Hepatitis B Related Liver Cirrhosis in Oman

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Abstract

Introduction: The estimated deaths because of chronic hepatitis B (CHB) related complications in 2015 were 887,000 patients worldwide. Most of these deaths were related to decompensated liver cirrhosis and hepatocellular carcinoma (HCC). Oman is a country with intermediate prevalence of CHB. Hepatitis B vaccine was introduced in Oman in 1990 with vaccine coverage rate of more than 95% as reported in 2005. Despite the association between CHB and liver cirrhosis and HCC, there is no available data from Oman demonstrating the CHB related liver cirrhosis.

Aim: To estimate the prevalence of CHB among patients with liver cirrhosis from Oman.

Method: A retrospective chart review of patients diagnosed with liver cirrhosis at Sultan Qaboos University Hospital and Armed Forces Hospital, between January 2006 and April 2013. All adult patients with liver cirrhosis were included. Demographic data and investigations of liver cirrhosis were collected.

Results: A total of 419 patients were included. Two thirds of patients were males. The median age was 59 years. Omani patients represent the majority (97.1%) of patients with cirrhosis. Diabetes mellitus was present in almost half of the patients and more than 20% had indicated alcohol consumption. Evidence of previous or current HBV infection was found in about half of the cohort (51.3%). Only 3% of CHB patients were positive for HBeAg. HBV DNA was detected in 47 patients (21.9%) of which 20 patients had high viral load > 2000IU/ml. More than a third (36%) had positive anti-HBs, indicating immunity to HBV, and 27% was due to previous HBV infection, 5% immune due to vaccination, and 4% had positive anti-HBs and unknown anti-HBc status. Negative anti-HBs was found in 34% of the cohort and 30% had unknown immunity status. HBV co-infection with hepatitis C virus (HCV) was found in 24.7% of HBV patients with cirrhosis.

Conclusion: Serological markers of CHB are common among liver cirrhosis patients in Oman. CHB related cirrhosis was more common in old age males compared to females (71% vs. 29% respectively, $p < 0.01$). Evidence of past or present HBV infection was found in more than 50% of the patients.

Key words: Hepatitis B virus, Chronic Hepatitis, Cirrhosis, Oman

Introduction

In 2015, the World Health Organization (WHO) estimated chronic hepatitis B virus (CHB) infection to be 3.5% of the world's population corresponding to 257 million. A report of deaths related to CHB complications in 2015 indicated 887,000 deaths worldwide [1]. Most deaths are related to decompensated liver cirrhosis and development of hepatocellular carcinoma (HCC) [1]. Hepatitis B virus (HBV) vaccine introduction has decreased the incidence of hepatitis B viral infection [2–6]. The risk of CHB infection is high among patients infected during early years of life [7].

The estimated prevalence of CHB in Oman before the introduction of HBV vaccination was 2-7% [8]. Hepatitis B vaccine was introduced in Oman in 1990. Catch up vaccination of school students born before the introduction of HBV vaccination complemented the introduction program of HBV vaccination. Follow up study in 2005 showed HBV vaccine coverage rate to be more than 95% [9]. In addition to the vaccination program, there were other preventative measures introduced to reduce the risk of HBV transmission such as blood donation screening, screening high risk population such as health care workers, patients on regular blood transfusion and hemodialysis patients [10].

In spite of the reported association between CHB and liver complications such as decompensated cirrhosis and development of HCC, there is no available data from Oman illustrating the CHB related liver cirrhosis that could support evaluating the burden of HBV and help planning preventative strategies and measures to reduce the burden of CHB outcome. The current study was conducted to evaluate the prevalence of CHB related liver cirrhosis in Oman.

Methods

This is a cross sectional study of patients diagnosed to have liver cirrhosis at Sultan Qaboos University Hospital and Armed Forces Hospital, between January 2006 and April 2013. These two hospitals are tertiary hospitals in the capital city of Oman, Muscat, where most of the cases from other regions in Oman are referred to. Therefore, the sample in this study could be a close representation of CHB related liver cirrhosis in the country. Patients' data were retrieved from the two computerized hospital information systems (HIS) as well as patients interviews during hospital visits.
All pediatric and adult patients with liver cirrhosis were included. Patients with missing data and those with pre and post hepatic portal hypertension were excluded from this study.

Data Collection

Demographic data such as age, gender, medical history that includes comorbidities such as drug history, diabetes mellitus or other components of metabolic syndrome,

heart failure, smoking and alcohol consumption, and family history of liver diseases were collected.
Blood investigations represented in complete blood count, coagulation profile, liver chemistry, electrolytes, renal function, hepatitis B and C serology, viral loads in positive cases, alpha 1 antitrypsin level, serum ceruloplasmin, iron profile and serum ferritin, and ANA and autoimmune profile were collected. Results of abdominal Ultrasound (US), Computed Tomography (CT) scan and/or Magnetic Resonance Imaging (MRI), gastroscopy findings, as well as liver biopsy results were collected.

The diagnosis of liver cirrhosis was based on laboratory and radiological investigations as well as the liver histology as the gold standard test. Patients were categorized into three categories based on the degree of accuracy of the diagnosis of liver cirrhosis. The categories are as follows: definite cirrhosis, probable cirrhosis, and possible cirrhosis. Description of the criteria used in categorize the patients is illustrated in **Table 1.**

Table 1: Categories depending on the accuracy of cirrhosis diagnosis

Category	Basis of diagnosis
Definite cirrhosis	• Either Histological features of cirrhosis • And/ or radiological features suggestive of liver cirrhosis (irregular or undulated liver surface with heterogeneous or coarse echotexture) with splenomegaly, collateral vessels, ascites and dilated PV. • With/ without biochemical tests showing raised aminotransferases (with AST>ALT usually), high bilirubin, low albumin associated with low platelet count and high PT or INR.
Probable cirrhosis	• Either irregular or undulated liver surface or heterogeneous or coarse echotexture on radiological images. With or without extrahepatic features such as enlarged spleen, collateral vessels, ascites and dilated PV. • With/ without biochemical tests showing high bilirubin, low albumin, low platelet count or increased INR or PT
Possible cirrhosis	• Biochemical tests show raised bilirubin, decreased albumin. Haematological tests showing low platelet count or high INR or PT but no histological or radiological tests to confirm the diagnosis.

PV = Portal Vein, AST = Aspartate Amino-Transferase, ALT = Alanine Amino-Transferase, PT = Prothrombin Time, INR = International Normalised Ratio

Statistical Analysis

Statistical analysis was done using Epi info ^{TM} version 7. This included calculating the frequencies of cirrhosis etiology, calculating the median values of age and laboratory data.

Results

The total number of identified patients with the diagnosis of cirrhosis from both hospitals was 469. Fifty patients were excluded due to different reasons. The final

analysis included 419 patients (**Figure 1).** When classified based on accuracy of cirrhosis diagnosis, 70.9%, 10.3%, 18.8% of the study cohort had definite, probable and suspected liver cirrhosis respectively (**Table 1).**

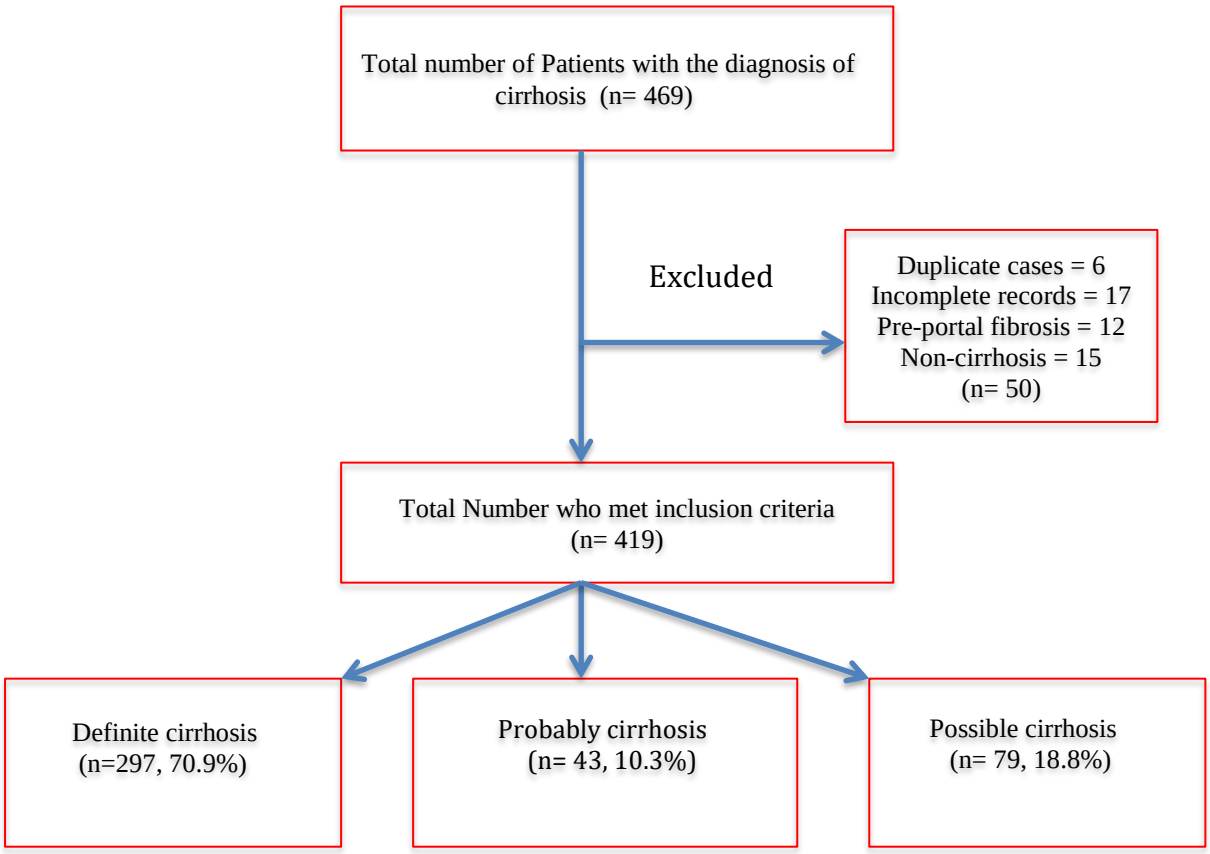


Figure 1: Flow chart showing the results of patient's selection process

The demographic characteristics are shown in **Table 2**. Two thirds of patients with cirrhosis were males. The median age of the study sample was 59 years (**Figure 2).** The majority (97.1%) of patients with cirrhosis were Omanis. Almost half of the cohort was also diabetic and more than 20% had indicated consumption of alcohol with no information available regarding the amount and duration of alcohol consumption. **Figure 3** illustrates the etiologies of cirrhosis in the study sample.

Table 2: Patients' demographics and clinical history

Variables	**Number**	**Percentage**
General demographic profile		
• No. of patients	419	
• Age (years; median)	59	
• Gender		
○ Male	283	67.5%
○ Female	136	32.5%

• Ethnicity		
○ Omani	407	97.1%
○ Non-Omani	12	2.9%
Patients' history		
• Diabetes mellitus	200	47.7%
○ Yes	59	14.1%
○ No	160	38.2%
○ Not available		
• Family history of liver disease	15	3.6%
○ Yes	31	7.4%
○ No	373	89%
○ Not available		
• Alcohol consumption	93	22.2%
○ Yes	86	20.5%
○ No	240	57.3%
○ Not available		
• Smoking	58	13.8%
○ Yes	84	20%
○ No	277	66%
○ Not available		

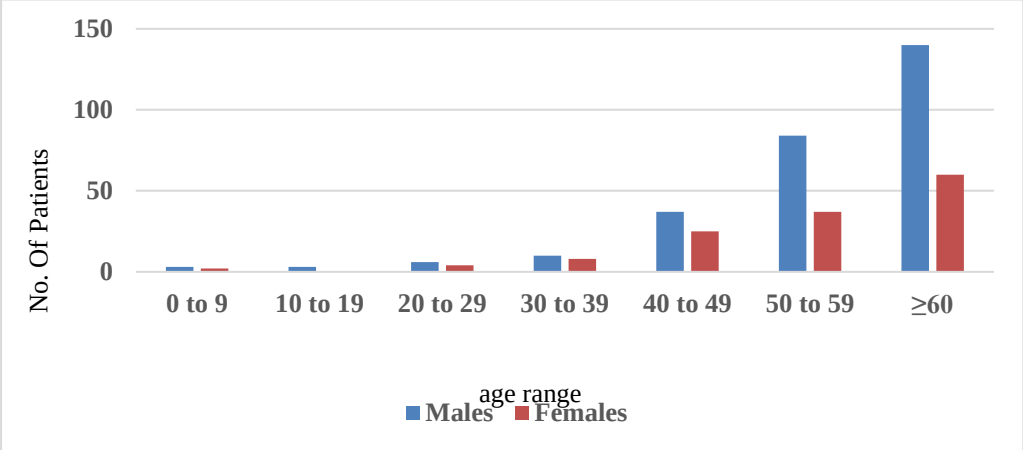
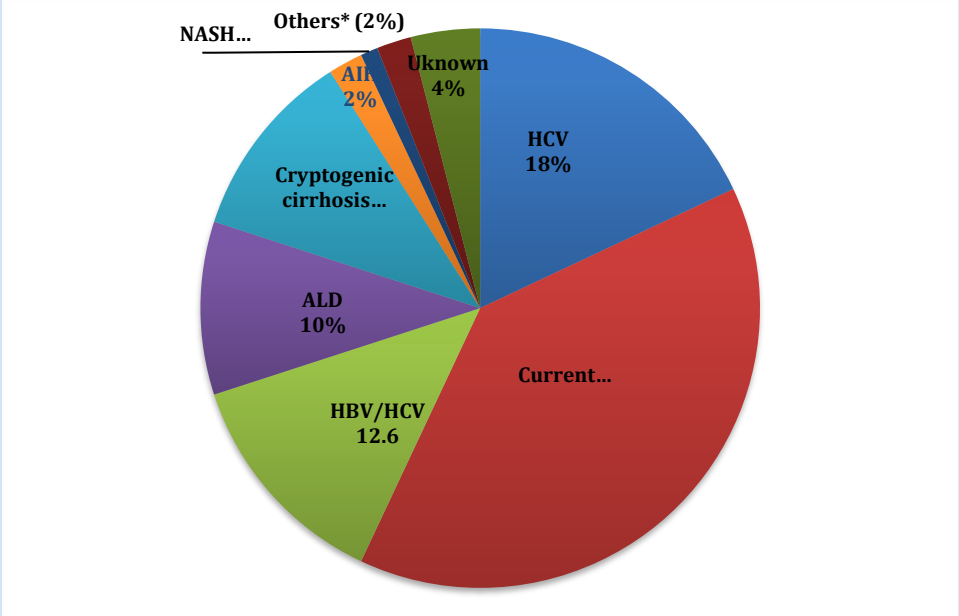


Figure 2: Age distribution of patients with Cirrhosis



- The percentage in this chart represent the percentage of the patients over the entire cohort of 419 patients
- * Others included the uncommon etiologies of liver cirrhosis in this study cohort. These were: two cardiac cirrhosis, two primary biliary cirrhosis, one primary sclerosing cholangitis, one secondary sclerosing cholangitis, one biliary atresia, one amiodarone induced cirrhosis, one Fanconi syndrome and one Wilson's disease.
- HCV = Hepatitis C Virus, HBV = Hepatitis B virus, AIH = autoimmune hepatitis, NASH = non-alcoholic steatohepatitis

Figure 3: Etiology of cirrhosis (Total No. of patients 419)

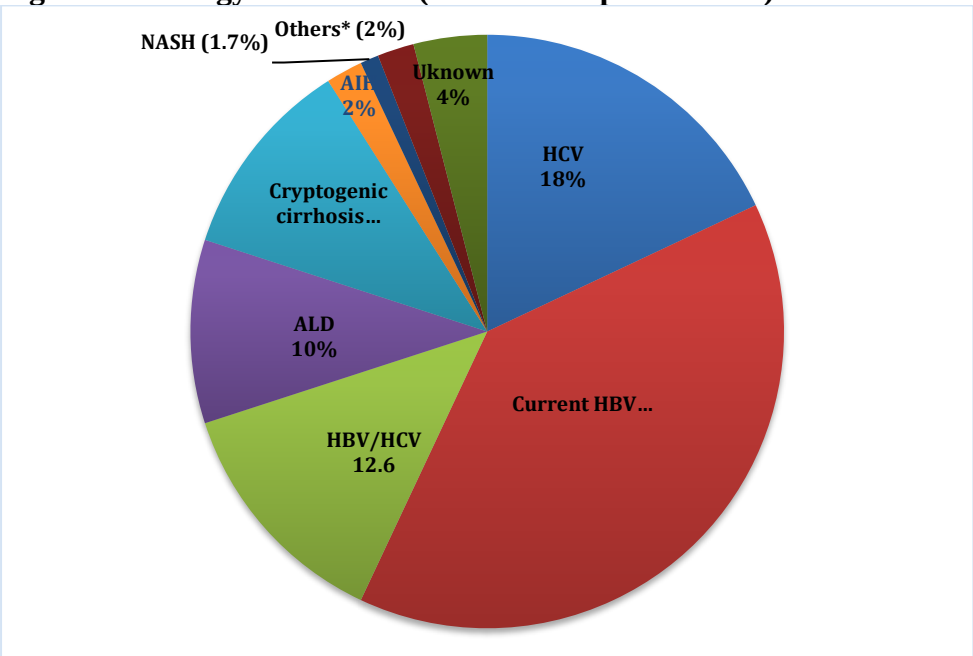


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Figure 3: Etiology of cirrhosis (Total No. of patients 419)

The majority of patients (69.3%) had viral hepatitis as etiology for liver cirrhosis. More than half of the study cohort (51.3%) had evidence of previous or current infection with HBV. Hepatitis B e Antigen (HBe-Ag) was found in 3.3% of CHB patients. Hepatitis B viral DNA (HBV DNA) was detected in 47 patients (21.9%), of which 20 patients had high viral load > 2000IU/ml (**Table 3).**

Table 3: HBV status of the study cohort (Total No. of patients 419, No. of HBV patients 215) ††

Definition	**Number (%)**	**Female (%)**	**Serologic findings**
Current and previous HBV infection	215 (51.3)	63 (29.3)	HBs-Ag Isolate anti-HBc
Current HBV infection	83 (38.6)	16 (18.8)	Positive HBsAg
Previous HBV infection (with or without HBV immunity)	79 (36.7)	26 (41.9)	Isolate anti-HBc and/or anti-HBv + anti-HBs
HBV with HCV co-infection†	53 (24.7)	21 (39.6)	anti-HBc + anti-HCV
Hepatitis B activity • Hepatitis B Viral Load • Hepatitis B e-Ag status	 • 47 (21.9) • 7 (3.3)	 • 19 (30.6) • 3 (4.8)	 • HBVDNA • HBe-Ag

HBV = Hepatitis B virus, HCV = Hepatitis C Virus, HBs-Ag = Hepatitis B surface antigen, anti-HBc = Hepatitis B core antibody, anti-HBs = Hepatitis B surface antibody, anti-HCV= Hepatitis C antibody.

†† The numbers and percentages in this table represent hepatitis B patients with cirrhosis (total 215) and not the entire cohort.

† 45 patients had past HBV with co-HCV infection

The majority of patients with HBV related liver cirrhosis were males (71%) compared to females (29%). HBV mono-infection is more common than HCV mono-infection (38.6% vs. 18%) p <0.01 **(Figure 3)**. Patients with hepatitis B related liver cirrhosis

were younger than those with other etiologies. Hepatitis B co-infection with hepatitis C virus (HCV) was found in 24.7% of HBV patients with cirrhosis **[Table 3].**

Data for HBV immunity was available for 328 patients (78.3%)**.** Of these**,** 36% were positive for hepatitis B surface antibody (anti-HBs). Negative anti-HBs was found in 34% of the studied cohort with 30% having unknown immunity status. The complete hepatitis B serology was not available in 4% of patients with anti-HBs. The majority of those with positive anti-HBs (27% out of the 36%) were immune due to previous infection (positive anti-HBs and antibodies to hepatitis B core antigen (anti-HBc)] with 5% only due to vaccination (positive anti-HBs and negative anti-HBc).

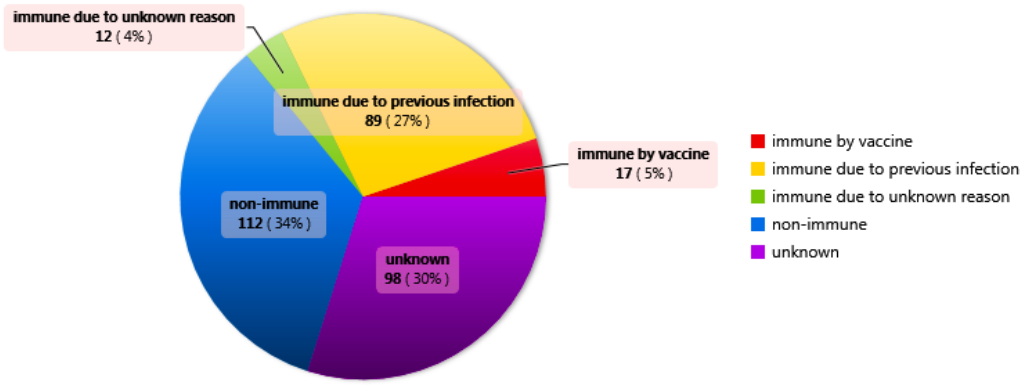

Figure 4: HBV immunity status (n=328)

Discussion

This study is conducted to investigate the association between CHB and liver cirrhosis in Oman. Majority of the patients (97.1%) were Omani. This high percentage of Omani patients included in this study can reduce the effect of synergistic factors that accelerate the process of fibrosis among CHB patients such as HBV genotypes and exposure to aflatoxins[11].

HBV infection among patients with cirrhosis is correlated with the prevalence of the virus in that region. It is estimated that HBV accounts for 5% of liver cirrhosis in low prevalence areas and up to 57% in high prevalence areas such as East Asia [12]. Based that estimation, the contribution of HBV to liver cirrhosis in the Eastern Mediterranean region including Oman would be around 35%. If the same estimation is applied to the contribution of HBV to liver cirrhosis in this study cohort, it would be equal to 19.6%. However, this estimated percentage is lower than what the current study indicates (38.7%). This discrepancy is likely to be due to multiple factors. Perz et al based their estimation on studies from Saudi Arabia and Tunisia. The prevalence of HBV in Oman is considered to be on intermediate prevalence before the introduction of HBV vaccination compared to Saudi Arabia which is considered to be of high prevalence for HBV [13] and Tunisia which is estimated to be of intermediate prevalence [14]. In addition to that, the quoted studies used to estimate the prevalence in different countries differ markedly in the design, population and methodology used.

There are certain factors that may accelerate the process of fibrosis among CHB patients and are present among our study patients. The probability of HBV clearance is higher among females due to unknown mechanism [15]. In addition, females tend to have lower rate of accelerated fibrosis due to inhibition of activated stellate cells by hormones mainly estrogen [16]. This could explain the majority of our patients in this study were males.

In countries with intermediate and high prevalence, the majority of patients acquire the infection in the early years of life [17]. With prolonged duration of HBV infection, the rate of fibrosis and hence cirrhosis is higher [18]. The estimated prevalence of CHB in Oman before the introduction of HBV vaccination is 2-7 % [19]. This factor can explain the median age of our patients is 59 years **(Table 2).**

Diabetes Mellitus (DM) and the associated NAFLD increase the risk for developing advanced fibrosis [20]. In a large prospective cohort study by Elserag et al, DM was found to double the risk of chronic non-alcoholic liver disease and HCC [21] Considering this factor, we might be able to explain one of the cirrhosis risk factors in this study population as almost half of the cohort had DM **(Table 2).**

Acute and chronic alcohol consumption is reported to cause significant necroinflammatory changes within the liver parenchyma [22] and alter cellular communication leading to cellular death [23]. The risk of liver fibrosis progression in patients with CHB is therefore increased with the synergistic effect of alcohol consumption [24]. The risk of cirrhosis among CHB patients who consume alcohol is also affected by other factors such as duration of alcohol intake, patients' gender, and presence of obesity [25]. In the current study, alcohol consumption was reported by 20% of the patients, however due to the retrospective design of our study, important information such as the amount and duration of alcohol consumption were not available. Therefore, the assessment of the synergetic effect of alcohol consumption on the CHB patients was not possible.

Fifty-seven percent (57.7%) of our patients had isolated anti-HBc (HBsAg negative). This is higher than the reported prevalence of isolated anti-HBc among Omani blood donor of 20.5% [26]. This difference could be related to the fact that blood donors in the previous study are younger than the patients in the current study cohort who were most likely HBV vaccinated and therefore the prevalence of isolated anti-HBc is likely to be low in their study.

Majority of our patients were HBe-Ag negative chronic hepatitis B. This finding is similar to the reported studies from areas of intermediate to high prevalence regions [27]. Once seroconversion from HBe-Ag to anti-HBe antibody is achieved, a suppression of HBV DNA is expected. Therefore, HBe-Ag negative chronic hepatitis B patients tend to have low viral load and favorable prognosis with low risk of progression to liver cirrhosis or HCC [28]. However, HBV of some of those HBe-Ag negative chronic hepatitis B patients may develop mutation in the pre-core or core promoter region leading to significant viremia and therefore progression to advanced fibrosis [29].

In this study, HBV DNA was detected in 21% of patients with cirrhosis. High viral load (more than 2000 IU/ml) was found in 43% of them. HBV DNA is the best measure of

HBV replication. However, HBV DNA levels may fluctuate in patients who are HBeAg-negative chronic hepatitis B reaching normal or high normal at times. Previous studies have shown reduction of HBV DNA with advanced liver fibrosis. Despite the reduction in HBV DNA, the liver inflammation continued leading to further fibrosis [30].

Anti-HBs seroconversion is considered to be the target clinical endpoints in patients with chronic HBV infection [31]. Anti-HBs was present in 36% of our patients. The majority (27% out of 36%) were due to previous infection. It is known that once seroconversion to Anti-HBs occurs, there should be no further liver inflammation or fibrosis. Therefore, we can postulate that cirrhosis occurred in this cohort before seroconversion unless other risk factors for progression toward cirrhosis such alcohol consumption, co-infection with HCV or presence of nonalcoholic steatohepatitis (NASH) exist in addition to Chronic Hepatitis B.

HBV co-infection with HCV accelerates liver fibrosis leading to early cirrhosis. The synergistic effect of HCV co-infection leading to advanced fibrosis has been mentioned in many studies [23-34]. The effect of HBV and HCV co-infection have been described among isolated anti-HBc [35-37].The global estimation of HBV and HCV co-infection is around 10-15% [16]. Our study showed that 12.6 % of patients with liver cirrhosis had HBV and HCV co-infection.
HCV is usually the dominant virus in HBV co-infection with HCV [38]. However, the persistence of low-level HBV replication within the hepatocytes induces chronic immune-related inflammation that increases severity of the liver disease and marked fibrosis [39,40].

The study showed that only 5% of patients were vaccinated for HBV, and 34% had no immunity against HBV. This is most likely due to the fact that most of those infected with hepatitis B were born before the introduction of vaccination in 1990.

The current study has multiple strengths. The sample size is relatively large with a good representation of the population given that the majority (97.1%) being Omani representing different parts of Oman. The classification of patients into three different groups using well-defined inclusion and exclusion criteria based on objective criteria add to the strength of the study.

The major limitation of our study is the retrospective nature. Data related to certain co-factors that can attribute to liver cirrhosis such as alcohol consumption, presence of metabolic syndrome, and other etiologies of liver cirrhosis was missing. Therefore, it was difficult to evaluate the synergistic effect of some cofactors and HBV in the etiology of cirrhosis in this study. Another limitation was the unavailability of complete HBV serological markers for some patient. This might underestimate the role of chronic HBV infection as a risk factor for liver cirrhosis.

Conclusion

Serological markers of chronic HBV infection are present in large number of patients with liver cirrhosis in Oman. The majority of the patients are male of older age group born before the introduction of HBV vaccination. Screening of high-risk patients is essential to reduce the complications of HBV infection in Oman. Further research is

essential to assess the role of contributing factors in the contribution of chronic hepatitis B to cirrhosis in Oman.

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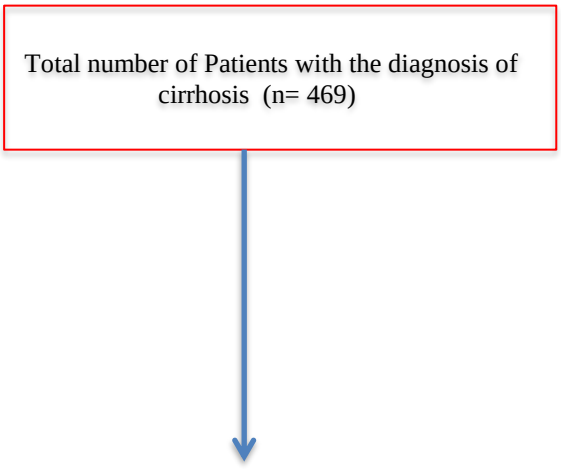


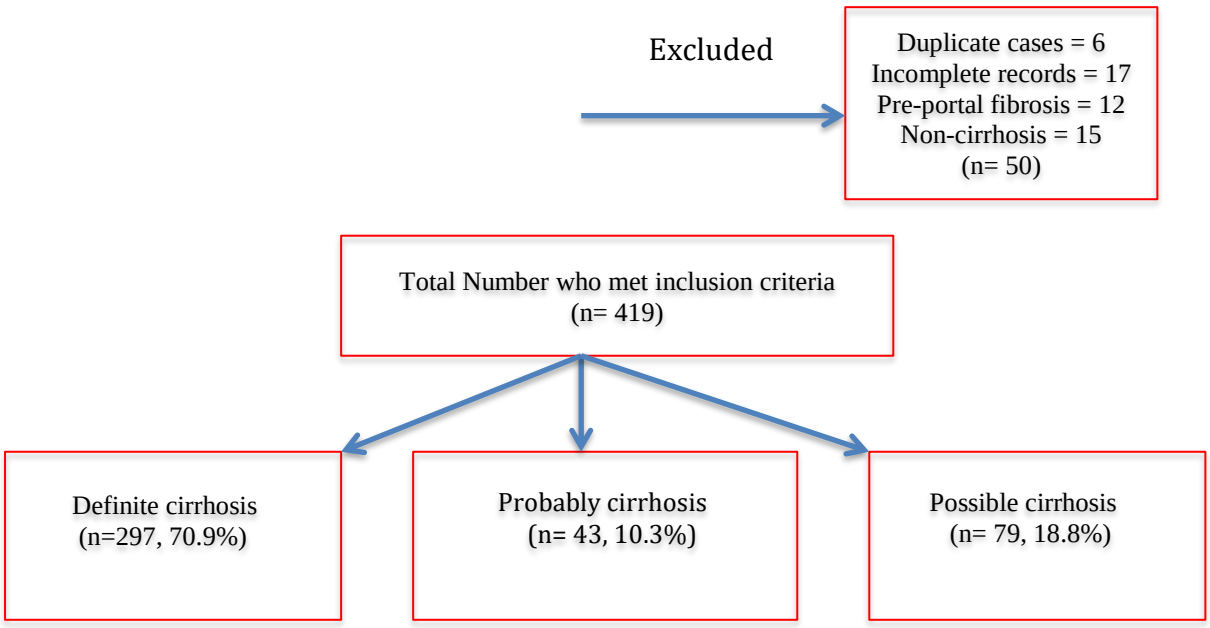


Figure 2: Age distribution of patients with Cirrhosis

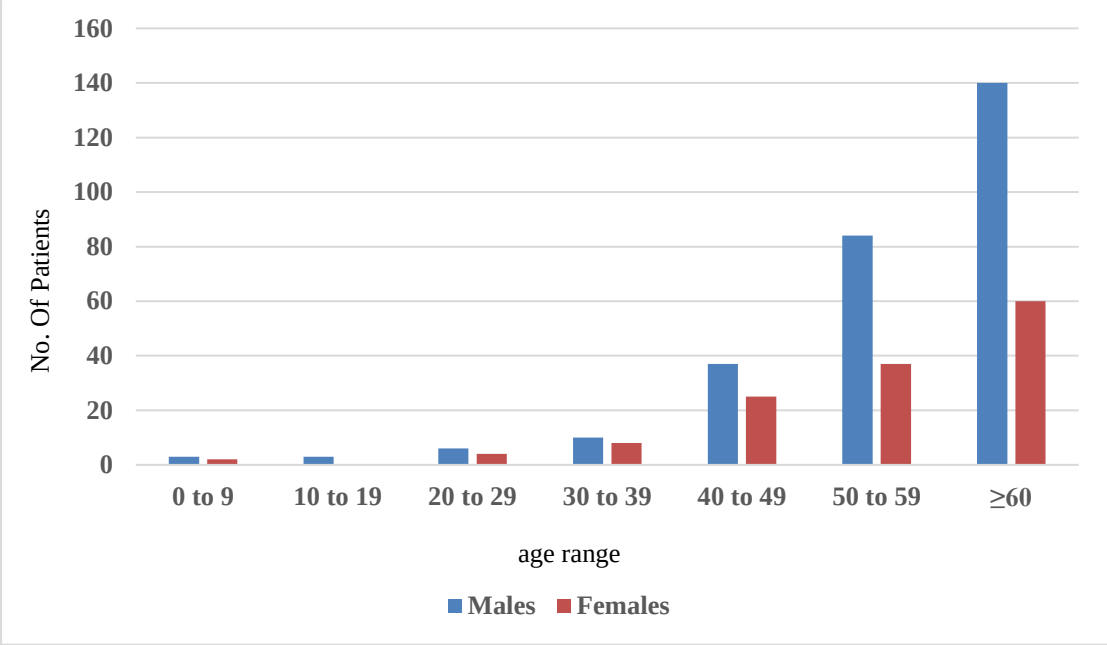
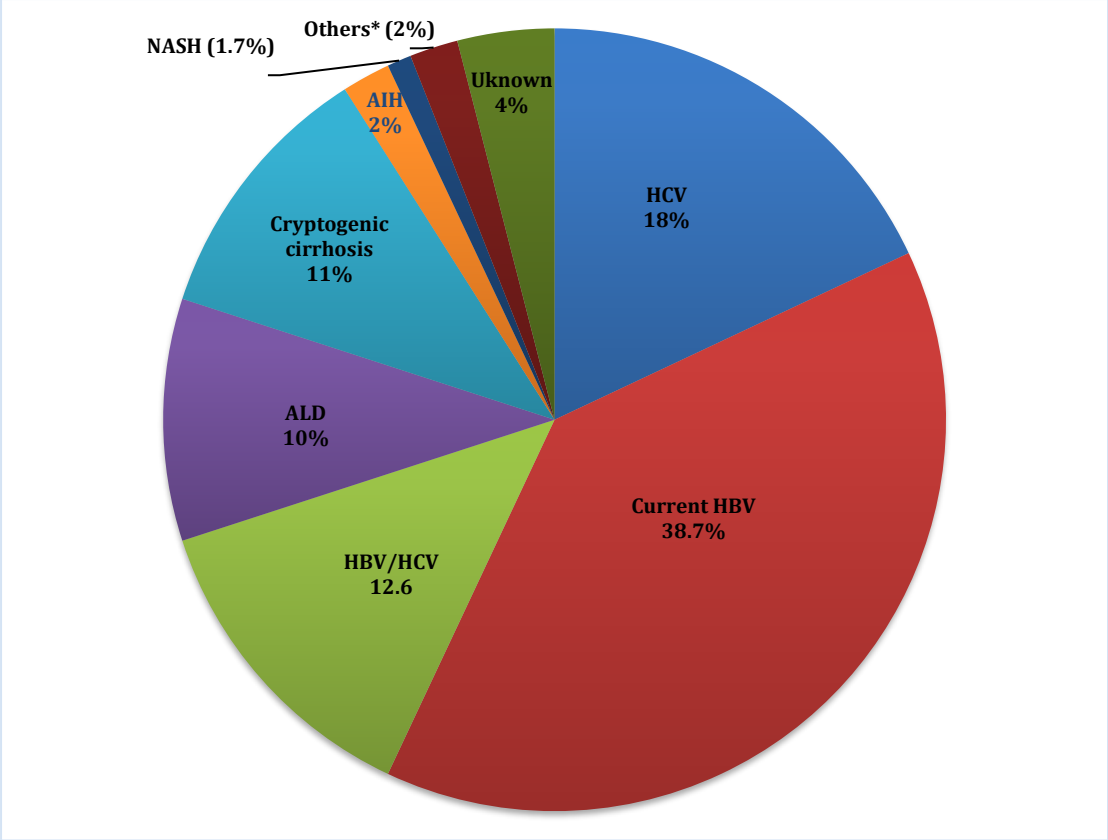


Figure 3: Etiology of cirrhosis (Total No. of patients 419)



- The percentage in this chart represent the percentage of the patients over the entire cohort of 419 patients
- * Others included the uncommon etiologies of liver cirrhosis in this study cohort. These were: two cardiac cirrhosis, two primary biliary cirrhosis, one primary sclerosing cholangitis, one secondary sclerosing cholangitis, one biliary atresia, one amiodarone induced cirrhosis, one Fanconi syndrome and one Wilson's disease.
- HCV = Hepatitis C Virus, HBV = Hepatitis B virus, AIH = autoimmune hepatitis, NASH = non-alcoholic steatohepatitis

Table 1: Categories depending on the accuracy of cirrhosis diagnosis

Category	Basis of diagnosis

Definite cirrhosis	• Either Histological features of cirrhosis • And/ or radiological features suggestive of liver cirrhosis (irregular or undulated liver surface with heterogeneous or coarse echotexture) with splenomegaly, collateral vessels, ascites and dilated PV. • With/ without biochemical tests showing raised aminotransferases (with AST>ALT usually), high bilirubin, low albumin associated with low platelet count and high PT or INR.
Probable cirrhosis	• Either irregular or undulated liver surface or heterogeneous or coarse echotexture on radiological images. With or without extrahepatic features such as enlarged spleen, collateral vessels, ascites and dilated PV. • With/ without biochemical tests showing high bilirubin, low albumin, low platelet count or increased INR or PT
Possible cirrhosis	• Biochemical tests show raised bilirubin, decreased albumin. Haematological tests showing low platelet count or high INR or PT but no histological or radiological tests to confirm the diagnosis.

PV = Portal Vein, AST = Aspartate Amino-Transferase, ALT = Alanine Amino-Transferase, PT = Prothrombin Time, INR = International Normalised Ratio

Table 2: Patients' demographics and clinical history

Variables	Number	Percentage

General demographic profile		
• No. of patients	419	
• Age (years; median)	59	
• Gender		
○ Male	283	67.5%
○ Female	136	32.5%
• Ethnicity		
○ Omani	407	97.1%
○ Non-Omani	12	2.9%
Patients' history		
• Diabetes mellitus	200	47.7%
○ Yes	59	14.1%
○ No	160	38.2%
○ Not available		
• Family history of liver disease	15	3.6%
○ Yes	31	7.4%
○ No	373	89%
○ Not available		
• Alcohol consumption	93	22.2%
○ Yes	86	20.5%
○ No	240	57.3%
○ Not available		
• Smoking	58	13.8%
○ Yes	84	20%
○ No	277	66%
○ Not available		

Table 3: HBV status of the study cohort (Total No. of patients 419, No. of HBV patients with liver cirrhosis 215) ††

Definition	Number (%)	Female (%)	Serologic findings

Current and previous HBV infection	215 (51.3)	63 (29.3)	Current HBV (HBs-Ag + anti-HBc) Previous HBV (Isolate anti-HBc alone)
Current HBV infection	83 (38.6)	16 (18.8)	HBsAg + Anti-HBc
Previous HBV infection (with or without HBV immunity)	79 (36.7)	26 (41.9)	Isolate anti-HBc • With Immunity (anti-HBc + anti-HBs) • No immunity (Isolated anti-HBc alone)
HBV with HCV co-infection†	53 (24.7)	21 (39.6)	Anti-HBc + Anti-HCV
Hepatitis B activity • Hepatitis B Viral Load • Hepatitis B e-Ag status	 • 47 (21.9) • 7 (3.3)	 • 19 (30.6) • 3 (4.8)	 • HBVDNA • HBe-Ag

HBV = Hepatitis B virus, HCV = Hepatitis C Virus, HBs-Ag = Hepatitis B surface antigen, anti-HBc = Hepatitis B core antibody, anti-HBs = Hepatitis B surface antibody, anti-HCV= Hepatitis C antibody.

†† The numbers and percentages in this table represent hepatitis B patients with cirrhosis (total 215) and not the entire cohort.

† 45 patients had past HBV with co-HCV infection