



Geographical pattern of chronic liver diseases in Italy: Results from two pooled national surveys

Tommaso Stroffolini^a, Evangelista Sagnelli^b, Caterina Sagnelli^b, Antonina Smedile^c,
Filomena Morisco^d, Nicola Coppola^b, Caterina Furlan^a, Piero Luigi Almasio^{e,*}

^a Department of Tropical and Infectious Diseases, Policlinico Umberto I, Rome, Italy

^b Department of Mental Health and Public Medicine, University of Campania Luigi Vanvitelli, Naples, Italy

^c Department of Medical Sciences, University of Turin, Turin, Italy

^d Department of Clinical Medicine and Surgery, Gastroenterology Unit, University of Naples "Federico II", Italy

^e Biomedical Department of Internal and Specialized Medicine (Di.Bi.M.I.S.), University of Palermo, Palermo, Italy

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ABSTRACT

Background: The information on the geographical characteristics of chronic liver diseases (CLD) in Italy is outdated.

Aim: To provide up-dated information on the geographical pattern of patients with CLD born in Italy.

Methods: Patients with CLD were enrolled in two national surveys performed in 2001 and 2014, which prospectively recruited subjects aged ≥ 18 years referring to Italian liver units located throughout the country that apply a similar clinical approach and analytical methods.

Results: The total number of patients enrolled was 11,676. Alcohol-related CLD was more frequently observed in northern/central areas (25.0% vs. 20.7%, $p < .001$), while HBV-related (15.4% vs. 13.3%, $p = .02$) and HCV-related (71.2% vs. 67.1%, $p < .001$) CLD prevailed in southern areas/main islands (Sicily and Sardinia). These differences were stable over time. Liver cirrhosis without HCC was diagnosed more frequently in southern area/islands than in northern/central areas (23.7% vs. 18.8%, $p < .01$). Moreover, an increased proportion over time of patients with cirrhosis without HCC was observed both in northern/central areas (17.3% vs. 27.4%, $p < .01$) and in southern area/islands (22.6% vs. 27.9%, $p < .01$).

Conclusions: These up-dated findings show different geographical patterns of CLD in Italy, reflecting different behavioural habits and socio-economic conditions across the country. They may be useful to apply more adequate preventive measures and to allocate economic resources.

1. Introduction

Italy is a country with wide regional differences regarding the demographic characteristics, behavioural habits, socio-economic conditions and income, which, among other things, favour a different geographical pattern in the distribution of diseases including chronic liver diseases (CLD).

Surveys performed several years ago [1–3] showed that alcohol-related CLD predominated in northern/central areas, where the economic conditions were better, while hepatitis B virus (HBV) and hepatitis C virus (HCV)-related CLD prevailed in southern areas and the main islands, areas with a higher frequency of large families and a lower socio-economic status.

These figures, however, are outdated, and up-dated information is needed to adequately allocate economic resources for preventive measures and treatment. By pooling the patients with CLD recruited in two national surveys performed in 2001 [4] and 2014 [5], we evaluated the current geographical pattern of CLD in Italy.

2. Patients and methods

The two national surveys have been previously described [4,5]. The first one enrolled 9997 subjects with CLD consecutively referring to 79 hospital liver units for a six-month period in 2001. The second one recruited 2557 CLD patients consecutively referring to 15 hospital liver units in 2014. In both studies, inpatients and outpatients were enrolled

* Corresponding author at: Biomedical Department of Internal and Specialized Medicine (Di.Bi.M.I.S.), University of Palermo, Piazza delle Cliniche, 2, 90127 Palermo, Italy.

E-mail address: piero.almasio@unipa.it (P.L. Almasio).

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Table 1
General characteristics of enrolled subjects according to geographical area.

Characteristics	Total (n = 11,676)	Northern/Central Italy (n = 4916)	Southern Italy/Islands (n = 6760)	p
Age (years) (mean \pm SD)	55.6 \pm 14.8	55.1 \pm 15.3	56.0 \pm 14.4	0.001
BMI (mean \pm SD)	25.4 \pm 3.8	24.9 \pm 3.7	25.8 \pm 3.8	< 0.001
Sex Ratio (M/F)	1.4	1.4	1.4	n.s.
Aetiology				
- HBsAg with other factors	1661 (14.2%)	656 (13.3%)	1005 (15.4%)	0.02
- HCV with other factors	8113 (69.5%)	3300 (67.1%)	4813 (71.2%)	< 0.001
- Alcohol abuse ^a with other factors	2628 (22.5%)	1229 (25.0%)	1399 (20.7%)	< 0.001
- NAFLD/NAASH	541 (4.6%)	239 (4.9%)	302 (4.5%)	n.s.
- Other ^b	473 (4.0%)	230 (4.7%)	243 (3.6%)	< 0.01
Diagnosis				
- Inactive carrier	2766 (2.3%)	122 (2.5%)	144 (2.1%)	n.s.
- Chronic hepatitis	8406 (72.0%)	3657 (74.4%)	4749 (70.3%)	< 0.01
- Liver cirrhosis without HCC	2531 (21.7%)	926 (18.8%)	1605 (23.7%)	< 0.01
- Liver cirrhosis with HCC	473 (4.1%)	211 (4.3%)	262 (3.9%)	n.s.

BMI: Body Mass Index; HCC: hepatocellular carcinoma.

^a ≥ 3 drinks/day for men; ≥ 2 drinks/day for women.

^b Including autoimmune, genetics, undefined.

for a given time and the criteria of enrolment were age over 18 years and altered hepatic biochemistry or a presence of etiological markers of liver damage. Subjects recruited in 2014 were different from those enrolled in 2001. The enrolling liver units were located throughout the country and most of the 15 hospitals participating in the second study had taken part in the first. The liver units participating in the two surveys had been cooperating in clinical investigations for nearly 15 years, had collected the data prospectively, had comparable access procedures and used a similar approach and similar analytical methods.

Personal data were collected in full compliance with the Italian law on personal data protection, and at the first observation each patient gave his/her informed consent to participate, in accordance with the instructions of the Ethics Committee of the coordinating centre, AUP University of Palermo. All procedures applied in the two studies were in accordance with the international guidelines, with the standards of human experimentation of the local Ethics Committees and with the Helsinki Declaration of 1975, revised in 1983. Patients who agreed to undergo liver biopsy signed an appropriate informed consent before the biopsy was performed. Patients were enrolled only once at their first observation. For each patient, a pre-coded questionnaire containing demographic, epidemiological and clinical data was filled out. No patient refused to participate in the studies.

2.1. Diagnostic criteria

In both surveys, the presence of serum hepatitis B surface antigen (HBsAg) identified an HBV aetiology and the presence of antibody to HCV, an HCV aetiology. Autoimmune chronic hepatitis, primary biliary cholangitis, hereditary hemochromatosis and Wilson's disease were diagnosed according to standardized international criteria [6–9]. An alcohol intake > 40 g/day for males (≥ 3 drinks a day) and > 30 g/day for females (≥ 2 drinks a day) for at least 5 years was considered an etiologic factor for alcoholic liver disease [10,11]. Non-alcoholic fatty liver disease was diagnosed based on abnormal serum alanine aminotransferase (ALT) values associated with hepatic steatosis identified by liver histology and/or ultrasound (US), in the absence of other known causes of liver disease [12]. CLD was considered cryptogenic in the absence of any viral, autoimmune or metabolic aetiology.

Chronic hepatitis was diagnosed based on liver histology, when available, or on the persistence (> 6 months) of abnormal ALT values in the absence of clinical, biochemical or US or transient elastography evidence of liver cirrhosis [13]. Liver cirrhosis was diagnosed by liver biopsy (LB) or, in the absence, on the presence of characteristic clinical, biochemical and ultrasound or transient elastography signs [13]. The diagnosis of hepatocellular carcinoma was based on histological and/or

imaging findings and alfa-1-fetoprotein serum levels [14]. Percutaneous LB was performed, if requested by the physician in care for diagnostic purposes, under US guidance using a disposable modified Menghini needle. In each liver unit, a skilled pathologist unaware of the clinical and laboratory data evaluated liver histology. Liver necroinflammation and fibrosis were assessed by the Ishak [15] or Metavir scoring system [16], and standardized criteria were used to convert the Ishak score to a Metavir score [17].

2.2. Serologic assays

Serum HBsAg and antibody to HCV were sought using commercial immune-enzymatic assays. Routine tests were applied to seek the etiologic markers of autoimmune hepatitis, primary biliary cholangitis, iron and copper overload and liver functions.

2.3. Statistical analysis

The data were collected in a pre-established electronic CRF database (web-based data collection, e-CRF provided by Air-Tel®, Airon Telematica, Milan, Italy). Differences in means and proportions were evaluated by Student's *t*-test and chi square test or Fisher's exact test, respectively. A *p* value $< .05$ was considered significant. All *p* values were two-tailed.

3. Results

Out of 12,405 subjects, the 729 patients born abroad were excluded and the 11,676 born in Italy were enrolled in the present study. Patients born in Northern/Central Italy were more frequently younger (mean age 55.1 years vs. 56.0 years, *p* = .001) and with alcohol-related CLD (25.0% vs. 20.7%, *p* $< .001$), whereas those born in Southern Italy or the main Islands (Sicily and Sardinia) more frequently had HBV-related (15.4% vs. 13.3%, *p* = .02) or HCV-related (71.2% vs. 67.1%, *p* $< .001$) CLD and a diagnosis of liver cirrhosis without HCC (23.7% vs. 18.8%, *p* $< .01$) (Table 1).

Stratifying by years of study, the geographical differences according to aetiology showed significant changes over time in virus-related CLD; while a presence of liver cirrhosis remained quite stable both in the 2001 and 2014 studies (Table 2).

The trend over time of the characteristics of subjects born in Northern/Central Italy showed an increasing mean age (55.4 years vs. 59.1 years, *p* $< .001$), a decreasing proportion both of HCV related cases (68.5% vs. 59.5%, *p* $< .001$) and alcohol-related cases (26.1% vs. 18.9%, *p* $< .001$) and an increasing rate of liver cirrhosis without

Table 2
Characteristics of subjects enrolled according to geographical area and year of study.

Characteristics	2001 Study		p	2014 Study		p
	Northern/Central Italy (n = 4153)	Southern Italy/Islands (n = 5294)		Northern/Central Italy (n = 763)	Southern Italy/Islands (n = 1466)	
Age (years) (mean ± SD)	54.4 ± 15.2	54.9 ± 14.6	n.s.	59.1 ± 15.0	60.1 ± 12.7	n.s.
BMI (mean ± SD)	24.8 ± 3.6	25.7 ± 3.8	< 0.001	25.6 ± 4.3	26.2 ± 4.1	0.005
Sex Ratio (M/F)	1.4	1.5	n.s.	1.2	1.6	0.002
Aetiology						
- HBsAg with other factors	550 (13.2%)	693 (13.1%)	n.s.	106 (13.9%)	312 (21.3%)	< 0.001
- HCV with other factors	2846 (68.5%)	3886 (73.4%)	< 0.001	454 (59.5%)	927 (63.2%)	n.s.
- Alcohol abuse ^a with other factors	1085 (26.1%)	1192 (22.5%)	< 0.001	144 (18.9%)	207 (14.1%)	0.003
- NAFLD/NASH	189 (4.6%)	234 (4.4%)	n.s.	50 (6.6%)	68 (4.6%)	0.02
- Other ^b	145 (3.5%)	149 (2.8%)	n.s.	85 (11.2%)	94 (6.4%)	< 0.001
Diagnosis						
- Inactive carrier	102 (2.5%)	113 (2.1%)	n.s.	20 (2.6%)	31 (2.1%)	n.s.
- Chronic hepatitis	3166 (76.2%)	3821 (72.2%)	< 0.01	491 (64.4%)	928 (63.3%)	< 0.01
- Liver cirrhosis without HCC	717 (17.3%)	1196 (22.6%)	< 0.01	209 (27.4%)	409 (27.9%)	< 0.05
- Liver cirrhosis with HCC	168 (4.0%)	164 (3.1%)	n.s.	43 (5.6%)	98 (6.7%)	n.s.

BMI: Body Mass Index; HCC: hepatocellular carcinoma.

^a ≥ 3 drinks/day for men; ≥ 2 drinks/day for women.

^b Including autoimmune, genetics, undefined.

Table 3
Characteristics of subjects enrolled in Northern/Central Italy according to year of study.

Characteristics	2001 Study (n = 4153)	2014 Study (n = 763)	p
Age (years) (mean ± SD)	54.4 ± 15.2	59.1 ± 14.9	< 0.001
BMI (mean ± SD)	24.8 ± 3.6	25.6 ± 4.3	< 0.001
Sex Ratio (M/F)	1.4	1.2	n.s.
Aetiology			
- HBsAg with other factors	550 (13.2%)	106 (13.9%)	n.s.
- HCV with other factors	2846 (68.5%)	454 (59.5%)	< 0.001
- Alcohol abuse with other factors ^a	1085 (26.1%)	144 (18.9%)	< 0.001
- NAFLD/NASH	189 (4.6%)	50 (6.6%)	0.02
- Other ^b	145 (3.5%)	85 (11.2%)	< 0.001
Diagnosis, N (%):			
- Inactive carrier	102 (2.5%)	20 (2.6%)	n.s.
- Chronic hepatitis	3166 (76.2%)	491 (64.4%)	< 0.01
- Liver cirrhosis without HCC	717 (17.3%)	209 (27.4%)	< 0.01
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HCC (17.3% vs. 27.4%, $p < .01$) (Table 3). The proportion of HBV related cases remained more or less stable over time (13.2% vs. 13.9%) (Table 3).

Similar changes over time were observed from 2001 to 2014 in Southern Italy/Islands regarding the mean age of patients (54.9 years vs. 60.1 years, $p < .001$), the proportion of subjects with HCV related (73.4% vs. 63.2%, $p < .001$) and alcohol-related (22.5% vs. 14.1%, $p < .001$) CLD, and the proportion of patients with liver cirrhosis without HCC (22.6% vs. 27.9%, $p < .01$). Surprisingly, the proportion of HBV-related CLD showed a marked increase from 13.1% to 21.3% ($p < .001$) (Table 4).

4. Discussion

The 2001 and 2014 nationwide prevalence surveys were structurally similar. Both studies were cross-sectional and prospectively enrolled for a given time inpatients and outpatients aged 18 or more with

Table 4
Characteristics of subjects enrolled in Southern Italy/Islands according to year of study.

Characteristics	2001 Study (n = 5294)	2014 Study (n = 1466)	p
Age (years) (mean ± SD)	54.9 ± 14.6	60.1 ± 12.7	< 0.001
BMI (mean ± SD)	25.7 ± 3.8	26.2 ± 4.1	< 0.001
Sex Ratio (M/F)	1.4	1.6	0.01
Aetiology, N (%):			
- HBsAg with other factors	693 (13.1%)	312 (21.3%)	< 0.001
- HCV with other factors	3886 (73.4%)	927 (63.2%)	< 0.001
- Alcohol abuse ^a with other factors	1192 (22.5%)	207 (14.1%)	< 0.001
- NAFLD/NASH	234 (4.4%)	68 (4.6%)	n.s.
- Other ^b	149 (2.8%)	94 (6.4%)	n.s.
Diagnosis, N (%):			
- Inactive carrier	113 (2.1%)	31 (2.1%)	n.s.
- Chronic hepatitis	3821 (72.2%)	928 (63.3%)	< 0.01
- Liver cirrhosis without HCC	1196 (22.6%)	409 (27.9%)	< 0.01
- Liver cirrhosis with HCC	164 (3.1%)	98 (6.7%)	< 0.01

BMI: Body Mass Index; HCC: hepatocellular carcinoma.

^a ≥ 3 drinks/day for men; ≥ 2 drinks/day for women.

^b Including autoimmune, genetics, undefined.

CLD of any aetiology referring for altered hepatic biochemistry or positivity of hepatitis virus serum markers to one of the participating liver units located throughout the country. The same clinical approach, analytical methods and facilities to access the liver units participating, whether district general or teaching hospitals, were adopted; several of these liver units had taken part in both the 2001 and 2014 surveys; the same threshold of risky alcohol intake was adopted in both surveys. For these reasons, pooling and comparisons of the two studies should not raise concerns. In addition, the large number of patients investigated and the geographical distribution of the liver units throughout the country support a generalization of the findings to the whole of Italy.

The patients were pooled together in the two macro areas (Northern/Central Italy and Southern Italy/main Islands, i.e. Sicily and Sardinia), based on a homogeneity in socio-economic conditions, behavioural habits and family size within these areas. The present findings show that the different geographical patterns of etiological factors of CLD in Italy remained stable from 2001 to 2014: alcohol-related

cases are prevalent in northern/central areas, while cases related to hepatitis viruses predominate in southern areas/islands, differences reflecting the behavioural habits and socio-economics conditions in these two macro areas. In fact, a higher proportion of alcohol consumption is reported in northern/central Italy, [18], while in southern regions/islands, HBV and HCV have largely spread in the past because of poorer socio-economic conditions and larger family size.

A significant downtrend over time both in alcohol-related and HCV-related CLD has occurred in both macro areas. The decreasing proportion of cases with alcoholic aetiology is in line with the consistent reduction in alcohol abusers of both sexes over the last decade in Italy [18], most probably due to the campaign by the Italian Healthcare Authorities to prevent alcohol abuse and to the economic crisis persisting in Italy for over a decade, which undoubtedly reduced the purchase of alcoholic beverages. The decreasing role over time of HCV infection observed in the present study reflects a decreasing spread of this infection over the last two decades in Italy, previously documented in a population-based survey performed in a town in southern Italy, where the rate of anti-HCV positivity in the general population decreased from 12.6% in 1996 to 5.7% in 2010; in addition, most of the cases observed in 2010 were aged over 70 [19]. Further evidence of this decrease comes from the data from a recent survey performed in five metropolitan areas of Italy showing anti-HCV positivity in the general population of 4.2% in subjects born before 1935 and of 0.2% in those born after 1984 [20]. Taken together these results show a cohort effect (i.e., decreasing exposure to the virus over generations) due to decreasing modes of virus transmission.

The increasing proportion of HBV-related CLD cases from 2001 to 2014, especially in southern areas/islands may reflect a referral bias. The availability since 2005 of highly effective, easy-to administer drugs such as Entecavir and Tenofovir for long-term suppression of HBV infection may have urged HBsAg-positive subjects to refer to the hospital centres issuing these drugs free of charge.

The shift over time in the proportion of CLD cases from chronic hepatitis to liver cirrhosis observed both in northern and southern Italy is cause for some concern because of the heavy burden of adequate healthcare and the high cost of therapy. The present study, however, provides up-dated figures for the geographical pattern of CLD in Italy, which may allow a better allocation of economic resources for prevention and treatment in the 20 Italian regions.

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Conflict-of-interest statement

All the authors (Tommaso Stroffolini, Evangelista Sagnelli, Caterina Sagnelli, Antonina Smedile, Filomena Morisco, Nicola Coppola, Caterina Furlan, Piero Luigi Almasio) of the manuscript: “Geographical pattern of chronic liver diseases in Italy: results from two pooled

national surveys” declare they have no conflict of interest regarding this paper.

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