Retrospective Study

Current trends of liver cirrhosis in Mexico: Similitudes and differences with other world regions

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Abstract

AIM
To investigate the main current etiologies of cirrhosis in Mexico.

METHODS
We performed a cross-sectional retrospective multicenter study that included eight hospitals in different areas of Mexico. These hospitals provide health care to people of diverse social classes. The inclusion criteria were a histological, clinical, biochemical, endoscopic, or imaging diagnosis of liver cirrhosis. Data were obtained during a 5-year period (January 2012-December 2017).

RESULTS
A total of 1210 patients were included. The mean age was 62.5 years (SD = 12.1), and the percentages of men and women were similar (52.0% vs 48.0%). The most frequent causes of liver cirrhosis were hepatitis C virus (HCV) (36.2%), alcoholic liver disease (ALD) (31.2%), and nonalcoholic steatohepatitis (23.2%), and the least frequent were hepatitis B virus (1.1%), autoimmune disorders (7.3%), and other conditions (1.0%).

CONCLUSION
HCV and ALD are the most frequent causes of cirrhosis in Mexico. However, we note that non-alcoholic fatty liver disease (NAFLD) as an etiology of cirrhosis increased by 100% compared with the rate noted previously. We conclude that NAFLD will soon become one of the most frequent etiologies of liver cirrhosis in Mexico.

Key words: Alcoholic liver disease; Hepatitis C virus; Nonalcoholic steatohepatitis; Liver cirrhosis

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Core tip: In 2004, a Mexican study reported the most common causes of liver cirrhosis were alcoholic liver disease (39.5%), hepatitis C virus (36.6%), and non-alcoholic fatty liver disease (10.4%). We believe that the epidemiology of cirrhosis has changed because of the increasing prevalence of obesity, metabolic syndrome, and autoimmune diseases. Therefore, we performed a cross-sectional multicenter study that included eight hospitals of different areas of Mexico in order to know the current epidemiology of liver cirrhosis in this country.

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INTRODUCTION

Liver fibrosis develops as a result of chronic injury to the liver in conjunction with the excessive accumulation of extracellular matrix proteins, which occurs in most chronic liver diseases (CLDs)[1]. The accumulation of extracellular matrix proteins distorts the hepatic architecture by forming fibrous scar tissue, and the subsequent development of regenerative nodules within hepatocytes defines cirrhosis[2]. Cirrhosis is the end stage of CLD and leads eventually to portal hypertension, hepatocellular carcinoma (HCC), and liver failure[3].

Liver cirrhosis is a major and underestimated global public health problem as well as an important cause of morbidity and mortality. In 2010, cirrhosis was responsible for an estimated 2% of all deaths worldwide[4]. Current global estimates show that 844 million people have a CLD, and 2 million people die per year because of CLD[5]. The worldwide prevalence rate for CLD is 4.5% to 9%, causing approximately 633000 cases of liver cirrhosis per year[6]. In the United States, CLDs and liver cirrhosis are the 12th leading cause of mortality and
account for about 60000 deaths per year\textsuperscript{(7)}. In European countries, liver cirrhosis affects about 0.1% of the populations and causes about 170000 deaths per year\textsuperscript{(8,9)}.

The most common etiologies of liver cirrhosis in developed countries include chronic hepatitis C virus (HCV) infection, alcoholism, and nonalcoholic steatohepatitis (NASH), whereas viral hepatitis, especially that caused by hepatitis B virus (HBV) infection, are the main causes in developing countries\textsuperscript{(10)}. However, in many countries, the proportion of liver cirrhosis caused by viral hepatitis is decreasing markedly and the proportion caused by NASH is increasing\textsuperscript{(10)}. Nonalcoholic fatty liver disease (NAFLD), the predecessor condition of NASH, has a current prevalence of 25%–30% worldwide and the highest prevalence rates are in Western countries\textsuperscript{(10)}. Some studies have reported that over 64 million people have NAFLD in the United States and 53 million have NAFLD in Europe\textsuperscript{(11)}. Therefore, it is expected that NAFLD will become the leading cause of liver-related morbidity and mortality in the next 20 years as well as the main indication for liver transplantation\textsuperscript{(12)}. Unfortunately, NASH is now the second most frequent indication for liver transplantation in the United States\textsuperscript{(13,14)}.

In Mexico, alcoholic liver disease (ALD) and HCV infection have been the most frequent causes of liver cirrhosis in the past decade\textsuperscript{(15)}. Nevertheless, the rising prevalence of obesity\textsuperscript{(16)}, metabolic syndrome\textsuperscript{(17)}, and autoimmune diseases\textsuperscript{(18)} has probably modified the epidemiology of cirrhosis in our country. Therefore, we aimed to investigate the main etiologies of liver cirrhosis in Mexicans. We believe that understanding the epidemiology of liver cirrhosis in the general population is the first step toward developing interventions to decrease this disease burden.

**MATERIALS AND METHODS**

A multicenter cross-sectional retrospective observational study was performed in eight tertiary referral hospitals from different cities of Mexico: Medica Sur Clinic and Foundation (Mexico City), Hospital “Juárez” of Mexico (Mexico City), Civil Hospital of Guadalajara “Fray Antonio Alcalde” (Jalisco), Christus Muguerza “Super Specialty” Hospital (Nuevo León), General Hospital of Mexico “Dr. Eduardo Liceaga” (Mexico City), Central Military Hospital (Mexico City), General Hospital of the Mexican Social Security Institute (Durango), and the General Regional Hospital, IMSS 1 (Cuernavaca). The hospitals in our sample come from three geographic regions of Mexico: North, Center, and Mexico City. These hospitals provide medical care to the Mexican population of all ages. The study was conducted from January 2012 to December 2017.

We included patients who were older than 20 years, of both genders, who had been diagnosed with liver cirrhosis of the compensated or decompensated stage. The medical records of all participants were reviewed to obtain information about liver disease categorization and biochemical and imaging data. All eligible patients had received a biochemical, clinical, imaging, or histological diagnosis of liver cirrhosis. The diagnosis of liver disease was categorized as HBV, HCV, autoimmune liver disease, ALD, NASH, or other conditions. Hereditary liver disease or liver cirrhosis resulting from hepatotoxic drugs or toxins was classified into the group of other causes.

We made the histological diagnosis of cirrhosis according to the American Association for the Study of Liver Diseases guidelines. The criteria for the categorization of viral hepatitis were positive serological enzyme-linked immunoassay test results for HCV antibody, immunoglobulin G to hepatitis core antigen, and positive surface antigen of HBV. ALD was diagnosed for patients with a history of ethanol consumption ≥ 30 g/d in men or ≥ 20 g/d in women and negativity to viral and autoimmune markers. Consumption of alcohol was assessed.

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### Table 1  Main causes of liver cirrhosis by hospital

| Hospital               | n   | Virus | Alcohol | NASH | Autoimmune | Others |
|------------------------|-----|-------|---------|------|------------|--------|
| MSC&F                  | 413 | B 8   | 169     | 123  | 71         | 42     | 0      |
| CHG                    | 156 | 0     | 91      | 45   | 20         | 0      | 0      |
| CMH                    | 100 | 0     | 23      | 25   | 41         | 11     | 0      |
| CMSSH                  | 113 | 3     | 20      | 26   | 47         | 8      | 9      |
| GHM                    | 73  | 1     | 6       | 40   | 25         | 1      | 0      |
| GHIM                   | 99  | 0     | 35      | 26   | 24         | 14     | 0      |
| GRH IMSS No.1          | 82  | 0     | 72      | 4    | 0          | 6      | 0      |
| HJM                    | 174 | 1     | 22      | 88   | 53         | 7      | 3      |
| Total                  | 1210| 13    | 438     | 377  | 281        | 89     | 12     |

The distribution of the etiology of liver cirrhosis was higher for hepatitis C virus 36.2%, alcoholic liver disease 31.2% and nonalcoholic steatohepatitis 23.2% and lower for hepatitis B virus 1.1%, autoimmune hepatitis 7.3% and other causes 1.0% (P < 0.001). MSC&F: Medica Sur Clinic and Foundation; HJM: Hospital “Juárez” of Mexico; CHG: Civil Hospital of Guadalajara “Fray Antonio Alcalde”; CMSSH: Christus Muguerza “Super Specialty” Hospital; GHM: General Hospital of Mexico “Dr. Eduardo Liceaga”; CMH: Central Military Hospital; GHD: General Hospital of Durango; GRH IMSS No.1: Regional General Hospital IMSS 1; NASH: Nonalcoholic steatohepatitis.
using the Alcohol Use Disorders Identification Test (AUDIT)\(^{19}\), a widely used screening instrument for unsafe and noxious alcohol consumption.

**Statistical analysis**
Continuous variables with a normal distribution are expressed as the mean ± SD. Categorical variables are expressed as frequencies and percentages. The chi-squared test was used to identify differences between the underlying cause of liver cirrhosis and age groups, gender, and the hospital where patients were treated. Data were analyzed using the statistical program Stata version 14 (Stata Corp, College Station, TX).

**RESULTS**
The sample comprised 1210 patients (male: female ratio 1:1; mean age 62.5 ± 12.1 years). HCV infection was the most frequent etiology (36.2%), followed by ALD (31.2%), and NASH (23.2%). Other causes of liver cirrhosis included autoimmune liver diseases (7.3%), HBV infection (1.1%), and other conditions (1%) (Table 1). Women accounted for most of the cirrhotic patients with HCV infection (64.8%) and NASH-related cirrhosis (60.5%), and men accounted for 86.7% of patients with liver cirrhosis caused by ALD \((P < 0.001)\). The underlying causes of liver cirrhosis and the gender distribution according to etiology are summarized in Table 2.

The prevalence of HCV infection, ALD, and NASH (38.6%, 32.6%, and 38.8%, respectively) was highest in the 61-70-year-old group. No significant differences in the etiology were found between age groups \((P = 0.166)\) (Figure 1).

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**Table 2 Main etiologies of liver cirrhosis by gender, n (%)**

| Hospital          | Male (n = 629) | Female (n = 581) |
|-------------------|---------------|-----------------|
|                   | Virus         | Virus           |
|                   | B   | C   | Alcohol | NASH | Auto-immune | Other | n   | B   | C   | Alcohol | NASH | Autoimmune | Other |
| MSC&F             | 217 | 5   | 56     | 110  | 29    | 17    | 0   | 196 | 3   | 113  | 13    | 42    | 25    | 0    |
| CHG               | 96  | 0   | 44     | 42   | 10    | 0     | 0   | 60  | 0   | 47   | 3     | 10    | 0     | 0    |
| CMH               | 35  | 0   | 8      | 13   | 12    | 2     | 0   | 65  | 0   | 15   | 12    | 29    | 9     | 0    |
| CMSH              | 70  | 2   | 11     | 23   | 11    | 2     | 5   | 43  | 1   | 9    | 3     | 20    | 6     | 4    |
| GHD               | 45  | 0   | 2      | 35   | 8     | 0     | 0   | 28  | 1   | 4    | 5     | 17    | 1     | 0    |
| GHM               | 45  | 0   | 1      | 10    | 72    | 0     | 0   | 20  | 1   | 1.4  | 10.0  | 10.0  | 1.5   | 0    |
| GRH IMSS No.1     | 14  | 0   | 12     | 1    | 0     | 1     | 0   | 68  | 0   | 60   | 3     | 0     | 5     | 0    |
| HJM               | 107 | 1   | 10     | 78   | 16    | 0     | 2   | 67  | 0   | 12   | 10    | 37    | 7     | 1    |
| Total             | 629 | 8   | 154    | 327  | 111   | 22    | 7   | 581 | 5   | 284  | 50    | 170   | 67    | 5    |

**RESULTS**
The sample comprised 1210 patients (male: female ratio 1:1; mean age 62.5 ± 12.1 years). HCV infection was the most frequent etiology (36.2%), followed by ALD (31.2%), and NASH (23.2%). Other causes of liver cirrhosis included autoimmune liver diseases (7.3%), HBV infection (1.1%), and other conditions (1%) (Table 1). Women accounted for most of the cirrhotic patients with HCV infection (64.8%) and NASH-related cirrhosis (60.5%), and men accounted for 86.7% of patients with liver cirrhosis caused by ALD \((P < 0.001)\). The underlying causes of liver cirrhosis and the gender distribution according to etiology are summarized in Table 2.

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Liver cirrhosis is the fourth leading cause of death in Mexico\(^\text{[20]}\). However, cirrhosis is the second leading cause of death in people aged 35-55 years\(^\text{[15]}\). In other countries, both developed and developing, CLD is also a major health problem\(^\text{[21­28]}\) (Figure 2).

As expected, we found that the epidemiology of cirrhosis in Mexico has changed with time. Previous epidemiological studies in Mexico have reported that ALD was the main cause of liver cirrhosis\(^\text{[21,29]}\). However, our recent results show that HCV infection and ALD are currently the most common causes of liver cirrhosis in Mexico. A recent study of 578 Mexicans with CLD by Torres-Valadez et al\(^\text{[30]}\), reported similar findings in patients assessed for liver damage. These authors reported that the leading etiologies in patients with liver cirrhosis were ALD (45%), HCV (43%), and NASH (10%). Similar to our findings, this study found that ALD was more prevalent in men, and NASH and HCV infection were more prevalent in women.

We found that NASH was the third leading cause of cirrhosis: 281 patients or 23.2%. This finding shows an increase in the prevalence of NASH of 100% compared with our report in 2004\(^\text{[21]}\). This increase in NASH prevalence corresponds to the current trends for liver cirrhosis worldwide. The recent obesity epidemic has contributed to the increase in the prevalence of NAFLD and its progressive form, NASH, which are becoming the leading causes of chronic liver disease in many countries\(^\text{[31]}\). Currently, the prevalence of NAFLD is very high in all regions, and the highest rates have been reported in South America (31%), the Middle East (32%), Asia (27%), the United States (24%), and Europe (23%). The current worldwide prevalence of NASH is 59.1%\(^\text{[32]}\).

Although NAFLD has been considered a problem only in Western countries, several Asian studies have reported a growing prevalence of NAFLD in Asian countries\(^\text{[33,34]}\). The increasing prevalence of NAFLD in Asia is due to the growing trend of obesity in this country which is why it has been reported that the currently prevalence of NAFLD in Asia is around 25% to 30%\(^\text{[32,33,35]}\), Shanghai, Hong Kong and Central China are the cities with the highest prevalence rates of NAFLD; 38.17%\(^\text{[36]}\), 28.8%\(^\text{[37]}\) and 24.5%\(^\text{[38]}\), respectively. These data are very alarming due to it is evident that obesity and its related diseases are becoming a serious problem worldwide.

In other Latin American countries such as Brazil, liver diseases are the eighth leading cause of death\(^\text{[39]}\). Cirrhosis related to alcohol consumption and to HBV and HCV infection represents 2.17% of disability-adjusted life years in Brazil\(^\text{[25,40]}\). In Brazil, the burden of liver disease is higher in young or middle-aged people\(^\text{[40]}\). By contrast, the age groups 61-70 and 51-60 years are the most affected in Mexico. This difference may reflect cultural differences because Mexicans normally do not seek medical attendance for cirrhosis until the disease has reached advanced stages. Brazilian studies have estimated that the prevalence of HCV infection in Brazilians is low (1.38%)\(^\text{[39,41]}\). However, in 2012, Gonçalves et al\(^\text{[37]}\) reported that the main etiologies of liver cirrhosis were ALD (39.7%), HCV (14.5%), HBV (13.1%), and NASH (4.4%). Interestingly, ALD is currently one of the leading causes of mortality and hospital admissions in Brazil\(^\text{[39]}\).

Similar to the trends in Mexico, ALD, viral hepatitis B and C, and metabolic syndrome related to overweight...
and obesity are the main underlying causes of liver cirrhosis in Europe and the United States. Alcohol is the strongest risk factor for chronic liver disease; alongside with NAFLD they represent 66% of liver diseases in the European population. The prevalence of NAFLD in this population is about 13%–44% which cause by itself the 13% of liver diseases and HCV with a prevalence of 0.13%–3.26% is related with 6% of liver disease. There is no percentage mentioned in European statistics about HBV (prevalence of 0.5%–0.7%) as cause of liver disease. NAFLD affects around 51.7% of Americans followed by ALD (20.7%), HCV (8.6%), and HBV (3.1%) [6,42]. It is interesting to
mention that United Kingdom (UK) had a high increase of liver cirrhosis in the last 2 decades compared to other European countries\[43\]. Nowadays, it is estimated that 30000 people live with cirrhosis and at least 70000 new cases are diagnosed each year in UK\[44\]. Although ALD is the first cause of cirrhosis in UK (Figure 2), a recent study has reported that NAFLD is the most common etiology for asymptomatic altered liver biochemistry, accounting for 26.4% of cases in UK\[45\].

Despite the expectation that NAFLD will soon become the main cause of end-stage liver disease and need for liver transplantation, we expect that the prevalence of HCV-related cirrhosis will continue to increase in Mexico because of the improved methods for diagnosing HCV infection and the difficulties in receiving care for this disease. Similarly, Davis et al\[46\] have estimated that the percentage of patients with HCV-related cirrhosis will reach 45% by 2030 in the United States.

In conclusion, in the present study, HCV, ALD, and NASH were the main etiologies of liver cirrhosis. Interestingly, the epidemiology of liver cirrhosis in Mexico is similar to that presented in the United States and Europe. Despite the differences between human populations they share similar cultural factors related to alcohol, hepatitis infection and obesity. CLDs will continue to cause significant morbidity and mortality. Therefore, it is necessary to implement preventive measures, particularly those related to viral hepatitis infection, obesity, and alcohol consumption, to decrease the rates of liver cirrhosis.

**ARTICLE HIGHLIGHTS**

**Research background**

Liver cirrhosis is the fourth leading cause of death in Mexico. In our previous study, the main causes of liver cirrhosis were: alcoholic liver disease (ALD), hepatitis C virus (HCV) and nonalcoholic steatohepatitis (NASH). However, the rising prevalence of obesity and metabolic syndrome has probably modified the epidemiology of cirrhosis in Mexico.

**Research motivation**

It is of great clinical significance to explore the methods for early diagnosis of liver cirrhosis. Moreover, it is necessary to implement preventive measures, particularly those related to viral hepatitis infection, obesity, and alcohol consumption, in order to decrease the mortality of liver cirrhosis.

**Research objectives**

We aimed to investigate the main etiologies of liver cirrhosis in Mexicans in the last five years.

**Research methods**

In this retrospective study, the clinical data of 1210 patients with liver cirrhosis were collected. The inclusion criteria were a histological, clinical, biochemical, endoscopic, or imaging diagnosis of liver cirrhosis. Data were obtained during a 5-year period (January 2012–December 2017).

**Research results**

The most frequent causes of liver cirrhosis were HCV (36.2%), ALD (31.2%), and nonalcoholic steatohepatitis (23.2%). The least frequent etiologies were hepatitis B virus (1.1%), autoimmune disorders (7.3%), and other conditions (1.0%).

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