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## **EVOLVING CLINICAL LANDSCAPE OF CHRONIC HEPATITIS B: A MULTICENTRE ITALIAN STUDY**

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Giovanni Battista Gaeta

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**EVOLVING CLINICAL LANDSCAPE OF CHRONIC HEPATITIS  
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Keywords:	Hepatitis B, HBeAg , HDV, cirrhosis



Stroffolini *et al.*

*Chronic Hepatitis B in Italy*

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*Stroffolini et al.**Chronic Hepatitis B in Italy*

## Abstract

The aim of the study was to evaluate the characteristics of chronic hepatitis B with special reference to the geographical origin of the patients and to the prevalence of HBeAg and viral and non-viral cofactors of liver disease. A cross-sectional multicentre survey was undertaken, which enrolled 1386 HBsAg chronic carriers observed consecutively in 21 referral centres over a six-month period. The prevalence of HBeAg in patients was 11%; the presence of HBeAg was associated independently with a younger age and coinfection with HIV. Anti-HDV, anti-HCV or anti-HIV antibodies were detected in 8.1%, 6.5% and 2%, respectively. However, among the patients first diagnosed during the study period (incident cases), 14.3% were anti-HDV positive. Seven percent of the patients were immigrants; they were younger than Italian patients and 18% were HBeAg positive; no difference was observed in the prevalence of anti-HDV, anti-HCV or anti-HIV antibodies. The presence of cirrhosis was associated independently with an age >52 years, the presence of anti-HDV or anti-HCV, alcohol use >4 drinks/day and a high BMI. The clinical epidemiology of chronic HBV infection shows a dynamic profile, with the potential for re-emergence of cases with HBeAg or anti-HDV and an emerging impact of metabolic factors on the evolution of liver disease.

Key words: Hepatitis B, HBeAg, HDV, cirrhosis

*Stroffolini et al.**Chronic Hepatitis B in Italy*

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Chronic hepatitis B is a major cause of cirrhosis and liver cancer worldwide despite the dramatic progress in controlling the spread of hepatitis B virus (HBV) and in the use of antiviral therapy in the last decade (Dienstag JL, 2008). This progress has led to rapid changes in the epidemiology of HBV infection that have impacted on liver disease. For example, in industrialised countries the proportion of HBeAg positive chronic hepatitis B fell during recent years and the age of the patients has increased significantly (Stroffolini et al, 2005; Zarski et al, 2006). These patients are often difficult to manage, with a wide range of severity of liver disease and may present comorbidities due to age or multiple viral infections.

In Italy, nationwide surveys of patients with chronic hepatitis B seen in clinical centres documented a fall in HBeAg positive cases from 60% in the years 1975-84 to approximately 10% in 1997 and 2001 and a decrease in hepatitis D virus (HDV) coinfections from more than 30% to 8% (Giusti et al, 1991; Gaeta et al, 2000; Gaeta et al, 2003; Stroffolini et al, 2005). Mass vaccination of newborns and twelve-year-old subjects since 1991 has contributed to the control of HBV infection along with the general improvement in hygiene and socio-economic conditions.

In recent years, new factors are modifying the clinical features of HBV infection. First, the availability of well-standardised and sensitive techniques for HBV DNA detection has led to a more precise definition of HBsAg carriers, based mainly on quantitative measurements of HBV DNA; secondly, increasing immigration, mostly from endemic areas with an intermediate or high prevalence of HBV, such as eastern Europe, Asia and sub-Saharan Africa and finally, the increasing number of HBV carriers treated with antiviral drugs can cause difficult-to-treat liver diseases and has the potential of introducing drug-resistant variants (Pawlotsky et al, 2008; Rantala and van de Laar, 2008; Locarnini and Warner, 2007).

Based on these facts, a multicentre survey was undertaken to provide an accurate picture of HBsAg positive chronic liver disease in Italy and to identify differences, if any, from previous studies.

## Patients and Methods

The study was performed in 21 tertiary hospitals selected among the members of the Italian Association for the Study of the Liver (AISF) on the basis of participation in previous nationwide surveys (Giusti et al, 1991; Gaeta et al, 2000; Gaeta et al, 2003; Stroffolini et al, 2005). All HBsAg positive subjects observed consecutively from September 1<sup>st</sup> 2006 to February 28, 2007 as either in-patients or out-patients were recruited. The patients were enrolled regardless of HBV DNA level or having a liver biopsy available. “Incident cases” were defined as those who were first diagnosed during the study period and as “prevalent cases” those observed during the study period but known to be HBsAg positive. For incident cases, the diagnosis of chronic hepatitis was established on the basis of a negative anti-HBc IgM test (using the cut-off for acute hepatitis B) and either an awareness of being HBsAg positive for >6 months or a confirmation period after enrolment in the study.

For each subject, the demographic, clinical and etiological data were recorded using a pre-coded questionnaire. The amount of alcohol intake was determined using a standard questionnaire containing information on the daily intake of various alcoholic beverages and lifetime duration of alcohol consumption. For the purposes of the study, alcohol abstainers were defined as not having consumed more than 12 drinks each year during the last five years.

Hepatitis B serum markers (HBsAg, HBeAg, anti-HBe) and anti-hepatitis D virus (anti-HDV) antibodies were determined by commercial immunoenzyme assays. Antibodies to hepatitis C virus (anti-HCV) were detected by 3<sup>rd</sup> generation commercial immunoenzymatic assays. Serum HBV DNA levels were assessed by polymerase chain reaction (PCR) amplification, with low detection limits of 50 or 200 IU/ml.

Chronic hepatitis was diagnosed by liver histology or, for patients without liver biopsy, on the basis of persistent or recurrent abnormal ALT values along with HBV DNA 10<sup>4</sup> copies/ml for more than six months, in the absence of clinical, biochemical and ultrasound markers of cirrhosis. Cirrhosis was diagnosed by either liver biopsy or the presence of unequivocal clinical, biochemical and ultrasound signs (Gaiani et al, 1997). The diagnosis of hepatocellular carcinoma (HCC) was made by imaging techniques plus histology, or by an  $\alpha$ 1-fetoprotein value greater than 400 ng/ml confirmed by at least one imaging procedure showing a typical vascular pattern (Bruix and Sherman, 2005).

*Stroffolini et al.**Chronic Hepatitis B in Italy**Statistical analysis*

Continuous variables were summarised as means and standard deviation and categorical variables as absolute and relative frequencies. Differences in the means were evaluated by the unpaired Student t-test; the chi-squared test was applied to categorical variables. The receiving operating characteristic (ROC) curve was used to identify the best cut-off point to categorise continuous variables.

Crude odds ratios (O.R.) and their 95% confidence intervals (C.I.) for the association of the outcome variable with potential risk factors were calculated by univariate analysis. Adjusted O.R. were calculated by stepwise logistic regression analysis to identify factors independently associated with the outcome variable (Rothman and Greenland, 1998).

## Results

During the study period, 1,396 HBsAg positive subjects were enrolled. Their main characteristics are shown in Table 1. The mean age was 49.7 years (range 18-83), with male preponderance (73.4%). The majority of the cases (92.5%) were seen as out-patients and were prevalent cases (90.5%). Two thirds had been HBsAg positive for more than 10 years. Nearly half of the cases were alcohol abstinent. Antiviral treatment, at some time, was reported by 60.4% of the patients and 46% had received lamivudine (data not shown). Cirrhosis was present in 21% of the cases

Table 2 shows the virological profile of the patients. The proportion of patients with an HBeAg positive test was 11%; anti-HDV antibodies were detected in 8.1% and anti-HCV or anti-HIV in 6.5% and 2% of the cases, respectively. Among untreated subjects, serum HBV DNA was undetectable in 26.8% and was  $>10^4$  copies/ml in 43%.

*Characteristics of patients according to HBeAg status.* HBeAg positive subjects were more likely to be younger, immigrants, co-infected with HIV and with higher HBV DNA and ALT levels compared to HBeAg negative cases (Table 3). No difference was observed in the proportions of co-infections with HCV or HDV or in the prevalence of cirrhosis. At multivariable analysis, the only factors associated independently with the presence of HBeAg were younger age and an HIV positive test.

*Characteristics of patients according to incident vs prevalent cases.* Incident cases, compared to prevalent cases (Table 4), were younger ( $p = 0.01$ ), more often female ( $p=0.01$ ), were more often from northern Italy or were foreigners ( $p<0.001$ ). The percentage with anti-HDV antibodies was higher, while no difference was observed in the prevalence of anti-HCV or anti-HIV antibodies. The liver disease was less advanced, as denoted by a higher percentage of subjects with normal ALT values and a lower percentage of subjects with cirrhosis, although about half of the patients had HBV DNA levels  $>10^4$  copies/ml.

*Characteristics of patients according to the area of birth.* One hundred and four subjects (7.4%) were immigrants, mostly from eastern Europe or Asia. As compared with Italian subjects (Table 5), they were considerably younger ( $p<0.001$ ) and more often incident cases. HBeAg positive cases were 18.6% vs. 10.3% ( $p=0.01$ ), while no difference was observed in the prevalence of anti-HDV,

Stroffolini et al.

Chronic Hepatitis B in Italy

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3 anti-HCV or anti-HIV antibodies. There was no difference in the distribution of the liver disease  
4 categories. The vast majority of them had never received antiviral treatment.  
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8 *Variables associated with cirrhosis.* At univariate analysis age greater than 52 years, male gender,  
9 the presence of anti-HDV or anti-HCV antibodies, alcohol use >4 drinks/day and a B.M.I. higher  
10 than 23 were associated with cirrhosis. After adjustment for the influence of all the variables  
11 considered, age (OR 3.81; 95% CI 2.79-5.21), an anti-HDV positive test (OR 2.46; 95% CI 1.5-  
12 4.05) , an anti-HCV positive test (OR 1.83; 95% CI 1.06-3.16), alcohol use (OR 2.54; 95% CI 1.47-  
13 4.31) and BMI (OR 1.64; 95% CI 1.13-2.38) were independent predictors of the likelihood of  
14 cirrhosis. Gender was no longer an associated factor (Table 6).  
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For Peer Review

## Discussion

This cross-sectional study evaluated the profile of chronic HBsAg carriers observed consecutively in liver disease centres over a short period of time. The choice of a short enrolment period was aimed at avoiding biases due to changes in the diagnostic methods or clinical classification over time, particularly in HBV DNA analysis.

Eighty-nine per cent of the subjects were HBeAg negative. Interestingly, the balance between HBeAg positive and negative cases has reached a steady state in Italy during the last 10 years. After a dramatic fall in the prevalence of HBeAg by the end of the 1980s, since the year 1997, it has ranged between 10-15% in different surveys performed with similar selection criteria. The presence of HBeAg was associated with a younger age and HIV coinfection. Despite the younger age, HBeAg positive patients had an advanced liver disease in similar proportions to HBeAg negative individuals. This feature stresses once again the role of persistently high viral replication in promoting disease progression (Iloeje, 2006). Some of these patients may have acquired HBV at birth or in childhood, and hence had a long history of ongoing viral replication and progressive liver damage (Chu *et al*, 2002; Fattovich *et al*, 2008). In contrast, HBeAg-negative patients represent the survivors of the cohort who acquired HBV 2-5 decades ago, when HBV was endemic in Italy. They presented lower HBV DNA levels, and about one third of them presented undetectable HBV DNA. In general, HBeAg-negative patients require a close longitudinal observation in order to establish virological and disease activity and the need for antiviral therapy. This cross-sectional observation did not allow a precise diagnostic allocation of all patients, particularly of those with an inactive carrier state, since ALT and HBV DNA levels may fluctuate over time (Chu *et al*, 2002; Fattovich *et al*, 2008).

*Stroffolini et al.**Chronic Hepatitis B in Italy*

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3 In contrast to other countries (Zarsky et al, 1994; Lin et al, 2007), the direct contribution of  
4 immigrants to the pool of HBsAg positive individuals is still marginal since only 7% of the patients  
5 were immigrants in our series, but the prevalence of HBeAg among them was 18%. Due to the  
6 recruitment modalities, barriers to accessing medical care by high risk populations cannot be  
7 excluded and may underestimate the actual number of HBeAg positive subjects. Indeed, where  
8 screening programs had been performed, the majority of HBsAg positive persons among the  
9 immigrant population were not aware of their condition or were reluctant to access the medical  
10 services (Lin et al, 2007). In this study, about one quarter of the immigrants were at their first  
11 diagnosis of hepatitis B vs. only 8% among Italians, suggesting that educational or screening  
12 programmes are warranted to identify new carriers.  
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28 An estimate of the number of immigrants in Italy is around 3.5 million (1° Rapporto sugli immigrati  
29 in Italia, 2007). Hence, for each prevalence point of HBsAg carriers, about 35,000 new HBsAg  
30 carriers are expected, that is, 170,000-200,000 HBsAg carriers based on a 5-6% prevalence in  
31 incoming populations (Stroffolini et al, 2003). A marginal impact on the risk of disease  
32 transmission to the resident population is expected, due to the sophisticated barrier based on mass  
33 vaccination, which at present covers all subjects from 0 to 30 years of age. In addition, new  
34 demands on the Health Care System can be expected to manage liver diseases and to provide  
35 education and prevention campaigns.  
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48 Overall, coinfections with HCV, HDV or HIV were present in 15% of the patients; none of these  
49 were associated with immigration. HIV was associated independently with HBeAg positivity,  
50 together with a young age, irrespective of geographical origin. One third of the patients did not  
51 receive anti-HIV testing, indicating that this need did not receive adequate emphasis in clinical  
52 practice.  
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60 Unexpectedly, the downtrend of HDV coinfection, which was well documented in past years (Gaeta  
et al, 2000), seems to have stopped. Overall, 8.1% of the cases had anti-HDV antibodies, a

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*Stroffolini et al.*

*Chronic Hepatitis B in Italy*

percentage in the range of those reported in previous studies; even among younger patients the prevalence remained stable over time at around 6% (data not shown). In contrast, among the incident cases the prevalence was 14.3%, suggesting the arrival of a new wave of HDV-infected individuals. A similar trend was reported elsewhere in Europe (Wedemeyer et al, 2007; Cross et al, 2008), but in contrast with these countries HDV infection was not associated directly with immigrants. Unprotected sexual practices are possibly the main cause of the re-emergence of HDV.

More than 60% of the patients had received or were receiving antiviral treatment, and most of them were lamivudine-experienced. This underscores the risk of circulating primary resistant HBV strains and prompts for a systematic use of resistance testing in chronic HBV carriers.

Independent of an association with cirrhosis were age, HCV or HDV co-infection, an elevated BMI and a daily alcohol consumption of more than 40 g. The role of BMI in the progression of liver disease has been studied extensively in chronic hepatitis C, while to date its role in hepatitis B is controversial or not well demonstrated (Tsochatzis et al, 2007; Yen et al, 2008). One explanation is that in most series, patients with chronic hepatitis C were substantially older than patients with hepatitis B and thus more likely to have metabolic derangements (Moucari et al, 2008). In the series described in this study, the mean age of the Italian patients was over 50 years and their mean BMI was 25.4; among the immigrants, the mean age was 35 and BMI 23.7 ( $p < 0.001$ ). Nutrition and lifestyle may contribute to this difference. In the near future, metabolic factors may assume increasing importance as disease cofactors in chronic hepatitis B in countries where the cohorts of persons infected with HBV become older. stress that the clinical epidemiology of chronic hepatitis B and related liver disease cofactors have a dynamic profile over time, which influence the clinical presentation and outcome of the liver disease. As a consequence, there is a need for continuous monitoring and targeted screening and prevention programmes.

*Stroffolini et al.**Chronic Hepatitis B in Italy*

Footnotes

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*Stroffolini et al.*

*Chronic Hepatitis B in Italy*

Zarsky JP, Marcellin P, Cohard M, Lutz JM, Bouche C, Rais A. French Multicentre Group. 1994.  
Comparison of anti-HBe-positive and HBe-antigen-positive chronic hepatitis B in France. *J Hepatol* 20:636

For Peer Review

**Table 1.** Baseline characteristics of HBsAg positive subjects.

Variables	
Age (years) (mean $\pm$ S.D.) (range)	49.7 $\pm$ 12.8 (18-83)
Gender	
male	1,025 (73.4%)
female	371 (26.6%)
Referral pattern	
in-patients	105 (7.5%)
out-patients	1,291 (92.5%)
prevalent cases	1,264 (90.5%)
incident cases	132 (9.5%)
BMI (kg/m <sup>2</sup> )	25.3 $\pm$ 3.4
Alcohol intake	
abstinent	771 (55.2)
$\leq$ 4 drinks/day	527 (37.8)
$>$ 4 drinks/day	98 (7.0)
Area of origin (birth)	
north	513 (36.7%)
centre	177 (12.7%)
south/islands	602 (43.1%)
abroad	104 (7.4%)
Years of awareness of HBsAg positivity	
$\leq$ 10	487 (34.9%)
11-20	517 (37.0%)
$>$ 20	392 (28.1%)
Antiviral therapy	
never treated	552 (39.5%)
under treatment	647 (46.4%)
- new treatment	184 (13.2%)
- retreatment	463 (33.3%)
past treatment	197 (14.0%)
Diagnostic category	
unclassified	186 (13.3%)
chronic hepatitis	876 (62.8%)
liver cirrhosis	293 (21.0%)
hepatocellular carcinoma	41 (2.9%)

BMI: body mass index.

**Table 2.** Baseline virological characteristics of HBsAg positive subjects.

	No. of patients
HBeAg status*	
HBeAg positive	148 (11.0%)
HBeAg negative	1,202 (89.0%)
Anti-HDV*	
negative	1,084 (91.9%)
positive	95 (8.1%)
Anti-HCV*	
negative	1,194 (93.5%)
positive	83 (6.5%)
Anti-HIV*	
negative	871 (98.0%)
positive	18 (2.0%)
HBV-DNA** (copies/ml)	
undetectable	162 (26.8%)
<10 <sup>3</sup>	54 (8.9%)
10 <sup>3</sup> - 10 <sup>4</sup>	129 (21.3%)
>10 <sup>4</sup>	260 (43.0%)

\*Some data are missing. #Only in untreated patients.

**Table 3.** Comparison of chronic HBsAg carriers according to HBeAg status.

	HBeAg positive (n=148)	HBeAg negative (n=1,202)	p
Age (years) (mean ± S.D.)	45.6 ± 14.7	50.2 ± 12.5	<0.001
Gender			0.2
male	115 (77.7%)	692 (72.9%)	
female	33 (22.3%)	268 (27.1%)	
Referral pattern			0.004
in-patients	20 (13.5%)	82 (6.8%)	
out-patients	128 (86.5%)	1,120 (93.2%)	
prevalent cases	131 (88.5%)	1,095 (91.1%)	0.3
incident cases	17 (11.5%)	107 (8.9%)	
Area of origin (birth)			0.035
north	59 (39.9%)	441 (36.7%)	
centre	15 (10.1%)	160 (13.3%)	
south/islands	55 (37.2%)	518 (43.1%)	
abroad	19 (12.8%)	83 (6.9%)	
Diagnostic category			0.03
unclassified	8 (5.4%)	153 (12.7%)	
chronic hepatitis	103 (69.6%)	755 (62.8%)	
liver cirrhosis	30 (20.3%)	261 (21.7%)	
hepatocellular carcinoma	7 (4.7%)	33 (2.8%)	
BMI (kg/m <sup>2</sup> )	25.2 ± 4.0	25.2 ± 3.4	0.9
Years of awareness of HBsAg positivity			<0.001
≤ 10	67 (45.3%)	391 (32.5%)	
11-20	60 (40.5%)	448 (37.3%)	
> 20	21 (14.2%)	363 (30.2%)	
Anti-HDV			0.9
negative	117 (92.1%)	958 (92.2%)	
positive	10 (7.9%)	81 (7.8%)	
Anti-HCV			0.2
negative	125 (91.2%)	1,039 (93.9%)	
positive	12 (8.8%)	67 (6.1%)	
Anti-HIV			<0.001
negative	100 (94.3%)	751 (98.8%)	
positive	6 (5.7%)	9 (1.2%)	
ALT* ≤ 1 U.L.N.	28 (41.2%)	396 (61.1%)	0.005
1-3 U.L.N.	30 (44.1%)	199 (30.7%)	
> 3 U.L.N.	10 (14.7%)	53 (8.2%)	
HBV-DNA*# (copies/ml)			<0.001
undetectable	5 (8.6%)	155 (28.7%)	
<10 <sup>3</sup>	3 (5.2%)	51 (9.4%)	
10 <sup>3</sup> - 10 <sup>4</sup>	6 (10.3%)	122 (22.6%)	
>10 <sup>4</sup>	44 (75.9%)	212 (39.3%)	
Alcohol intake			0.02
abstinent	78 (52.7%)	675 (56.1%)	
≤ 4 drinks/day	52 (35.1%)	453 (37.7%)	
> 4 drinks/day	18 (12.2%)	74 (6.2%)	
Antiviral therapy			0.4
never treated	48 (32.4%)	474 (39.4%)	
past treatment	20 (13.5%)	174 (14.5%)	
under treatment	80 (54.1%)	574 (46.1%)	
- new treatment	22 (14.9%)	159 (13.2%)	
- retreatment	58 (39.2%)	395 (32.9%)	

\* Some data are missing. # Only in untreated patients

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For Peer Review

**Table 4.** Comparison of chronic HBsAg carriers according to referral pattern.

	Incident cases (n = 132)	Prevalent cases (n = 1,264)	p
Age (years) (mean ± S.D.)	46.9 ± 13.8	49.9 ± 12.6	0.01
Gender			0.01
male	85 (64.4%)	940 (74.4%)	
female	47 (35.6%)	324 (25.6%)	
Referral pattern			<0.001
in-patients	21 (15.9%)	84 (6.6%)	
out-patients	111 (84.1%)	1,180 (93.4%)	
Area of origin (birth)			<0.001
north	76 (57.5%)	437 (34.6%)	
centre	10 (7.6%)	167 (13.2%)	
south/islands	22 (16.7%)	580 (45.9%)	
abroad	24 (18.2%)	80 (6.3%)	
Diagnostic category			<0.001
unclassified	37 (28.0%)	149 (11.8%)	
chronic hepatitis	70 (53.0%)	806 (63.8%)	
liver cirrhosis	23 (17.4%)	270 (21.3%)	
hepatocellular carcinoma	2 (1.6%)	39 (3.1%)	
BMI (kg/m <sup>2</sup> )	24.8 ± 3.3	25.3 ± 3.5	0.1
HBeAg			0.3
negative	107 (86.3%)	1,095 (89.3%)	
positive	17 (13.7%)	131 (10.7%)	
Anti-HDV			0.018
negative	84 (85.7%)	1,000 (92.5%)	
positive	14 (14.3%)	81 (7.5%)	
Anti-HCV			0.9
negative	112 (93.3%)	1,082 (93.5%)	
positive	8 (6.7%)	75 (6.5%)	
Anti-HIV			0.6
negative	75 (98.7%)	796 (97.9%)	
positive	1 (1.3%)	17 (2.1%)	
HBV-DNA <sup>*#</sup> (copies/ml)			0.03
undetectable	12 (18.8%)	150 (27.7%)	
<10 <sup>3</sup>	11 (17.2%)	43 (8.0%)	
10 <sup>3</sup> - 10 <sup>4</sup>	10 (15.6%)	119 (22.0%)	
>10 <sup>4</sup>	31 (48.4%)	229 (42.3%)	
Alcohol intake			0.9
abstinent	71 (53.8%)	700 (55.4%)	
≤ 4 drinks/day	52 (39.4%)	475 (37.6%)	
> 4 drinks/day	9 (6.8%)	89 (7.0%)	

\* Some data are missing. # Only in untreated patients

**Table 5.** Comparison of chronic HBsAg carriers according to country of birth.

	<b>Italian cases (n = 1,292)</b>	<b>Immigrant cases (n = 104)</b>	<b>p</b>
Age (years) (mean ± S.D.)	50.8 ± 12,3	35.8 ± 10.5	<0.001
Gender			
male	958 (74.1%)	67 (64.4%)	0.02
female	334 (25.9%)	37 (35.6%)	
Referral pattern			
in-patients	99 (7.7%)	6 (5.8%)	0.7
out-patients	1193 (92.3%)	98 (94.2%)	
prevalent cases	1184 (91.6%)	80 (76.9%)	<0.001
incident cases	108 (8.4%)	24 (23.1%)	
Diagnostic category			
unclassified	164 (12.7%)	22 (21.0%)	0.06
chronic hepatitis	813 (62.9%)	63 (60.6%)	
liver cirrhosis	275 (21.3%)	18 (17.3%)	
hepatocellular carcinoma	40 (3.1%)	1 (1.1%)	
BMI (kg/m <sup>2</sup> )	25.4 ± 3.5	23.7 ± 3.3	<0.001
HBeAg			
negative	1,119 (89.7%)	83 (81.4%)	0.01
positive	129 (10.3%)	19 (18.6%)	
Anti-HDV			
negative	1,007 (92.0%)	77 (91.7%)	0.9
positive	88 (8.03%)	7 (8.3%)	
Anti-HCV			
negative	1,105 (93.6%)	89 (92.7%)	0.7
positive	76 (6.4%)	7 (7.3%)	
Anti-HIV			
negative	795 (97.9%)	76 (98.7%)	0.6
positive	17 (2.1%)	1 (1.3%)	
HBV-DNA*# (copies/ml)			
undetectable	148 (27,4%)	14 (21,5%)	0.2
<10 <sup>3</sup>	44 (8,2%)	10 (15,4%)	
10 <sup>3</sup> - 10 <sup>4</sup>	114 (21,1%)	15 (23,1%)	
>10 <sup>4</sup>	234 (43,3%)	26 (40,0%)	
Alcohol intake			
abstinent	696 (53.9%)	75 (72.1%)	0.001
≤ 4 drinks/day	506 (39.2%)	21 (20.2%)	
> 4 drinks/day	90 (7.0%)	8 (7.7%)	
Antiviral therapy			
never treated	480 (37.2%)	72 (69.2%)	<0.001
past treatment	190 (14.7%)	7 (6.7%)	
under treatment	622 (48.1%)	25 (24.1%)	
- new treatment	172 (13.3%)	12 (11.5%)	
- retreatment	450 (34.8%)	13 (12.5%)	

\* Some data are missing. # Only in untreated patients.

**Table 6.** Factors associated with cirrhosis. Crude and adjusted Odds Ratios (O.R.) derived by multiple logistic regression analysis. Patients with HCC were excluded from the analysis.

Variable	Absence of cirrhosis	Cirrhosis	Crude O.R. (95% C.I.)	Adjusted O.R. (95% C.I.)	p
Age					
≤ 52 years	656 (61.8%)	92 (31.4%)			
> 52 years	406 (38.2%)	201 (68.6%)	3.53 (2.68-4.65)	3.81 (2.79-5.21)	<0.001
Gender					
female	308 (29.0%)	60 (20.5%)			
male	754 (71.0%)	233 (79.5%)	1.59 (1.16-2.17)	1.22 (0.83-1.79)	0.3
HBeAg					
negative	908 (89.1%)	261 (89.7%)			
positive	111 (10.9%)	30 (10.3%)	0.94 (0.61-1.44)		
Anti-HDV					
negative	819 (93.4%)	229 (86.4%)			
positive	58 (6.6%)	36 (13.6%)	2.22 (1.43-3.45)	2.46 (1.50-4.05)	<0.001
Anti-HCV					
negative	907 (94.5%)	248 (89.5%)			
positive	53 (5.5%)	29 (10.5%)	2.01 (1.25-3.22)	1.83 (1.06-3.16)	0.03
Anti-HIV					
negative	644 (97.9%)	196 (98.0%)			
positive	14 (2.1%)	4 (2.0%)	0.94 (0.31-2.89)		
Alcohol intake					
abstinent	622 (61.8%)	131 (50.4%)			
≤ 4drinks/day	384 (38.2%)	129 (49.6%)	1.60 (1.21-2.10)	1.11 (0.81-1.51)	0.5
> 4drinks/day	56 (8.3%)	33 (20.1%)	2.80 (1.75-4.47)	2.54 (1.47-4.39)	0.001
BMI (kg/m <sup>2</sup> )					
≤ 23	285 (26.8%)	51 (17.4%)			
> 23	777 (73.2%)	242 (82.6%)	1.74 (1.25-2.42)	1.64 (1.13-2.38)	0.01