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Concise review

A landscape of liver cirrhosis and transplantation in Mexico: Changing leading causes and transplant as response

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ABSTRACT

Liver cirrhosis causes include alcoholism, viral infections (hepatitis B virus (HBV) and hepatitis C virus (HCV)), alcohol-associated liver disease (ALD), and metabolic dysfunction associated with steatotic liver disease (MASLD), among others. Cirrhosis frequency has increased in recent years, with a prevalence of 1395 cases per 100,000 and a mortality rate of 18 per 100,000, which corresponded to 1,472,000 deaths during 2017. In Mexico, liver disease is a public health problem since it was associated to 41,890 deaths in 2022, including liver cirrhosis (>25,000) and ALD (14,927). This represents 114 daily deaths due to these causes, and corresponds to the 4th or 5th place of all causes. The global prevalence of MASLD is estimated to affect 25% of the world's population, while in the pediatric population it could be higher. In Mexican population it is more prevalent since estimations were around 41.3% in 2023. Alcohol consumption, a global health issue due to its high prevalence and associated morbidities, is associated to ALD in 32.9%, with a mortality rate of 23.9%, primarily due to liver-related causes. In Mexico, ALD is present in 23% of all cirrhosis cases, already surpassed by hepatitis B cases in 2009. HCV and HBV frequencies changed due to programs implementing screening detection, vaccines and direct-acting antivirals during the last years. A switch of causes has occurred, increasing MASLD and diminishing viral causes. Efficient performed liver transplantation has grown as a response to increasing cirrhosis cases, including recent authorized centers. These efforts are necessary, whereas preventive strategies should be implemented according to leading causes.

Abbreviations: ALD, Alcohol-associated liver disease; CENATRA, National Transplant Center; DAAs, Direct-acting antivirals; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HCV, Hepatitis C virus; MASLD, Metabolic dysfunction associated with steatotic liver disease; NAFLD, Nonalcoholic Fatty Liver Disease; NASH, Nonalcoholic steatohepatitis; T2DM, Type 2 diabetes mellitus; WHO, World Health Organization

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1. Introduction

Liver cirrhosis refers to replacing normal liver tissue with fibrosis due to various chronic diseases [1]. Major causes include alcoholism, viral infections (hepatitis B virus (HBV) and hepatitis C virus (HCV)), alcohol-associated liver disease (ALD), metabolic dysfunction associated with steatotic liver disease (MASLD), and others like immunologic, infections and metabolism defects. These causes can exist singly or coexist in the same patient [2]. In recent years, the proportion attributed to certain causes has changed due to the use of new drugs and vaccines, leading to a decrease in cirrhosis associated with viral infections [3]. While vaccines and the availability of antivirals impact this condition, they have no effect on alcohol-related cirrhosis, which is responsible for the majority of cases [4]. Additionally, the high prevalence of diabetes and obesity has contributed to the rise of non-alcoholic fatty liver disease, whichin turn, contributes to cirrhosis cases [2]. Patients with cirrhosis can remain clinically compensated for several years, but may progress to hepatocellular carcinoma, decompensation due to various causes, and ultimately death [5]. The transition from compensated to decompensated cirrhosis has increased in recent years at a rate of 5−12% annually [1,3-5], despite the ability to maintain alcohol-associated and fatty liver-related cirrhosis with lifestyle changes and therapies. According to The Global Burden of Disease Study (GBD) [6-8], in 2017 there were 112 million people with compensated cirrhosis. Cirrhosis was the cause of death for 1,472,000 people, with a cirrhosis rate of 1,395 cases per 100,000 and a prevalence between populations ranging from 0.3% to 0.8%, with a mortality rate of 18 per 100,000 [9]. On the other hand, acute-on-chronic liver failure, characterized by organ failure, poses a high mortality risk. Alcohol consumption accounts for 45% of acute-on-chronic liver failure cases (24-55%), and 3-month mortality can be as high as 68% of cases that could be preventable. Worldwide, liver cirrhosis is on the rise, representing one of the leading causes of mortality globally, responsible for 2.4% of deaths in 2019, ranking fourth among different causes of adult mortality [9]. Additionally, liver disease is often underdiagnosed, leading to detection when the disease is decompensated [1,10,11]. It is estimated that 40% of diagnoses are made in decompensated cirrhosis with ascites or hepatic encephalopathy data limiting benefits from different medical interventions to extend survival and making liver transplantation a viable treatment option. In Mexico, the frequency of liver disease and cirrhosis is also increasing, following global trends with changes in causality due to the rising prevalence of MASLD and the high frequency of alcohol-related liver disease [4,9,12]. Also, the number of liver transplants in the country has increased, along with the number of institutions performing them.

1.1. Objective

The aim of this review is to present an overview of the changing frequencies of cirrhosis causes in Mexico, emphasizing the last 10 years. We describe epidemiological aspects such as the frequency and mortality of these causes and aspects related to liver transplants in Mexico in recent years, including three newly performed in Hospital Juárez de México. Finally, we briefly point out the necessity of implementing strategies to prevent the development and progression of cirrhosis according to leading causes.

2. General aspects of cirrhosis in Mexico

In Mexico, liver disease is a public health problem since it was responsible for 41,890 deaths in 2022, including liver cirrhosis (>25,000 deaths) and ALD (14,927 deaths). This represents 114 daily deaths due to these causes. Over the past decade, liver diseases ranked 4th to 5th in mortality (representing 5% of all deaths). However, it dropped to sixth place since 2020, surpassed by COVID-19, influenza, and pneumonia cases. But it is the third cause of death in men and seventh in women [13,14]. Fig. 1 illustrates the annual number of deaths from liver diseases in the Mexican population over the

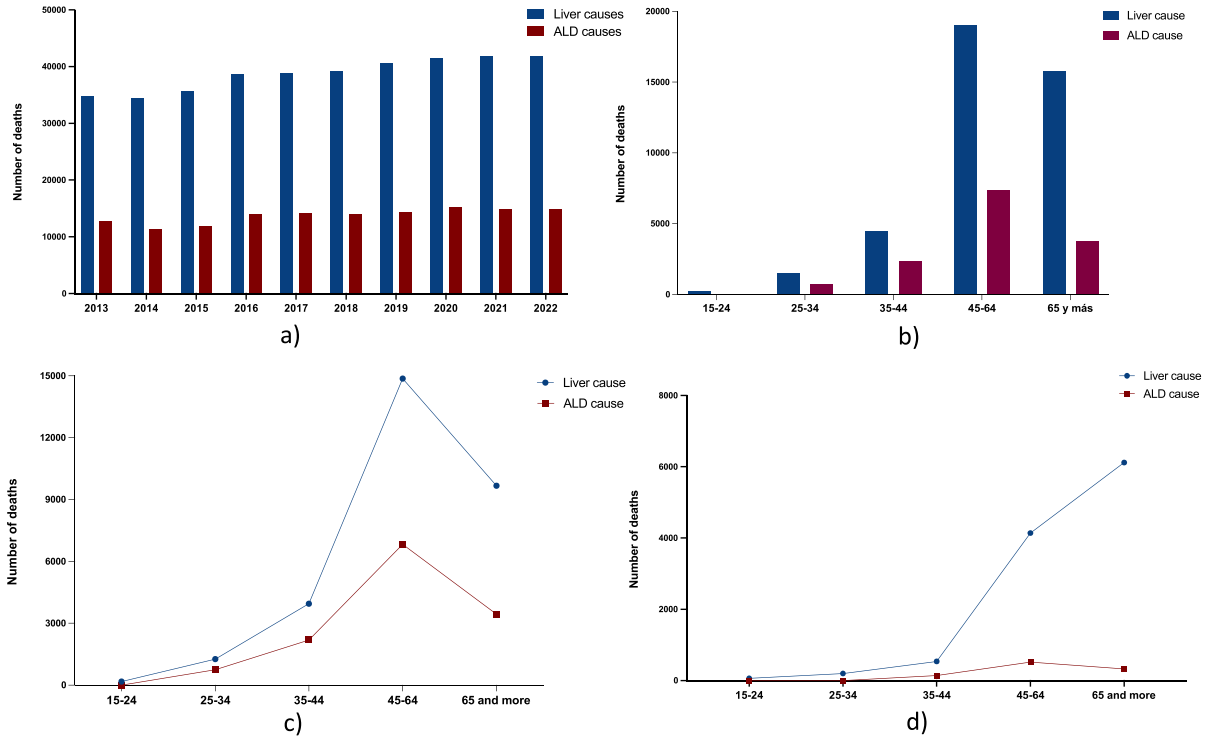

Fig. 1. Number of deaths caused by all liver diseases and ALD during the last 11 years. a) Number of deaths caused by all liver diseases and ALD annually in Mexico from 2013 to 2022. b) Number of deaths caused by all liver diseases and ALD by group age during 2022. c) Number of deaths caused by all liver diseases and ALD in men by group age. d) Number of deaths caused by all liver diseases and ALD in women by group age.

last 10 years (2013-2022), including ALD, according to age and gender.

3. Causes of cirrhosis

3.1. Metabolic dysfunction-associated steatotic liver disease

MASLD is currently the leading cause of liver disease globally, affecting an estimated 25% of the world's population. It is associated with increasing metabolic disorders such as obesity, type 2 diabetes mellitus (T2DM), serum glucose levels, blood pressure, triglyceride levels, and HDL cholesterol. Although there are few studies considering the term MASLD due to its recent nomenclature, the condition known as Nonalcoholic Fatty Liver Disease (NAFLD) is currently the most prevalent cause of chronic liver disease worldwide, encompassing steatosis and progressing to nonalcoholic steatohepatitis (NASH). The global prevalence of NAFLD is estimated at 30.1%, reflecting an increase over the last three decades (1990-2019), rising from 25.3% in 1990-2006 to 38.2% between 2016-2019 [15,16].

The significance of metabolic-driven liver disease is notable due to various factors such as a higher risk of progressing to chronic liver disease, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). These alterations affect a high population of the population including children and adolescents, occur frequently in young and/or working-age patients, and are associated with increased mortality. Notably, the frequency of MASLD correlates with the rise in obesity and diabetes, demanding greater attention [17].

Globally, in 2017, the prevalence of diabetes was 6059 cases per 100,000 (6.28% in the general population, approximately 462 million affected individuals). The prevalence increases to 15% in individuals aged 50 to 69 and 22% in those aged 70 or older [18]. Obesity has also grown alarmingly, with the World Health Organization estimating that in 2016, over 1 billion people were affected (13% of the population), including 650 million adults, 340 million teenagers, and 39 million children under 5 years old. Additionally, overweight prevalence is higher, reaching 39% in adults aged 18 or older. Overweight and obesity prevalence tripled from 1975 to 2016 [19], and it is projected that by 2025, there will be an additional 167 million individuals affected by overweight and obesity [20,21]. Mortality due to liver-related causes in people with NAFLD is 0.77 per 1,000 persons per year, while for NASH, it is 11.77 per 1,000 persons per year. However, all-cause mortality rises to 15.44 and 25.26 per 1,000 persons per year for NAFLD and NASH, respectively [17,22].

In the pediatric population, the MASLD estimated global prevalence (including reports up to 2020) is 33.78% in boys and girls (36.05 and 26.84, respectively). Still, it increases to 44.94% in the presence of obesity (50.20 in boys and 35.34% in girls) [23]. It is currently the leading cause of liver disease in children. Considering NAFLD, the prevalence is estimated at 7.4% in children overall, but it increases to 52.4% in obese children and 39.17% in overweight children. The prevalence has increased in recent years, from 4.62% in 2000 to 9.02% in 2017, representing an annual increase of 0.26%. It is estimated that in 2040, it will affect 30.7% of this population. Alarming rates of overweight and obesity are also present in children; it was estimated in 2016 that 51 million children under 5 years and 340 million children aged 5 and older and adolescents were overweight or obese, and this is expected to increase over time [21,22]. Complications related to obesity, including NAFLD, are expected to rise as the prevalence of these conditions is proportional to the increase in BMI [5]. The prevalence of diabetes is also significant in children, with 0.26% of those under 19 years having it, altering frequency patterns by age group [24-28].

NAFDL progression risk to cirrhosis is 3% over 15 years, with a decompensation risk at 4 years 33%, and during these 4 compensated years, there is a 10% risk of decompensation or death per year [29]. However, if NAFLD coexists with metabolic disorders, cirrhosis risk increases; for example, there is a double risk in the presence of T2DM. Metabolic factors also impact mortality in patients with MASLD; as such, T2DM, hyperlipidemia, obesity, a sedentary lifestyle, and an unhealthy diet elevate mortality due to both liver and non-liver causes (such as cardiovascular disorders, diabetes, and cancer). In contrast, liver fibrosis presence is a predictor of all-cause mortality. The highest values imply a 9.16 times higher risk of liver-related mortality for NASH and a 2.09 times higher risk in the presence of diabetes, controlling for other variables [15].

Globally, in 2017, cirrhosis mortality in males was caused by hepatitis B in 25.5%, hepatitis C in 31.5%, ALD in 27.3%, and 7.7% by NAFLD; in females, it was caused by NASH (11.3%), HBV (24%), ALD (20%) [30-32]. In recent years in Mexico, MASLD prevalence has changed according to consumption of certain foods and sedentary lifestyles. Reports on its frequency in the Mexican population show this trend. An initial report in 2000 identified a frequency of 10%, which increased to 14.3% in 2006, 20.9% in 2019, and 41.3% in 2023. These frequencies are even higher if the individual has poor eating habits, is sedentary, and is male. Additionally, the prevalence is higher after age 30, with the highest values in the age group of 50 to 59 years [9]. It is also much higher than the global frequency, corresponding to 25% of the world's population. However, reported frequencies have variability; other estimates place MASLD in Mexico at 17% of the general population.

On the other hand, metabolic alterations in the Mexican population have also been on the rise, with Mexico being among the countries with the highest number of overweight and obese individuals [33], with rates of 70% and 33%, respectively. According to data from the National Health and Nutrition Survey (ENSANUT) [34], 39.1% of adults aged 20 and older are overweight, and 36.1% are obese. Regarding T2DM, it affects 13.5% of the Mexican population but increases to 25% in adults aged 60 or older, according to ENSANUT. T2DM is relevant since it confers a risk twice as high for developing NAFLD, affecting 60% of patients with type 2 diabetes.

The metabolic syndrome is also gaining importance in Mexico, with its prevalence in Mexican adults increasing over time: 40% in 2006, 57% in 2012, 59% in 2016, and 56% in 2018 [9]. Its presence increases the risk of progression from fibrosis to cirrhosis and HCC, as well as mortality. The coexistence of these conditions with liver disease is significant, as 51% of NAFLD patients are obese, 23% have T2DM, 69% have hyperlipidemia, 39% have hypertension, and 42% have metabolic syndrome. Furthermore, the presence of diabetes accelerates the progression of NAFLD to fibrosis and increases mortality [7,35].

In Mexican children, the prevalence of overweight, obesity, and diabetes has also been on the rise. In 2018, 17.5% and 36.5% of children aged 5 to 11, respectively, and 23% and 14% of teenagers were overweight and obese, respectively. According to the National Registry of Weight and Height [36], in 2019 in Mexico, the frequency of overweight and obesity was 37.2% in children aged 6 to 11 (40% in boys and 34% in girls) [37]. Even in children aged 0 to 4, 22% are at risk of overweight. There are few studies on hepatic metabolic alterations in Mexican children. A report from 2004 on 833 overweight and obese children aged 5.5 to 12 found a frequency of MASLD of 12.6%. Another study with 102 overweight and obese children aged 1 to 15 detected non-alcoholic fatty liver disease in 11%, but in children aged 10 or older 14.1% met the criteria for metabolic syndrome [5]. More recently, in children aged 6 to 16 with obesity, 40% had hepatic steatosis, but 54% showed an increase in serum alanine aminotransferase [4]. The metabolic syndrome frequency could be up to 2.4–45.9% in children aged 9 to 13 and 14% in children aged 10 or older with overweight or obesity [5,38,39]. Additionally, it is suggested to consider non-alcoholic fatty liver disease in children from families with obesity, insulin resistance, or diabetes, all of which are common in the Mexican population [40].

3.2. Alcohol-associated liver disease (ALD)

Alcohol consumption is a global health issue due to its high prevalence and associated morbidities, including cardiovascular, gastrointestinal, and cancer-related conditions, leading to significant mortality. In 2016, it was estimated that alcohol was responsible for 5.3% of global deaths, equivalent to 3 million people (2,307,300 men and 681,000 women). Of these, approximately 25% were related to digestive causes, including 607,000 caused by ALD and 30,000 by pancreatitis [41-43].

Globally, it's estimated that 2.3 billion people are alcohol consumers, with an average consumption of 32.8 grams of pure alcohol per day. According to age groups, 26.5% of individuals aged 15-19 are alcohol consumers, equivalent to 155 million adolescents. As such, in May 2022, the global prevalence of ALD was estimated at 4.8%, with variations based on gender, age, region, years of alcohol intake, obesity, genetic factors, and viral infections. Notably, 90% of heavy alcohol consumers develop steatosis, and ALD is developed in 32.9%, with a mortality rate of 23.9%, primarily due to liver-related causes [41,42,44].

ALD is a chronic disease associated with long-term and excessive alcohol consumption. Initially presenting as alcohol-related fatty liver, it encompasses a wide range of liver damage and can progress to alcohol-related hepatitis, liver fibrosis, cirrhosis, and cancer. In 2017, the estimated global frequencies of compensated and decompensated alcohol-related cirrhosis were approximately 23.6 million and 2.46 million, respectively. Besides, hospitalization risk for these cases has increased by 32.8% annually, with an 8% increase in mortality, predominantly affecting individuals under 40 years old [32,43-49].

In Mexico, alcohol consumption is also a significant health problem. In 2016, 34.2% of the population aged 15 or older were drinkers (37.3% women and 30.9% men). The per capita consumption of pure alcohol was estimated at 6.5 liters in individuals aged 15 and older (11.1 in men and 2.1 in women) [50,51]. The prevalence of heavy episodic drinking in the population was 18% in individuals aged 15 or older, with a significant predominance in men (30.1%) compared to women (6.2%), rising to 28.7% in drinkers aged 15-19 (39.8% in men and 17.2% in women). Different alcohol-related disorders in the population have a prevalence of 2.3%, including alcohol dependence in 1.3% and alcohol-related harm in 1%. However, deaths attributable to alcohol account for 6% of total deaths (9.8% in men and 1.3% in women) [43]. Regarding ALD in 2020, according to SUAVE, it corresponds to 0.1% of the total cases of non-communicable diseases, with an incidence of 3.2 per 100,000 inhabitants. The incidence varies across the country, with a wide range between 1 to 11.1 per 100,000 inhabitants, based on characteristics such as age and gender, with those aged 60-65 being the most affected by cirrhosis [43]. ALD frequencies are variable among different studies. One study covering five centers over five years (2012 to 2017) identified ALD as the second cause of liver cirrhosis (31.2%). In contrast, a more recent study spanning 20 years in five hospitals (2000-2019) reported that ALD accounted for 23% of all cirrhosis cases and identified it was surpassed by hepatitis B cases in 2009, with a mortality rate of 75.7%, primarily due to liver-related causes [42].

The frequency of patients with alcohol-related cirrhosis undergoing transplantation varies by hospital and the analyzed time period [52,53]. For example, over 16 years (1996-2011) at Hospital General de México (HGM) and Centro Médico Nacional La Raza (CMNLR), 15% of adult transplant recipients had alcohol-related cirrhosis, ranking second in the frequency [54]. In the Hospital General de México, during one year (July 2011 to May 2012), 25% of eight transplants were attributed to ALD, ranking second. In a later four-year period (2019-2022) at the same hospital, ALD accounted for 33% of transplants, ranking first [55]. At the Instituto Nacional de Nutrición Salvador Zubirán (INNSZ), where the first transplant was performed, less than 10% of transplants corresponded to patients with alcohol-related cirrhosis. These data confirm that, until 2012, alcohol was the leading cause of liver cirrhosis in Mexico, but now is the second. It is important to note that 7.4% of registered cirrhosis patients have had the benefit of liver transplantation [47].

3.3. HBV and HCV

The importance of liver infections in cirrhosis is primarily due to the involvement of hepatitis B (HBV) and hepatitis C (HCV) viruses, contributing to 57% of global cirrhosis cases and 78% of primary liver cancer cases (WHO 2022). Although 25% (15-45%) of infections result in virus clearance within the first 6 months, most individuals will develop chronic infection (nearly 71 million people in 2017, causing approximately 400,000 deaths due to complications such as cirrhosis and hepatocellular carcinoma) [56,57].

3.3.1. HBV

Regarding HBV, the global prevalence of chronic infection was estimated at 4.1% in 2019, affecting 316 million people. Hepatitis B is the leading cause of liver cancer deaths (40%) and the third leading cause of cirrhosis deaths (22.5%), accounting for 192,000 and 331,000 deaths in that year, respectively. Although the prevalence of the disease has decreased at least from 2015 (by 38% from 1990 to 2019), mortality has increased among the infected, contributing to 555,000 deaths in 2019 (7.2 deaths per 100,000 people) and representing almost 50% of deaths from hepatitis [58-63].

Its impact is not only due to its frequency but also to contributes to up to 25% risk of developing cancer or 10% of developing a chronic infection in adults, which confers more than 20% risk of progression to terminal liver damage [64]. Prevalence is higher in at-risk groups, such as HIV-positive patients, where the frequency of HBV infection can be up to 30%, and progression to cirrhosis is faster. This group of patients represents 1% of HVB chronic patients (approximately 2.7 million in 2019). Also, individuals who inject illicit drugs and men who have sex with men have a higher frequency. Another at-risk group is children due to the high risk of developing chronic infection: up to 90% if the infection occurs in the first year of life and up to 50% if it occurs in the first 5 years. Additionally, most infections occur through vertical transmission and in the early years of life. Fortunately, the vaccine has significantly reduced the proportion of chronic infections in children, decreasing from 5% (between 1980 and 2000) to only 1% in 2019. The hepatitis B vaccine has a 95% efficacy and has reduced seroprevalence globally, especially in children under 5 years, with estimates of 76.8% fewer infections from 1990 to 2019, as shown in Tables 1 and 2 [8,65].

On the other hand, a third of the total disease burden and progression to cirrhosis involves different factors such as age and gender, and multiple modifiable or treatable factors like smoking, alcohol consumption, obesity, and other metabolic disorders, exposure to toxins such as aflatoxin and tobacco, and comorbidities [66]. These factors can have an additive or synergistic effect on infection, emphasizing the need to identify and address them [49].

Table 1
Global and Mexico HBsAg seroprevalence and number of deaths in 1990, 2015, and 2019.

Region	1990	2015	2019
	Prevalence		
Global	6.0%	4.4%	4.1%
Mexico	0.3%	0.2%	0.2%
	Number of deaths related to HBV		
Global	9.8	7.3	7.2
Mexico	1.7	1.4	1.7

Rates per 100 000.

Table 2
HBsAg prevalence in children younger than 5 years in 1990, 2015, and 2019 in Mexico and worldwide.

Region	1990 (%)	2015 (%)	2019 (%)
Global	4.4	1.2	1
Mexico	0.1	0.02	0.02

In Mexico, data from the Annual Epidemiological Report on Viral Hepatitis Surveillance in Mexico 2019 identified an average of 737 annual cases of Hepatitis B in Mexico over 10 years (2010-2019). These data imply an incidence of 0.63 cases per 100,000 inhabitants in 2019. The male gender was more affected (70.6%), and the age group 25 to 44 years was most affected [61,67-71]. However, a significant decrease in 2020 to less than 300 cases was described. The cirrhosis associated with HBV frequency varies in different reports. In 2004, it was identified in 5% of Field [18], while in 2008, VHB was identified in 2.8% of 534 adults with cirrhosis (59% women, average age 55 years), 3 cases coexisting with HCV, with a predominance of ALD (38%) and HCV (31%). At-risk groups such as blood donors, healthcare workers, pregnant women, sex workers, HIV-positive individuals, transfused individuals, and those on hemodialysis should be considered because the frequencies increase [61]. However, its frequency has decreased mainly in children, attributable to the hepatitis B vaccination implemented in 1999, as shown in Table 2 [8,72].

3.3.2. HCV

HCV is the main responsible associated with liver disease and overall mortality in individuals with liver diseases, with a global prevalence estimated by the WHO in July 2023 of 58 million people affected by chronic hepatitis C virus infection, with an annual incidence of 1.5 million new cases. These data include 3.2 million children and adolescents with the chronic form. In addition, a mortality of 290,000 people was estimated in 2019 due to cirrhosis and hepatocellular carcinoma associated with HCV. However, other reports estimate higher frequencies, with around 71 million people living with chronic HCV infection worldwide [59]. Since most infections are asymptomatic, they go undetected, but 30% of cases eliminate the virus, and 70% develop chronic infection. Of these, 15 to 30% develop cirrhosis within a period of 20 years (WHO). Cirrhosis presence also increases the risk of liver cancer, with a risk of up to 8% in people with cirrhosis and 4% in the absence of cirrhosis [73]. Other factors influence this progression, such as age, gender, inoculum size, viral genotype, coinfection with other viruses, alcohol consumption, smoking, exposure to toxins, and the individual's immune competence [58]. Despite no vaccine for HCV, direct-acting antivirals are effective in 95% of people, making a revolutionary impact [57].

In Mexico, reports from 2007 and 2008 estimate an average prevalence of HCV ranging from 1.2 [62] to 1.4% [63], although with variations according to the region (up to 2% in the northern region, 1.5% in the south). In 2012, an HCV seroprevalence of 0.27% was estimated in the population aged 15 to 49, and in 2018, the estimated prevalence was 0.38%, considering individuals over 20 years old [59]. In 2020, the prevalence of hepatitis C is estimated at approximately 1,590,000 individuals, but only 20% of these cases have a known diagnosis. Data from the National Health and Nutrition Survey (ENSANUT) [59,69] 2018 identified the seroprevalence of hepatitis C in Mexican adults over 20 years which was 12,389, implying a national seroprevalence of 0.38%, equivalent to 307,000 individuals over 20 years old. In high-risk groups, similar to VHB, the frequency is higher; the estimated prevalence from 2008 to 2019 was from 11.8 to 39.6%. These frequencies change according to specific characteristics, such as age and gender. For example, it is lower in individuals aged 20 to 49 and males (and in urban areas). While seroprevalence has not varied much from 2010 to 2020, with 22,578 cases identified (equivalent to 2,182 cases annually), there is a slight decrease between 2012 and 2018. This represents a national incidence rate of 1.88 cases per 100,000 inhabitants in 2019, with a predominance in males (62.82%). The age group of 25-44 years has the highest number of cases, although the incidence rate is higher in individuals aged 60 to 64, with 5.73 cases per 100,000 inhabitants [47,74].

3.3.3. HCV and HBV

The frequencies have been modified by screening for detection in blood donors starting in 1993. Furthermore, in 2020, Mexico initiated the National Plan for the Elimination of Hepatitis C, which includes detection and management campaigns in high-risk groups [75]. Since its implementation, diagnostic and care units have expanded from 42 to 629, and more than 333,000 healthcare professionals have been trained in timely detection and early management of the disease. 356,000 detection tests have been conducted, identifying, treating, and curing 22,748 individuals. Higher-risk groups such as individuals with human immunodeficiency virus (HIV), incarcerated individuals, users of psychoactive substances, healthcare workers, transfused persons, or organ transplant recipients before 1994, as well as descendants of infected women, have received special attention with detection tests. By August 2021, it was estimated that more than 1,200 people with HIV were diagnosed with HCV infection and received treatment. By July 2023, screening and registration of more than 78% of people with HIV were completed so that the prevalence of HCV in this population is known). Additionally, the number of units attending to individuals without entitlement who live with HIV and HCV has increased from 18 in 2019 to 137 in 2020 nationwide. The impact of this program will be known in the coming years.

4. Changes in frequencies in Mexico

According to the previously mentioned data, it is visible that there have been changes in the incidence and prevalence of hepatic cirrhosis in recent years, globally and in Mexico. These changes are associated with highly relevant different actions. The first is access to direct-acting antivirals in health institutions, which have a response of up to 98% and can reduce more than 70% of the risk of developing hepatocellular carcinoma, around 90% of mortality from hepatic causes, and the need for a liver transplant [76]. The second action is the implementation of the HBV vaccine, which was nationally implemented in 2016. Considering this data, the number of hepatitis B cases has been gradually decreasing. In the 10 years prior to 2012, there were an average of 786 cases annually. Since 2012, there has been an average of 565 cases per year, which have gradually decreased to 317 cases registered in 2023 [77]. A more recent action, implemented in July 2020, is The National Program for the Elimination of Hepatitis C, which includes free screening, diagnosis, and treatment [60].

Despite these efforts, based on data from 2012 to 2019 on cirrhosis causes from Mexico, a significant increase in MASLD is observed (from 14% to 36%), a pronounced decrease in HCV (from 45% to 11%), and a minor increase in ALD are seen, as shown in Fig. 2. This implies that MASLD is already the leading cause while HCV and HBV causes are diminishing and that these trends are expected to persist. Despite these decreases, mortality in 2022 in Mexico from hepatic causes ranked sixth (with 41,281 deaths, corresponding to 4.8% of all deaths). Within these, 35% are deaths from ALD (with 14,395 deaths, corresponding to 25% of those related to hepatic diseases and 1.6% of total deaths), pointing to the alcohol consumption importance. Trends in the affected gender have not changed, as most deaths from hepatic causes correspond to men, including those caused by ALD, as shown in Fig. 1 [68].

Further factors that must be considered are diet and lifestyle, as they are linked to an increase in the prevalence of MASLD in the general population, with important frequency in younger patients, including children and adolescents. In Mexico, MASLD already leads

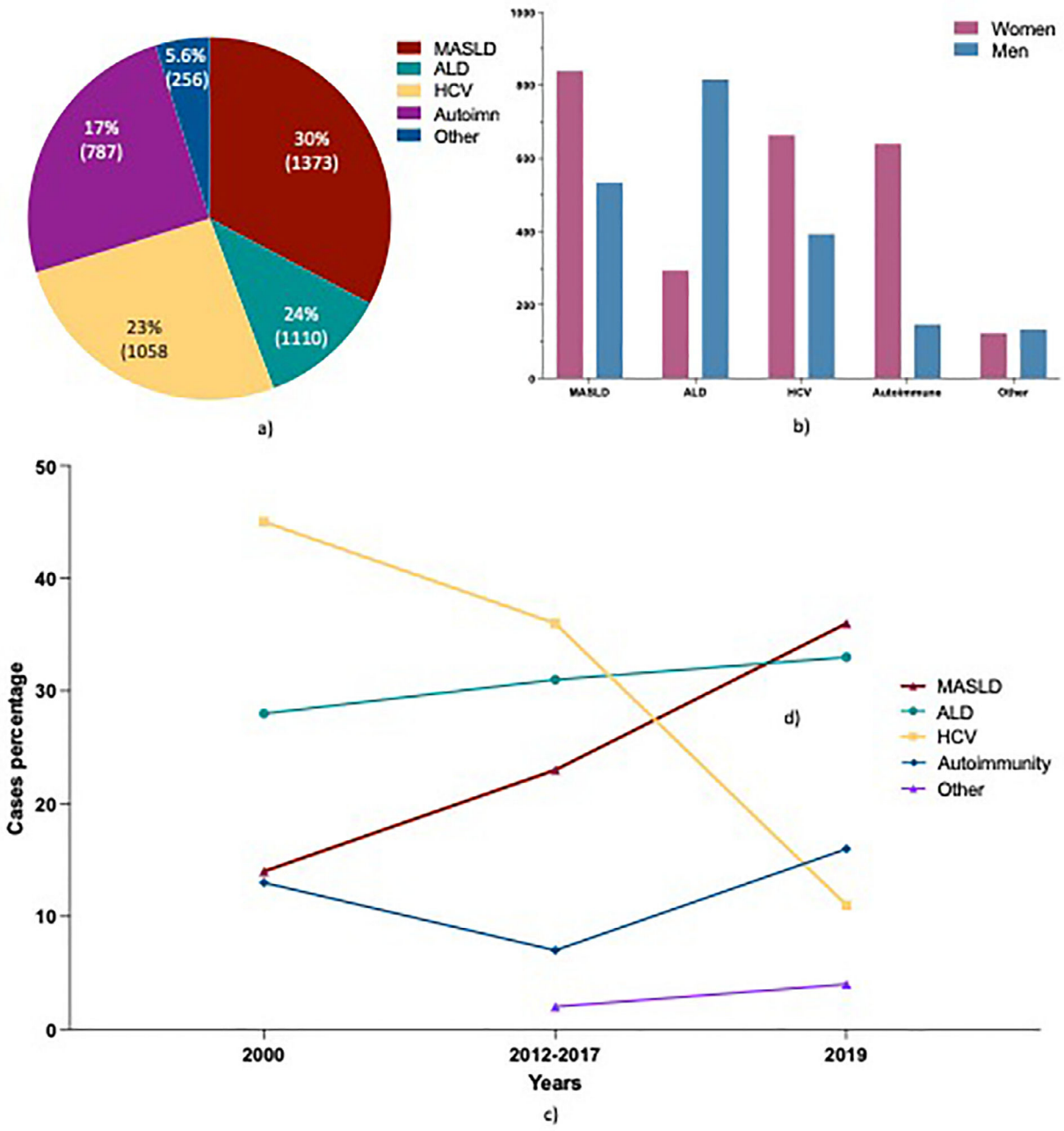

Fig. 2. Changes in liver cirrhosis causes from 2000 to 20019. a) Percentage of cirrhosis causes frequency from cases registered in 5 health centers from 2000 to 2019 (*n*=3562). b) Cirrhosis causes frequency according to gender from cases registered in these health centers from 2000 to 2019 (2560 women and 2024 men). c) Changes of cirrhosis frequency causes for 20 years, according to data from 2000, 2012-2017 and 2019 (as reported by González-Chagolla and Mendez Sanchez) [47].

as the primary cause of cirrhosis (30%), followed by ALD (25%) and HCV (23%) in cases aged 20 years (from 2000 to 2019). The transition from viral causes occurred in 2007 when MASLD, in conjunction with cryptogenic causes, surpassed HCV as the leading cause of cirrhosis in Mexico [78,79].

5. Liver transplantation as a response in Mexico

It is important to consider that the high efficacy of liver transplantation to treat chronic and acute liver diseases without satisfactory therapy is very high, with a high survival rate. Since the beginning of liver transplantation, the number of procedures has increased. Although HCV and ALD still lead theunderlying causes, the growing proportion of patients with MASLD is becoming and will be the next significant cause [80]. Although few patients with MASLD progress to cirrhosis, the number of affected individuals will increase significantly, thereby increasing the number of transplant candidates. Patients with MASLD undergoing liver transplantation show an excellent response [81]. In Mexico, the number of transplants performed has increased, except for the decline observed in 2019-2021 due to the COVID-19 pandemic and a rebound in 2022, almost equal to 2018. These data are shown in Fig. 3A, covering 2007 to 2022.

In 2023, an increase in liver transplants was expected since the reactivation of authorized centers post-COVID, as well as the initiation of the Liver Transplant Program at the Juárez Hospital of Mexico, where the first transplant was performed in November 2023, and three more were completed by the end of the year. Despite the growing number of transplants, the number of patients on the liver

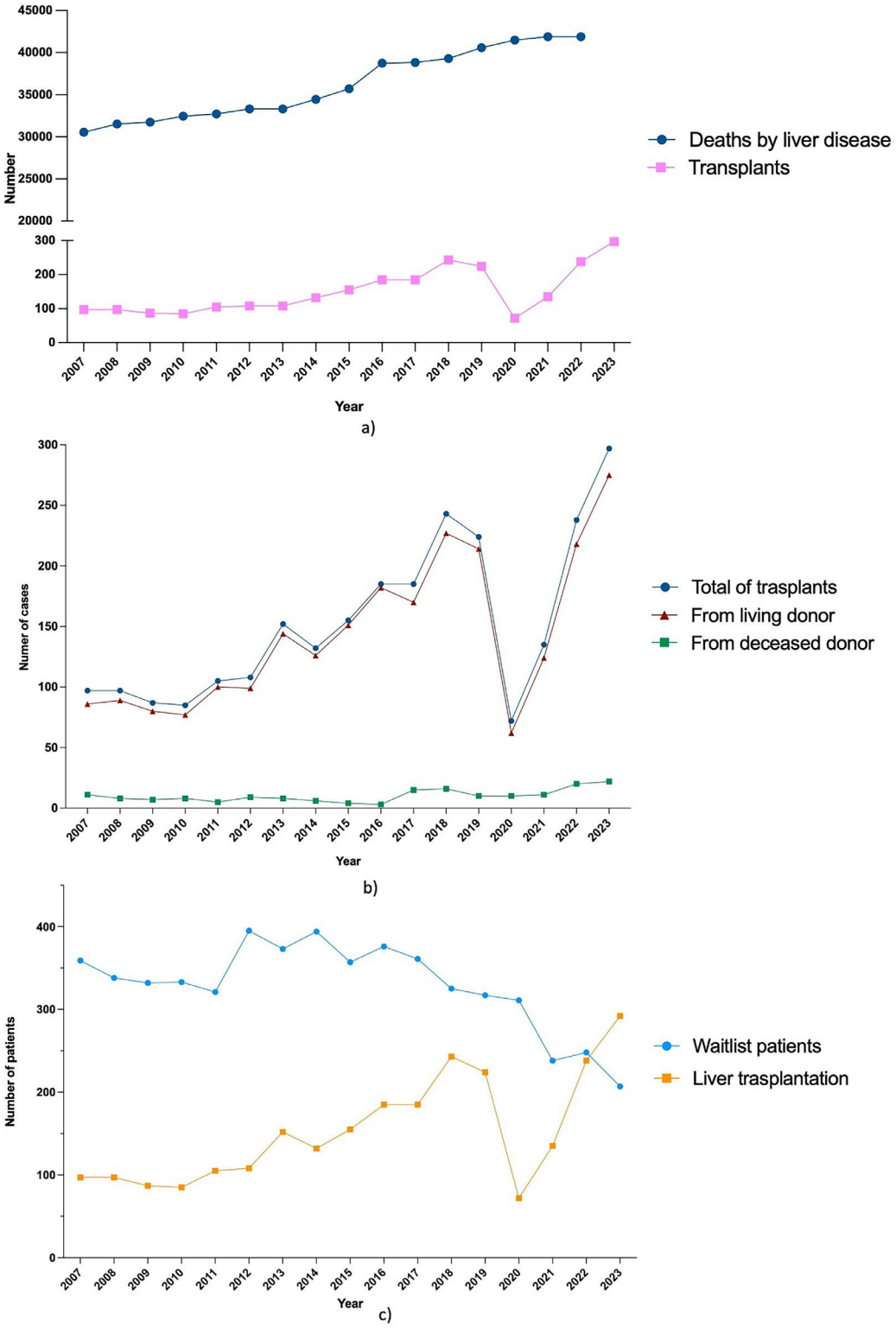

Fig. 3. Number of liver transplanted patients and patient in the liver waitlist as receptor since 2007. a) Number of performed liver transplantations and number of deaths associated to liver disease. b) Number of liver transplantation cases, including successful and non-successful. c) Number of liver transplantation cases and patients waiting for liver donation at the end of each year. c) Frequencies obtained of CENATRA.

receptor waitlist is important; since 297 transplants were performed in 2023, 207 patients remained on the list. These data are presented in Fig. 3B from 2007 to December 2023, according to the Natnal Center of Transplants (CENATRA) data [82,83].

Taking into account that the waiting list in December 2022 was 229 and that 248 transplants were performed in 2023, the number of new patients added to the waiting list by December 2023 was 208 [84]. This implies that the likelihood of being transplanted has increased for patients already registered on the waiting list. However, considering the high number of deaths due to liver-related causes in the country (41,890 in 2022) [13], a significant percentage die before being listed or while on the waiting list [85].

The effectiveness of liver transplantation in Mexico reflects the gradual increase in the number of authorized transplant centers, along with physical infrastructure, financial and human resources. The number of authorized transplant hospitals has grown among tertiary referral hospitals, counting 84 authorized centers by CENATRA. These hospitals are located in 20 states of the country (Baja California, Chiapas, Chihuahua, Mexico City, Coahuila, Durango, Guanajuato, Guerrero, Jalisco, State of Mexico, Morelos, Nuevo León, Puebla, Querétaro, San Luis Potosí, Sinaloa, Sonora, Tabasco, Veracruz and Yucatán) as shown in Fig. 4. However, if we consider the transplants performed in the last five years (966), the majority were conducted by a few hospital centers. It's worth noting that in 2022, there were 84 authorized centers, but only 31 were active [83]. Although the SSA (Secretaría de Salud) had 5 active centers out of the 9 authorized during 2022, over the last 5 years, they performed 35% of the 944 transplants. Meanwhile, IMSS (Instituto Mexicano del Seguro Social) performed 31% while having six active programs out of nine authorized. Together, they account for approximately 66% of all procedures. Among the five hospitals with the highest activity are the INNSZ and the HGM of the SSA, which performed 19% and 16% of the procedures respectively. Regarding the IMSS, the UMAE (Unidad Médica de Alta Especialidad) Hospital de Especialidades "Dr. Antonio Fraga Mouret" at the CMNLR performed 7.60%, and the UMAE Hospital de Especialidades No. 25 performed 7.50%. Other public hospital, the Centro Médico Nacional "20 de noviembre" of the ISSSTE (Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado), performed 6% of the transplants. On the other hand, the role of private hospitals is relevant, as they have 47 authorized programs (more than 50%) and 17 active ones, and they performed approximately 25% of the transplants in the last five years. As such, the burden to attend to patients affected with liver cirrhosis depends on public resources and implies that only two hospitals of the SSA perform 35% of the procedures, and adding the two IMSS hospitals with the highest activity, they account for 50% of all transplants [83,84].

On the other hand, if we consider the population in Mexico, which in 2022 was estimated at 130.1 million, mostly represented by the State of Mexico (13.4%), Mexico City (7.3%), Jalisco (6.6%), Puebla (5.2%), and Nuevo León (4.5%) [86]. Considering the transplants performed over the past 5 years in different states of the republic, Mexico City performed 65% of the procedures, the state of Jalisco 16%, the state of Nuevo León 13%, the State of Mexico less than 1%, and Puebla had no activity. These proportions highlight a discrepancy between the proportion of transplants performed and the corresponding population density, coupled with a low number of liver transplant centers (the State of Mexico had one active center and Puebla had no activity in 2022) [83,84].

Further, considering the population covered by the country's health system during 2022, 41.4% have coverage from IMSS, 8.1% from ISSSTE, 0.5% have private insurance, and 48.8% of the population have no social security. As can be seen, 36% of the transplants were handled by SSA, an institution that serves almost half of the population, while IMSS performed 27% of the transplants even though it serves 41% of Mexicans [87]. Additionally, private medical services, which serve 0.5% of the population, performed a significantly higher number of transplants and had 17 active centers out of 19 authorized [83,84]. These data confirm the need to increase resources for authorized and active centers in all public health institutions in the country, considering the needs according to the population of each state, in order to increase the number of transplants. Limitations such as a low number of organ donors, limited economic resources to have sufficient and timely materials and supplies, and trained personnel with the necessary profiles (surgeons, anesthesiologists, intensivists, transplant coordinators, nursing staff, etc.) are aspects that need attention and must be addressed, due to the significant increase in MASLD and liver transplant demands.

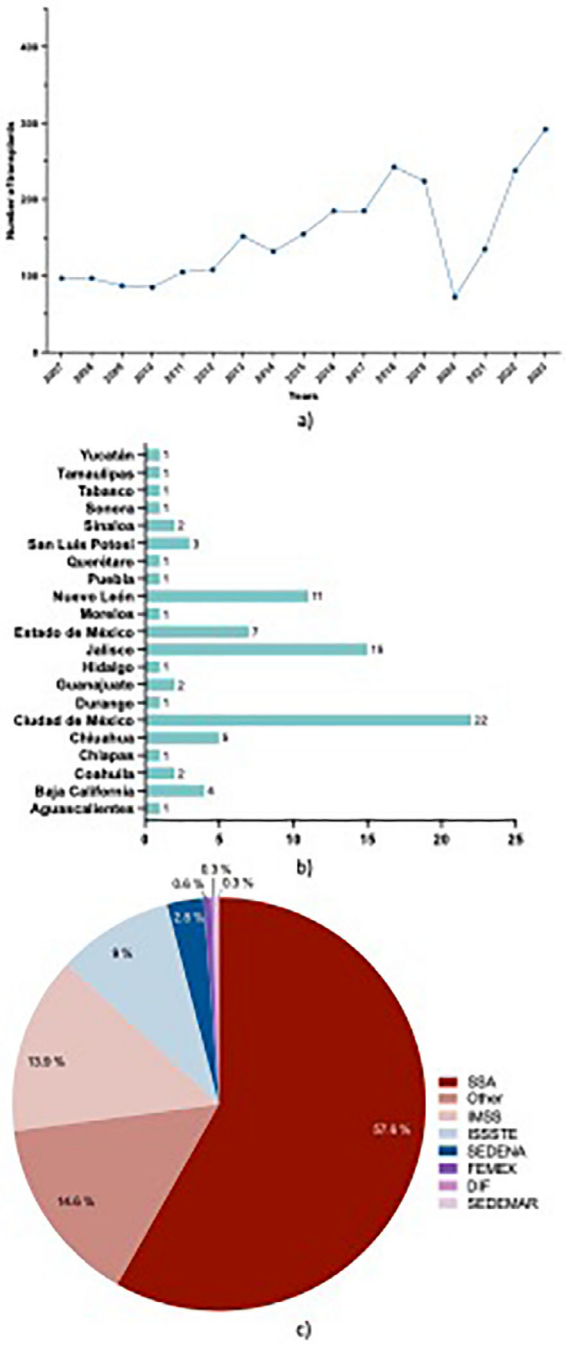

Fig. 4. Authorized liver transplant centers and cirrhosis cases attended. a) Number of authorized liver transplant centers per state. centers public health centers. b) Percentage of cirrhosis cases attended by public health centers, corresponding to different health institutions. (SSA: Secretaría de Salud, IMSS: Instituto Mexicano del Seguro Social, ISSSTE: Instituto de Salud y Seguridad Social de los Trabajadores del Estado, SEDENA: Secretaría de la Defensa Nacional, DIF: Sistema Nacional para el Desarrollo Integral de la Familia, SEDEMAR: Secretaría de la Marina). Data obtained from CENATRA [83].

5.1. Liver transplant results (survival rate)

Although there are no official data on liver transplant outcomes, CENATRA started including recipient and graft survival for transplants performed from January 1, 2022, onwards. Therefore, there are no records yet. However, case reports have been published evaluating the short- and long-term survival of transplanted patients in Mexico since 1991. At Centro Médico Nacional de Occidente, a survival report of 49 patients, including children and adults (one patient

was re-transplanted and another patient underwent a liver-kidney transplant), treated over almost 7 years (from July 1999 to November 2006), identified perioperative survival of 70%, one-year survival of 64%, and five-year survival of 58% [88]. At the University Hospital UANL Dr. José Eleuterio González, the survival of 96 transplants in 94 patients over 20 years (from 1991 to 2011) was 66.1%, 53.3%, and 46.2% at one, five, and ten years, respectively (Pérez-Rodríguez 2011). A study of 51 transplants performed in 15 children and 36 adults (with two re-transplants) over 8-9 years (from 2003 to 2011) at the UMAE 25 IMSS Monterrey identified an overall survival of 57.1% at one year and 54.2% at five years [89]. At the General Hospital CMN La Raza, 40 adult transplant patients were evaluated over 16 years (from 1996, the year of their first transplant, to 2011), identifying perioperative survival of 82.5%, a one-year survival rate of 41.5%, five-year survival of 27.2%, and ten-year survival of 13.6% [54]. In transplant results from Hospital San José-Tec de Monterrey, a survival rate of 83% and 76% at one and five years, respectively, was identified in 55 transplants performed over 13 years (between 1999 and 2011) in 54 patients [90]. At INNSZ, a report includes 248 transplanted patients over 13 years (from 2002 to 2015), describing a mortality rate of 6% at two years of follow-up, with no differences between those younger and older than 60 years [91]. At this same institute (INNSZ), a second report evaluates the mortality of 112 transplanted patients (including 3 re-transplants) over a period of 27 years (from 1985 to 2012) divided into three periods. In a first group of 22 patients transplanted from 1985 to 1999, perioperative mortality was 29%, one-year survival was 47%, and five-year survival was 29% (with 45% medical complications and 36.3% surgical complications). In a second group of 37 patients transplanted from 2000 to 2007, perioperative mortality was 50%, one-year and five-year survival was 77.6% and 66.17%, respectively (with 43% medical complications and 48.6% surgical complications). In a third group of 56 patients transplanted from 2008 to 2012, perioperative mortality was 3.5%, one-year survival was 94.4%, and five-year survival was 87.8% (with 48% medical complications and 21.4% surgical complications). Overall, across the three periods, perioperative mortality was 25%, one-year survival was 73%, and five-year survival was 61%. However, as time progresses, survival improves, and there are fewer surgical complications, with the third group achieving perioperative mortality of 3.5% and one-year and five-year survival rates of 94.4% and 87.8%, respectively [92].

Data from children include an initial report from 35 transplants in 34 children at the Hospital Infantil de México Federico Gómez between June 1998 (the date of the first transplant at this center) and march 2004 (including 80% deceased whole-organ grafts and 20% segmental grafts, with 11% from cadaveric and 9% from living donors), identified a survival rate of 77.1% and 74.2% at 1- and 5-years, respectively. However, when sequential times were considered, the survival rate for transplants performed during 2001−2004 was 91.6% (compared with 1998−2000) [93]. A second report from this center, increasing the number of transplanted children to span 13 years (from June 1998 to May 2011), which includes 76 transplants in 74 recipients (12% from living donors), identified a better one- and five-year survival, of 85% and 75%, respectively (reference) [94]. A second center reporting results in children is the UMAE 25, Centro Médico Nacional del Noreste, Monterrey, N.L., with data from 12 patients treated over 9 years (2003 to 2012), identifying a three-year survival of 50% [95]. Finally, a recent report from 2022, of 40 transplants performed at Hospital Angeles Pedregal over 5 years (2017-2021), identified a two-year survival of 95.8% [96].

Survival might differ according to the type of donation. The number of transplants from deceased donors is the majority, with 92.5% (893) of the procedures, and only 7.5% from living donors (73), considering the last 5 years. These data are consistent with 222 livers procured from brain dead donors in 2022, resulting in 218 transplants from deceased donors and 20 from living donors [83]. To date, there are no records of donations after circulatory death. This is important since a greater number of living donors, could increase the possibility for current patients and new ones on the waiting list.

6. Conclusions

The causes of liver cirrhosis in Mexico have changed significantly in recent years. HCV has been decreasing, and this trend will likely continue as hepatitis elimination programs continue. Meanwhile, NAFLD has increased notably, a trend that will probably persist due to its association with metabolic alterations in the population, which have also been increasing. Although showing a slight increase in the population, ALD needs more consideration since it is related to MASLD. Regarding liver transplantation as a response to cirrhosis cases, it has yielded good results, and the number of performed transplants has increased gradually. Despite limitations and the resources involved, the number of authorized hospital centers for performing liver transplants has also increased. These changes can benefit patients, help them acquire more experience, and positively impact survival rates. During the COVID-19 pandemic, the number of transplants and patients on the waiting list decreased, but by 2022, it has increased, and this trend is likely to continue. While there are better conditions for performing transplants, given the growing number of cirrhosis cases in the country, it is essential to consider the causes to act earlier and identify individuals at risk of developing it. At present MASLD is the leading cause of liver cirrhosis, and it is associated with highly prevalent metabolic alterations, it is necessary to address its causes. Therefore, preventive measures such as healthy dietary habits and lifestyles, are necessary to reduce the development of liver cirrhosis. Besides, viral hepatitis prevention programs should continue. Furthermore, early identification of individuals with cirrhosis or complication risks should be mandatory to diminish cirrhosis frequency and mortality, as well as future associated liver transplant demands.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chat-gpt in order to improve language and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Conflicts of interests

None.

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