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ORIGINAL ARTICLE

Retrospective Cohort Study

Etiology of chronic liver diseases in the Northwest of Italy, 1998 through 2014

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Abstract

AIM

To assess the etiology of chronic liver diseases (CLD) from 1998 to 2014 at the outpatient clinic of Gastroenterology of the main hospital in Northwest of Italy among those dedicated to hepatology.

METHODS

A random sample of charts of patients referred to for increased liver enzymes between January 1998 and December 2006, and between January 2012 and

December 2014 were reviewed. Etiology search included testing for hepatitis B virus (HBV), hepatitis C virus (HCV), autoimmune hepatitis, primary biliary cirrhosis, Wilson's disease and hereditary hemocromatosis. A risky alcohol consumption was also considered. Non-alcoholic fatty liver disease (NAFLD) was diagnosed in patients with histological and/or ultrasound evidence of steatosis/steatohepatitis, and without other causes of CLD.

RESULTS

The number of patients included was 1163. Of them, 528 (45%) had positivity for HCV and 85 (7%) for HBV. Among the virus-free patients, 417 (36%) had metabolic disorders whereas the remaining had history of alcohol abuse, less prevalent causes of CLD or concomitant conditions. In comparison to 1998-2000 (41%), a reduction of HCV alone-related cases was detected during the periods 2001-2003 (35%, OR = 0.75, 95%CI: 0.53-1.06), 2004-2006 (33%, OR = 0.70, 95%CI: 0.50-0.97) and 2012-2014 (31%, OR = 0.64, 95%CI: 0.46-0.91). On the contrary, in comparison to 1998-2000 (31%), metabolic-alone disorders increased in the period 2004-2006 (39%, OR = 1.37, 95%CI: 0.99-1.91) and 2012-2014 (41%, OR = 1.53, 95%CI: 1.09-2.16). The other etiologies remained stable. The increase of incidence of metabolic-alone etiology during the period 2004-2006 and 2012-2014 tended to be higher in older patients ($\geqslant$ 50 years) compared to younger (P = 0.058).

CONCLUSION

In the Northwest of Italy, during this study period, the prevalence of HCV infection decreased notably whereas that of NAFLD increased.

Key words: Chronic liver diseases; Cirrhosis; Hepatitis C virus; Hepatitis B virus; Nonalcoholic steatohepatitis

Core tip: The epidemiological knowledge of variations of etiology of chronic liver diseases (CLD) is crucial for health policy of resource allocation and for planning strategies of prevention and treatment. Our study, carried out in a large population from 1998 to 2014 period, shows that, in Northwest Italy, viral CLD decreased and CLD due to metabolic disorders remarkably increased. These results suggest the need to perform a strategy of rigorous education and counseling, in particular in overweight and obese subjects.

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INTRODUCTION

The epidemiology of chronic liver diseases (CLD) in Italy is now changing due to the decreasing rate of viral hepatitis[1] and the increasing new epidemic of a wide spectrum of metabolic disorders like steatosis, non-alcoholic fatty liver disease (NAFLD) and steatohepatitis (NASH)[2]. The last three decades witnessed extensive diagnosis of the major hepatitis viruses, such as hepatitis C virus (HCV), hepatitis B virus (HBV) and hepatitis D virus (HDV) and their diffuse treatment with antiviral therapy. In addition, vaccination programs against HBV, which in Italy became mandatory since 1991, helped to achieve the complete immunization of newborn, teenagers and young adults[3,4]. This active approach for HBV prevention was also effective against the risk of acquiring a superimposed HDV infection. As a result, Italy has become a country with a low (< 0.3%) endemicity for HBV infection, and HDV infection is almost vanishing[3]. However, HCV infection alone, despite the lowest rate of infection occurring to date in young adults, remains at risk of spread among subjects with a lifestyle prone to high risk behaviours or undergoing invasive medical procedures.

Unfortunately, the amelioration of hygiene and social conditions, has been accompanied by a rapid change in eating habits of Italian people, with a diet richer in sugar and lipids compared to the past healthy Mediterranean regimen. Furthermore, overweight and obesity in children and adults have reached prevalence rate of 10%-15%[5]. Such figures, although lower compared to those reported in North America[6], are substantial. We are thus facing a significant change in the main causes of CLD compared to the recent past. Hence, the knowledge of the new etiological pattern of CLD has became very important in planning both the strategy of health policy and clinical recommendations for the next decades.

The Unit of Gastroenterology of Molinette Hospital represents the main facility in the Northwest of Italy (with a population of around 6 million people) among those dedicated to the management of liver diseases. Since, in this area, there are no updated data on the trend of the etiology of CLD, the aim of the present study was to address this issue over the period 1998-2014.

MATERIALS AND METHODS

A sample of charts of patients referred to by the general practitioners for hepatology reasons, from January 1998 to December 2014, was reviewed. In our outpatient facility, the medical personnel is organized in work teams that follow cohorts of patients with specific pathologies. The mean number of consultations is from 10000 to 12000 per year[7]. Patients were divided into three main cohorts: (1) with suspected or known chronic liver disease; (2) with suspected or known bowel diseases; and (3) with suspected or known diseases of the upper

Table 1 Patients characteristics *n* (%)

Variable	*n* = 1163
Age, median (IQR)	52 (40-62)
Males	644 (55)
Etiology	
HCV	528 (45)
HCV alone	407 (35)
Metabolic	557 (48)
Metabolic alone	417 (36)
HBV	85 (7)
HBV alone	67 (6)
Period	
1998-2000	295 (25)
2001-2003	251 (22)
2004-2006	336 (29)
2012-2014	281 (24)

HBV: Hepatitis B virus; HCV: Hepatitis C virus.

gastrointestinal tract. Consultations are usually assigned into "first" and "control" in order to check the number of incidental cases in comparison to prevalent cases. For the purpose of this study, only patients with the first consultation were included. We analyzed the triennial prevalence of different causes of liver disease during the periods 1998-2000, 2001-2003, 2004-2006 in order to detect early changes in etiological trends. The cohort 2012-2014 was included to confirm the previous trend also in recent years. Since in the period 2007-2012 the outpatient clinic changed location, part of the data have not been homogeneously collected, due to logistic problems. Hence, to avoid biases we excluded this period from the analysis.

The more prevalent indication for hepatology consultations was the increase in liver enzymes. The search for etiology included testing for HBV serological markers (hepatitis B surface antigen, antibodies to hepatitis B core antigen), HDV serological markers (antibodies to HDV, IgG and IgM), and HCV serological markers (antibodies to HCV). Viral replication was measured by testing serum HBV-DNA, HDV-RNA, or HCV-RNA, using quantitative assays mainly based on PCR techniques to amplify the target nucleic acid (*i.e.*, COBAS TaqMan HBV and COBAS TaqMan HCV, Roche Diagnostics). We also collected a lifetime drinking history. The threshold for a risky alcohol consumption was set at 40 g/d for men or 20 g/d for women.

Autoimmune chronic hepatitis and cholestatic liver diseases were diagnosed on the basis of international standard criteria[8-11]. Organ- and non-organ-specific autoantibodies were tested at the dedicated laboratory: Anti-nuclear, anti-mitochondrial, anti-smooth muscle and anti-liver/kidney microsome type 1 autoantibodies. Autoantibodies were evaluated by indirect immunofluorescence on murine liver and kidney. IgA, IgG and IgM were detected with fluorescein isothiocyanate.

Hereditary hemocromatosis was diagnosed according to the presence of abnormal ferritin and saturated transferring serum values, genetic test, or liver histology. Wilson's disease was diagnosed on the basis of accepted international criteria[12,13]. Patients without known causes of CLD but serum aminotransferases elevation, histological and/or ultrasound evidence of hepatic steatosis/steatohepatitis, were considered as suffering from NAFLD or NASH[14].

The study conformed to the guidelines of the 1975 Declaration of Helsinki and was approved by the local Hospital ethical committee. Data were managed with respect of patients' privacy.

Statistical analyses

Since the patient records were not available in electronic format, assessments of the etiologies of the CLD were evaluated in a review of random samples from physical files. No formal power analysis was performed respect to a statistical comparison and the sample size was determined on the basis of resources available for in-depth review of the medical records. A mean sample of 900 medical records (in order to obtain approximately 100 patients per year) have been extracted according to an ordered sequence generated using a uniform distribution. For each patient with confirmed CLD, demographic, clinical, and etiological data were recorded. The change of (1) HCV; (2) HCV alone; (3) metabolic; and (4) metabolic alone, etiology during the analyzed periods (1998-2000, 2001-2003, 2004-2006, 2012-2014) was evaluated using logistic regression models, adjusting for age and sex. Potential effect modification by age (< 50, $\geqslant 50$ years) was evaluated in the logistic model including an interaction between the variables age and period.

RESULTS

The features of the cohort included in the study are reported in Table 1. The overall number of enrolled patients was 1163 (644 males, 55%), with a median age of 52 (interquartile range: 40-62). Of this cohort, 528 (45%) had positivity for anti-HCV (35% HCV-alone) and 85 (7%) for HBV (6% HBV-alone). Among the virus-free patients, 417 (36%) had metabolic disorders. The remaining group included patients with history of alcohol abuse, less prevalent causes of CLD or concomitant conditions.

To gain insight into the temporal trend of the etiological pattern of CLD, four periods (1998-2000, 2001-2003, 2004-2006, 2012-2014) were analyzed. Focusing on the main etiologies, in comparison to 1998-2000 (41% of HCV alone), a reduction in HCV-related cases was detected during the periods 2001-2003 (35% of HCV alone, OR = 0.75, 95%CI: 0.53-1.06), 2004-2006 (33% of HCV alone, OR = 0.70, 95%CI: 0.50-0.97) and 2012-2014 (31%, OR = 0.64, 95%CI: 0.46-0.91) (Table 2). On the contrary, liver disease due to metabolic disorders increased from 31.2%, during the period 1998-2000, to 39% during the period 2004-2006 (OR = 1.37, 95%CI: 0.99-1.91)

Table 2 Hepatitis C virus Etiology by period

Period	Patients, *n*	HCV			HCV alone		
		n (%)	OR (95%CI)	*P* value	*n* (%)	OR (95%CI)	*P* value
1998-2000 (Ref.)	295	157 (53)	1	-	121 (41)	1	-
2001-2003	251	127 (51)	0.89 (0.63-1.24)	0.487	87 (35)	0.75 (0.53-1.06)	0.107
2004-2006	336	140 (42)	0.61 (0.45-0.84)	0.002	112 (33)	0.70 (0.50-0.97)	0.031
2012-2014	281	104 (37)	0.51 (0.36-0.71)	< 0.001	87 (31)	0.64 (0.46-0.91)	0.012

ORs were estimated by a logistic regression model adjusting for age and gender. HCV: Hepatitis C virus.

Table 3 Metabolic etiology by period

Period	Patients, *n*	Metabolic			Metabolic alone		
		n (%)	OR (95%CI)	*P* value	*n* (%)	OR (95%CI)	*P* value
1998-2000 (Ref.)	295	136 (46)	1	-	92 (31)	1	-
2001-2003	251	121 (48)	1.08 (0.77-1.51)	0.663	78 (31)	0.98 (0.68-1.41)	0.907
2004-2006	336	167 (50)	1.14 (0.83-1.56)	0.418	131 (39)	1.37 (0.99-1.91)	0.061
2012-2014	281	133 (47)	1.01 (0.73-1.41)	0.947	116 (41)	1.53 (1.09-2.16)	0.015

ORs were estimated by a logistic regression model adjusting for age and gender.

Table 4 Subgroup analysis hepatitis C virus etiology

Subgroup	Period	Patients, *n*	HCV (interaction *P* = 0.407)		HCV alone (interaction *P* = 0.252)	
			n (%)	OR (95%CI)	*n* (%)	OR (95%CI)
Age < 50 yr	1998-2000 (Ref)	132	68 (52)	1	61 (46)	1
	2001-2003	114	53 (46)	0.80 (0.48-1.32)	35 (31)	0.51 (0.30-0.86)
	2004-2006	155	70 (45)	0.74 (0.46-1.18)	55 (35)	0.62 (0.38-1.00)
	2012-2014	111	45 (41)	0.55 (0.32-0.93)	37 (33)	0.52 (0.30-0.89)
Age ⩾ 50 yr	1998-2000 (Ref)	163	89 (55)	1	60 (37)	1
	2001-2003	137	74 (54)	0.96 (0.61-1.52)	52 (38)	1.03 (0.64-1.65)
	2004-2006	181	70 (39)	0.51 (0.33-0.79)	57 (31)	0.77 (0.49-1.20)
	2012-2014	170	59 (35)	0.46 (0.30-0.72)	50 (29)	0.75 (0.47-1.19)

ORs were estimated by a logistic model including an interaction between the variables age and period. HCV: Hepatitis C virus.

Table 5 Subgroup analysis metabolic etiology

Subgroup	Period	Patients, *n*	Metabolic (interaction *P* = 0.300)		Metabolic alone (interaction *P* = 0.058)	
			n (%)	OR (95%CI)	*n* (%)	OR (95%CI)
Age < 50 yr	1998-2000 (Ref.)	132	56 (42)	1	44 (33)	1
	2001-2003	114	54 (47)	1.21 (0.73-2.00)	41 (36)	1.10 (0.65-1.87)
	2004-2006	155	64 (41)	0.93 (0.58-1.49)	52 (34)	0.97 (0.59-1.59)
	2012-2014	111	52 (47)	1.08 (0.64-1.82)	44 (40)	1.16 (0.67-1.99)
Age ⩾ 50 yr	1998-2000 (Ref.)	163	80 (49)	1	48 (29)	1
	2001-2003	137	67 (49)	0.98 (0.62-1.55)	37 (27)	0.87 (0.52-1.44)
	2004-2006	181	103 (57)	1.36 (0.89-2.08)	79 (44)	1.81 (1.15-2.83)
	2012-2014	170	81 (48)	0.97 (0.63-1.50)	72 (42)	1.86 (1.18-2.94)

ORs were estimated by a logistic model including an interaction between the variables age and period.

and 2012-2014 (41%, OR = 1.53, 95%CI: 1.09-2.16) (Table 3).

Stratifying by age groups, no significant differences were observed in CLD incidence due to HCV alone between younger patients (< 50 years) and older ones (⩾ 50 years) (P = 0.252) (Table 4), whereas the incidence of metabolic causes alone during the period 2004-2006 and 2012-2014 in comparison to 1998-2000 tended to be higher in older patients (⩾ 50 years) than in younger ones (from 29% to 44% and 42% in the former *vs* from 33% to 34% and 40% in the latter group; OR = 1.81 *vs* 0.97, OR= 1.86 *vs* 1.16, P = 0.058) (Table 5).

DISCUSSION

The asymptomatic nature of mild CLD impedes the accurate determination of its epidemiology. Hence,

it is crucial, periodically, to perform studies aiming at defining detailed incidence and prevalence of liver diseases as well as their etiology.

The findings of our study show that in Northwest Italy, the incidence and prevalence of HCV infection decreased notably. This feature is supported by studies reporting a sharp decline in viral infections in hepatology settings more in Northern than in Central and Southern Italy. In a multicentre study including more than 6000 inpatients and outpatients, admitted for increase in liver enzymes in the year 2001, 62.6% had HCV alone, 9.2% HBV alone and about 13% non-viral causes. With regard to Northern Italy, HCV alone was reported in the 33.2% of cases, equivalent to our 33.3%, while NAFLD was diagnosed in the 34.2% of cases[1], similarly to 39% of our study in the period 2004-2006. Hence, the findings of our facility, that was not involved in the above reported study, independently confirm the changes in epidemiology of CLD of the same area. Quite different is the situation in Southern Italy, where results of the SCIROCCO Study Group for Liver Disease, have found that 62.9% of cases of CLD were HCV positive, 11.9% were HBV positive, 1.3% were HBV/HCV co-infected, 11.6% had an alcoholic liver disease and 10.1% had NAFLD[15]. Thus, in the South of Italy, viral infection still remains the most common etiology and the main cause for referral to centers dedicated to hepatology. These findings are similar to those obtained in a US population-based study, performed in Connecticut (New Haven County), Oregon (Multnomah) and California (Oakland) in the period 1999-2001, where HCV alone (42%) or in combination with alcoholic liver disease (22%) were the principal causes of CLD, followed by NASH for 9% and HBV for 3%[16].

Considering the general population, in Northern Italy, the Dionysos study, collecting data of 6917 inhabitants of 2 towns (Campogalliano and Cormons), reported that the overall prevalence of anti-HCV-positivity was 3.2%. When classified by age, the prevalence was rather low (< 1%) in subjects younger than 40 years but it raised markedly in subjects older than 60 years reaching a value of 10%[17]. According to some studies, this trend is in keeping with the so-called "cohort-effect"[18]. For instance, La Torre *et al*[18] estimated the HCV infection trends in Italy during the years 1996-2006. A strong reduction in HCV infection was observed (-12.45%), with no differences according to gender (-12.23% in males and females -12.8% in females). When stratified by age, the incidence rate decreased significantly, from 2.02 (age < 65 years) to 0.55 (age > 65 years) per 100000, without differences among groups. Moreover, with the new treatments based on direct antiviral agents (DAAs), that directly inhibit HCV replication targeting different viral-encoded proteins, a further drop in the prevalence of HCV can be expected in the next years[19]. Currently, since the DAA treatment for HCV has been introduced in our region in January 2015, an impact in the reduction of HCV prevalence found in our cohort could be excluded. Whether immigration is affecting the hepatitis virus epidemiology in Italy remains to be clarified.

Tightly linked to obesity and metabolic syndrome, NAFLD is emerging as potentially the overriding liver disease of the near future[20]. In our study there was an increase in rate of diagnosis of NAFLD. Although the latter was present in all cohorts, it was significantly higher in older than in younger subjects. Considering that an Italian multicentre cross-sectional study has shown that 23% of cases of hepatocellular carcinoma (HCC) occurred in virus-free patients with an increasing prevalence in the elderly, the issue of the age needs to be highlighted. Surveillance resulted an independent predictor for either single HCCs less than 2 cm or HCCs meeting the Milan criteria detection[21]. Moreover, in a cohort of US veterans, NAFLD and metabolic syndrome resulted the principal risk factors of 13% of patients with HCC without signs of cirrhosis[22]. Thus, the strict surveillance of these type of patients, in particular in elderly, is mandatory. This is more relevant considering that almost half of NAFLD patients have normal liver enzyme levels[2].

As part of the prevention program, an important role is played by behavior therapy for NAFLD. This is supported by previous observational studies[23,24] and finally by a more recent randomized controlled trial[25]. In the near future, therapeutic and behavior interventions might be supported by new technologies, such as smartphone applications and web-based platforms in order to permit an interactive engagement between patients and physicians[26].

In contrast with several studies conducted in general populations or in specific cohorts (for example blood donors) with short period analysis, our study evaluated the incidence of the main etiologies in a hepatology setting during a long period. This could be important for health policy of resource allocation. The health sector is characterized by vast demand and a lack of funds due to budget constraints. Prioritization is therefore necessary. Updating disease burden data is thus crucial in developing policy and prevention strategies, prioritizing research and appropriately allocating resources.

Some limitations of the present study have to be recognized. Estimates resulting from our outpatient clinic does not represent the general population. Nevertheless, data sources were critically assessed to avoid under- or over-estimation and to make sure that the results were consistent with general Italian population epidemiology[18]. The potential heterogeneity in collecting data is limited both by the fact that, in our outpatient clinic[7], all authors follow International Guidelines and that data were not collected in an outpatient clinic dedicated to a specific etiology (for example, exclusive for NASH or for viral hepatitis) but in a general hepatology one. As the primary aim

of our study was the definition of the epidemiologic pattern of these diseases over time, no data regarding CLD stages are provided. Another limitation is the lack of data in the period 2007-2012, due to the logistic problems above described.

In conclusion, our study carried out in a large population shows that, in Northwest Italy, there is a trend towards a decline in viral CLD and a relevant increase in liver diseases due to metabolic disorders. These results suggest the need for a strategy of rigorous counseling in the whole population, and particularly, in subjects with metabolic disorders.

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COMMENTS

Background

The epidemiology of chronic liver diseases (CLD) in Italy is now changing due to the decreasing rate of viral hepatitis and the increasing new epidemic of a wide spectrum of metabolic disorders like steatosis, non-alcoholic fatty liver disease and steatohepatitis. Since, in North-West Italy, there are no updated data on the trend of the etiology of CLD, the aim of the present study was to address this issue over the period 1998-2014.

Research frontiers

The epidemiological knowledge of variations of etiology of CLD is crucial for health policy of resource allocation and for planning strategies of prevention and treatment.

Innovations and breakthroughs

The present study included 1163 patients with CLD. Of them, 528 (45%) had positivity for hepatitis C virus (HCV) and 85 (7%) for hepatitis B virus. Among the virus-free patients, 417 (36%) had metabolic disorders whereas the remaining had history of alcohol abuse, less prevalent causes of CLD or concomitant conditions. In comparison to 1998-2000 (41%), a reduction of HCV alone-related cases was detected during the periods 2001-2003 (35%, OR = 0.75, 95%CI: 0.53-1.06), 2004-2006 (33%, OR = 0.70, 95%CI: 0.50-0.97) and 2012-2014 (31%, OR = 0.64, 95%CI: 0.46-0.91). On the contrary, in comparison to 1998-2000 (31%), metabolic-alone disorders increased in the period 2004-2006 (39%, OR = 1.37, 95%CI: 0.99-1.91) and 2012-2014 (41%, OR = 1.53, 95%CI: 1.09-2.16).

Applications

The study presented, carried out in a large population from 1998 to 2014 period, shows that, in Northwest Italy, viral CLD decreased and CLD due to metabolic disorders remarkably increased. These results suggest the need to perform a strategy of rigorous education and counseling, in particular in overweight and obese subjects.

Peer-review

In this study, the authors' give a brief overview of the epidemiology of chronic liver disease in their region over a 16 year period. However, there are several important methodological flaws, the most obvious of which is the lack of data between the years 2007-2010. This should undoubtedly be addressed by the authors before their manuscript is considered for publication. Furthermore, there also exists the question of the relevance of these data. The authors present a limited vision of the epidemiological trends, with no additional data such as concomitant diseases, obesity rates, antiviral treatment received, *etc*.

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