

ASSOCIATION OF AGE AND GENDER WITH DEVELOPMENT OF LIVER CIRRHOSIS AMONG HEPATITIS B VIRUS INFECTED INDIVIDUALS IN SUDAN

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Article Received on
08 Feb. 2019,

Revised on 02 March 2019,
Accepted on 23 March 2019

DOI: 10.20959/wjpr20195-14594

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ABSTRACT

The progress of liver cirrhosis among HBV patients can be affected by the viral load, immunity of the patient and environmental factors. This study aimed to associate age and gender as factor for development of liver cirrhosis in HBV patients. Information of gender, age and liver cirrhosis were collected from ninety HBV patients in different clinical status through instructed interview questionnaire, and sera from the participants were collected and tested for HBV viral load and liver enzymes alanine transaminase (ALT) and aspartate transaminase (AST). Liver cirrhosis was significantly associated with male gender ($P= 0.034$), older age ($P= 0.000$) and aging in both of males ($P=0.007$) and females ($P=0.001$). HBV infection and liver cirrhosis are significantly most frequent in males than females with significant increase among females older than 45 years old. The serum levels of

HBV viral load was elevated among male and female with older age and liver cirrhosis. AST and ALT are elevated in males and younger age group.

KEYWORDS: Age, Gender, HBV, Liver cirrhosis.

INTRODUCTION

Hepatitis B virus infection is one of the major health problems in the world. It is estimated that more than 2 billion people worldwide are HBV infected, with more than 350 million being chronic carriers of the virus and more than one million annual deaths due to HBV-related chronic liver diseases.^[1,2,3] The virus is transmitted through sexual contact, vertically, via transfusion of blood and blood products, and through sharing of sharp objects specially needles during drug abuse. The disease can be manifested as acute or chronic or even asymptomatic hepatitis.^[4]

The main complications of HBV infections are liver cirrhosis, liver de-compensation and hepatocellular carcinoma. The progress of liver cirrhosis can be identified based on main factors that include viral load, the presence of fibrosis on liver biopsy, and elevated serum ALT. Other co factors include viral genotype, being positive for HBeAg, the level of HBsAg, co-infection with other viruses, such as hepatitis D virus (HDV) and HIV, and alcohol consumption.^[5]

Many studies regarded disparity of gender and age with hepatitis B infection and development of liver cirrhosis. Males are more likely than females to become chronic carriers for HBV.^[6] Some workers found the concentration of viral DNA copies (viral load) and the titer of HBsAg to be higher in sera of males than females.^[7,8] Male gender and HBeAg positivity were both associated with about a 2 times greater risk of developing more severe liver diseases. This may be contributed to hormonal or genetic factors rather than personal life style.^[9]

Sex hormones, such as androgen and estrogen may play an important role in pathogenesis of cirrhosis and HCC by binding specific cellular receptors and affecting the corresponding signaling pathways. These hormones can regulate the transactivation of HBx, cause the chronic release of inflammatory cytokines in the hepatocellular microenvironment, and participate in epigenetic and genetic alternations in hepatocytes.^[10]

Estrogen may influence the protection and defense of hepatic cells against the development of chronic liver disease,^[11] but the protective effect of female gender against cirrhosis gradually lost with increasing age.^[12]

MATERIALS AND METHODS

During the period from June 2016 to June 2017 a total of 90 HBV infected patients attending Ibn Sina specialized hospital-Khartoum town-Sudan were enrolled in this study. All the participants were confirmed to be positive for HBV infection serologically by detection of HBsAg using ELISA technique with Fortress[®] ELISA kit. One third of the participants were suffering from liver cirrhosis as confirmed by ultrasound and histopathology.

After having a written consent of each patient to participate in the study, data were collected using a questionnaire. The required information include age and gender.

5 milliliter of venous blood was collected from the antecubital area under aseptic condition. The blood specimens were drawn into plain blood containers, allowed to clot, then centrifuged and the sera separated and stored at -20°C until used.

For each blood specimen the sera level of ALT and AST was estimated using chemical auto analyzer (Mindray Bs120[™]) with reagent kits from (BioSystem[™]). As well as HBV viral load was determined by real time PCR.

Independent t-test and chi-square test were used for statistical analysis of this study, and calculated by SPSS[®] version 21.

RESULTS

The mean age of the participants was (41.7±13.8) range from 18-75 years, and frequency of patients under the age of 45 years (56.7%) was a little bit higher than those above 45 years (43.3%) (Table 1).

Regarding the 30 HBV infected patients with liver cirrhosis, 21(70%) were male and the remaining 30% were female (Table 2) the frequency of male is slightly higher than the female (P value 0.034).

Regarding age groups, most of the HBV infected patients with liver cirrhosis were within the age group ≥45 years old. The frequency of HBV infected patients with liver cirrhosis is statistically significant at the age group equal or above 45 years old (P value 0.000).

21(70%) out of the 30 cirrhotic patients were males, this gives significant association between male gender and development of liver cirrhosis (P= 0.034). (Table 2).

Most of the patient with liver cirrhosis occurred in the group of 45 years and above 22 (73.3%) this gives a strong significant association ($P= 0.000$) of older age with development of liver cirrhosis among HBV positive individuals. (Table 3).

8(88.9%) of the females and 14(66.7%) of the males in cirrhosis group were belonged the age group more than 45 years old. This give high significant association of liver cirrhosis with aging in both of male ($P=0.007$) and females ($P=0.001$).

The highest concentration of viral load ($>10^7$) was more frequent among both males and females in younger age group, but when regarding the complications of cirrhosis, the highest concentrations of viral load ($>10^7$) occur among females with liver cirrhosis particularly among age group more than 45 years old whereas male gender showed the highest concentration of HBV load among cirrhotic and non cirrhotic and both age groups less and more than 45 years old. Tables (6, 7, 8, 9).

There were insignificant differences in the concentration of AST and ALT between male and female and between older and younger group.

Tables (10 and 11) illustrate insignificant increase in the mean of viral load among males in comparison to female within group of HBV infected without liver cirrhosis, and insignificant increase in means of AST and ALT among females comparing to the males in both groups of hepatitis b patients either with or without liver cirrhosis.

Table (11) shows the insignificant increase of viral load among the age group less than 45 years old whereas the AST and ALT are insignificantly elevated among the elder group.

AST and ALT are insignificantly higher among females in overall study population including the subgroups of HBV infected with and without liver cirrhosis except ALT among non cirrhotic group which higher among males.

Table 1: Distribution of age and gender among study population.

| | | Frequency | Percent |
|-------------------|--------------|-----------|---------|
| Age groups | Less than 45 | 51 | 56.7 |
| | 45 and more | 39 | 43.3 |
| | Total | 90 | 100.0 |
| Gender | Male | 74 | 82.2 |
| | Female | 16 | 17.8 |
| | Total | 90 | 100.0 |

Table 2: Association of gender with study cirrhosis.

| Gender | Total number tested | HBV infected | | | | P value |
|--------|---------------------|----------------------|------|-------------------------|------|---------|
| | | With liver cirrhosis | | Without liver cirrhosis | | |
| | | Frequency | % | Frequency | % | |
| Male | 74 | 21 | 28.4 | 53 | 71.6 | 0.034 |
| Female | 16 | 9 | 56.3 | 7 | 43.7 | |
| Total | 90 | 30 | 33.3 | 60 | 66.7 | |

Table 3: Association of age groups with cirrhosis.

| Age groups | Total number tested | HBV infected | | | | P value |
|--------------|---------------------|----------------------|------|-------------------------|------|---------|
| | | With liver cirrhosis | | Without liver cirrhosis | | |
| | | Frequency | % | Frequency | % | |
| Less than 45 | 51 | 8 | 15.7 | 43 | 84.3 | 0.000 |
| 45 and more | 39 | 22 | 56.4 | 17 | 43.6 | |
| Total | 90 | 30 | 33.3 | 60 | 66.7 | |

Table 4: Association of age groups with cirrhosis among male gender subgroups.

| Age groups with male gender | Total number tested | HBV infected | | | | P value |
|-----------------------------|---------------------|----------------------|------|-------------------------|------|---------|
| | | With liver cirrhosis | | Without liver cirrhosis | | |
| | | Frequency | % | Frequency | % | |
| Less than 45 | 43 | 7 | 16.3 | 36 | 83.7 | 0.007 |
| 45 and more | 31 | 14 | 45.2 | 17 | 54.8 | |
| Total | 74 | 21 | 28.4 | 53 | 71.6 | |

Table 5: Association of age groups with cirrhosis among female gender subgroups.

| Age groups with female gender | Total number tested | HBV infected | | | | P value |
|-------------------------------|---------------------|----------------------|------|-------------------------|------|---------|
| | | With liver cirrhosis | | Without liver cirrhosis | | |
| | | Frequency | % | Frequency | % | |
| Less than 45 | 8 | 1 | 12.5 | 7 | 87.5 | 0.001 |
| 45 and more | 8 | 8 | 100 | 0 | 0.0 | |
| Total | 16 | 9 | 56.3 | 7 | 43.7 | |

Table 6: Distribution of viral load among gender.

| Viral load | Gender | | | |
|----------------------------------|-------------|------|---------------|------|
| | Male (n=74) | | Female (n=16) | |
| | N | % | N | % |
| 0-10 ⁴ | 37 | 50 | 5 | 31.3 |
| 10 ⁴ -10 ⁵ | 17 | 22.9 | 2 | 12.5 |
| 10 ⁵ -10 ⁶ | 12 | 16.2 | 3 | 18.8 |
| 10 ⁶ -10 ⁷ | 3 | 4.1 | 2 | 12.5 |
| >10 ⁷ | 5 | 6.8 | 4 | 25 |

Table 7: Distribution of viral load among gender within groups of liver cirrhosis.

| Viral load | HBV infected with liver cirrhosis (n=30) | | | | HBV infected without liver cirrhosis (n=60) | | | |
|----------------------------------|--|------|--------------|------|---|------|--------------|------|
| | Male (n=21) | | Female (n=9) | | Male (n=53) | | Female (n=7) | |
| | N | % | N | % | N | % | N | % |
| 0-10 ⁴ | 10 | 47.6 | 2 | 22.2 | 27 | 50.9 | 3 | 42.8 |
| 10 ⁴ -10 ⁵ | 5 | 23.8 | 2 | 22.2 | 12 | 22.6 | 0 | 0.0 |
| 10 ⁵ -10 ⁶ | 4 | 19 | 0 | 0.0 | 8 | 15.1 | 3 | 42.8 |
| 10 ⁶ -10 ⁷ | 1 | 4.8 | 2 | 22.2 | 2 | 3.8 | 0 | 0.0 |
| >10 ⁷ | 1 | 4.8 | 3 | 33.3 | 4 | 7.6 | 1 | 14.2 |

Table 8: Distribution of viral load among gender within age groups of liver cirrhosis patients.

| Viral load | HBV infected with liver cirrhosis (n=30) | | | | | | | |
|----------------------------------|--|------|--------------|-----|-------------------------------|------|--------------|------|
| | Less than 45 years old (n=8) | | | | More than 45 years old (n=22) | | | |
| | Male (n=7) | | Female (n=1) | | Male (n=14) | | Female (n=8) | |
| | N | % | N | % | N | % | N | % |
| 0-10 ⁴ | 1 | 14.3 | 0 | 0.0 | 9 | 64.3 | 2 | 25 |
| 10 ⁴ -10 ⁵ | 2 | 28.6 | 0 | 0.0 | 3 | 21.5 | 2 | 25 |
| 10 ⁵ -10 ⁶ | 3 | 42.8 | 0 | 0.0 | 1 | 7.1 | 0 | 0.0 |
| 10 ⁶ -10 ⁷ | 0 | 0.0 | 1 | 100 | 1 | 7.1 | 1 | 12.5 |
| >10 ⁷ | 1 | 14.3 | 0 | 0.0 | 0 | 0.0 | 3 | 37.5 |

Table 9: Distribution of viral load among gender within age groups of non cirrhotic patients.

| Viral load | HBV infected without liver cirrhosis (n=60) | | | | | | | |
|----------------------------------|---|------|--------------|------|-------------------------------|------|--------------|-----|
| | Less than 45 years old (n=43) | | | | More than 45 years old (n=17) | | | |
| | Male (n=36) | | Female (n=7) | | Male (n=17) | | Female (n=0) | |
| | N | % | N | % | N | % | N | % |
| 0-10 ⁴ | 19 | 52.8 | 3 | 42.9 | 8 | 47.1 | 0 | 0.0 |
| 10 ⁴ -10 ⁵ | 8 | 22.2 | 0 | | 4 | 23.5 | 0 | 0.0 |
| 10 ⁵ -10 ⁶ | 5 | 13.8 | 3 | 42.9 | 3 | 17.6 | 0 | 0.0 |
| 10 ⁶ -10 ⁷ | 2 | 5.6 | 0 | | 0 | 0.0 | 0 | 0.0 |
| >10 ⁷ | 2 | 5.6 | 1 | 14.2 | 2 | 11.8 | 0 | 0.0 |

Table 6: Statistics and mean differences of viral load, AST and ALT among gender.

| Variable | Male (n=74) | Female(n=16) | P value |
|-------------------|---------------------------------|---------------------------------|---------|
| AST IU/L of serum | 66.101±64.839 (15.00-345.00) | 74.125±76.122 (16.00-300.00) | 0.665 |
| ALT IU/L of serum | 45.687±62.766 (9.00-520.00) | 49.313±39.402 (17.00-170.00) | 0.825 |

Table 7: Statistics and mean differences of viral load, AST and ALT among age groups

| Variables | Less than 45 (n=51) | 45 and more (n=39) | P value |
|-------------------|---------------------------------|---------------------------------|---------|
| AST IU/L of serum | 65.167±60.934 (15.00-300.00) | 70.615±74.048 (16.00-345.00) | 0.703 |
| ALT IU/L of serum | 40.682±26.185 (9.00-115.00) | 53.718±84.761 (12.00-520.00) | 0.303 |

Table 8: Statistics and mean differences of viral load, AST and ALT among gender within groups of liver cirrhosis.

| Variables | HBV infected with liver cirrhosis (n=30) | | HBV infected without liver cirrhosis (n=60) | |
|-------------------|--|---------------------------------|---|---------------------------------|
| | Male (n=21) | Female (n=9) | Male (n=53) | Female (n=7) |
| AST IU/L of serum | 56.524±40.244 (18.00-155.00) | 64.111±59.788 (16.00-210.00) | 69.896±72.300 (15.00-345.00) | 87.000±96.831 (30.00-300.00) |
| ALT IU/L of serum | 33.571±16.480 (15.00-90.00) | 52.333±47.244 (17.00-170.00) | 50.487±73.098 (9.00-520.00) | 45.429±29.563 (20.00-105.00) |

DISCUSSION

The present study revealed high increase in male gender than female among HBV infected individuals, this finding agreed with the work of *Baig et al*, who found 79.5% males and 20.5% females among his study population.^[11] Other study by *Khan et al* reported 68.15% males and 31.85% females. Male were more frequently exposed to the risk factors as compared to female.^[13]

The overall frequency of males having liver cirrhosis is much higher than females, this gives significant association between male gender and development of liver cirrhosis independently to level of viral load, AST and ALT, this finding concurred with work of *You et al* who found (73.1%) of cirrhotic patients were males whereas (26.9%) were females.^[12] This study also agreed with *Başıyigit et al* who reviewed data of liver cirrhosis patients during four years, and they found liver cirrhosis in 67.4% males and 32.6% females.^[14] And the work of *Mair et al* reported 65% males and 35% females with liver cirrhosis in nine years cohort study.^[15]

Most of the patient with liver cirrhosis occurred in the group of older than 45 years this gives a strong significant association of liver cirrhosis and older age among both genders. This finding agreed with *You et al*, who reported (70.7%) of females and (52%) of the males with liver cirrhosis belong to age group more than 50 years old and the conclusion was that; the liver fibrosis was lower among female patients aged 15–59 years, whereas it significantly higher among female patients aged ≥ 60 years.^[12]

The present study shows that the highest concentration of viral load ($>10^7$) was associated with male gender and older female with liver cirrhosis. This agreed with work of *Moyen Uddin et al* who observed the high viral load among age group less than 50 years old and higher among females in comparison to males.^[16]

AST and ALT are insignificantly higher among females in overall study population including the subgroups of HBV infected with and without liver cirrhosis except ALT among non cirrhotic group which higher among males. This finding is disagreed with the work of *You et al* who reported slightly increases in the means of HBV viral load, AST and ALT among males in both groups of HBV infection with and without liver cirrhosis.^[12]

CONCLUSIONS

HBV infection and liver cirrhosis are significantly most frequent in males than females, with significant increase among females older than 45 years old. The serum levels of HBV viral load was elevated among male and older female particularly with liver cirrhosis, generally viral load, AST and ALT are elevated in males and younger age group.

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