A) divided by the proportion of non- diseased subjects with a test result in the same range (group B). The percentiles method for calculation of the SSLR is as follows: Step 1. Establish the strata and tabulate the stratum specific test results. Step 2. Compute proportion of patients with the disease with those results. Step 3. Compute proportion of patients without the disease with those results. Step 4. Divide the fractions with the disease by the fractions without the disease (7).

4. Results

Baseline tumor and patients characteristics are shown in table (1). As regard the hepatic condition as evaluated by Child-Turcotte-Pugh (CTP) score, Child class A

represented 43.2%, Child class B represented 42.3% while Child class C represented 14.4% in group A. In group B, Child class A represented 89.5%, Child class B represented 8.6% while Child class C represented 1.8%. As regard the tumor burden in group A, the tumor size was smaller than 2cm in 9 % , 2-3cm in 11.7 % and larger than 3cm in 79.3 %. The tumor was unifocal in 33.3%, multifocal in 63.1% and diffuse in 3.6% . Mean tumor size was 5.56 ± 2.1 cm. The smallest tumor diagnosed non - invasively was 1.3 cm. The distribution of Seventh edition TNM tumor stage (8) in group A was as follows: stage I represented (19.8%), stage II represented (25.2%), stage IIIa represented (19.8%), stage IIIb (18.1%), stage IIIc (1.8%), stage IVa (8.1%) and stage IVb (7.2%). Regarding group A, both FI and FIB4 scores reported significantly higher values. The value of FIB4 in group A was 7.15±5.78 compared to 3.42±3.14 in group B (P≤0.000). The value of FI in group Awas 3.57±1.07 compared to 2.43±1.08 in group B (P≤0.000). The score of FIB4reportedacut off value (≥2.32) above which there was a high risk of development of HCC with area under the curve (AUC) (77.7%), sensitivity (91.2%), specificity (56%), positive predictive value (PPV) (49.5%), negative predictive value (NPV) (93.1%), accuracy (67.3%) and positive likelihood ratio (LR) (2.07). Also, FI reported the cut off value (≥3.13) above which there was a high risk of development of HCC with AUC (78.1%), sensitivity (70.4 %), specificity (78.4 %), PPV (64.4%), NPV (82.6%), accuracy (75.5%) and positive (LR) (3.26) (Figure3). FIB4 score reported SSLR for presence of HCC as follow; (0.07, 1.22 and 2.43) in scores of (< 2, 2 to 4 and >4) respectively. Also, FI score reported SSLR for presence of HCC as follows; (0.22, 1.02 and 5.05) in scores of (< 2, 2 to 4 and>4) respectively.

Table 1: Baseline patient's characteristics

Variable	Group	Mean	Std. Deviation	P value
Age	A	59.34	7.61	0.000
	B	48.18	8.39	
CTP score	A	7.36	2.06	0.000
	B	5.48	1.07	
ALT (0-41 U/L)	A	62.00	59.27	0.871
	B	62.90	38.64	
AST (0-37 U/L)	A	88.48	83.07	0.007
	B	64.99	41.07	
Albumin (3.5-5 g/dl)	A	3.23	0.62	0.000
	B	3.94	0.57	
Platelet ($\times 10^3/\mu l$)	A	123.83	67.45	0.000
	B	160.76	69.26	
INR	A	1.31	0.28	0.000
	B	1.11	0.16	
Total bilirubin (up to 1mg/dl)	A	1.68	1.07	0.000
	B	1.01	0.57	
Creatinine (up to 1.2 mg/dl)	A	0.93	0.28	0.017
	B	0.87	0.20	
FIB4	A	7.15	5.78	0.000
	B	3.42	3.14	
FI	A	3.57	1.07	0.000
	B	2.43	1.08	

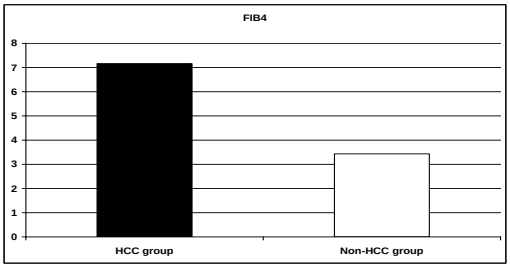

Figure 1: Value of FIB4 in HCC and non HCC CHC patients

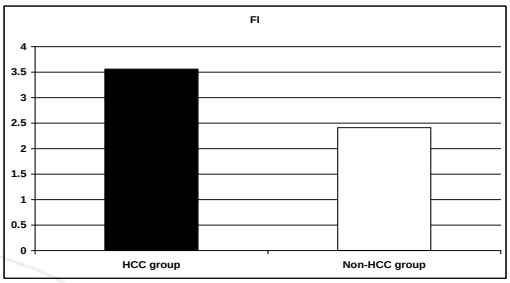

Figure 2: Value of FI in HCC and non HCC CHC patients

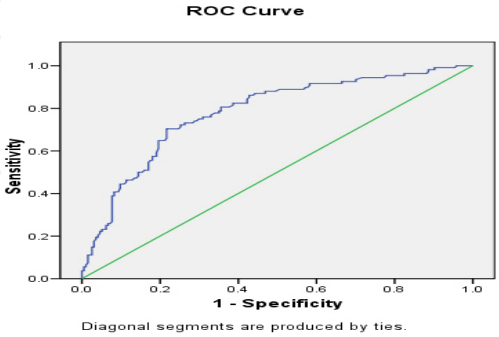

Figure 3: ROC analysis curve of FI in prediction of HCC in CHC patients

FI reported acut off value (≥3.13) above which there wasa high risk of development of HCC with AUC (78.1%), sensitivity (70.4 %), specificity (78.4%), PPV (64.4%), NPV (82.6%), accuracy (75.5 %) and positive LR (3.26)

5. Discussion

HCC is still a main problematic health issue in Egyptian patients and represents the first etiology of death in cancer patients (1). Chronic hepatitis C is the major risk factor of HCC in Egypt. The very early diagnosis of HCC permits the application of effective curative therapies and improves patient outcome. The definition of population at highest risk, the surveillance method and frequency of its application is controversial. In EASL clinical practice guidelines, abdominal ultrasonography (US) is recommended every six months in chronic HCV patients with liver fibrosis stage equal to or more than F3. The period is shortened to three months if a nodule smaller than one centimeter (cm) is encountered. Contrast enhanced abdominal CT is indicated if abdominal ultrasonography is unreliable as in obese patients (6). In the Japanese clinical practice guidelines, abdominal US and three HCC markers (AFP, PIVKAII, AFP L3) are done every three months with contrast enhanced abdominal CT or MRI examinations every six to twelve

months (as an optional surveillance method) in extremely high risk (cirrhotic) CHC patients. In high risk CHC patients, abdominal US plus the three HCC markers every six months are recommended (9). In the United States, only about (12%) of new HCC in chronic HCV patients are diagnosed through surveillance programs (10) and 20% or less of cirrhotic patients with emerging HCC have undergone regular surveillance (11). The addition of prediction method to the surveillance program could improve the cost-effectiveness by giving attention to the extremely high risk groups. Attempts to define patients who need a much closer follow up have been done. In Egypt, Yosry et al concluded that patients with chronic HCV and fibroscan score >25 k Pa are eagerly in need for meticulous follow up by imaging examinations (12). Ethoxibenzyl-magnetic resonance imaging (EOB-MRI) was used to calculate Liver-Intervertebral (LI) disc ratio as follows: (post-contrast liver intensity/post-contrast intervertebral disc intensity) / (pre-contrast liver intensity/pre-contrast intervertebral disc intensity). Nojiri et al concluded that LI < 1.46 was an independent factor that is related to the risk of HCC development in chronic CHV patients, and that LI may substitute liver biopsy for evaluating this risk. Also, combination of LI and FIB-4can provide a better prediction of HCC progression (13).

The present study reported a strong male predominance that may be due to the differences in sex-specific exposure to risk factors, like viral hepatitis, which is more common in males and may also be due to hormonal factors. Androgens promote the development of HCC via induction of oxidative stress and DNA damage [14]. High percent of HCC cases were diagnosed with large tumor (≥3 cm) & multifocal HCC despite adherence to surveillance program, denoting the need for better stratification of Egyptian CHC patients who are at risk of HCC development.

In clinical practice, however, FIB 4 and FI are not used as diagnostic tests of HCC, but used as an indicator of increasing risk of HCC. In this issue, SSLR is much valuable than a fixed cutoff value (12). The present study indicates that FIB4 >4 is 2.43 times as likely to occur in patients with chronic HCV related HCC than those without HCC. This finding agrees with that of Tamaki et al who concluded that patients with a FIB-4 score >3.25 were at high risk to develop HCC (15). It also indicates that FI >4 is 5.05 times as likely to occur in patients with chronic HCV related HCC than those without HCC. This denotes that FI score is a stronger predictor of HCC development than FIB4 score in CHC Egyptian patients. This can be attributed to the fact that FI score calculation is more dependent on hepatic disease specific variables, like serum albumin and platelet count, thanFIB4 in which age & transaminases are included beside the platelet count.

6. Conclusion

Both FIB4 and FI scores could be useful tools to predict the risk of development of HCC in Egyptian subjects with chronic HCV. Nevertheless, FI was superior to FIB4 in this aspect. FI ≥ 4 is 5.05 times more likely to occur in chronic HCV patients with HCC than those without. So, patients with chronic HCV with FI ≥ 4 must be subjected for meticulous follow-up.

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