MAR Medicine (2025) 1:2

Research Article

Assessment of Liver Fibrosis using Fibroscan in Immunotolerant and Inactive Carrier HBV Infected Patients in the Gastroenterology Unit at IBN SINA Hospital "from September to December 2021

Dr. Aalaa Salih Fadel*

***Correspondence to:** Dr. Aalaa Salih Fadel, Sudan.

Received: 16 April 2025

Published: 23 April 2025

Abstract

Background: *Hepatitis B virus (HBV) infection is currently the most common cause of chronic hepatitis worldwide. Liver disease by HBV covers a wide clinical spectrum ranging from fibrosis to, cirrhosis and hepatocellular carcinoma. Noninvasive alternatives such as FibroScan (transient elastography) have been developed to evaluate liver fibrosis and to monitor disease progression. Fibrosis assessment in HBV is essential for prediction of long-term prognosis and proper treatment decision.*

Objective: *To assess liver fibrosis in immune tolerant and inactive carrier HBV infected patients by using FibroScan.*

Methods: *A cross-sectional study enrolled 50 HBV patients in in GI unit at Ibn-Sina Specialized Hospital during the period from September to December 2021. Data regarding demographics, comorbidities, laboratory investigations were collected. The liver fibrosis grade was evaluated by transient elastography.*

Results: *Among 50 patients, 26(52%) were males and 24(48%) were females, their mean age was 35±12 years. In immune statuses, 33(66%) patients were inactive carriers and 17(34%) were immune tolerants. The mean of fibrosis score was 6±2.5 KPa, mild fibrosis (F2) was found in 10(20%) patients, moderate fibrosis (F3) in 3(6%) and advanced fibrosis (F4) in 3(6%) patients. The liver fibrosis among inactive carriers was mild in 21.2%, moderate and advanced in 9.1% (for both). In immune tolerant patients the liver fibrosis was mild only in 17.6%. Liver fibrosis was not significantly associated with age (P= 0.195), gender (P= 0.872), comorbidities (P= 0.106) and HB viral load (P= 0.520).*

Conclusion: *About one-third of HBV patients had liver fibrosis and mainly mild in both inactive carrier and immune tolerants. Serial transient elastography measurements for monitoring both immune-tolerant phase and inactive carrier state patients is recommended.*

Abbreviations:

ALT Alanine Aminotransferase

APRI Aspartate Transaminase To Platelet Ratio Index

AST Aspartate Transaminase

AUROC Area Under The Receiver Operator Characteristic

BMI Body Mass Index

cccDNA Covalently Closed Circular Deoxyribonucleic Acid

CHB Chronic Hepatitis B

CTLs Cytotoxic T Lymphocytes

DM Diabetes Mellitus

DNA Deoxyribonucleic Acid

ESRD End Stage Renal Disease

FIB-4 Fibrosis 4 Scoring System

FS Fibroscan

HBeAg Hepatitis B E Antigen

HBsAg Hepatitis B Surface Antigen

HBV Hepatitis B Virus

HCC Hepatocellular Carcinoma

HCV Hepatitis C Virus

HDV Hepatitis D Virus

HEV Hepatitis E Virus

HTN Hypertension

IC Inactive Carrier

Ig Immunoglobulin

IT Immune Tolerant

IU International Unit

LF Liver Fibrosis

LMS Liver Stiffness Measurement

NPV Negative Predictive Value

PLT Platelet

PPV Positive Predictive Value

SPSS Statistical Package For Social Sciences

TE Transient Elastography

ULN Upper Limit Of Normal

US Ultrasonography

WHO World Health Organization

Introduction

Worldwide, more than 2,000 million people have been infected with hepatitis B virus (HBV) during their lifetime. Of these, about 350 million remain chronically infected (CHB). Three-quarters of the world‘s population live in areas with high levels of infection. An estimated 1 million people die each year from HBV-related cirrhosis or primary liver cancer.

The natural history of chronic HBV infection can be divided into five phases, not necessarily sequential, that depend on the virus–host interaction: (i) Immune-tolerant (IT) phase: This phase may persist for 10–30 years in individuals infected perinatally or in the first years of life. (ii) Immune-reactive phase (HBeAg-positive): This phase is more frequent and/or more easily achieved in individuals infected in adulthood. (iii) ―State of inactive HBV carrier‖: It may occur after HBeAg seroconversion to anti-HBe. It is characterized by the absence of HBeAg and presence of anti-HBe, serum HBV DNA levels <2000 IU/mL, normal ALT levels and histologically minimal or no necroinflammation, slight fibrosis or even normal liver. (iv) HBeAg-negative chronic hepatitis B (v) HBsAg-negative phase: In these patients immunosuppression, such as chemotherapy or after transplantation, can lead to reactivation of hepatitis B, hence antiviral treatment is indicated (1).

HBV has a complex natural history, centered in the liver, where the interaction between viral proteins and the immune system leads to a cycle of hepatocyte damage and tissue repair. This repair involves the repeated deposition of extracellular matrix leading to progressive liver fibrosis over time. The HBV X protein may also have particular fibrogenic and oncogenic effects on liver. Progression to advanced fibrosis can be rapid, slow, or sporadic depending on disease state and the degree of active liver inflammation and injury (2).

Liver fibrosis by HBV covers a wide clinical spectrum ranging from the inactive carrier (IC) state to chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (3,4).

There are currently few studies evaluating the degree of liver damage in this type of patients, inactive carriers or immunotolerance , because until recently estimation of the degree of liver damage was based on histological analysis of the sample obtained in a liver biopsy, an invasive technique not without complications (5-7).

Liver biopsy is the gold standard for detection of liver fibrosis in subjects with chronic HBV infection, but is painful and invasive. The aspartate transaminase (AST) to platelet ratio index (APRI) and fibrosis 4 scoring system (FIB-4) were developed as clinical noninvasive predictors of liver fibrosis, but their sensitivity and

specificity are insufficient. Liver stiffness measurement (LSM) by transient elastography (TE) is noninvasive, does not involve radiation, and can be performed repeatedly. LSM has been extensively validated in subjects with chronic HBV infection, and LSM findings correlate well with METAVIR fibrosis scores graded in biopsy tissue specimens (8).

The introduction of transient elastography (FibroScan) has greatly improved evaluation of liver damage of different etiologies, since it is able to estimate liver fibrosis (LF) in a non-invasive and painless manner (6,9). This technique has shown an excellent ability to exclude the stage of hepatic cirrhosis and is good for identifying patients with different grades of fibrosis. In addition, it is a technique that is easy to use, rapid, highly reproducible and reliable (7).

These characteristics have made it the most used technique in current daily practice as an alternative to liver biopsy for evaluation of the degree of liver damage in patients with chronic infection of viral origin (6,7). Patients with HBV infection with normal transaminase levels are also ideal for patients for evaluating the LF grade using techniques such as TE, since in these patients there is no confounding factor from inflammatory activity expressed as elevated serum transaminases on laboratory tests and which can cause overestimation of LF. It is therefore the most accurate technique for evaluation of LF in these patients (6,10,11).

Problem statement and justification

Hepatitis B virus (HBV) infection is globally highly prevalent and is one of the major causes of liver cirrhosis and hepatocellular carcinoma worldwide. Hepatitis B virus is highly endemic among Sudanese patients (8%) according to major health organization (WHO; CDC, USA and CDC, Africa)

Patients in young age (< 40) have presented with end stage liver disease (31-61%)or hepatocellular carcinoma (43 – 60 %) .

Recent studies indicated that hepatocarcinogenesis may occur in immune tolerant (IT) and inactive carrier phase HBV patients.

Liver biopsy is consider the gold stander test to diagnose underline pathology, but currently is not recommended in IT-phase and inactive carrier patients unless the patient is 40 years or more.

Therefore, a noninvasive assessment by measuring liver stiffness model (FibroScan) has been suggested to evaluate liver fibrosis, specifically in HBV-infected patients, owing to its high applicability, inter-laboratory reproducibility, wide availability for repeated assays and reasonable cost in developing countries.

Identification of fibrosis on FibroScan among IT and inactive carrier phase patients has potentially important clinical significance during the decision-making for an antiviral treatment.

According to our best knowledge, information regarding the liver fibrosis of Sudanese patients with HBV is

scarce. Therefore in this study we aimed to assess liver fibrosis in immune tolerant and inactive carrier HBV infected patients by using FibroScan in our context.

Objectives

General objective

To assess liver fibrosis in immune tolerant and inactive carrier HBV infected patients by using FibroScan

Specific objectives

- To determine prevalence of fibrosis in immune tolerant and inactive carriers HBV patients.
- To detect association between comorbidities and immune statues regarding the results of FibroScan.
- To detect association between the viral load and the results of FibroScan.

Methodology

Study design:

This is a descriptive cross sectional hospital based study.

Study area:

The study was conducted in GI unit at Ibn-Sina Specialized Hospital in Khartoum state.

Study duration

The study was conducted in the period from June - December 2020

Study population:

All inactive carriers HBV patients (negative HBe Ag, viral load < 2000 ,pressistant normal ALT and AST or slightly elevated and normal abdominal ultrasound.).

All immunotolerance HBV patients (positive HBe Ag ,viral load > 1million, normal AL T or and normal abdominal ultrasound.)

Inclusion criteria:

- Adult patients (>18 years)
- All IT-phase HBV patients and inactive HBV carriers

Exclusion criteria

- Patients has diagnosed with another etiology.
- Patients with significant alcohol consumption.
- Patients with fatty liver disease or PPF on ultrasound.
- Patients of chronic HBV on treatment.

Sample size

Total coverage of all immune tolerant and inactive carrier HBV infected patients who fulfill the inclusion criteria of the study. The estimated number of patients according to statistical records is 50 patients during the study period

Data collection tools and methods:

Data collection carried out by the principal investigator. Data was collected through structured questionnaires consisting of: demographics, comorbidities, laboratory investigations were collected

Case definition

• IT-phase HBV: positive HBeAg , viral load >1000,000 and ALT is normal or mini elevated (3- 35 IU/l) and normal abdominal ultrasound

• Inactive HBsAg carrier: persistent normal ALT and AST serum levels, positive HBsAg, negative HBeAg, and HBV DNA viral load < 2000 IU/ml

FibroScan (transient elastography)

FibroScan (Echosens machine) was conducted by expert gastroenterologist in private area and patient should be fasting for 4 hours and lying in prone position with right arm above the head .to detect LMS scores

It is required 10 valid readings and average for each patient recorded interpretation done as follows, the results of fibroscan were interpreted as follow:

• F0 – F1(KPa 2-7) indicate no liver scaring to mild

• F2 (KPa 7-9.5) indicating moderate scaring

• F3 (KPa 9.5-12.5) indicating severe liver scaring

• F4 (KPa >12.5) indicating advance liver scaring

Study variables

Independent variables:

Age

Gender

Comorbidities

Viral load

HBeAg

ALT and AST

Platelets count

Abdominal US

Immune status Dependent variables:

FibroScan measurements

Data analysis:

Data was analyzed by using a computer program Statistical Package for Social Sciences (SPSS V. 21.0). The analyzed data presented in tables and figures designed by Microsoft Excel 2007. Chi-Square test was used as significance test for categorical data and ANOVA test for continuous data. The P. value was considered as significant at level 0.05.

Ethical consideration:

An ethical approval was obtained from Sudan medical specialization board (SMSB). Approval acceptance to the hospital authority was being given. Data used anonymously by using identity numbers instead of names is order to protect patient‘s identity and kept securely and in separate file. No reference to any individual participant made in study reports. Subject identities were being known only by the study staff.

Results

In total this study enrolled 50 HBV patients, 26(52%) were males and 24(48%) were females, their mean age was 35±12 years and most of them 28(56%) belonged to age group from 20-39 years (table 1)

Figure (1) showed that, 13(26%) patients had comorbidities as hypertension in 4(8%) patients, DM in 3(6%), hypertension and DM in 3(6%) and ESRD in 3(6%) patients

According to immune statuses, 33(66%) patients were inactive carriers and 17(34%) were immune tolerants (figure 2)

Among inactive carriers, the averages of HB viral load was 365 IU/ml, ALT was 20.7±8 U/l and AST was 20.3±8.1 U/L (table 2)

Among immune tolerant patients, the averages of HB viral load was 52,717,000IU/ml, ALT was 23.3±7.2 U/l and AST was 25±6 U/L (table 3)

The FibroScan results showed that, the mean of fibrosis score was 6±2.5 KPa, mild fibrosis (F2) was found in 10(20%) patients, moderate fibrosis (F3) in 3(6%) and advanced fibrosis (F4) in 3(6%) patients (figure 3)

Among inactive carriers, 20(60.6%) patients had normal or mild fibrosis (F0-F1), 7(21.2%) had moderate fibrosis (F2), 3(9.1%) had severe fibrosis and 3(9.1%) patients had advanced fibrosis (table 4)

Among immune tolerant patients, 14(82.4%) patients had normal or mild fibrosis (F0- F1), and 3(17.6%) had moderate fibrosis (F2) (table 5)

The association between demographic characteristics and fibrosis score showed that, the age (P= 0.195) and the gender (P= 0.872) of the patients were not significantly associated with liver fibrosis (table 6)

Table (7) revealed that, the presence of comorbidities were not significantly associated with liver fibrosis (P= 0.106)

As detailed in table (8), the averages of HB viral load was not significantly correlated with the presence of liver fibrosis (P= 0.520)

Table 1: The demographic characteristics of HBV patients

	N	**%**
Age (Yrs.); mean ± SD	**35±12**	
• <20	4	8.0
• 20-39	28	56.0
• 40-59	15	30.0
• 60+	3	6.0
Gender		
• Male	26	52.0
• Female	24	48.0

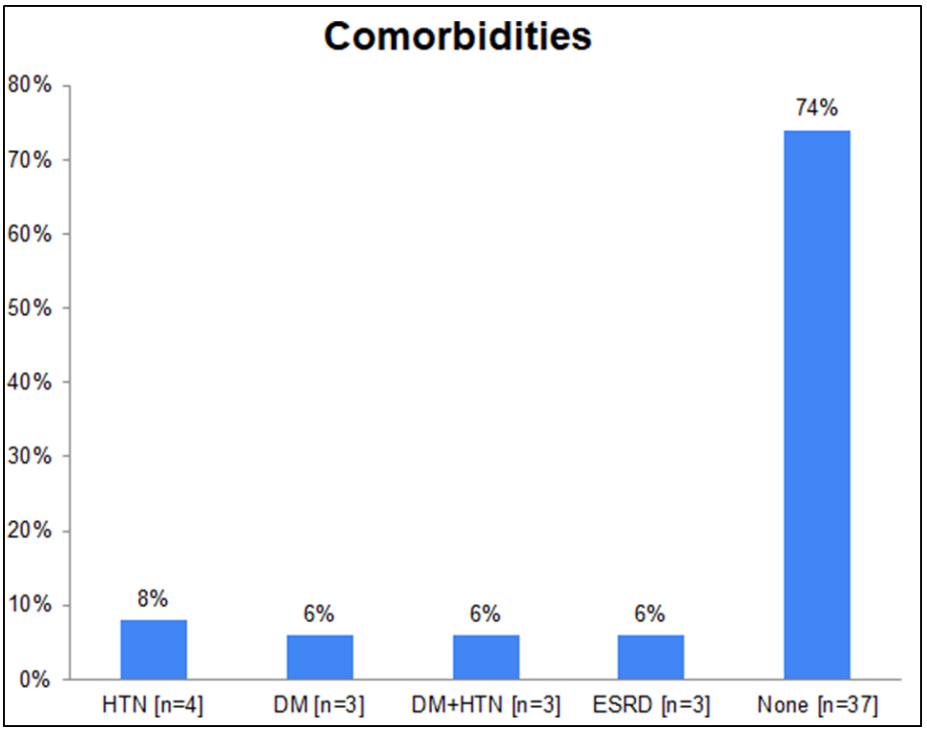

Figure 1: The comorbidities of HBV patients

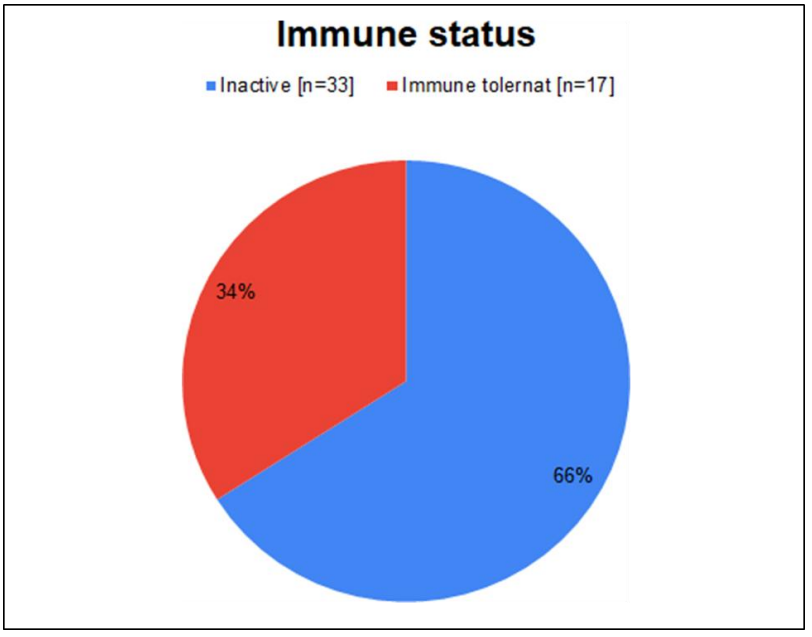

Figure 2: The distribution of immune statuses among of HBV patients

Table 2: The laboratory investigations of inactive carriers (N=33)

	Mean	SD
HB viral load (IU/ml); Median	365	
ALT (U/L)	20.7	8.0
AST (U/L)	20.3	8.1

Table 3: The laboratory investigations of immune tolerant patients (N=17)

	Mean	SD
HB viral load (IU/ml); Median	52,717,000	
ALT (U/L)	23.3	7.2
AST (U/L)	25.0	6.0

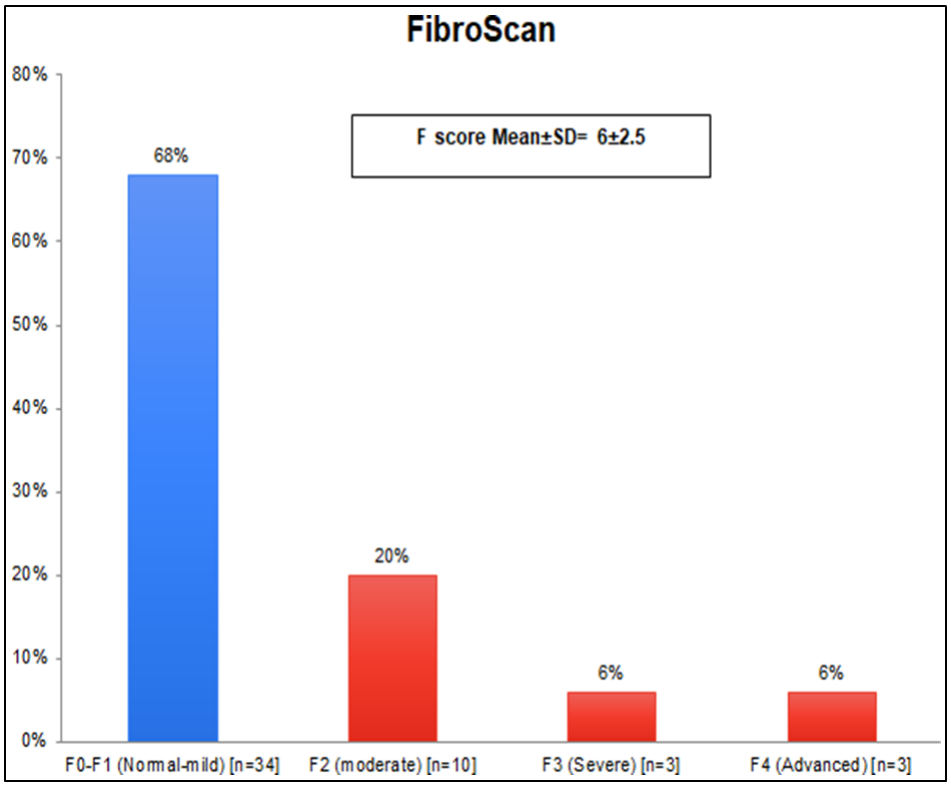

Figure 3: The FibroScan results of HBV patients

Table 4: The FibroScan results of inactive carriers (N=33)

	N	%
FibroScan		
• **F0-F1**	20	60.6
• **F2**	7	21.2
• **F3**	3	9.1
• **F4**	3	9.1

Table 5: The FibroScan results of immune tolerant patients (N=17)

	N	%
FibroScan		
• **F0-F1**	14	82.4
• **F2**	3	17.6
• **F3**	0	0
• **F4**	0	0

Table 6: The association between fibrosis and demographic characteristics

	FibroScan				**P**
	F0-F1	**F2**	**F3**	**F4**	
Age (Yrs.)					
• <20	3	0	1	0	0.195
	75.0%	0.0%	25.0%	0.0%	
• 20-39	21	6	0	1	
	75.0%	21.4%	0.0%	3.6%	
• 40-59	8	4	2	1	
	53.3%	26.7%	13.3%	6.7%	
• 60+	2	0	0	1	
	66.7%	0.0%	0.0%	33.3%	

Gender					
• Male	18	5	1	2	0.872
	69.2%	19.2%	3.8%	7.7%	
• Female	16	5	2	1	
	66.7%	20.8%	8.3%	4.2%	

Table 7: The association between fibrosis and comorbidities

	FibroScan				**P**
	F0-F1	**F2**	**F3**	**F4**	
Comorbidities					
• DM	1	1	0	1	0.106
	33.3%	33.3%	0.0%	33.3%	
• HTN	3	0	0	1	
	75.0%	0.0%	0.0%	25.0%	
• DM+HTN	1	2	0	0	
	33.3%	66.7%	0.0%	0.0%	
• ESRD	1	1	1	0	
	33.3%	33.3%	33.3%	0.0%	
• None	28	6	2	1	
	75.7%	16.2%	5.4%	2.7%	

Table 8: The association between fibrosis and viral load

	HB Viral load (IU/ml)	**P. value**
FibroScan		
• F0-F1	1485.00	0.520
• F2	1193.50	
• F3	596.00	
• F4	404.00	

Discussion

Liver fibrosis is an important factor associated with liver disease prognosis. Liver biopsy has been used to assess patients with viral hepatitis, especially those with HBV, to define the stage of the disease and to decide starting treatment. Because of many limitations of liver biopsy, noninvasive alternatives, including FibroScan, have been developed. In this study we aimed to liver fibrosis in 50 HBV patients by using FibroScan.

In this study there was males (52%) showed slightly predominance compared to female (48%) patients. Similar finding was reported by Sara E. et al who found that, the prevalence of HBV was found to be high in male (64%) than females (36%) (90). Also, these findings came close to the studies of El-Zayadi et al in Egypt (91). This could be attributed to males are more exposed to HBV risk factors more than females.

The mean age of our study cases was 35±12 years and most of them 28(56%) belonged to age group from 20-39 years. These results similar to the study of Hatim M et al in Sudan who reported among 404 subjects were screened with a mean age of 35 years (92). Also, Hatim M. in his study reported that, exposure to HBV infection increased from 47.5% in those 20 years of age to 80% in those 39 years of age (93). Also, Tajeldin M et al in Eastern Sudan found that the mean of the age among 31 HBV patients was 27.2±11.4 years (94). Correspondingly, in the study of Saleh S et al the mean age was 38.3±9.9 years (71).

This study demonstrated that, HBeAg was positive in 34% of the cases. The rate of HBeAg in this study was comparable to the study of Wong V et al who reported HBeAg was positive in 36% of patients (89). However, the Sudanese study conducted by Mukhlid Y et al in Khartoum, showed the rate of HBeAg was encountered in 12.1% (95).

DNA levels is corner stone in pathogenesis of HBV, in the current study showed that, the median of HBV viral load was 1008.5 IU/ml. These findings comparable with the study of Monika S et al in USA who reported the most of the patients had HBV DNA levels less than 2,000 IU/ml (96). Also, in Italy Stroffolini T et al found that the most of HBV patients (44.9%) had HBV DNA level <2,000 IU/ml (97).

Immune tolerant phase diagnosed by the presence of serum HBeAg and very high levels of HBV (>1 million IU/ml), while the inactive HBsAg carrier state is diagnosed by absence of HBeAg and undetectable or low levels of HBV DNA in PCR-based assays (<20,000 IU/ml). In this study showed that, 33(66%) patients were inactive carriers and 17(34%) were immune tolerants.

The FibroScan results showed that, the mean of fibrosis score was 6±2.5 KPa, and 12% of patients had significant fibrosis (F3 and 4). Our rate was in accordance with studies of San Juan L et al (15%) (7), Amr A et al (20%) (88) and Wong V et al (15%) (89).

Among inactive carriers, 20(60.6%) patients had normal or mild fibrosis (F0-F1), 7(21.2%) had moderate fibrosis (F2), 3(9.1%) had severe fibrosis and 3(9.1%) patients had advanced fibrosis, which are similarly to the study of Amr A et al, 6.7% were no fibrosis , 73.3% were stage 1 fibrosis (F0 - F1)and 20% were stage 2 fibrosis (F2).(88)

Among immune tolerant patients, 14(82.4%) patients had normal or mild fibrosis (F0- F1), and 3(17.6%) had moderate fibrosis (F2). Unfortunately, during my study l did not find previous studies regarding immunotolerance HBV patients to compare my results to them.

The present study showed that, the age (P= 0.195) and the gender (P= 0.872) of the patients were not significantly associated with liver fibrosis. These results were confirmed by numerous of studies (7,88). Although, Jia-Feng W et al reported male sex and age ≥18 years were independent predictors of a liver fibrosis (8).

The presence of comorbidities like hypertension, DM and ESRD were not significantly associated with liver fibrosis (P= 0.106). This observation was in agreement with the study of Wong V et al who also reported DM and hypertension were not significantly associated with liver fibrosis progression (89).

In the current study, the HB viral load was not significantly correlated with the presence of liver fibrosis (P= 0.520). This result was similar to the studies of Saleh S et al (86) and Amr A et al (88).

Conclusion

This study concluded that, about one-third of HBV patients had liver fibrosis and mainly mild in both inactive carrier and immune tolerants. The presence of liver fibrosis was not significantly associates with age, gender, comorbidities, HB viral load and immune statuses of patients.

Recommendations

• Using serial transient elastography measurements for monitoring both immune- tolerant phase and inactive carrier state patients is recommended to early detection of progression of liver fibrosis.

• Further a larger scale follow-up study of inactive HBsAg carriers for several years to monitor any pathological progress of the disease.

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