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Diagnostic Efficacy of Serum Factor IV Collagen of Hepatic Fibrosis Regression in Chronic Hepatitis B Virus Infected Patients

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Abstract

Purpose: Chronic hepatitis B virus infection affects more than 3 million people worldwide. The present study aimed to evaluate the role of pretreatment factor IV collagen as predictor of post treatment virological response with hepatic fibrosis regression. **Materials and Methods:** This prospective cohort study has been conducted on 74 naieve patients with chronic HBV infection with variable degree of hepatic fibrosis (F2, F3, ≥F4), viral load, and variable degree of abnormality in laboratory parameters of liver functions. All patients treated with Entecavir 0.5 mg/day or 1 mg/day according to severity of hepatic condition for 1 year. Liver fibrosis assessed using fibroscan, factor IV collagen, (APRI) and (FIB-4) scores evaluation. **Results:** All included patients in our study achieve post treatment Virological response with undetectable HBV DNA PCR (<16 IU/ml). With significant post treatment reduction in mean fibroscan value 10.70 ± 5.80 ($p < 0.001$). There were also significant end treatment improvements in mean FIB score and APRI score 1.56 ± 1.02 ($p < 0.0001$) and 0.50 ± 0.28 ($p < 0.0001$) respectively. There is significant end treatment improvement of mean factor IV collagen. In our study 49 (66.22%) of included patients showed post treatment reduction in their level of hepatic fibrosis (Responder) opposite to 25 (33.78%) had no post treatment improvement in degree of hepatic fibrosis (Non-responder). **Conclusion:** Low pretreatment factor IV collagen is significantly correlated with virologial response and hepatic fibrosis regression post Entecavir therapy in patients with chronic HBV infection.

Keywords

Entecavir, Hepatic Fibrosis, HBV

1. Introduction

Hepatitis B virus (HBV) infection is one of the major public health problems in Egypt; its prevalence was (1.4%) with higher prevalence in urban than rural area [1].

All patients with untreated chronic hepatitis B virus infection have a high risk of development of cirrhosis and hepatocellular carcinoma [2].

The aim of treatment is decreasing HBV DNA levels, decreasing hepatic inflammation and improving laboratory parameters of disease activity [3].

Entecavir is a potent oral guanosine nucleoside analogue for treatment of HBeAg-positive or negative chronic HBV infection; it's safe and effective in treatment of naive and lamivudine resistant patients [4].

Chronic liver injury causes necrosis and apoptosis of parenchymal cells and replacement by extracellular matrix, with disease progression the liver parenchyma replaced by scar tissues with abnormal vascular architecture and finally organ dysfunction [5].

Coagulation cascade is one of main factors in development of hepatic fibrosis, in which Thrombin is cause change of fibrinogen to fibrin which appear in the hepatic tissue during acute and chronic liver injury [6].

Thrombotic risk factors play an important role in hepatic fibrosis in patients with chronic HBV or chronic HCV [7].

Type IV collagen is a direct marker of hepatic fibrosis which indicate hepatic extracellular matrix transformation, and its concentration affected by degree of liver cell loss and disturbed hepatic function [8].

Hepatic fibrosis is the main complication of chronic hepatic disease that eventually leads to cirrhosis with subsequent complications [9].

So, in this study we aimed to evaluate the role of pretreatment serum level of factor IV collagen as a predictor of post antiviral therapy virological response with hepatic fibrosis regression.

2. Aim of the Work

To evaluate the role of serum factor IV collagen level as a predictor of post antiviral therapy virological response with hepatic fibrosis regression.

3. Materials and Methods

3.1. Study Participants

This prospective cohort study has been conducted on 74 naieve patients with chronic HBV infection with variable degree of hepatic fibrosis (F2, F3, ≥F4), viral load (HBV DNA) from 16 up to >1,000,000 copies/ml, and variable degree of abnormality in laboratory parameters of liver functions. All patients attend out patient's clinic of Tropical Medicine and Gastroenterology Departments during the period from April 2017 till May 2018.

Exclusion criteria included: 1) co-infection with HCV, HDV, or HIV; 2) excessive alcohol consumption (>21 drinks per week in men and >14 drinks per week in women); 3) dynamic CT imaging of HCC or history of HCC.

All patients treated with Entecavir 0.5 mg or 1 mg according to severity of hepatic condition, once daily oral on empty stomach for 1 year. Patients were treated according to EASL 2017 guidelines for HBV infection treatment [2].

At base line and one year post antiviral treatment all included patients subjected to complete history taking , full clinical examination, liver function tests, liver fibrosis assessment (F2- ≥ F4) using fibroscan, factor IV collagen measurement as a serum direct fibrosis markers, aspartate aminotransferase-to-platelet ratio index (APRI) score [10] and fibrosis index based on four factors (FIB-4) score [11] where increase in FIB-4 and APRI scores correlate with increase in hepatic fibrosis [12] [13], they calculated according to the following equation.

$$\text{FIB-4} = \left(\text{age} \times \text{AST}\right) \Big/ \left(\text{platelet count} \times \left(\text{ALT}\right)^{1/2}\right)$$

$$\text{APRI} = \left(\left[\text{AST}/\text{UNL}\right] \Big/ \text{platelet count}\right) \times 100$$

3.2. Sampling

8 ml of venous blood were collected from each patients under aseptic precautions and divided in 4 tubes: 1) 2 tubes containing EDTA (sterile EDTA containing Vacutainer) one for platelet count used directly and the other for HBV-DNA centrifuged, separated in sterile tube and frozen at −20˚C till the time of the assay. 2) Plain glass tube for liver function tests, then after clotting, the tube was centrifuged at 3000 rpm for 5 min at room temperature and then the serum was separated to be used for estimation of liver function (including liver enzymes, albumin, bilirubin-total and direct) and type IV collagen. 3) Sodium citrate containing tube (Vacutainer) for prothrombin time, prothrombin concentration and INR.

3.3. The Laboratory Tests

1) The platelet count was done by Celtak haematology analyzer (Nihon Kohden, Japan).
2) The liver function tests (total and direct bilirubin, serum albumin, AST and ALT) were done by BT 1500 full automated chemistry analyzer (Bioticnica, Italy).
3) The prothrombin time, concentration and INR was done by done using Thromborel S kits (Siemens, Germany) using BE coagulator (Germany).
4) HBV-DNA was done by StepOnePlus™ Real-Time PCR System (ThermoFisher Scientific, USA) using Taqman PCR mastermix (ThermoFisher Scientific, USA) after DNA extraction by Qiagen kit (Qiagen, inc, USA) and according the manufacture's pamphlet.
5) Type IV collagen was assayed using quantitative sandwich ELISA technique with Human col IV ELISA kit (Mybiosource, inc, USA) and according the manufacture's pamphlet.

3.4. Transient Elastography

Liver fibrosis assessment was done for all patients with Transient Elastography

(FS-502 touch device, France) using both the M and XL probes. Transient elastography provides a continuous measure of liver stiffness measured in kilopascals (kPa). Transient elastography was performed after overnight fasting. Mild amplitude and low-frequency waves were transmitted through the liver and liver stiffness directly correlate with wave velocity [14].

10 valid measurements were done for every patient, which considered reliable when success rate ≥60% and an interquartile range (IQR)/median liver stiffness measures ≤30%. 10 All patients did ultrasound transient elastography examination at the baseline and one year after end of treatment. Results of transient elastography were correlated to METAVIR histological staging system. The cut-off values in our study were [15]:

F0: till 5.4 kPa **F0-F1:** 5.5 - 5.9 kPa **F1:** 6 - 6.9 kPa **F1-F2:** 7 - 8.7 kPa

F2: 8.8 - 9.4 kPa **F3:** 9.5 - 12.4 kPa **F3-F4:** 12.5 - 14.4 kPa **F4:** ≥14.5 kPa

3.5. Therapeutic Efficacy According to Degree of Fibrosis

Responder patients to treatment: include any patients who show any decrease in their degree of fibrosis after one year of regular treatment in comparison to pretreatment one.

Non-Responder patients to treatment: include any patients with no change in their level of hepatic fibrosis or those who show any progression in hepatic fibrosis after one year of regular treatment compared to their pretreatment level.

Virological response during NA therapy: is defined as undetectable HBV DNA by a sensitive polymerase chain reaction (PCR) assay with a limit of detection of 10 IU/ml [2].

3.6. Ethical Approval

The study protocol was approved by the ethical committee of our institution and all our patients provided informed consent before inclusion in the study

3.7. Statistical Analysis

The data were coded and verified prior to data entry. Computer program Statistical Package for Social Sciences (SPSS) (ver.21) Chicago. USA was used for analyzing the collected data and for drawing figures. Data expressed as mean ± standard deviation and number, percentage. Student-t-test used to determine significant for numeric variable. P value is considered significant if P value < 0.05 and not significant if P value > 0.05.

To calculate sample size in this study by "EBI" program at power 80%, with confidence 95.0%, Alpha 0.5 equal 74 patients.

4. Results

4.1. Demographic Data of the Study Participants

The present study included 74 patients with naive chronic HBV-infection with their mean ages were 43.85 ± 10.12; 21 females (28.77%) and 53 males (72.6%)

and their mean FIB-4 score and APRI score were 2.80 ± 1.61 and 1.24 ± 0.67 respectively.

The mean value for pretreatment fibroscan was 11.99 ± 4.96 kPa; twenty nine of them (39.19%) were F2, 30 (40.54%) were F3 and 15 (20.27%) were ≥F4 (Table 1).

4.2. The Mean Laboratory Measures, Liver Fibrosis Level, FIB Score and APRI Score before and One Year after Regular Therapy

Regarding the post treatment fibroscan assessments of the included patients, the mean value was 10.70 ± 5.80 ($p < 0.001$**), 4 (5.41%) of them were F0, 17 (22.97%) were F1, 24 (32.43) were F2, 15 (20.27%) were F3 and 14 (18.92%) were F4 with evidence of cirrhosis.

The laboratory measures among chronic HBV infected patients including factor IV collagen, mean platelet count, and liver function tests together with mean FIB score and APRI score before and one year of regular therapy are presented in Table 2, with significant improvement of them except INR which show non-significant post treatment improvement ($p < 0.111$).

All included patients achieve Virological response with undetectable HBV DNA PCR (<16 IU/ml) during regular treatment with Entecavir 0.5 mg/d or 1mg/day for one year (100%).

There were also significant end treatment improvements in mean FIB score and APRI score 1.56 ± 1.02 ($p < 0.0001$***) and 0.50 ± 0.28 ($p < 0.0001$***) respectively (Table 2).

In our study 49 (66.22%) of included patients showed post treatment reduction in their level of hepatic fibrosis (Responder) opposite to 25 (33.78%) had no post treatment improvement in degree of hepatic fibrosis (Non-responder).

4.3. Pretreatment and Post Treatment Improvement in Degree of Liver Fibrosis in Responder Patients

As regard hepatic fibroscan of the responder group:

- 26 (53.06%) patients were F2 and after one year of regular treatment 4 (15.40%) of them became F0, 17 (65.40%) became F1and 5 (19.20%) didn't show any change in their degree of hepatic fibrosis.
- 20 (40.82%) patients were F3 and post treatment 17 (85.00%) of them became F2 and 3 (15%) of them showed no post treatment improvement in their hepatic fibrosis.
- 3 (6.12%) patients were F4 and post treatment 2 (66.70%) of them became F2 and only one patients (33.30%) become F3.

With significant p value (<0.0001***). This is illustrated in Table 3.

4.4. Pretreatment Laboratory Measures, Mean Fibroscan Values, APRI Score and FIB-4 Score between Responder and Non-Responder Patients

By comparing baseline laboratory parameters between responder and

non-responder patients, the responder group had mild pretreatment impairment in their laboratory parameters.

This is illustrated in Table 4.

4.5. Laboratory Parameters in Responder Patients That Show Statistically Significant Difference Compared to Non-Responder Group

ROC curve analysis of different pretreatment variables that show statistically significant difference between responder and non-responder group, revealed that pretreatment low level of serum bilirubin, mild impairment of serum INR, mild degree of liver stiffness as detected by fibroscan and low level of serum factor IV collagen were statistically significant factors associated with post treatment improvement in the level of hepatic fibrosis in naive chronic hepatitis B virus infected patients (Table 5, Figure 1).

Table 1. Demographic and baseline laboratory and radiologic data of the included patients.

Variables	
Number	74
Age (y) (Mean ± SD)	43.85 ± 10.12
Male (N.%)	53 (72.6%)
Female (N.%)	21 (28.77%)
Platelet count (Mean ± SD) PLT (10^3/µl)	147.03 ± 70.04
Liver function tests (Mean ± SD)	
Bilirubin (mg/dl)	1.55 ± 0.58
Albumin (gm/dl)	3.52 ± 0.67
ALT (U/L)	66.70 ± 32.76
AST (U/L)	60.35 ± 23.67
INR	1.31 ± 0.29
HBV DNA PCR level (IU/ml) (N. %) Mild (16 - 100,000 IU/ml) Moderate (100,000 - 1,000,000 IU/ml) High (>1,000,000 IU/ml)	 25 (33.80%) 25 (33.80%) 24 (32.40%)
Factor IV collagen (mg/dl)	219.04 ± 108.76
Liver Fibroscan (Kilo Pascal" kPa") (Mean ± SD)	11.99 ± 4.96
Fibrosis stage (N.%) (Mean ± SD)	
F2	29 (39.19%) 8.12 ± 0.59

Continued

F3	30 (40.54%) 11.49 ± 1.43
F4	15 (20.27%) 20.46 ± 3.85
FIB-4 score (Mean ± SD)	2.80 ± 1.61
APRI score (Mean ± SD)	1.24 ± 0.67

Abbreviations: ALT: Alanine transaminase, **AST**: Aspartate transaminase, **INR:** International normalization ratio, **HBV:** Hepatitis B virus, **FIB-4:** Fibrosis index based on four factors APRI**:** Aspartate aminotransferase-to-platelet ratio index.

Table 2. Factor IV collagen, laboratory measures, liver fibrosis level, FIB score and APRI score among patients with chronic HBV infection before and one year after regular therapy.

Variables (n = 74)	Before therapy	After one year of entecavir therapy	P. value
Platelet count (Mean ± SD) PLT (103/µl)	147.03 ± 70.04	182.97 ± 76.22	0.002**
Liver function tests (Mean ± SD)			
Bilirubin (mg/dl)	1.55 ± 0.58	1.31 ± 0.42	0.224
Albumin (gm/dl)	3.52 ± 0.67	3.62 ± 0.55	0.0001***
ALT (U/L)	66.70 ± 32.76	37.38 ± 20.46	0.0001***
AST (U/L)	60.35 ± 23.67	31.89 ± 14.87	0.0001***
INR	1.31 ± 0.29	1.23 ± 0.24	0.111
HBV DNA PCR level (IU/ml) (N%) Mild viral load Moderate viral load High viral load	25 (33.80%) 25 (33.80%) 24 (32.40%)	Undetectable	------
Factor IV collagen (mg/dl)	219.04 ± 108.76	171.34 ± 78.25	0.012*
Liver Fibroscan (Kilo Pascal" kPa") (Mean ± SD)	11.99 ± 4.96	10.70 ± 5.80	0.001 **
Fibrosis stage (N %) (Mean ± SD)			
F0	-------	4 (5.41%) 5.17 ± 0.20	----------
F1	-------	17 (22.97%) 6.11 ± 0.19	----------
F2	29 (39.19%) 8.12 ± 0.59	24 (32.43) 7.76 ± 0.80	0.018*
F3	30 (40.54%) 11.49 ± 1.43	15 (20.27%) 12.45 ± 1.03	0.023*
F4	15 (20.27%) 20.46 ± 3.85	14 (18.92%) 21 ± 4.01	0.972
FIB-4 score (Mean ± SD)	2.80 ± 1.61	1.56 ± 1.02	0.0001***
APRI score (Mean ± SD)	1.24 ± 0.67	0.50 ± 0.28	0.0001***

$p < 0.05$ indicate significant difference. Student-t-test was used, *$P < 0.05$ significant, **$P < 0.001$ moderate significance ***$p < 0.000$ highly significance.

Table 3. Pretreatment and post treatment improvement in degree of liver fibrosis in responder patients.

		Degree of liver fibrosis after treatment in responder					P value
		F0	**F1**	**F2**	**F3**	**F4**	
Degree of liver fibrosis before treatment in responder	**F2**	4	17	5	0	0	<0.0001***
		15.40%	65.40% (17/26)	19.20% (5/26)	0.00%	0.00%	
		100.00%	100.00% (17/17)	22.70% (5/22)	0.00%	0.00%	
	F3	0	0	17	3	0	
		0.00%	0.00%	85.00% (17/20)	15% (3/20)	0.00%	
		0.00%	0.00%	77.30% (17/22)	60.00% (3/5)	0.00%	
	F4	0	0	0	2	1	
		0.00%	0.00%	0.00%	66.70% (2/3)	33.30% (1/3)	
		0.00%	0.00%	0.00%	40.00% (2/5)	100.00% (1/1)	

***p < 0.000 highly significance.

Table 4. Comparison between responder and Non-responder patients as regard Pretreatment laboratory measures, mean fibroscan values, APRI score and FIB-4 score.

Variables (n = 74)	Pretreatment Responder (n = 49)	pretreatment parameters of Non-responder (n = 25)	P value
Platelet count (Mean ± SD) PLT (10^3/µl)	168.57 ± 64.49	104.80 ± 61.65	<0.0001***
	Liver function tests (Mean ± SD)		
Bilirubin (mg/dl)	1.33 ± 0.37	1.96 ± 0.68	<0.0001***
Albumin (gm/dl)	3.77 ± 0.61	3.03 ± 0.49	<0.0001***
ALT (U/L)	65.35 ± 25.39	69.36 ± 44.33	0.622
AST (U/L)	62.22 ± 19.40	56.68 ± 29.00	0.331
INR	1.19 ± 0.22	1.54 ± 0.26	<0.0001***
Factor IV collagen (mg/dl)	179.37 ± 76.04	296.80 ± 122.06	<0.0001***
	HBV DNA PCR level (IU/ml) (N.%)		
Mild viral load	17 (34.69%)	8 (32%)	
Moderate viral load	16 (32.65%)	9 (36%)	0.118
High viral load	16 (32.65%)	8 (32%)	
Liver Fibroscan (kPa") (Mean ± SD)	9.89 ± 2.92	16.10 ± 5.59	<0.0001***
FIB-4 score (Mean ± SD)	2.09 ± 1.10	4.19 ± 1.56	<0.0001***
APRI score (Mean ± SD)	1.09 ± 0.61	1.53 ± 0.70	0.007**

**p < 0.001 moderate significance ***p < 0.000 highly significance.

Table 5. Pretreatment laboratory parameters in responder patients that show statistically significant difference compared to non-responder group.

Area Under the Curve					
Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Bilirubin (mg/dl)	0.872	0.043	0.000	0.788	0.956
Albumin (gm/dl)	0.186	0.056	0.000	0.077	0.295
Platelet count (10^3/µl)	0.460	0.067	0.579	0.329	0.591
INR	0.838	0.053	0.000	0.734	0.943
Liver Fibroscan (kPa")	0.957	0.022	0.000	0.913	1.000
Factor Iv collagen (mg/dl)	0.743	0.067	0.001	0.612	0.874

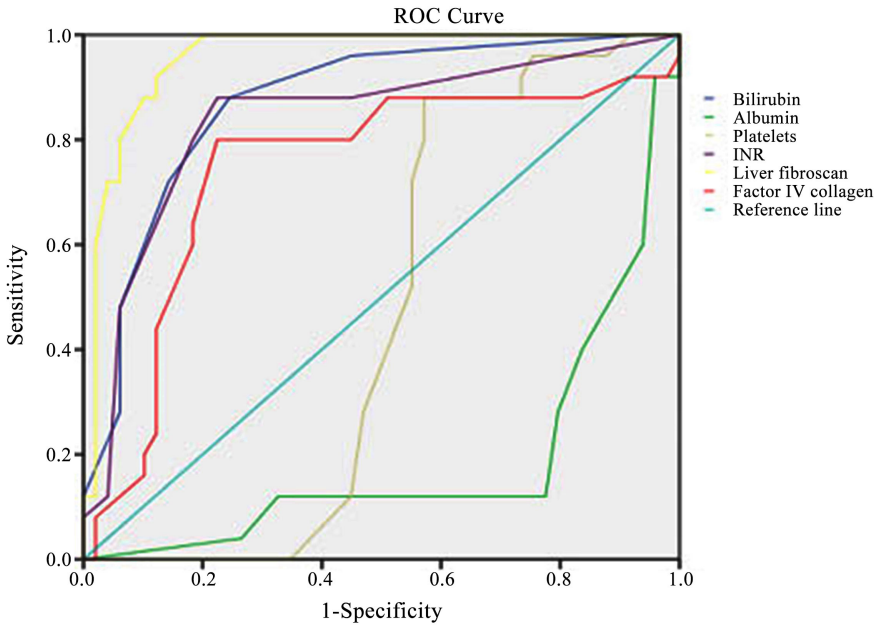

Figure 1. ROC curve of pretreatment laboratory parameters in responderpatients, that show statistically significant difference compared to non-responder group.

5. Discussion

Progression of hepatic fibrosis is associated with increased risk of liver decompensation, and development of hepatocellular carcinoma (HCC) [16].

Chronic hepatitis B virus treatment with nucleotide analogs (NUCs) leads to clinical improvement and reduces risk of HCC development [17].

Entecavir is potent new NAs generation with low risk of resistance, however NAs don't have immunomodulatory effects so, prolonged treatment is usually required to prevent viral relapse [18].

In this prospective study we try to assess degree of improvement in hepatic fibrosis after one year of regular treatment with entecavir 0.5 mg/day in naive

chronic hepatitis B virus infection patients with different base line degree of fibrosis evaluated using hepatic fibroscan.

We have significant post treatment improvement in the level of hepatic fibrosis in 66.22% of our patients which assessed by evaluated by the decrease parameters of hepaticfibroscan.

This was in accordance with Chon *et al.* [19] who found significant decreased in level of hepatic fibrosis over 5 years of nucleat(s) ide therapy with the best fibrosis level reduction in the first year.

Also Kose *et al.* [20] and Xu *et al.* [21] found that entecavir is an effective treatment for patients with chronic hepatitis B, with both histological improvement and virological suppression.

Both APRI and FIB-4 scores are suitable non-invasive markers for detecting marked hepatic fibrosis and liver cirrhosis in patients with chronic hepatitis B virus infection [22].

In our study we have significant improvement in both FIB-4 and APRI scores after one year or regular antiviral treatment compared to baselines values ($P < 0.0001^{***}$).

With our study, Koksal *et al.* [23] found marked decrease in both APRI and FIB-4 scores one year post entecavir antiviral therapy and both of them could be used for monitoring treatment response.

In contrary, Chon *et al.* [19] found that no annual significant improvement in both FIB-4 and APRI scores with regular antiviral therapy, however, significant post treatment improvement in both FIB-4 and APRI scores were detected after 5 years of regular antiviral treatment.

On the other hand Kim *et al.* [24] reported that post entecavir antiviral therapy reduction in APRI or FIB-4 scores didn't correlate with reduction of hepatic fibrosis estimated by liver biopsy.

In our study we have significant post treatment increase in platelet count.

This come in agreement with Wang *et al.* [25], who found significant increase in Platelets count after entecavir therapy and it was correlated with improvement of hepatic fibrosis.

In our study, we have significant improvement of bilirubin, albumin and liver enzymes after one year of regular antiviral therapy.

This come in agreement with Chang *et al.* [26] who conclude that naive chronic hepatitis B virus infected patients even those with advanced hepatic fibrosis achieve normalization of ALT after entecavir antiviral therapy.

Also Kim *et al.* [24] found significant decrease in mean values of ALT, AST, and bilirubin with significant increase in mean albumin level after entecavir antiviral therapy.

In contrary, Wong *et al.* [27] reported that entecavir treatment in patients with acute exacerbation of chronic hepatitis B (which considered in their study as ALT above 10 time normal level and bilirubin above 3 times normal value) is associated with early mortality with jaundice, ascites and hepatic encephalopathy.

In our patients pretreatment ALT and bilirubin don't exceed 4 times and 3 times upper limit of normal respectively.

The results of the current study as regard the therapeutic efficacy of entecavir as oral antiviral therapy revealed 100% virological response with undetectable HBV DNA after one year of regular therapy.

In agreement with this findings, Myung *et al.* [28], who reported that entecavir therapy had excellent efficacy in naive chronic hepatitis B virus infected patients. Also our findings were in line with Akbar and Fallatah [29], who reported that entecavir was effective for the treatment of naive and experienced chronic hepatitis B virus infected patients.

On the opposite side, Chon *et al.* [30] reported that some naive chronic hepatis B virus infected patients develop partial virological response which defined according to EASL guideline[2] as a decrease in HBV DNA of more than 1 $\log^{10}$ IU/ml but detectable HBV DNA > 35 IU/ml after at least 12 months of therapy.

Factor IV collagen is non-invasive serological marker to identify significant fibrosis in patients with chronic hepatitis B [31].

In our study we have significant decrease in factor IV collagen one year post entecavir antiviral therapy ($p < 0.012$).

This come in agreement with Liang and Li [32], who found significant decrease of factor IV collagen in patients treated with entecavir antiviral therapy ($p < 0.05$).

Our study reveals that pretreatment low level of serum bilirubin, mild impairment of serum INR, mild degree of liver stiffness as detected by fibroscan and low level of serum factor IV collagen are associated with post treatment improvement in the level of hepatic fibrosis in naive chronic hepatitis B virus infected patients.

In conclusion, in chronic HBV infected patients, low pretreatment serum level of factor IV collagen are good predictor of post treatment virological response and hepatic fibrosis regression.

Study Limitations

Lack of a long-term follow-up period after the treatment completion is the major limit of this study especially for non-responder patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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