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ABOUT COVER

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AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical epidemiology of chronic viral hepatitis B: A Tuscany real-world large-scale cohort study

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Informed consent statement: The demographic data of the study were appropriately encrypted in the database and the exported file (containing the "anonymized" data) was sent from the system to the Regional Health Agency of Tuscany *via* a secure channel.

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Abstract

AIM

To build a regional database of chronic patients to define the clinical epidemiology of hepatitis B virus (HBV)-infected patients in the Tuscan public health care system.

METHODS

This study used a cross-sectional cohort design. We evaluated chronic viral hepatitis patients with HBV referred to the outpatient services of 16 hospital units. Information in the case report forms included main demographic data, blood chemistry data, viral hepatitis markers, instrumental evaluations, and eligibility for treatment or ongoing therapy and liver transplantation.

RESULTS

Of 4015 chronic viral hepatitis patients, 1096 (27.3%) were HBV infected. The case report form was correctly completed for only 833 patients (64% males, 36% females; mean age 50.1 ± 15.4). Of these HBV-infected patients, 73% were Caucasian, 21% Asian, 4% Central African, 1% North African and 1% American. Stratifying patients by age and nationality, we found that 21.7% of HBV-infected patients were aged < 34 years (only 2.8% were Italian). The most represented routes of transmission were nosocomial/dental procedures (23%), mother-to-child (17%) and sexual transmission (12%). The most represented HBV genotypes were D (72%) and A (14%). Of the patients, 24.7% of patients were HBeAg positive, and 75.3% were HBeAg negative. Of the HBV patients 7% were anti-HDV positive. In the whole cohort, 26.9% were cirrhotic (35.8% aged < 45 years), and 47% were eligible for or currently undergoing treatment, of whom 41.9 % were cirrhotic.

CONCLUSION

Only 27.3% of chronic viral hepatitis patients were HBV infected. Our results provide evidence of HBV infection in people aged < 34 years, especially in the foreign population not protected by vaccination. In our cohort of patients, liver cirrhosis was also found in young adults.

Key words: Hepatitis B virus infection; Liver fibrosis; Cirrhosis; Public health; Epidemiology

Core tip: Although the introduction of a vaccine against hepatitis B virus (HBV) has been highly effective in reducing the incidence and prevalence of HBV infection in many countries, an estimated 257 million people worldwide are chronically infected. In 2015, WHO published the guidelines for prevention, care and treatment of HBV infected people promoting treatment based on noninvasive assessment. This real-world large-scale cohort study provides appropriate planning for public health programs, as well as the specific characteristics of patients, thus contributing to the successful, efficient translation of new knowledge to management and treatment of HBV patients to eradicate HBV.

Stasi C, Silvestri C, Berni R, Brunetto MR, Zignego AL, Orsini C, Milani S, Ricciardi L, De Luca A, Blanc P, Nencioni C, Aquilini D, Bartoloni A, Bresci G, Marchi S, Filipponi F, Colombatto P, Forte P, Galli A, Luchi S, Chigiotti S, Nerli A, Corti G, Sacco R, Carrai P, Ricchiuti A, Giusti M, Almi P, Cozzi A, Carloppi S, Laffi G, Voller F, Cipriani F. Clinical epidemiology of chronic viral hepatitis B: A Tuscany real-world large-scale cohort study. *World J Hepatol* 2018; 10(5): 409-416 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i5/409.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i5.409

INTRODUCTION

While the introduction of an effective vaccine has been highly effective in reducing the incidence and prevalence of hepatitis B virus (HBV) infection in many countries, an estimated 257 million people worldwide are chronically infected[1].

HBV prevalence is > 8% in parts of sub-Saharan Africa. An intermediate prevalence (2%-8%) is present in some regions of the eastern Mediterranean, Central Asia, Southeast Asia, China, parts of South America and some European countries (Albania, Bulgaria, Romania, Turkey and Italy). There is a low prevalence (< 2%) in parts of North America and in some European countries (Belgium, the Czech Republic, Denmark, France), as well as Australia and New Zealand[2].

High levels of viremia, or the infection contracted at a young age (affecting mainly males) are associated with an increased risk of death or of developing hepatocellular carcinoma[3]. In 2015, hepatitis B resulted in 887000 deaths, mostly from complications (including cirrhosis and hepatocellular carcinoma)[1].

In 2015, WHO published guidelines for the prevention, care and treatment of persons with chronic HBV infection. These promote the use of simple, noninvasive tests to assess liver disease stage and eligibility for treatment. For adult patients in countries with limited resources, the test for ratio of aspartate aminotransferase to platelets (APRI) is recommended as a noninvasive diagnostic to assess the presence of cirrhosis (APRI score > 2), while transient elastography (*e.g.,* fibroscan) or fibrotest are recommended in countries where these tests are available and cost constraints are not significant. These guidelines are based on a public health approach to the use of antiviral drugs for the treatment of chronic HBV. Such an approach considers the feasibility and effectiveness of treatment, even in countries with limited resources-for example, in areas where diagnostic methods such as HBV DNA and liver biopsy are unable to be used[4].

According to the latest Italian recommendations[5], treatment with nucleoside or nucleotide analogues is indicated in the following instances: HBeAg-positive patients with moderate or severe fibrosis who have failed seroconversion after a cycle of Peg-IFN, for whom treatment with Peg-IFN is not indicated at diagnosis; in HBeAg-negative patients with moderate or severe fibrosis who have already been treated with Peg-IFN without success or those for whom treatment with PegIFN is not indicated at diagnosis; in HBeAg-positive or HBeAg-negative patients who (for family, work or social reasons) are unable to practice or do not accept Peg-IFN therapy; in HBeAg-positive or HBeAg-negative patients with compensated or decompensated cirrhosis, regardless of the likelihood of seroconversion, serum HBV DNA levels and ALT values.

The aim of this study was to build a regional database of patients diagnosed with chronic HBV infection in specialised outpatient services in our region to define the clinical epidemiology of HBV-infected patients in the Tuscan public health care system.

MATERIALS AND METHODS

This prospective observational study is fully in line with the objectives of the National Plan for the Prevention of Viral Hepatitis, in particular the Address Line 1 (LI 1)-Epidemiology, which seeks to "define the epidemiology of viral hepatitis B and C and to strengthen surveillance systems". Objective 3 is of particular focus: It outlines the importance of the quality of reporting system data and the monitoring of HBV and HCV as acute or chronic infections[6].

All patients with HBV-related chronic liver disease referred to the hepatology outpatient services of 16 hospital units from January 1, 2015, to December 31, 2015, and who agreed to participate in the study, were evaluated. These 16 hospital units were: Hepatology Unit, University Hospital of Pisa, Pisa, Italy; Centre for Systemic Manifestations of Hepatitis Viruses (MaSVE), Internal Medicine and Liver Unit, Department of Experimental and Clinical Medicine, Careggi University Hospital, Florence, Italy; Gastroenterology Research Unit, Department of Experimental and Clinical Biomedical Sciences Mario Serio, Careggi University Hospital, Florence, Italy; Infectious Disease Unit, Hospital of Lucca, Italy; Infectious Diseases Unit, Siena University Hospital, Siena, Italy; Infectious Disease Unit, S. Maria Annunziata Hospital, Florence, Italy; Infectious Disease Unit, Hospital of Grosseto, Italy; Infectious Disease Unit, Hospital of Prato, Italy; Infectious and Tropical Diseases Unit, Careggi

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Study design

The Regional Health Agency of Tuscany provided all units with a computerised clinical database to collect the main socio-demographic, clinical and treatment data for all patients with chronic HCV and HBV infection admitted at each centre. A record was created for each patient containing his or her main personal data, blood chemistry data, viral hepatitis markers, HCV-RNA and HBV-DNA viral load, histology and instrumental evaluation (FibroScan®, liver ultrasound), previous treatment (with outcome), eligibility for treatment, or therapy already in progress, and liver transplantation details.

Liver ultrasound and elastography are among the main diagnostic procedures used in patients with chronic hepatitis. Liver ultrasound allows clinicians to diagnose and monitor chronic liver diseases, including the diagnosis of liver tumours and the identification of signs of portal hypertension. Liver surface irregularities detected by ultrasound techniques define the presence of micro- and macronodules and are considered the most sensitive and reproducible signs of liver cirrhosis[7]. Elastography characterises the properties and mechanical response of tissues, measuring their stiffness[8]. Elastography is currently used to determine clinical priorities based on the estimated fibrosis stage. In HBV naïve patients with normal ALT, the cut-offs used were < 6 kPa (no significant fibrosis), 6-9 kPa (grey area), and > 9 kPa (severe fibrosis/cirrhosis). In HBV-naïve patients with elevated ALT (but < 5 × ULN), the cut offs used were < 6 kPa (no significant fibrosis), 6-12 kPa (grey area), and > 12 kPa (severe fibrosis/cirrhosis)[9].

To estimate the number of patients with more severe liver disease, we considered those patients with a Child-Pugh score (used only to assess the severity of liver cirrhosis), and/or with a liver stiffness either > 9 kPa (normal ALT) or > 12 kPa (elevated ALT)[9] at elastography, and/or with a histological diagnosis of cirrhosis (METAVIR score equal to F4 or Ishak equal to S5-6), and/or with a nodular structure of the liver identified by ultrasound examination. Duplicate cases were excluded.

The demographic data were appropriately encrypted in the database. The software not only allowed the research team to include guided and controlled information using a combo-box but also to export files ready to be sent.

The exported file (containing the "anonymized" data) was sent from the system to the Regional Health Agency of Tuscany *via* a secure channel (SSL). After logging in and connecting to the Agency's web page, the user was then able to upload the file.

The research topic was described to the patients. The local Ethics Committee approved the study. Each participant gave written informed consent prior to the study, in accordance with the principles of the Declaration of Helsinki (Sixth Revision, Seoul 2008).

Statistical analysis

All data were validated, checking for out-of-range values and values that were logically inconsistent were handled. All results are expressed as mean ± SD. The numerical comparison of continuous data was performed using the Student's *t*-test for unpaired and for paired samples with Bonferroni correction, after checking similar variances in the groups by Levine's test for equality of variances. To avoid the potential bias related to the missing data, the analysis of the variables was conducted only on the completed fields.

Statistical significance was set at a value of $P < 0.05$. Statistical analysis was obtained using statistical software Stata 12 (College Station, TX, United States).

RESULTS

Demographic and epidemiological features

A total of 23 hepatology units were invited to participate in the study. Data were obtained from 16 hospital units for a total of 4654 cases of chronic HBV and HCV infections. Diagnoses were specified for 4015 (86.3%) patients, of whom 1096 (27.3%) were HBV infected (Figure 1). However, the case report form was correctly completed for only 833 patients (64% males, 36% females; mean age 50.1 ± 15.4). For HBV patients, 73% were Caucasian, 21% Asian, 4% Central African, 1% North African and 1% American. Of these HBV-infected patients, 106 (12.7%) were referred to the clinics for the first time during the period in question. Table 1 shows the patients stratified by age and gender.

Analysis of the calendar year of diagnosis and of the first access to specialised services reveals that about 98.1% of these cases occurred after 1990.

Stratifying patients by age and nationality, we found that 21.7% of HBV-infected patients were aged < 34 years (only 2.8% were Italian). Table 2 shows the most represented routes of transmission were nosocomial/dental procedures (23%), mother-to-child (17%) and sexual transmission (12%).

Clinical data

The most represented HBV genotypes were D (72%) and A (14%), shown in Table 3, seen in 135 HBV patients.

The total population displayed the following parameters: mean ALT = 59.84 ± 108.49 IU/L; mean AST

Table 1 Percentage of hepatitis B virus infected patients stratified by age group *n* (%)

Age group	Males	Females	Total
⩽ 34	54 (18.3)	46 (27.9)	100 (21.7)
35-44	60 (20.3)	26 (15.7)	86 (18.7)
45-54	68 (23.1)	33 (20.0)	101 (22.0)
55-64	58 (19.7)	27 (16.4)	85 (18.5)
65-74	36 (12.2)	22 (13.3)	58 (12.6)
> 75	19 (6.4)	11 (6.7)	30 (6.5)
Total	295 (100)	165 (100)	460 (100)
Missing			479

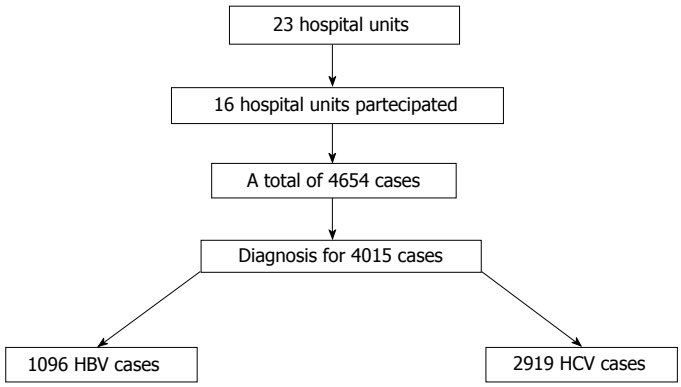

Figure 1 A total of 23 hepatology units were invited to enrol patients in the study, but 16 hepatology units have participated for a total of 4654 cases of chronic viral hepatitis. The diagnoses were specified for 4015 patients, of whom 1096 (27.3%) were hepatitis B virus infected. HBV: Hepatitis B virus; HCV: Hepatitis C virus.

= 48.20 ± 87.02 IU/L; mean Platelets = 195.23 ± 72.13 cells/L. The number of patients with PLT < 100000 was 31. In the population, 24.7% of HBV patients were HBeAg positive, 75.3% were HBeAg negative, and 7% were anti-HDV positive.

In non-treated HBeAg and anti HBeAg positive patients, the HBV DNA levels were $7.26 \times 10^7 \pm 1.71 \times 10^8$ and 8358838 ± 2.71×10^7 UI/mL, respectively.

In non-treated HBeAg and anti-HBeAg-positive patients, the ALT levels were 42.05 ± 29.70 U/L and 33.96 ± 33.49 U/L, respectively.

Staging of liver disease

A total of 89 HBV patients underwent liver biopsy. Of these, 66 also had elastography, with 45% of total liver biopsies performed before 2007 (*i.e.*, before liver elastography was used in clinical practice). Of 89 patients underwent liver biopsy, 70% were evaluated with an Ishak score (supplementary material), providing a better definition of liver fibrosis compared to METAVIR score. Twenty-three patients underwent liver biopsy alone, while 283 underwent elastography, with the latter performed exclusively after 2008.

Ultrasound examination revealed liver structure alteration in 29.4% of cases, and the presence of a nodular structure in 12%.

In the whole cohort, 26.9% of patients were cirrhotic (35.8% were aged < 45 years). The Child-Pugh score was specified in 156 patients. Most cirrhotic patients were classified as Child-Pugh Class A (*n* = 150, 96.2%), with an early stage severity of liver cirrhosis, with 4 classified as Child B (2.5%) and 2 as Child C (*n* = 1.3%). One hundred and six patients displayed signs of portal hypertension, which mostly occurred in those < 45 years (26%). Eight patients received liver transplantations. Forty-seven percent of patients were either eligible for or currently undergoing treatment, of whom 41.9% were cirrhotic. Dividing the cohort into treated (*n* = 162) and untreated HBeAg-positive patients (*n* = 182), we found significant differences between liver stiffness values (7.83 ± 3.56 *vs* 5.3 ± 2.3, *P* = 0.02). Similar differences were observed (7.84 ± 5.05 *vs* 4.82 ± 1.88, *P* < 0.001) when dividing the cohort into treated (*n* = 163) and untreated anti-HBeAg-positive patients (*n* = 181).

DISCUSSION

To our knowledge, this study involves the largest cohort of HBV patients in Italy. HBV infection was responsible for 27.3% of cases of chronic liver disease, whereas a previous study by Sagnelli *et al*[10] found an HBV prevalence of 20.2%.

We also found HBV-infected patients in those aged < 34 who would normally be covered by vaccination. Analysis of the nationality of HBV-infected patients highlights the prevalence of infection in the non-Italian population (only 2.8% of Italians were infected). Similar data was found in a previous study conducted in an industrialised city in the Tuscany region[11]. Further efforts are needed to improve vaccination coverage for

Table 2 Distribution of hepatitis B virus transmissions-multiple-choice analysis *n* (%)

Routes of transmission	Distribution
Intravenous drug users	15 (3.5)
Coagulation factors/blood transfusions	26 (6.0)
Sexual transmission	53 (12.3)
Piercing and tattooing	9 (2.1)
Vertical transmission	73 (16.9)
Nosocomial/dental cure	101 (23.4)
Undefined	255 (59.0)

Table 3 Distribution of the major hepatitis B virus genotypes *n* (%)

Genotypes	Distribution
A	19 (14.1)
B	4 (3.0)
C	4 (3.0)
D	97 (71.9)
E	5 (3.6)
F	6 (4.4)
Total	135 (100)

non-infected and non-vaccinated immigrants who are susceptible to infection.

According to national data on risk factors associated with the HBV infection in the Integrated Epidemiological System of Viral Acute Hepatitis (SEIVA), nosocomial/dental procedures (23%) are some of the most represented risk factors for HBV transmission, followed by mother-to-child (17%) and sexual transmission (12%). Recently, cosmetic treatment with percutaneous exposure (28% of patients), sexual exposure (24.7%), and dental therapy (11.5%) have been recognized as the main risk factors in acute viral hepatitis B in Italy. The risk of maternal-infant transmission is related to the mother's HBV replicative status (90% correlation with HBeAg-positive mothers compared to 10%-20% for HBeAg-negative mothers)[12]. Many studies[13-16] have highlighted that pregnant women in particular with high levels of HBV DNA (more elevated in HBeAg positive patients compared to HBeAg-negative patients) have an increased risk of transmitting infection. As recently shown by Sagnelli *et al*[17], the screening of pregnant women to detect circulating HBsAg and prophylaxis procedures for new-born babies, the universal vaccination against HBV infection introduced in 1991, and national media campaigns against HIV infection are considered the main reasons for the significant reduction in this type of transmission. Heterosexual (and, to a greater extent, homosexual) activity remain significant means of transmission. A study of Zuccaro *et al*[14] for an HBV cohort of 103 patients in 15 Italian hospital units showed a high prevalence of sexual transmission. In a study by Hahné *et al*[15], HBsAg prevalence estimates in men who have sex with men (MSM) ranged from < 1% to 4% in 3 of the 34 countries. This prevalence was 22 times higher than that of the general population for countries with available data[15].

As reported by Liaw *et al*[16], HBV genotype D is predominant in Mediterranean countries. In line with this finding, our study found that the most represented HBV genotype were D (72%), followed by A (14%). As concerns the potential bias of missing data, the statistical advantage of data that are missing completely at random is that the estimated parameters are not biased by the absence of the data.

To our knowledge, this is one of the few Italian studies to consider both infection rates and liver fibrosis stage based on international guidelines for a large cohort of patients.

We found a higher prevalence of HBeAg positive patients (24.7%) compared to Sagnelli *et al*[10] (7.2%) and a lower anti-HDV prevalence (7% *vs* 11.9%). It is well established that ongoing HBV replication or the presence of HBeAg may accelerate the progression of liver fibrosis. In a study of the natural course of HBV infection during the HBeAg-positive phase, Chu *et al*[18] showed that the annual incidence of cirrhosis was 0.5%, and the cumulative probability of cirrhosis after 17 years was 12.6%. Hence, age at anti-HBe seroconversion and hepatitis relapse were independent risk factors for cirrhosis. In particular, deferred HBeAg seroconversion (patients > 40 years) were associated with an increased risk of cirrhosis[18]. Moreover, HDV coinfection is associated with an accelerated progression towards liver cirrhosis, decompensation in existing cases of cirrhosis, and an increased risk of hepatocellular carcinoma[19].

In our cohort, almost all untreated patients were represented by inactive HBV carriers (HBV DNA < 2000 IU/mL), and by patients in an immune-tolerant phase (HBV DNA > 20000 IU/mL) with liver stiffness measurements < 6 kPa and normal ALT. These results are in agreement with national guidelines for treatment[5]. A study of 361 patients with inactive HBeAg-negative chronic hepatitis B patients demonstrated that liver fibrosis progression is rare given serum HBV DNA < 20000 IU/mL and normal ALT[21]. Brunetto *et al*[20] demonstrated that after a mean follow-up of six years, anti-HBe positive chronic hepatitis B progressed to cirrhosis in 45% of patients, with end-stage complications occurring in 24% of those presenting with cirrhosis. These outcomes seem to be associated with older age and persistent viral replication or hepatitis exacerbations in chronic hepatitis or cirrhotic patients. A recent study by Olivieri *et al*[22] showed that HBeAg-negative HBsAg-carriers with baseline HBV-DNA ⩽ 20000 IU/mL, and normal transaminases were associated with transition to inactive carrier status in 43% of low-viremic active carriers, and to occult HBV infection in 20% of inactive carrier, within five years.

We found that almost all patients with liver stiffness > 6 kPa were treated. There are several instances of evidence showing that antiviral therapy stops the progression of liver fibrosis and induces fibrosis regression. A recent study by Stasi *et al*[23] conducted in anti-HBeAg-positive patients before and during antiviral treatment using liver stiffness measurements with

transient elastography at different time points to assess changes in liver fibrosis showed a statistically significant reduction in stiffness values at 18 and 24 mo from those observed prior to therapy.

In the whole cohort, 26.9% were cirrhotic patients; it should be stressed here that 35.8% of these were aged < 45 years. The majority of cirrhotic patients showed signs of portal hypertension (43%). This data was different to that of Sagnelli *et al*[10] for a cohort of 513 HBV patients, 24% of whom had liver cirrhosis.

In conclusion, our data showed that 27.3% of chronic viral hepatitis patients were HBV infected. Evidence of HBV infection in people aged < 34 years was apparent, especially in the foreign population not protected by vaccination. The main routes of transmission were consolidated by data reported in several other studies. In our cohort of patients, we found an elevated prevalence of HBeAg-positive patients. In line with other Italian data, we found a high prevalence of liver cirrhosis in young adults. Antiviral treatment seems to be fully in line with national guidelines. Further efforts are necessary to increase vaccine coverage in immigrant populations.

ARTICLE HIGHLIGHTS

Research background

While the introduction of an effective vaccine has been highly effective in reducing the incidence and prevalence of hepatitis B virus (HBV) infection in many countries, an estimated 257 million people worldwide are still chronically infected. In 2015, WHO published guidelines for the prevention, care and treatment of persons with chronic HBV infection. These promote the use of simple, noninvasive tests to assess liver disease stage and eligibility for treatment.

Research motivation

Few data are currently available concerning the real-word large-scale staging and treatment of HBV patients followed in specialised outpatient services. The knowledge of the specific characteristics of patients could lead to appropriate planning for public health programs, thus contributing to the successful, efficient translation of this knowledge to management and treatment of HBV patients to eradicate HBV.

Research objectives

The main objective of this study was to build a regional database of patients diagnosed with chronic HBV infection in specialised outpatient services in our region to define the clinical epidemiology of HBV-infected patients in the Tuscan public health care system.

Research methods

This prospective observational study is fully in line with the objectives of the National Plan for the Prevention of Viral Hepatitis, in particular with those outlining the importance of the quality of reporting system data and of the monitoring of HBV and hepatitis C virus as acute or chronic infections. This study used a cross-sectional cohort design to evaluate all patients with HBV-related chronic liver disease referred to the hepatology outpatient services of 16 hospital units from January 1, 2015, to December 31, 2015. A computerised clinical database was used to collect the main socio-demographic, clinical and treatment data for all patients with chronic HBV infection admitted at each centre. The exported file (containing the "anonymized" data) was then sent to the Regional Health Agency of Tuscany *via* a secure channel (SSL).

Research results

The results of this study demonstrated that 27.3% of chronic viral hepatitis patients were HBV infected. Of these HBV-infected patients, 73% were Caucasian, 21% Asian, 4% Central African, 1% North African and 1% American. Stratifying patients by age and nationality, we found that 21.7% of HBV-infected patients were aged < 34 years. Among these only 2.8% were Italian. The most represented routes of transmission were nosocomial/dental procedures (23%), mother-to-child (17%) and sexual transmission (12%). The most represented HBV genotypes were D (72%) and A (14%). Of the patients, 24.7% were HBeAg positive, and 75.3% were HBeAg negative. Of the HBV patients, 7% were anti-HDV positive. In the whole cohort, 26.9% were cirrhotic (35.8% aged < 45 years), and 47% were eligible for or currently undergoing treatment, of whom 41.9% were cirrhotic.

Research conclusions

The informatization of clinical data and the real-word large-scale staging and treatment of these kinds of patients would allow health planners to assign specific healthcare resources to targeted populations. This observational research may provide a public health opportunity to screen and treat specific groups of patients. In particular, to eradicate HBV infection further efforts are necessary to increase vaccine coverage in immigrant populations.

Research perspectives

Based on the data collected in the course of this investigation, it is necessary to implement a series of preventive measures and strengthen the entire care process to eliminate, or at least reduce, risk factors for HBV infection and progression toward advanced liver fibrosis stages and to adopt care protocols suitable for immigrant populations.

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ORIGINAL ARTICLE

Retrospective Study

Isolated hepatic non-obstructive sinusoidal dilatation, 20-year single center experience

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Abstract

AIM

To characterize isolated non-obstructive sinusoidal dilatation (SD) by identifying associated conditions, laboratory findings, and histological patterns.

METHODS

Retrospectively reviewed 491 patients with SD between 1995 and 2015. Patients with obstruction at the level of the small/large hepatic veins, portal veins, or right-sided heart failure were excluded along with history of cirrhosis, hepatic malignancy, liver transplant, or absence of electrocardiogram/cardiac echocardiogram. Liver histology was reviewed for extent of SD, fibrosis, red blood cell extravasation, nodular regenerative hyperplasia, hepatic

peliosis, and hepatocellular plate atrophy (HPA).

RESULTS

We identified 88 patients with non-obstructive SD. Inflammatory conditions (32%) were the most common cause. The most common pattern of liver abnormalities was cholestatic (76%). Majority (78%) had localized SD to Zone Ⅲ. Medication-related SD had higher proportion of portal hypertension (53%), ascites (58%), and median AST (113 U/L) and ALT (90 U/L) levels. Nineteen patients in our study died within one-year after diagnosis of SD, majority from complications related to underlying diseases.

CONCLUSION

Significant proportion of SD and HPA exist without impaired hepatic venous outflow. Isolated SD on liver biopsy, in the absence of congestive hepatopathy, requires further evaluation and portal hypertension should be rule out.

Key words: Sinusoidal dilatation; Sinusoidal obstruction syndrome; Hepatic plate atrophy

Core tip: We identified 88 patients with diagnosis of non-obstructive sinusoidal dilatation (SD) over the period of twenty years. Inflammatory conditions (32%) were the most common cause identified. Medication related SD was associated with higher proportion of portal hypertension, ascites, and elevated transaminases. The finding of non-obstructive SD on liver biopsy should prompt a review of patient's medical history and drug exposure. Additionally, portal hypertension should be rule out either clinically, endoscopically, or radiographically. There does not appear to be any relationship between histological patterns and medical conditions, which may suggest overlapping biological pathways in the development of non-obstructive sinusoidal dilatation.

Sunjaya DB, Ramos GP, Braga Neto MB, Lennon R, Mounajjed T, Shah V, Kamath PS, Simonetto DA. Isolated hepatic non-obstructive sinusoidal dilatation, 20-year single center experience. *World J Hepatol* 2018; 10(5): 417-424 Available from: URL: http://www.wjgnet.com/1948-5182/full/v10/i5/417.htm DOI: http://dx.doi.org/10.4254/wjh.v10.i5.417

INTRODUCTION

Hepatic sinusoidal dilatation (SD) is usually attributed to either hepatic venous outflow obstruction at the level of small or large hepatic veins, supra-hepatic inferior vena cava, or right-sided heart failure. A proportion of patients demonstrate SD in the absence of post-sinusoidal venous outflow impairment or portal vein thrombosis and the clinical significance of this finding is unclear[1]. Histologically, non-obstructive SD is often characterized by distended sinusoidal spaces, most evident in zone Ⅲ and, sometimes accompanied by hepatocellular plate atrophy, and/or red blood cell (RBC) extravasation (Figure 1). These findings are non-specific and have been reported with systemic inflammatory states, hematological malignancies, granulomatous disease, medications, and inflammatory bowel disease[2-10]. Sinusoidal dilatation may also be seen on wedge biopsies of the liver obtained intra-operatively. The long-term outcomes of patients with SD are not known. Moreover, there is no clear guidance on how such patients are to be investigated.

The purpose of this study was to better characterize non-obstructive SD by: (1) identifying associated conditions, such as: Vascular disorder, neoplastic disease, inflammatory disease, infections, surgery, or medications; (2) describing the long-term outcomes of these patients; and (3) identifying distinct laboratory or histological patterns that may identify the potential cause or disease association of the SD.

MATERIALS AND METHODS

We identified 491 patients from the Mayo Clinic, Rochester Minnesota electronic medical record between 1995 and 2015 with histological findings consistent with SD on high quality liver biopsy. SD was defined as sinusoidal lumen greater than one liver cell plate wide, observed in several lobules in a high-quality liver specimen devoid of artefactual tearing[9]. We defined high quality liver specimen by the presence of seven or more portal tracts from either needle or wedge biopsy. Patients with confirmed obstruction at the level of the small hepatic veins (veno-occlusive disease or sinusoidal obstruction syndrome), large hepatic veins/inferior vena cava (Budd-Chiari syndrome), portal vein thrombosis, evidence of vascular infiltration (sickle cell, hemophagocytic syndrome, or malignancy) or right-sided heart failure (moderate to severe tricuspid regurgitation, constrictive pericarditis, restrictive cardiomyopathy, or elevated right ventricle systolic pressure on echocardiogram) were excluded from the study (Figure 2). In addition, patients with cirrhosis, hepatic malignancy, liver transplant recipients, or absence of electrocardiogram or echocardiogram on medical records (to rule out heart failure) were also excluded from our study. Liver transplant recipients were excluded from the study due to the high likelihood of anastomotic vascular complications resulting in sinusoidal dilatation in this group.

The remaining cases were investigated for associated medical conditions. The electronic records were reviewed for clinical, laboratory values and imaging data (Supplementary Table 1). Imaging studies include abdominal ultrasound, abdominal/ pelvis CT with or without contrast, and abdominal/ pelvis MRI if available. Patients were classified into 1 out of 4 possible categories: inflammatory/auto-immune disorder, malignancy, medication, or undefined based on review of clinical history, histological findings, history of medication exposure, and laboratory findings. Patients with diagnosis of long standing inflammatory/ auto-immune disorder in

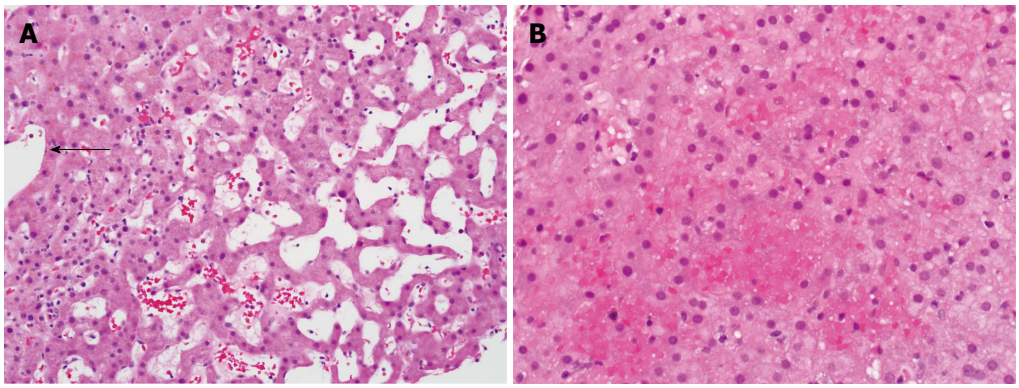

Figure 1 Sinusoidal dilatation and hepatocellular plate atrophy in zone 3 (arrow marks hepatic vein branch) (20 ×) (A); Zone 3 congestion and red blood cell extravasation (20 ×) (B).

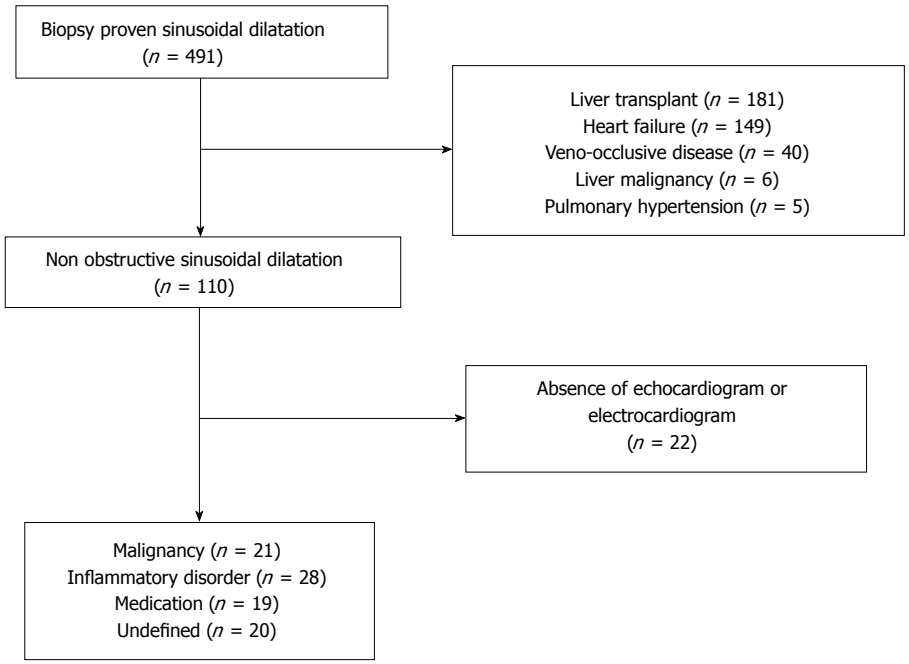

Figure 2 Flow chart of the screening process.

the absence of other plausible etiology were categorized to the inflammatory/auto-immune category. Patients with history of malignancy without previous exposure to medications associated with SD (including chemotherapy drugs) were assigned to the malignancy group. Patients with exposure to medications known to be associated with SD, such as oxaliplatin or estrogen, in the absence of other plausible etiology were categorized into the medication-related category. Patients without history of inflammatory/auto-immune disorder, malignancy, or exposure to medications associated with SD were assigned to the undefined category.

We reviewed the quality of liver biopsies by evaluating for the number of samples, size of biopsies, and number of portal tracts. Standard histologic staining such as: trichrome and reticulin, were performed on all samples. Special staining, such as PAS- diastase, Congo red, and copper, were performed on select samples based on the degree of clinical or histologic suspicion. The following information was recorded: (1) Extent of SD; (2) extent of fibrosis; (3) RBC extravasation; and presence of (4) hepatocellular plate atrophy. For this study, RBC extravasation was defined as the presence of red blood cells in the space of Disse. Extent of fibrosis was staged using the METAVIR system, which assigns 0 = no fibrosis, 1 = portal fibrosis without septa, 2 = portal fibrosis with few septa, 3 = numerous septa without cirrhosis or 4 = cirrhosis. Histopathological data on nodular regenerative hyperplasia and peliosis hepatis were also obtained. Nodular regenerative hyperplasia was defined as the presence of regenerative nodules on reticulin stain, and no or minimal fibrosis on trichrome staining[11]. Peliosis hepatis was defined as presence of round or oval cavities randomly distributed between areas of normal hepatic parenchyma[12].

Although early sinusoidal obstruction syndrome

Table 1 Study demographics *n* (%)

Variables	*n* = 88
Age	56 (6-85)
Gender	
Female	48 (54.5)
Ethnicity	
Caucasian	75 (85.2)
Mortality within 1 yr	19 (21.6)
Portal hypertension	31 (35.2)
Radiological Findings	
Hepatic nodule(s)	15 (17.0)
Splenomegaly	35 (39.8)
Ascites	29 (33.0)
Pattern of liver injury	
Hepatocellular	8 (9.1)
Cholestatic	67 (76.1)
Mixed	9 (10.2)
Normal	4 (4.5)
Primary medical condition	
Malignancy	21 (23.9)
Inflammatory disorder	28 (31.8)
Medication	19 (21.6)
Undefined	20 (22.7)

(SOS) cannot be entirely ruled out in patients exposed to chemotherapy drugs, those with typical histologic features of SOS including centrilobular fibrosis and hepatocyte necrosis were not included in this study. Therefore, we defined possible SOS based on liver injury arising within 20 d of chemotherapy exposure with at least two of the following: (1) Rise of serum bilirubin above 2.0 mg/dL; (2) hepatomegaly and/or right upper quadrant tenderness; and (3) sudden weight gain (> 2% of body weight) attributable to fluid accumulation.

The presence of portal hypertension was identified by either: (1) hepatic vein pressure gradient > 6 mmHg; (2) splenomegaly and thrombocytopenia (< 150000); (3) Serum Ascites Albumin Gradient > 1.1 g/dL; or (4) porto-systemic venous collaterals identified on ultrasound, CT, or MRI scans.

The pattern of liver test abnormality was categorized as either as: (1) hepatocellular; (2) cholestasis; (3) mixed; or (4) normal. Normal was defined as the absence of liver test abnormality. The pattern of liver injury was classified using the R factor score[13]. An R value of > 5.0 is used to define hepatocellular injury, R < 2.0 as cholestatic injury, and R between 2.0 to 5.0 as mixed hepatocellular-cholestatic injury. If serum ALT level was not available for R factor score calculation, we utilized our best clinical judgment based on serum AST, alkaline phosphatase, and bilirubin level.

Overall mortality and death within one year of diagnosis of non-obstructive SD were collected.

Statistical review of this study was performed by a biomedical statistician from the Mayo Clinic division of biomedical statistics and informatics. Dichotomous data were expressed as frequency (percentage). Continuous data were expressed as median and range. Kruskal-Wallis test was used to compare continuous variables between different groups. For nominal variables, chi-square test was used. All tests were two-sided and a *P* value of $\leqslant$ 0.05 was considered statistically significant. Analysis were done using SPSS version 20.0.

RESULTS

We identified a total of 88 patients with non-obstructive SD, which accounts for 17.9% of all cases with histologic evidence of SD in our center (Figure 2). Abnormal liver enzymes and presence of ascites were the most common indications for the liver biopsy. Needle biopsy accounts for majority of samples (97%). The median number of tissue sample collected was 2 (1-10) with a median number of 8 portal tracts identified and a median biopsy dimension of 1.5 cm (0.5-3.9). The majority of patients were female (55%) and Caucasian (85%) with a median age of 56 years old (6-85) at diagnosis. The most common medical conditions associated with SD were inflammatory conditions or autoimmune disorder (32%) followed by malignancy (24%) and medications (22%). We were not able to identify a potential etiology for twenty patients (23%) (Table 1). The list of complete medical conditions identified in our cohort can be found on Table 2. The most common autoimmune or inflammatory conditions identified were granulomatous hepatitis (*n* = 4), mixed connective tissue disease (*n* = 3), and inflammatory bowel disease (*n* = 3). Hematological malignancies and myeloproliferative diseases, accounted for the majority of the neoplasms in our study cohort. Oxaliplatin based chemotherapy (*n* = 7) was the most common medication identified in our study cohort followed by purine analogs (*n* = 3). Oral contraceptive use was identified as a probable cause of non-obstructive SD in two patients.

The most common radiological findings associated with SD were splenomegaly (40%) followed by ascites (33%), and hyperechoic liver lesion or hepatic nodule(s) (17%). Portosystemic collateral veins were identified in five patients (6%). Medication related non-obstructive SD had a significantly higher proportion of ascites (58%, *P* = 0.044) than the other associated clinical conditions (Table 3).

The median serum AST was 43 U/L, ALT was 44 U/L, total bilirubin 0.9 mg/dL, direct bilirubin 0.4 mg/dL, alkaline phosphatase 271 IU/L, GGT 123 U/L, serum protein 6.4 g/dL, albumin 3.2 g/L, and INR 1.1. Median ESR and CRP were 45.5 mm/h and 5.1 mg/L respectively. ESR and CRP were collected in a subset of patients where clinical suspicion for inflammatory disorder was high. We found medication-related non-obstructive SD was associated with higher median serum AST (113 U/L, *P* < 0.008) and ALT level (90 U/L, *P* = 0.002). Five of the thirteen patients (39%) in the medication related SD group had serum total bilirubin greater than 2.0 mg/dL. Four out of five patients in this subgroup had ascites and splenomegaly on imaging suggesting a possible diagnosis of early SOS. We also found lower median platelet counts in medication related SD group (80 x 10^3, *P* = 0.022), consistent with higher prevalence of non-cirrhotic portal hypertension (Table 4). Malignancy related

Table 2 Medical conditions associated with non-obstructive sinusoidal dilatation

Variables	*n*
Malignancy	
Hematological malignancies	
Leukemia	
AML	2
CLL	1
CML	1
Lymphoma	
B-cell lymphoma	4
T-cell lymphoma	1
Solid organ tumor	
Gastric adenocarcinoma	2
Angiosarcoma	1
Myeloproliferative disorder	9
Inflammatory condition	
Granulomatous hepatitis	4
Connective tissue disorder	3
Ulcerative colitis	2
Castleman's disease	2
Polyarthritis nodosa	2
Other[1]	15
Medications	
Oxaliplatin	7
Purine Analogs	3
Other[2]	9

[1]Acute inflammatory demyelinating polyradiculopathy, autoimmune hepatitis, amyloidosis, CINCA syndrome, Crohn's disease, IgA nephropathy, non-alcoholic steatohepatitis, primary biliary cirrhosis, psoriatic arthritis, and sarcoidosis; [2]Alcohol, atorvastatin, allopurinol, cyclophosphamide, decitabine, ethinyl estradiol and norgestimate, vincristine, and ibritumomab tiuxetan. AML: Acute myelocytic leukemia; CLL: Chronic lymphoblastic cytic leukemia; CML: Chronic myelocytic leukemia.

non-obstructive SD had higher median total bilirubin (1.6 mg/dL, $P = 0.008$).

The most common pattern of liver abnormalities was cholestasis (76%) followed by mixed (10%) and hepatocellular (8%) (Table 5). We did not identify a difference in the pattern of liver test abnormalities between varying causes of non-obstructive SD ($P = 0.54$). The majority of patients (78.4%) had SD localized to Zone Ⅲ. Fibrosis was found in 37 patients and 17 of them were limited to portal fibrosis without septa involvement (stage 1/4) (Table 6). Patients with autoimmune or inflammatory diseases had higher proportion of fibrosis on liver biopsy (39%) followed by medication (32%) and malignancy (19%) (Table 6). Hepatocellular plate atrophy and RBC extravasation were found in 58% and 32% of the study population respectively. Patients with autoimmune or inflammatory disorder also had higher proportion of hepatocellular plate atrophy (75%) followed by malignancy (52%) and medication related (42%). Nodular regenerative hyperplasia and hepatic peliosis were identified on histopathology in nine patients (10%) and one patient (1%) respectively. Lymphocytic infiltration was identified in twenty-four patients (27%) (Table 6).

The median follow up for all patients was 437 d (0-5616 d). Thirty seven patients (42%) died during the study follow up. Nineteen patients in our study died within one year after diagnosis of SD. The one-year mortality was highest in the medication related group (47%) followed by malignancy group (19%) and inflammatory group (14%). Ten patients died from complications of their respective underlying disease, such as: High burden of malignancy or infections related to immunosuppression. Four patients died from conditions unrelated to the cause of non-obstructive SD and in five patients the cause of death was not identified. Fifty out of sixty-nine patients (72%) that survived had at least 1 year of follow-up with a median follow-up time of 1943 d (370-5616 d).

Our cohort included 20 patients with unspecified cause of non-obstructive SD. The median age of diagnosis in this subgroup was 53 years (range: 16-85 years) with a median follow up of 636 d (range: 11-4120 d). Six patients (30.0%) from this subgroup died with median time to death of 2711 d (range: 146-5518 d) and 2 patients (10%) died within one-year of SD diagnosis.

DISCUSSION

The main findings of this study are that a significant proportion of SD occurs in the absence of impaired hepatic venous outflow. Twenty-eight percent (19/69) of patients with follow-up of at least one year died within one year after non-obstructive SD diagnosis, which might reflect poor clinical status or high disease burden in this study population. Medication related non-obstructive SD was associated with elevated serum AST and ALT levels but lower platelet counts compared to other causes. This observation correlates with a higher prevalence of non-cirrhotic portal hypertension in this group. A subset of these patients may have developed early SOS in the setting of recent chemotherapy exposure, such as oxaliplatin, despite the lack of typical histologic features. No patients had a history of stem cell transplantation. We did not identify a relationship between the extent of SD, hepatocellular plate atrophy, lymphocytic infiltration, or RBC extravasation with a specific etiology of non-obstructive SD. Our findings suggest that non-obstructive SD likely occurs through a common pathway associated with various medical conditions. Several studies have suggested the role of both IL-6 and VEGF overexpression in the development of SD[2,3]. Furthermore, the same IL-6 and its soluble receptor (sIL-6R) have been shown to be upregulated in chronic inflammatory or autoimmune conditions. In our cohort, one patient had a markedly elevated serum IL-6 level (249.1 pg/mL, normal range: 0-12.2 pg/mL). This was obtained as part of his extensive rheumatological work up. Unfortunately, this patient was not included in our final analysis due to the absence of echocardiogram to exclude right-sided heart failure, although he had no suggestive cardiac symptoms. Furthermore, the median serum CRP in our cohort was significantly elevated suggesting a role of chronic inflammatory state in the development of SD.

The prevalence of SD without hepatic venous outflow impairment has been reported in several small

Table 3 Clinical and radiological features stratified by conditions *n* (%)

	Malignancy (*n* = 21)	Inflammatory state (*n* = 28)	Medication (*n* = 19)	Not specified (*n* = 20)	*P*
Hepatic nodules	4 (19)	4 (14)	4 (21)	3 (15)	0.922
Portal hypertension	10 (48)	8 (29)	11 (58)	6 (30)	0.144
Ascites	7 (33)	5 (18)	11 (58)	6 (30)	0.04
Splenomegaly	9 (43)	11 (39)	9 (47)	6 (30)	0.719

Table 4 Laboratory findings stratified by conditions

	Malignancy	Inflammatory state	Medication	Not specified	*P*
AST (U/L)	46 (14-120)	43 (9-222)	113 (21-2351)	36 (14-80)	0.008
ALT (U/L)	36 (15-283)	46 (6-237)	90 (23-785)	28 (13-84)	0.002
Total bilirubin (mg/dL)	1.6 (0.3-28)	0.6 (0.2-9.1)	1.3 (0.4-12.8)	0.5 (0.3-8)	0.008
Direct bilirubin (mg/dL)	0.9 (0.1-24)	0.3 (0.1-6.2)	0.6 (0.1-8.2)	0.3 (0.1-5.8)	0.141
Alk Phosphotase (IU/L)	323 (71-1616)	355 (50-2288)	313 (104 - 1905)	135 (50-801)	0.057
GGT (U/L)	140 (82-1856)	106 (51-1066)	233 (50-418)	125 (N/A)	0.881
Albumin (g/L)	3.2 (1.7-4.3)	3.3 (2.1-4.1)	3.1 (2.5-4.5)	3.6 (1.2-4.3)	0.826
INR	1.2 (1-2.4)	1.1 (0.9-1.7)	1.1 (0.9-1.9)	1.1 (0.9-1.5)	0.106
Total protein (g/dL)	5.8 (1.6-9.2)	6.4 (4.7-8.6)	5.8 (4.8-8.2)	7.1 (5.2-10)	0.111
Platelets (10^3)	161 (25-907)	187 (10-708)	80 (17-339)	188 (78-352)	0.022
ESR (mm/h)	59 (3-132)	43 (0-121)	24 (13-117)	35 (6-127)	0.687

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; ESR: Erythrocyte sedimentation rate.

case series[1,14]. Bruguera *et al*[14] reported the a 2.9% incidence of non-obstructive SD on consecutive liver biopsy, while Kakar *et al*[1] reported one in three patients with diagnosis of SD occurred in the absence of venous outflow impairment. In our study, we found that 18% of all cases of sinusoidal dilatation occurred in the absence of venous outflow obstruction, or hepatic malignancy. This supports the previous studies indicating that non-obstructive SD may be more common than expected. The clinical significance of non-obstructive SD on histopathology is unclear, although we identified a high one-year mortality rate in our cohort. The majority of patients that died had coexisting malignancy (58%) and/or an autoimmune/inflammatory condition (29%). Seventy nine percent of patients died from either high burden of disease or complications of their underlying medical condition, such as malignancy. This brings forward a question of whether or not asymptomatic patients with abnormal liver enzymes and non-obstructive SD on biopsy require further evaluation for occult malignancy or inflammatory conditions. In our cohort of patients with undefined cause of SD, the one year mortality rate was low and interestingly all patients died from systemic infections. Future studies should evaluate the utility of screening for inflammatory/autoimmune condition or malignancy in patients with abnormal liver enzymes without an obvious cause of non-obstructive SD.

We were also interested in determining whether or not there is distinct biochemical, radiological, or histological patterns associated with specific medical conditions in patients with non-obstructive SD. We found that medication associated non-obstructive SD, such as previous exposure to platinum-based chemotherapy or purine analogs, were associated with higher median serum AST (113 U/L, $P = 0.008$) and ALT (90 U/L, $P = 0.002$) levels. This was consistent with previously reported findings highlighting the hepatotoxic nature of both oxaliplatin and 5-FU even after cessation of treatment[10,15-20].

We did not identify a relationship between the presence of hepatic nodules on imaging with nodular regenerative hyperplasia or peliosis hepatis on histopathology.

The strengths and weaknesses of our study merit further discussion. The major strength of our study was that this is the largest study to date on isolated non-obstructive SD. Previous studies were limited to case reports or small case series[1,14]. In addition, we have lon-

Table 5 Pattern of liver injury stratified by conditions

	Malignancy	Inflammatory state	Medication	Not specified	*P*
Liver injury					0.536
Hepatocellular	1	2	4	1	
Cholestasis	16	21	14	16	
Mixed	3	4	1	1	
Normal	1	1	0	2	

Table 6 Histology features stratified by conditions

	Malignancy (*n* = 21)	Inflammatory state (*n* = 28)	Medications (*n* = 19)	Not specified (*n* = 20)	Total	*P*
Zone						0.82
Ⅲ	17 (81)	22 (79)	16 (84)	14 (70)	69	
Ⅱ and Ⅲ	1 (5)	3 (11)	1 (5)	3 (15)	8	
Ⅰ, Ⅱ, and Ⅲ	1 (5)	0 (0)	1 (5)	0 (0)	2	
Other	2 (10)	3 (11)	1 (5)	3 (15)	9	
METAVIR score						0.60
0	15 (71)	14 (50)	13 (68)	9 (45)	51	
1	3 (14)	6 (21)	3 (16)	5 (25)	17	
2	1 (5)	4 (14)	1 (5)	3 (15)	9	
3	0 (0)	1 (4)	2 (11)	2 (10)	5	
Nodular regenerative hyperplasia	1(5)	2 (7)	4 (21)	2 (10)	9	0.33
Hepatic peliosis	1 (5)	0	0	0	1	0.36
Lymphocytic infiltration	6 (29)	8 (29)	6 (32)	4(20)	24	0.77
RBC extravasation	8 (38)	8 (29)	7 (37)	5 (25)	28	0.76
Hepatocellular plate atrophy	11 (52)	21 (75)	8 (42)	11 (55)	51	0.13

gitudinal data, up to 10 years after the initial diagnosis in majority of the patients. There were several limitations to our study: (1) As a tertiary center, a significant proportion of our cohort was referred for a second opinion of abnormal liver enzymes and had significant medical comorbidities, which may affect our one-year mortality rates and duration of follow up; (2) follow up data was not available in all patients, but the majority (69 out of 88 patients) had at least one-year follow up; (3) there were a large proportion of undefined causes of non-obstructive sinusoidal dilatation, which reflects the need for high quality prospective studies on this condition; and (4) we utilized our best clinical judgment based on available clinical data and histologic findings when selecting the primary etiology of non-obstructive SD in the setting of multiple medical conditions and/or history of medication exposure.

In conclusion, the finding of non-obstructive SD on liver biopsy should prompt a review of patient's medical history and drug exposure. Additionally, portal hypertension should be rule out either clinically, endoscopically or radiographically. There does not appear to be a relationship between histological patterns and medical conditions, which may suggest overlapping biological pathways in the development of non-obstructive sinusoidal dilatation.

ARTICLE HIGHLIGHTS

Research Background

A proportion of patients demonstrate (SD) in the absence of post-sinusoidal venous outflow impairment or portal vein thrombosis and the clinical significance of this finding is unclear. Long-term outcomes of patients with SD are not known. Moreover, there is no clear guidance on how such patients are to be investigated.

Research motivation

To better understand the clinical relevance and long-term outcomes of patients with non-obstructive SD.

Research objectives

To better characterize isolated non-obstructive SD by identifying associated conditions, laboratory findings, and histological patterns.

Research methods

Retrospective chart review of patients with isolated non-obstructive SD.

Research results

Inflammatory conditions (32%) were the most common cause identified. The most common pattern of liver abnormalities was cholestatic (76%). The majority (78%) had localized SD localized to Zone III. Medication-related SD had higher proportion of portal hypertension (53%), ascites (58%), and median AST (113 U/L) and ALT (90 U/L) levels. Nineteen patients in our study died within one-year after diagnosis of SD. Ten patients died from complications related to underlying diseases associated with SD.

Research conclusions

Significant proportion of SD may exist without impaired hepatic venous outflow. There does not appear to be any relationship between histological patterns and medical conditions. High one-year mortality rate in our cohort may suggest relationship between clinical status and development of SD. Isolated SD on liver biopsy, in the absence of congestive hepatopathy, requires further evaluation and portal hypertension should be rule out.

Research perspectives

Future studies should evaluate the utility of screening for inflammatory/autoimmune condition or malignancy in patients with non-obstructive SD

without an obvious cause.

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