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Determinants of disease in Italian patients at the time of their first diagnosis of liver cirrhosis

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List of abbreviations in order of appearance: HBV – Hepatitis B virus, HCV – Hepatitis C virus, HDV – Hepatitis delta virus, SVR – Sustained virological response, WHO – World Health Organization, MASLD – Metabolic dysfunction–associated steatotic liver disease, T2DM – Type 2 diabetes mellitus, PBC – Primary biliary cholangitis, AIH – Autoimmune hepatitis, BMI – Body mass index, HBsAg – Hepatitis B surface antigen, SD – Standard deviation, HBV-DNA – Hepatitis B virus DNA, HDV-RNA – Hepatitis delta virus RNA
HCV-Ab – Hepatitis C virus antibody, HCV-RNA – Hepatitis C virus RNA, FIB-4 – Fibrosis-4 index, HDL – High-density lipoprotein, PWID – People who inject drugs

ABSTRACT

Background: The epidemiology, etiologies and clinical presentation of cirrhosis have changed markedly in recent years; however, national-level data remain limited.

Aims: To describe the epidemiological profile and metabolic and non-metabolic determinants of cirrhosis in Italy in 2024.

Patients and methods: In this cross-sectional, multicentre observational study, 1195 consecutive patients with cirrhosis were enrolled from 11 tertiary hepatology centres across Italy. Eligible participants had a new diagnosis of previously unknown cirrhosis or a previous diagnosis with first evaluation at a participating centre in 2024. Demographic, socioeconomic, etiological, clinical and laboratory data were collected. Metabolic and non-metabolic determinants of cirrhosis were ranked by prevalence using Pareto chart analysis.

Results: Among 1195 patients, metabolic dysfunction-associated steatotic liver disease (MASLD) was the most prevalent etiology (321 patients, 26.9%), followed by alcohol-related liver disease (ALD) (269, 22.5%), viral etiologies (263, 22.0%) and other causes (116, 9.7%). Mixed etiologies were identified in 226 patients (18.9%), including Met-ALD, Met-virus, ALD-virus, Met-ALD-virus and PBC-AIH overlap. In the Pareto analysis, arterial hypertension ranked first, followed by type 2 diabetes mellitus, obesity, HCV infection, alcohol abuse and HBV infection. Despite the growing metabolic burden, viral hepatitis remained a major contributor, accounting for 28% of etiologies (137/490) among patients with a previous diagnosis of cirrhosis.

Conclusions: Cirrhosis epidemiology in Italy is shifting toward metabolic predominance, with MASLD emerging as the leading etiology. Nevertheless, viral hepatitis remains a substantial contributor. The frequent overlap of etiologies highlights the increasing complexity of cirrhosis management.

STATEMENTS AND DECLARATION

Conflicts of interest: All the other authors reported no conflict of interest.

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Data availability: All the data generated within the study will be available from the corresponding author upon reasonable request.

Ethics approval: The study was approved by the Ethic Committee of Palermo (Italy) with code SORPRESA (Reference 225) in January 2024. The study protocol is in accordance with the ethical guidelines of the 2013 Declaration of Helsinki and 2018 Declaration of Instanbul.

Patients consent: All subjects provided written informed consent prior inclusion in the study.

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INTRODUCTION

Liver cirrhosis represents the end stage of chronic liver disease, and is associated with high morbidity and mortality; it is estimated to be the twelfth leading cause of death in the United States [1]; it accounts for 2.4% of deaths worldwide [2] and 1.7% in Europe [3].

The most common causes of cirrhosis are represented by viral etiologies (hepatitis B virus, HBV; hepatitis C virus, HCV; and HBV/hepatitis delta virus, HDV), hazardous alcohol consumption, metabolic causes, cholestatic and/or autoimmune diseases, a combination of these factors, and other less frequent etiologies such as Wilson's disease, hemochromatosis, genetic disorders, and vascular diseases. A study conducted in Italy in 2001 identified HCV infection as the predominant etiology (51.1%), followed by the association of HCV and alcohol (15.7%), and alcohol alone (12.4%) [4]; a further study conducted in Italy in 2014 identified HCV as the predominant single etiology of cirrhosis (49.4%), although at a lower prevalence than reported in 2001, followed by HBV (15%), NAFLD/NASH (7.3%), and alcohol-related liver disease (7%) [5].

However, over the past decade, a paradigm shift has occurred in the treatment of HCV infection with the introduction of second-generation direct-acting antivirals achieving sustained virological response (SVR) rates over 96% [6]. In Italy, screening programs targeting at-risk populations and treatment of patients already in care have resulted in 279,247 antiviral prescriptions [7], leading to a substantial reduction in viral circulation, although the World Health Organization (WHO) targets for 2030 have not yet been fully achieved [8]. Furthermore, both the incidence of new infections and the prevalence of HBsAg-positive individuals have also markedly declined in Italy, reflecting the impact of mandatory neonatal vaccination introduced in 1991, behavioral prevention measures, and the widespread use of nucleos(t)ide analogues [9, 10].

Following this major transformation in hepatology, nationwide data on the epidemiology of liver cirrhosis in Italy remain lacking. Partial insight into the current landscape is provided by a retrospective study conducted in the Veneto region, located in northeastern Italy, which analyzed regional healthcare data from 2013 to 2020 among patients with cirrhosis. The study found that HCV ranked as the third most common etiology, preceded by alcohol-related liver disease and the "other" category, which also included MASLD [11]. However, these findings were derived from a single region accounting for less than 10% of the total Italian population. As such, they are likely influenced by regional lifestyle patterns and environmental factors and may not accurately reflect the epidemiology of cirrhosis across the entire country.

In parallel, the increasing prevalence of metabolic disorders has shifted attention toward metabolic etiologies. As a matter of fact, metabolic dysfunction–associated steatotic liver disease (MASLD) is currently considered the leading cause of chronic liver disease worldwide, with an estimated prevalence of approximately 30% [12]. The recent revision of nomenclature allows for the diagnosis of metabolic-related cirrhosis even in the presence of single metabolic risk factor, including arterial hypertension, type 2 diabetes mellitus (T2DM), obesity, or dyslipidemia, when other causes are excluded [13].

Finally, also an increased prevalence of cholestatic- and autoimmune-related liver cirrhosis has been reported [14], mostly attributable to increased diagnostic awareness and more systematic investigation of these conditions , as well as to improved diagnostic accuracy promoted by clinical practice guidelines for cholestatic liver diseases—particularly primary biliary cholangitis (PBC) [15]—and autoimmune hepatitis (AIH) [16]. Consequently, the number of liver cirrhosis cases classified as cryptogenic is decreasing.

Collectively, these trends suggest that the etiological landscape of liver cirrhosis has evolved over the past decade. Therefore, an updated and comprehensive picture of the current epidemiology of liver cirrhosis—including demographic, clinical, and etiological characteristics—is required. Based on these premises, we conducted a cross-sectional, multicentre observational study called SORPRESA (Studio Osservazionale multicentRico sulla PREsentazione clinica della cirroSi in ItAlia nel 2024), enrolling all patients with new diagnosis of unknown cirrhosis or those evaluated for the first time at participating centres. The primary aim was to characterize the profile of newly diagnosedously cirrhotic patients, assessing the impact of etiology, examining the prevalence of metabolic and non-determinants of cirrhosis, and assessing the residual burden of viral-related liver disease in the era of effective prevention and antiviral therapy.

PATIENTS AND METHODS

SORPRESA is a cross-sectional, multicentre observational study conducted between January 2024 and December 2024 and included 1,195 patients consecutively enrolled from eleven tertiary hepatology centres evenly distributed across Italy (Northern Italy, n=404; Central Italy, n=155; Southern Italy, n=636). Eligibility criteria comprised a new diagnosis of unknown liver cirrhosis or first clinical evaluation at the participating centre of patients with a previous diagnosis of cirrhosis. At enrolment, after obtaining informed consent, the following data were collected: demographic characteristics; alcohol consumption; metabolic comorbidities (obesity, dyslipidemia, arterial hypertension, and T2DM); cirrhosis etiology; viral serology; stage of liver disease (compensated or decompensated); and routine laboratory parameters. The study was approved by the Ethic Committee of Palermo (Italy) with code SORPRESA (Reference 225) in January 2024.

Liver cirrhosis was diagnosed by liver biopsy or on the presence of characteristic clinical, biochemical and ultrasound sign.

Etiology of cirrhosis was classified by the treating physician based on the available clinical history, laboratory and serological data. Regarding etiology, the MASLD etiology was assigned based on the presence of liver steatosis evidenced through imaging or histology, at the time of evaluation or in previous exams, associated with at least one cardiometabolic risk factor (CMRF) [17] and alcohol intake not exceeding 20g/day in women and 30g/day in men [13]. Viral etiology was assigned in case of HCV or/and HBV (± HDV) infection (for HCV based on HCV-Ab positivity, for HBV based on HBsAg positivity). Alcohol-related liver disease (ALD) was assigned in patients with cirrhosis considered primarily related to harmful alcohol use (with reported alcochol consumption >50g/day in women and >60g/day in men), and MetALD was assigned when metabolic dysfunction coexisted with alcohol exposure of 20-50g/day in women and 30-60g/day in men.

STATISTICAL ANALYSIS

Continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are reported as counts and percentages. Comparisons of variances between two groups were performed using t-test, while categorical variables were compared using Fisher's exact test. A two-tailed p-value < 0.05 was considered statistically significant.

Pareto Chart

Pareto Chart analysis, in combination with the Lorenz curve, was performed to describe the prevalence of metabolic and non-metabolic determinants of cirrhosis in patients.
The following determinants were analyzed: obesity (BMI ≥30), T2DM, arterial hypertension, dyslipidemia, alcohol abuse for ALD (>60g/day in men and >50g/day in women), alcohol abuse for

MetALD (20-50g/day in women and 30-60g/day in men), HBV infection (HBsAg positivity), HCV infection (anti-HCV positivity), autoimmunity (PBC and/or AIH), and other causes (including hemochromatosis, Wilson's disease, right-sided heart failure, vascular causes, cryptogenic cirrhosis).

RESULTS

Clinical and demographic characteristics

Clinical and demographic characteristics of patients are shown in Table 1. Of the 1,195 patients included, 872 (72.9%) were male, with a mean age of 64.2 years (± 11.6). Newly diagnosed liver cirrhosis was present in 705 patients (59%), whereas 490 patients (41%) had a previously established diagnosis and were evaluated for the first time at the participating center. At enrolment, 599 patients (51%) were classified as Child–Pugh A, 412 (35%) as Child–Pugh B, and 164 (14%) as Child–Pugh C. The mean age was lower among newly diagnosed patients compared with those with an established diagnosis (63.5 ± 12 vs 65.2 ± 11 years; p = 0.0129, −1.7 (−3.02−0.38)). Male sex was less represented in newly diagnosed cases compared with previously known cirrhosis (n:499 patients, 70.8% vs n:373 patients, 76.1%; p = 0.041, OR 0.76 (0.58–0.99)).

Etiologies

The etiological distribution of liver cirrhosis is shown in figure 1. MASLD was the most prevalent etiology (n:321 patients, 26.9%), followed by alcohol-related cirrhosis (n:269 patients, 22.5%), viral causes (n:263 patients, 22.0%), PBC (n:30 patients, 2.5%), and AIH (n:23 patients, 1.9%). Furthermore, 209 patients (17.5%) exhibited a mixed etiology involving two causes, while 17 patients (1.4%) had cirrhosis attributable to three concurrent etiologies. The "other" category (n:63 patients, 5.3%) included cryptogenic cirrhosis as well as cirrhosis related to vascular, genetic, or right-sided heart failure–associated causes. Figure 2 shows the distribution of cirrhosis etiologies stratified by newly diagnosed cases and first evaluation of previously established cirrhosis. By comparing the etiologies of the two subgroups, significant differences emerged for viral, alcohol-related, MASLD, and autoimmune etiologies. Viral etiology was more prevalent among patients with previously known cirrhosis (28% vs 17.9%, p=0.0001, OR 0.55 (0.42–0.71)), whereas alcohol-related (24.5% vs 19.6%, p=0.044, OR 1.30 (0.98–1.72), MASLD (29.6% vs 22.9%, p=0.0092, OR 1.39 (1.06–1.83)), and autoimmune cirrhosis (3% vs 0.4%, p=0.0014, OR 7.56 (1.77–32.3) were more frequent among newly diagnosed cases.

Metabolic and non-determinants of cirrhosis

The prevalence of determinants of cirrhosis in our cohort was evaluated using Pareto Chart analysis integrated with the Lorenz curve enabling the assessment of cumulative frequencies (Figure 3). The determinants analyzed included obesity, T2DM, arterial hypertension, dyslipidemia, alcohol abuse for ALD (>60g/day in men and >50g/day in women), alcohol abuse for MetALD (20-50g/day in women and 30-60g/day in men), HCV infection (HCV-Ab+), HBV infection (HBsAg+), autoimmune liver disease (AIH and/or PBC), and other causes (including cryptogenic cirrhosis and other etiologies). Arterial hypertension was the most prevalent determinants (592 patients), followed by T2DM (451patients); 299 patients were classified as obese. Alcohol abuse counted for 324 patients but 191 of them had ALD criteria while 133 had an alcohol abuse for Met-ALD criteria. Among viral etiologies, HCV infection was more prevalent than HBV infection (261 vs 159). Overall, metabolic and viral factors, together with alcohol abuse, accounted for a cumulative frequency of 94.2%.

Viral etiology stratification

Viral etiology ranked third in the overall population and among newly diagnosed cases but represented the leading cause among patients with previously established cirrhosis at evaluation. HBV, HCV, and HDV serological data are reported in Table 2. In the overall cohort, 159 patients

(13.3%) were HBsAg-positive; among these, 83 (52.2%) had newly diagnosed cases and 76 (47.8%) had a previously established diagnosis. The prevalence of HBsAg positivity was higher among patients with previously known cirrhosis compared with the overall study population (15.5% vs 13.3%, p 0.0614, OR 0.73 (0.52–1.02)). HBV-DNA was detectable in 55/159 (34.6%) HBsAg-positive patients, with a significantly higher prevalence in newly diagnosed cases than in previously known cirrhosis (36 vs 19, p=0.015, OR 2.30 (1.16–4.55)). HBV/HDV coinfection was identified in 23/159 (14.5%) HBsAg-positive patients, of whom 16 (69.6% of anti-HDV patients) had detectable HDV-RNA. Overall, 261 patients (21.8%) were HCV-Ab–positive; among these, 112 (9.3% of the total cohort, 42.9% of anti-HCV patients) were HCV-RNA–positive. When stratified by cirrhosis status, HCV-RNA positivity was more frequent in newly diagnosed cases than in previously known cirrhosis (81 vs 31, p=0.003, OR 1.92 (1.25-2.95)). Conversely, HCV-Ab-positive/HCV-RNA–negative status was more commonly observed among patients with previously established cirrhosis (101 vs 48, p<0.0001, OR 0.28 (0.20–0.41)).

DISCUSSION

Liver cirrhosis underwent profound epidemiological changes over the past fifteen years, and our prospective nationwide study provides an updated real-world snapshot of these transformations in Italy. Despite persistently high morbidity and mortality, we observed a clear shift in the etiological landscape, with MASLD emerging as the leading cause of cirrhosis, while viral etiologies continue to account for a substantial burden, particularly among patients with previously established diseases.

Although MASLD is widely considered the predominant etiology worldwide [12], contemporary real-world epidemiological data from Western countries remain limited, and in Italy available estimates date preceding the widespread use of direct-acting antivirals [4-6]. Our findings therefore reflect the combined impact of effective antiviral therapies, vaccination strategies, and the growing prevalence of metabolic risk factors on the current cirrhosis population.

Our analysis identified statistically significant demographic differences between patients with newly diagnosed cirrhosis and those evaluated for the first time with a previous diagnosis of cirrhosis, with newly diagnosed cases being slightly younger and less frequently male.

In particular, the increasing contribution of metabolic-related liver disease—characterized by a more balanced sex distribution—together with the progressive decline of alcohol and virus-related risk exposures traditionally more prevalent among males, may partially explain the observed demographic changes. This pattern is consistent with the evolving epidemiology of chronic liver disease in Western countries and suggests a transition toward different risk profiles at the time of cirrhosis diagnosis.

We also observed a significantly higher proportion of Child–Pugh A patients among newly diagnosed cirrhosis cases, suggesting increased awareness of individual risk factors and improved referral pathways to specialist outpatient clinics. The widespread implementation of risk stratification and non-invasive diagnostic tools likely explains the lower proportion of hepatic decompensation among newly diagnosed patients, reflecting earlier recognition rather than reduced disease severity [18, 19].

The most substantial change in liver cirrhosis over recent decades concerns its etiological profile. Historically, viral infection represented the leading etiological cause, particularly in Southern Europe [4]. However, the implementation of mandatory vaccination for HBV [10], together with major therapeutic advances achieved with nucleos(t)ide analogues [20] and direct-acting antiviral agents [6], has rapidly reshaped this landscape. In the current scenario, MASLD—either as a single

etiology or in combination with other causes—has emerged as the predominant driver of liver cirrhosis. The findings of the present study capture this pivotal transition, with MASLD representing the leading etiology both in the overall cohort and among patients with newly diagnosed cirrhosis, whereas viral etiologies remain predominant among patients evaluated for the first time with a previously established diagnosis of cirrhosis. This pattern likely reflects the long-term legacy of viral liver disease in older cohorts, alongside the growing impact of metabolic risk factors on contemporary cirrhosis incidence [21].

The increasing prevalence of metabolic-related cirrhosis likely reflects both the growing burden of metabolic risk factors and greater identification of at-risk individuals. In this context, the widespread adoption of non-invasive risk stratification tools, including simple fibrosis scores such as FIB-4 and transient elastography [18], allows clinicians to identify patients who warrant further diagnostic evaluation. These strategies facilitate the detection of advanced fibrosis and cirrhosis at earlier, often preclinical stages, contributing to a shift in the clinical presentation of metabolic-related cirrhosis rather than necessarily indicating a true decrease in disease severity.

Consistent with global epidemiological evidence indicating that alcohol consumption remains highest in Europe and the Americas [22], in our cohort alcohol-related cirrhosis accounts for a relevant proportion of cases, slightly increasing in respect to the past, underscoring its persistent social, healthcare, and economic impact, despite changes in the overall etiological burden.

Nevertheless, the complexity of the current etiological landscape remains substantial and often defies strict classification. In our cohort, a considerable proportion of patients presented with cirrhosis attributable to dual or triple etiology, reflecting variable exposure and contribution of individual determinants of cirrhosis. In parallel, the continuous refinement of clinical practice guidelines for cholestatic and autoimmune liver diseases improved diagnostic accuracy, facilitating the identification of previously unrecognized causes [15, 16] and contributing to a progressive reduction in the proportion of cryptogenic cirrhosis [23].

The scenario is further complicated by the marked heterogeneity of patients with MASLD-related cirrhosis. Current clinical practice guidelines allow classification of metabolic etiology in the presence of a single metabolic risk factor— such as arterial hypertension, type 2 diabetes mellitus, visceral obesity, hypertriglyceridemia, or low HDL cholesterol [13]—even though these conditions are characterized by distinct pathogenic mechanisms of liver injury. This heterogeneity challenges a uniform interpretation of metabolic-related cirrhosis and underscores the need for a more nuanced understanding of risk profiles within this broad etiological category.

To explore the prevalence of metabolic and non-determinants of cirrhosis in our patients we applied Pareto Chart analysis combined with the Lorenz curve, allowing a hierarchical exposure of their cumulative impact. Arterial hypertension emerged as the most prevalent determinant, followed—among metabolic factors—by type 2 diabetes mellitus and obesity. Although arterial hypertension is directly involved in MASLD [24], this finding may be likely influenced by the high prevalence of arterial hypertension in the general Italian population [25], which is estimated to be more than twice that of dyslipidemia, obesity, and type 2 diabetes mellitus [26, 27]. This observation further reinforces the concept that patients with cirrhosis are affected by multiple comorbidities.

However, despite the current shift of attention toward metabolic etiologies, our findings highlight the persistence of a highly relevant burden of viral-related liver disease in the overall study population. Furthermore, a consistent, non-negligible proportion of patients among newly diagnosed cirrhosis cases, still presented as active HBV or HCV carriers, very likely becoming

aware of their viral infection concomitantly with their diagnosis. These findings clearly underscore the fact that viral hepatitis continues to contribute to cirrhosis in the era of effective antiviral countermeasures.

In the case of HBV, given the long-standing implementation of mandatory vaccination program in Italy, which primarily protect the younger generations [10], the residual burden of viral-related cirrhosis may reasonably be attributed to older individuals as well as migrants from regions with lower vaccination coverage. By contrast, the HCV scenario appears substantially different. Italy's current national screening strategy targets selected populations such as PWID, incarcerated individuals, and those born between 1969 and 1989 [28]. In parallel, the decline in direct-acting antiviral therapies prescriptions observed since 2020 [7], raises concerns on the possibility to achieve the World Health Organization 2030 elimination targets [8].

Our findings support the need to further strengthen current screening and linkage-to-care strategies. This should be obtained by expanding community-based screening to older individuals [29] and implementing hospital-based screening programs [30]. These approaches may identify older adults and underserved individuals, facilitating earlier antiviral treatment before cirrhosis or hepatic decompensation develops.

Notably, active HCV infection was detected not only among patients with newly diagnosed cirrhosis, but also among those with a previously established cirrhosis. These findings highlighted missed opportunities for earlier diagnosis and treatment, underscoring the need to strengthen preventive strategies, optimize integrated care pathways, and address persistent gaps in linkage-to-care.

CONCLUSIONS

Liver cirrhosis is an increasingly complex disease with a markedly evolving clinical and etiological profile. In the current scenario, MASLD has emerged as the predominant etiology highlighting the growing importance of risk stratification strategies and non-invasive diagnostic tools to identify advanced fibrosis or compensated cirrhosis at earlier stages. Alcohol-related liver disease, together with cholestatic and autoimmune etiologies—previously largely underrecognized— continues to contribute substantially to the overall burden of cirrhosis and warrants sustained clinical attention. Importantly, despite widespread availability of effective antiviral therapies, viral etiology remains a relevant cause of cirrhosis. Migration flows, ongoing globalization, heterogeneous global health policies, and suboptimal screening strategies currently implemented in Italy, all contribute to a significant proportion of this burden, which could be substantially reduced through more effective and targeted preventive measures.

Finally, the frequent coexistence of many etiologies and determinants underscores the multifactorial nature of cirrhosis and the multiple comorbidities affecting these patients.

LIMITATIONS

The present study provides an overview of liver cirrhosis in Italy in 2024, without stratifying the analysis according to geographic region or patients' nationality.

The Pareto chart analysis is purely descriptive. The observed ranking of determinants represents their frequency in the study cohort and does not imply causality, etiological importance, or the magnitude of their contribution to the development of cirrhosis.

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