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Original article

Occult liver disease: A multinational perspective

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ABSTRACT

Occult liver disease refers to the presence of unrecognized chronic liver disease and cirrhosis. Liver disease is currently the eleventh cause of death globally, representing 4% of all deaths in the world. Alcohol consumption is the leading cause of cirrhosis globally, accounting for approximately 60% of cases. The estimated global prevalence of non-alcoholic fatty liver disease (NAFLD) is 32.4% and has been steadily increasing over the last years. Viral hepatitis B and C accounted for 1.3 million deaths in 2020.

Several studies in populations at high risk of chronic liver disease (elevated liver enzymes, type 2 diabetes, excessive alcohol consumption) have found an elevated prevalence of occult liver disease. Attempts should be made to assess the prevalence of occult liver disease in Latin America, a region with one of the highest rates of metabolic diseases and excessive alcohol consumption.

Screening for NAFLD in high-risk subjects and screening for excessive drinking and alcohol use disorders at every level of medical care is relevant. Efforts should also focus on the early treatment of occult liver disease to try to reduce liver disease burden and, in the case of occult viral hepatitis infection, prevent further spreading.

1. Introduction

Occult liver disease refers to the presence of unrecognized chronic liver disease and cirrhosis. Chronic liver disease is a significant cause of morbidity and mortality globally. However, data on prevalence of occult chronic liver disease is scarce.

A considerable number of patients with compensated chronic liver disease are undiagnosed since most of them remain asymptomatic; therefore, they dont receive appropriate management and follow up.

Chronic liver disease can be caused by different etiologies such as excessive alcohol consumption, metabolic dysfunction associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, hemochromatosis, α-1 antitrypsin deficiency, Wilson's disease, autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis [1] amongst others. From here onwards, the terms NAFLD and MASLD will be used as originally published by the authors.

2. Epidemiology

Liver disease is currently the eleventh cause of death globally, accounting for >2 million deaths per year (cirrhosis, viral hepatitis, and liver cancer), representing 4% of all deaths in the world [2]. Cirrhosis can be categorized into compensated and decompensated. Compensated cirrhosis is usually asymptomatic and can last for several years until the development of overt clinical signs; it often goes undiagnosed [3]. In 2017, it was estimated that the global prevalence of compensated cirrhosis was 112 million [4] and of decompensated cirrhosis 10.6 million [5].

Alcohol consumption increases the risk of liver disease-related mortality 260-fold, it is also the leading cause of cirrhosis globally, accounting for approximately 60% of cases [2]. A recent meta-analysis estimated the global prevalence of NAFLD to be 32.4%, and has been steadily increasing over the last years [6]. Viral hepatitis B and C accounted for 1.3 million deaths in 2020, the highest prevalence of HBV was in Africa, the highest area of prevalence for HCV was Eastern Europe, followed by Central Asia [2].

Abbreviations: chronic hepatitis B virus, (HBV); chronic hepatitis C virus, (HCV); immunodeficiency virus, (HIV); Non-alcoholic fatty liver disease, (NAFLD); Occult HBV infection, (OBI); Occult HCV infection, (OCI); peripheral blood mononuclear cells, (PBMCs); transient elastography, (TE)

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There are approximately 626 million people in Latin America. Nonetheless, epidemiological data on the prevalence and mortality of cirrhosis is very limited [7]. A multinational study including 20 countries in Latin America estimated that the mortality rate of cirrhosis was 19.9 per 100,000 habitants [8]. Cirrhosis and liver cancer combined account for 3.5% of all deaths globally; noteworthy, since 1990, deaths from cirrhosis have been steadily increasing from 1.9% (1.8-2%) to 2.4% (2.3-2.6%) in 2017 [5].

3. Detection of occult liver disease

Several studies have been conducted using different surrogate markers to identify populations at risk of chronic liver disease and to estimate the prevalence of occult liver disease. A study in Sweden, including asymptomatic patients with increased liver enzymes for at least six months, found that 52.6% had chronic liver disease of different etiologies, such as viral hepatitis, autoimmune disease, hereditary disorders, and metabolic disease [9].

A large study conducted in Italy found that 21.3% of subjects were not previously diagnosed. However, they finally were considered to have occult chronic liver disease, and specially found occult cirrhosis in 1.3% of the population using thrombocytopenia as a surrogate marker [10]. A study including patients referred for bone marrow biopsy found that 51% of patients with normal bone marrow had cirrhosis, compared to 3% of patients with abnormal bone marrow results; the most common causes were non-alcoholic steatohepatitis, excessive alcohol consumption, and HCV infection [11].

Occult cirrhosis also occurs in the elderly; a study found that the prevalence of undiagnosed cirrhosis in a series of autopsies in a geriatric hospital in Tokyo was 1.12%, and HCV infection was the leading etiology of cirrhosis [12].

A single-center retrospective cohort study including patients with compensated chronic liver disease who underwent transient elastography (TE) found a prevalence of 37% of occult cirrhosis [13]. Another study in the United Kingdom performed TE in patients with risk factors for chronic liver disease (excessive alcohol consumption and/or type 2 diabetes) found a prevalence of cirrhosis of 2.9% [14].

A study in France used TE as a tool for screening occult cirrhosis in the general population; this study included 1190 healthy subjects > 45 years attending for a medical check-up and found that 7.5% had > 8 kPa, of which 10.1% had occult cirrhosis, the most frequent cause was NAFLD [15]. To the best of our knowledge, there is no data on the prevalence of occult cirrhosis in Latin America.

4. Occult hepatitis B infection

Occult HBV infection (OBI) is defined by the presence of detectable HBV DNA by PCR in the serum or the liver of a patient who is otherwise negative for HBV surface antigen; it was first described in the late 1970s [16,17]. OBI can be categorized as seropositive OBI (HBV core antibody and/or HBV surface antibody positive) or seronegative OBI (HBV core antibody and HBV surface antibody negative) [18]. In Latin America, HBV prevalence ranges from 7 to 12 million people infected; the most frequent genotypes are F and H [19].

A systematic review and meta-analysis found that the prevalence of OBI in blood donors in low-endemicity countries was 0.06% (95% CI 0.00-0.26%), 0.12% (95% CI 0.04-0.23%) in intermediate-endemicity countries, and 0.98% (95% CI 0.44-1.72 %) in countries with high-endemicity [20]. This study also estimated the prevalence in high-risk groups; in low-endemicity countries, it was 5.5% (95% CI 2.9-8.7), 5.2% (95% CI 2.5-8.6%) in intermediate-endemicity countries, and 12.0% (95% CI 3.4-24.7%) in countries with high-endemicity countries (I^2=95.2%; p=0.41) [20], they did not perform regional analysis.

A study in Mexico evaluated the presence of OBI in blood donors and found a prevalence of 6.4%; genotype H was detected in 66.7% of the samples with detectable HBV DNA [21]. There is a residual risk of HBV transfusion-transmission in blood donors with OBI; factors associated with an increased risk are the volume of plasma transfused and the anti-HBV immune status of the donor and recipient; residual transmission risk has been estimated to be 3-14% [22].

Patients with human immunodeficiency virus (HIV) infection are considered at high risk of being coinfected with HBV. A study in Mexico, including patients with HIV, found that 18.4% had OBI [23]. A more recent study in Mexico found a prevalence of 36% of OBI among HIV-positive patients; all the sequences corresponded to the H genotype [24]. Another study in Africa among HIV-positive patients found a prevalence of OBI of 11.2% [25]. These studies emphasize the importance of evaluating high-risk populations for OBI.

A study in China evaluated the prevalence of OBI in patients with autoimmune hepatitis and found that 23.3% of the patients had OBI with positive HBV-DNA and negative HBV surface antigen; genotype C was the most frequent (57.89%) [26]. This study highlights the importance of looking for occult viral diseases in patients receiving immunosuppressive therapy, especially in the endemic areas.

Although the association between OBI and hepatocellular carcinoma has been controversial, a meta-analysis found that OBI significantly increases the risk of hepatocellular carcinoma when compared with non-infected subjects in retrospective (OR 6.08; 95% CI 3.45-10.72), and prospective studies (RR 2.86; 95% CI 1.59-4.13) [27].

A study in Japan including patients with hepatocellular carcinoma found that OBI was detected in 38% of patients with cryptogenic cirrhosis and 25.6% of patients with chronic HCV infection; fewer patients with OBI had high inflammatory activity, suggesting other factors involved in the development of hepatocellular carcinoma associated with OBI [28].

5. Occult hepatitis C virus infection

Occult HCV infection (OCI) was first described in 2004, and it is defined by the presence of HCV RNA in the hepatocytes or peripheral blood mononuclear cells (PBMCs) with no detectable HCV RNA in the serum; there are two types: seronegative (anti-HCV antibody negative and serum HCV RNA negative) and, seropositive (anti-HCV antibody positive and serum HCV RNA-negative) [16,29].

A study in China evaluated blood donors who were seronegative for HCV and found a prevalence of 2.2% of positive HCV RNA when tested in PBMC; all the patients had mild elevations in alanine aminotransferase [30]. In Mexico, another study was conducted using randomly selected blood donors considered eligible by the local norms; the prevalence of OCI was 3.4%; they found that homosexual relationships (OR 5.52; 95% CI 1.53-10.92; $p < 0.05$), and the use of acupuncture (OR 3.56; 95% CI 1.41-9.98; $p < 0.05$) were risk factors associated with OCI [31].

Populations at high risk of infection by HCV have been the focus of several studies to determine the prevalence of OCI. A study conducted in Iran demonstrated a prevalence of 3% of OCI in patients undergoing chronic hemodialysis [32]. A study including patients with HIV in Georgia found that OCI was detected in 2% of patients without evidence of liver disease, 12% of patients with cryptogenic liver disease, and 31% of patients with HIV/HBV co-infection; liver fibrosis was more frequent and with higher scores in patients with OCI compared with patients without OCI [33].

It is crucial to consider relatives of patients with chronic HCV infection for screening for OCI. A study including family members of patients with HCV infection found that 6.36% had OCI [34]. The presence of OCI has been assessed in the general population; a small study in Italy included healthy subjects who tested negative for HCV antibodies, and 3.3% were positive for HCV-RNA in PBMCs [35].

A systematic review and meta-analysis in a population of the Middle East and Eastern Mediterranean countries estimated the overall prevalence rate of OCI to be 10.04% (95% CI; 7.66-13.05%); the higher

rates were assessed in patients with other chronic liver diseases (12.04%, 95% CI 5.87-23.1%), and in multi-transfused patients (8.71%; 95% CI 6.05-12.39%) [36].

A recent meta-analysis estimated the global prevalence of OCI; the pooled prevalence of seronegative OCI was estimated to be 9.6% (95% CI 6.8-12.7%, I^2= 94.7%; 95% CI 93.8-95.4%; $p < 0.0001$), the pooled prevalence of seropositive OCI was estimated to be 13.3% (95% CI 7.8-19.9%, I^2= 93.0%; 95% CI 90.8-94.7%; $p < 0.0001$) [37].

6. Liver fibrosis in HIV carriers

As mentioned above, subjects positive for HIV are at an increased risk of OBI and OCI. A study found that HIV co-infection in patients with chronic HBV or HCV infection was a risk factor for occult cirrhosis (OR 3.53; 95% CI 1.85-6.76) [13].

Additionally, it has been reported that patients with HIV have a high prevalence of NAFLD, estimated between 13 and 55% in the ART era; the estimated prevalence is higher in patients with HIV/HCV co-infection (23 to 72%). [38]

One study performed TE in patients infected with HIV (51% were coinfected with HCV), 2.7% had occult cirrhosis, defined as preclinical compensated cirrhosis without any clinical findings, and 10.7% had overt undiagnosed cirrhosis. Moreover, the presence of occult cirrhosis increased the risk of liver-related events in these patients (aHR 7.1; 95% CI, 1.3-38.0) [39].

7. Unsuspected liver fibrosis in alcohol consumers

Excessive alcohol consumption is the leading cause of cirrhosis in Argentina, Brazil, Chile, Mexico, and Peru [7]. In 2017, the estimated number of deaths from alcohol liver disease in Latin America was 54,000 [40]; alcohol abuse is the leading cause of cirrhosis (60%) in the region [7]. In 2016.

In Latin America, the estimated consumption of alcohol per capita was 6.84 L of pure alcohol [8], and alcohol-attributable fractions for all-cause disability-adjusted life years were 6.7% and 5.5% for all-cause deaths in 2016 [41]. A prospective study in the United Kingdom included patients with alcohol use disorder, excluding patients with known liver disease; 29% were categorized to have advanced fibrosis using liver fibrosis test, ELF ≥ 10.5 [42].

8. Liver fibrosis in patients with metabolic diseases

In 2021 the global prevalence of diabetes was estimated to be 6.1% (5.8-6.5%), type 2 diabetes mellitus accounts for 96% (95.1-96.8%) of the cases, the age-standardized disability-adjusted life-years rate in 2021 in Latina America was 1446.1 (1240.9-1673.7) per 100,000, the highest globally, with a prevalence increase for the region of >100% from 1990 to 2021; it was estimated that by 2050 the global prevalence of diabetes will be >10% [43].

From 1980 to 2013, the proportion of adults with a body-mass index ≥ 25 kg/m2 increased from 28.8% (95% UI 28.4-29.3) to 36.9% (95% UI 36.3-37.4) in men and from 29.8% (95% UI 29.3-30.2) to 38.0% (95% UI 37.5-38.5) in women, Latin America has one of the highest prevalence globally [44].

A study in the United Kingdom found that the prevalence of occult cirrhosis is increased in patients with obesity and type 2 diabetes mellitus (OR 9.4; 95% CI 2.2-40.9) [14]. A study in Italy calculated the Fibrosis-4 index in a database of patients with type 2 diabetes and found a prevalence of advanced fibrosis of 24%, of which only 19% had been previously diagnosed with cirrhosis [45].

Patients with type 1 diabetes mellitus are also at increased risk of occult cirrhosis. A study that included patients with type 1 diabetes who underwent liver biopsy found that cirrhosis was diagnosed in 24.6% of patients, with an increased risk when comparing patients ≤ 55 years to the general population (OR 1.87; 95% CI 0.93-3.57) [46].

Another study estimated the proportion of candidates for bariatric surgery with liver fibrosis evaluated by transient elastography, 23.1% (95% CI 17.8-29.3%) had ≥ 9.5 kPa, body mass index was an independent predictor of elevated liver stiffness (OR 1.14; 95% CI 1.07-1.21; $p < 0.01$) [47].

Patients with NAFLD are at high risk of presenting liver fibrosis and progression to cirrhosis. The estimated global prevalence of NAFLD is 25%, although data from Latin America is scarce; the estimated prevalence in Latin America is estimated to be ~30.45% (95% CI 22.74-39.4%), one of the highest globally [48].

9. Future perspectives

There is little data on the prevalence of occult cirrhosis and occult liver disease globally. To the best of our knowledge, there is no data on the prevalence of occult cirrhosis in Latin America. Efforts should be made to assess the prevalence since Latin America is a region with one of the highest rates of metabolic diseases and excessive alcohol consumption.

Screening for NAFLD in high-risk subjects and screening for excessive drinking and alcohol use disorders at every level of medical care is relevant. Patients with persistent thrombocytopenia without hematologic disease should be screened for occult liver disease.

Efforts should also focus on the early treatment of occult liver disease to try to reduce liver disease burden and, in the case of occult viral hepatitis infection, prevent further spreading.

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Author contributions

Paulina Vidal-Cevallos: conceptualization, writing original draft, writing review and editing. Nayeli Flores-García: conceptualization, supervision, writing review and editing. Norberto Chávez-Tapia: Corresponding author, conceptualization, funding acquisition, supervision, writing review and editing. Naga Chalasani: Corresponding author, conceptualization, supervision, writing review and editing.

Conflicts of interest

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