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BRIEF ARTICLE

Impact of comorbidities on the severity of chronic hepatitis B at presentation

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Abstract

AIM: To evaluate the clinical relevance of each cofactor on clinical presentation of chronic hepatitis B.

METHODS: Out of 1366 hepatitis B surface antigen (HBsAg) positive subjects consecutively observed in 79 Italian hospitals, 53 (4.3%) showed as the only cofactor hepatitis D virus (HDV) infection [hepatitis B virus (HBV)/HDV group], 130 (9.5%) hepatitis C virus (HCV) (group HBV/HCV), 6 (0.4%) human immunodeficiency virus (HIV) (group HBV/HIV), 138 (10.2%) alcohol abuse (group HBV/alcohol); 109 (8.0%) subjects had at least two cofactors and 924 were in the cofactor-free (CF) group.

RESULTS: Compared with patients in group CF those in group HBV/alcohol were older and more frequently had cirrhosis ($P < 0.001$), those in group HBV/HDV were younger ($P < 0.001$), more frequently resided in the south of the country and had cirrhosis ($P < 0.001$), those in group HBV/HCV were older ($P < 0.001$) and more frequently had cirrhosis ($P < 0.001$). These cofactors were all independent predictors of liver cirrhosis in HBsAg positive patients. Multivariate analysis showed that an older age [odds ratio (OR) 1.06, 95% CI: 1.05-1.08], alcohol abuse with more than 8 drinks daily (OR 2.89, 95% CI: 1.81-4.62) and anti-HDV positivity (OR 3.48, 95% CI: 2.16-5.58) are all independently associated with liver cirrhosis. This association was found also for anti-HCV positivity in univariate analysis, but it was no longer associated (OR 1.23, 95% CI: 0.84-1.80) at multivariate analysis.

CONCLUSION: Older age, HDV infection and alcohol abuse are the major determinants of severe liver disease in chronic HBV infection, while HCV replication plays a lesser role in the severity of hepatic damage.

Key words: Chronic hepatitis B; Hepatitis B virus/hepatitis D virus dual infection; Hepatitis B virus/hepatitis C virus dual infection; Alcohol abuse

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INTRODUCTION

Seroepidemiological studies on the aetiology of chronic hepatitis in Italy performed in the 1980s, 1990s[1-3] and in 2001[4] showed a progressive reduction in the prevalence of hepatitis B surface antigen (HBsAg) positive cases from 60.7% observed in cases collected from 1976 to 1981[1] to 13% found in 2001[4]. Despite this, infection by the hepatitis B virus (HBV) is still responsible for a sizable number of cases of chronic hepatitis and/or hepatocellular carcinoma (HCC), and the burden of HBV infection on the healthcare system in Italy is still heavy.

In a multicentre study carried out on 1829 patients with cirrhosis in 1992, the prevalence of HBV-related cases was 13.8%; in particular, HBV was the only aetiological factor in 4.2% of cases, most cases being associated with cofactors (9.6%): hepatitis D virus (HDV) in 3.4%, hepatitis C virus (HCV) in 3.2% and alcohol abuse in the remaining 3%[5]. In human immunodeficiency virus (HIV)/HBV dual infection, found in 3.7%-4.6% of HIV positive subjects in Italy but estimated around 10% in people with HIV infection worldwide[6], the prevalence of patients with cirrhosis is reported as higher than in HIV-negative/HBV-positive cases[7]. Cofactors may therefore play a substantial role in the progression of HBsAg positive chronic hepatitis to the more severe clinical forms[8-10].

The gradual reduction in the percentage of HBsAg positive cases was associated with a dramatic decrease in the prevalence of cases with HBV/HDV dual infection[11-13]. About a quarter of HBsAg positive patients with chronic hepatitis were anti-HDV positive in 1978-1981[14] and in 1987[15]; this prevalence was lower in 1992 (14.4%)[16], in 1997 (8.3%)[17] and in 2001 (9.9%)[4]. No data to this effect are available on HBV/HCV dual infection and on the association of HBV infection/alcohol intake[18].

Our survey on the largest series of patients with chronic hepatitis ever studied in Italy showed an overall low HDV prevalence in HBsAg chronic carriers (9%), a high prevalence of patients with HBV/HCV dual infection (16.9%) and alcohol abuse (10.4%)[4]. The data from this study allow us to evaluate the current main characteristics of patients with HBV/HDV or HBV/HCV chronic infection or HBV infection/alcohol abuse compared with a large control group of HBsAg chronic carriers with no evident cofactor.

MATERIALS AND METHODS

The study design was more extensively described in a previous paper[4]. Seventy-nine centres participated in the study, 25 in the North, 24 in the Centre and 30 in the South of Italy and the two main islands (Sicily and Sardinia).

All subjects consecutively referred from February 1 to July 31, 2001 as in-patients or out-patients to one of the 79 Italian centres were recruited; 9997 patients with chronic hepatitis were enrolled. Both tertiary and peripheral centres were randomly selected by a systematic cluster sampling procedure. For each of these three geographical areas, all of the hospitals were identified and listed numerically according to an assigned number. In each list, a single hospital was considered as a cluster. The first cluster was randomly chosen, whereas the others were selected with a probability proportional to the required number of hospitals at systematic intervals. Both prevalent and incident cases were recruited. We defined as "incident cases" all new diagnoses of chronic liver disease made during the enrolment period, and as "prevalent cases" all subjects with a previous diagnosis of chronic liver disease observed during the study period.

For each subject, the demographic, clinical and aetiological 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. An alcohol intake of more than 40 g daily for males and 30 g daily for females for at least 10 years was considered as an aetiological cofactor[19,20].

HBV serum markers, HBsAg, anti-HBc, hepatitis B e antigen (HBeAg), anti-HBeAg and anti-HDV were determined by commercial immunoenzymatic assays. Antibodies to HCV were detected by 3rd generation commercial immunoenzymatic assays. Antibodies to HIV 1 and 2 were determined by commercial enzyme-linked immunosorbent assay (Diasorin Biomedica, Saluggia, Vercelli, Italy; Abbott Labs, North Chicago, Illinois, United States) and the positive results were confirmed by a Western Blot analysis (Genelabs Diagnostics, Science Park Drive, Singapore). Patients were enrolled in 2001 when various methods of different sensitivity were used to detect HBV viral load in different centres in Italy. For this reason, we preferred not to evaluate the predicting value of HBV viral load; data on HBV-DNA were given as positive or negative.

Data on HDV-RNA and HDV-Ag were not available. We classified patients as asymptomatic carriers when alanine aminotransferase (ALT) values were persistently normal in the absence of clinical, biochemical and ultrasound signs of chronic liver disease. Chronic hepatitis was diagnosed only on the basis of liver histology. Liver cirrhosis was diagnosed from a liver biopsy or the presence of unequivocal clinical, biochemical and ultrasound signs[20]. HCC diagnosis was based on histology, imaging techniques or biochemical parameters (α_1-feto protein greater than 400 ng/mL)[21,22]. Patients with serum markers suggesting autoimmune liver disease and those with liver disease associated with genetic disorders were excluded from the study.

Statistical analysis

Continuous variables were summarised as mean ± SD or median and interquartile range, and categorical variables as absolute and relative frequencies. Differences in the means were evaluated by an unpaired Student *t* test or Kruskal-Wallis one-way analysis of variance, and the χ^2 test was applied to categorical variables. Crude odds ratios (OR) and their 95% CI for the association of liver cirrhosis with potential risk factors were calculated by univariate analysis. Adjusted OR were calculated by stepwise logistic regression analysis to identify factors independently associated with liver cirrhosis. Only factors associated with liver cirrhosis by univariate analysis were included in the logistic regression analysis. In the logistic model liver cirrhosis was the outcome variable, while age, sex, anti-HDV, anti-HCV, alcohol intake, and body mass index were the independent variables.

RESULTS

Of the 1366 HBsAg positive patients, 924 (67.6%) lacked all the cofactors investigated (HDV, HCV, HIV and alcohol abuse); this group of patients was named the cofactor-free (CF) group. Fifty-nine (4.3%) patients showed HDV infection (anti-HDV positive) as the only cofactor (group HBV/HDV), 130 (9.5%) HCV infection (group HBV/HCV), 6 (0.4%) HIV infection (group HBV/HIV), 138 (10.2%) alcohol abuse (group HBV/alcohol) and 109 (8.0%) had more than one cofactor (group with two or more cofactors). Overall, 333 (24.4%) patients had no liver biopsy at presentation; of the remaining 1033 cases, 278 subjects (26.9%) were classified as asymptomatic carriers, 453 (43.9%) as having chronic hepatitis, 249 (24.9%) as having liver cirrhosis and 53 (5.1%) patients had a diagnosis of HCC. Interferon treatment was given in 365 (26.7%) patients and 244 (17.9%) patients received Lamivudine. Excluding cases under immunosuppressive therapy, approximately all HBeAg positive and half of HBeAg negative cases showed active HBV replication. Fifty-seven (4.2%) patients were born outside Italy, and only 4 of them were born in China.

Characteristics of the CF group

The 924 HBsAg positive subjects with none of the cofactors investigated were more frequently males (66.5%) and observed as out-patients (81.1%) and as prevalent cases (83.2%); they aged 48.1 ± 14.3 years, were infrequently HBeAg positive (12.6%) and frequently showed a mild clinical presentation: 26.9% of cases were asymptomatic carriers, 56.9% of patients showed chronic hepatitis, 12.4% liver cirrhosis and 3.8% had HCC.

Comparison according to anti-HDV status

The 59 anti-HDV positive patients were younger than those in group CF (46.7 ± 11.8 years *vs* 48.1 ± 14.3 years; $P < 0.001$) and showed higher ALT levels (128 ± 116 IU/L *vs* 98 ± 290 IU/L, $P = 0.008$); they were more frequently observed as in-patients (25.4% *vs* 18.9%, $P = 0.3$), were more frequently born in southern Italy or on one of the two main islands (67.8% *vs* 52.9%, $P = 0.029$) and more frequently had liver cirrhosis (37.3% *vs* 12.4%, $P \leqslant 0.001$); none of the 59 anti-Delta positive patients had HCC (Table 1).

Comparison according to anti-HCV status

The 130 subjects co-infected with HCV were older than those in group CF (55.2 ± 14.7 years *vs* 48.1 ± 14.3 years, $P < 0.0001$), and more frequently showed liver cirrhosis (23.1% *vs* 12.4%, $P < 0.001$); this group contained the highest prevalence of patients with HCC observed in the study (6.2%) (Table 1). Active HCV replication as evaluated by positive HCV-RNA by RT-PCR was found in 115 subjects (88.5%).

Comparison according to anti-HIV status

Only 6 patients showed HBV/HIV dual infection; all of these patients were males and younger than those in group CF. Four of them were HBeAg positive and none had liver cirrhosis (Table 1).

Comparison according to alcohol abuse

Compared with patients in group CF, the 138 HBsAg positive patients with alcohol abuse as the only cofactor were older (52.6 ± 11.8 years *vs* 48.1 ± 14.3 years, $P < 0.0001$), were more frequently males (92.6% *vs* 66.5%, $P < 0.0001$), had had fewer years of schooling (85.9% *vs* 67.0%, $P < 0.001$) and more frequently showed liver cirrhosis (31.1% *vs* 12.4%, $P < 0.0001$) and HCC (5.1%).

Comparison according to the presence of two or more cofactors

Of the 109 patients in this group, 21 had HBV/HDV/HCV concurrent infection, 12 HBV/HDV dual infection plus alcohol abuse, 64 had HBV/HCV dual infection plus alcohol abuse, and 12 had HBV/HDV/HCV concurrent infection plus alcohol abuse. Compared with group CF, patients with two or more cofactors were more frequently males (86.8% *vs* 66.5%, $P < 0.001$), in-patients (28.0% *vs* 18.9%, $P = 0.003$) and had liver cirrhosis (35.8% *vs* 12.4%, $P < 0.001$). They more frequently belonged to larger families (24.5% *vs* 14.6%, $P < 0.01$) and had had fewer years of schooling (84.3% *vs* 67.0%, $P < 0.001$). Only 4 patients showed HCC (Table 1).

Variables associated with the presence of cirrhosis

At the univariate analysis older age, anti-HCV, HCV-RNA positivity, alcohol abuse, anti-HDV and anti-HIV positivity were all associated with liver cirrhosis. Multivariate analysis showed that age (OR 1.10, 95% CI: 1.08-1.11), alcohol abuse (between 4 and 8 drinks daily: OR 2.30, 95% CI: 1.29-4.10; more than 8 drinks daily: OR 2.42, 95% CI: 1.31-4.46), HDV positivity (OR 2.68, 95% CI: 1.56-4.61) and anti-HIV (OR 5.78, 95% CI: 1.50-22.27) were independent predictors of the development of cirrhosis, whereas anti-HCV and HCV-RNA positivity were no longer associated (Table 2).

Table 1 Comparison of baseline features of hepatitis B surface antigen positive patients, according to different cofactors (mean ± SD) *n* (%)

Variable	HBsAg positive (*n* = 924)	HBsAg/anti-HDV positive (*n* = 59)	HBsAg/anti-HCV positive (*n* = 130)	HBsAg/anti-HIV positive (*n* = 6)	HBsAg/alcohol abuse (*n* = 138)	HBsAg/two or more cofactors (*n* = 109)	*P* value
Age (yr)	48.4 ± 14.0	46.5 ± 11.7	55.2 ± 14.7	37.0 ± 3.6	52.7 ± 11.7	45.8 ± 12.1	< 0.001
Males	606 (66.5)	41 (71.9)	87 (68.0)	6 (100)	126 (92.6)	92 (86.8)	< 0.001
In-patients	171 (18.9)	15 (25.4)	29 (22.7)	0	20 (14.7)	30 (28.0)	0.060
Out-patients	732 (81.1)	44 (74.6)	99 (77.3)	6 (100)	116 (85.3)	77 (72.0)	
Prevalent cases	769 (83.2)	53 (89.8)	111 (85.4)	6 (100)	115 (83.3)	95 (87.2)	0.500
Incident cases	155 (16.8)	6 (10.2)	19 (14.6)	0	23 (16.7)	14 (12.8)	
Born in Italy							
North	192 (21.0)	11 (18.6)	36 (27.7)	3 (50.0)	32 (23.7)	35 (32.4)	0.010
Centre	195 (21.3)	5 (8.5)	16 (12.3)	0	26 (19.3)	21 (19.4)	
South/islands	484 (52.9)	40 (67.8)	76 (58.5)	2 (33.3)	73 (54.1)	49 (45.4)	
Born Abroad	44 (4.8)	3 (5.1)	2 (1.5)	1 (16.7)	4 (2.9)	3 (2.8)	
Asymptomatic carrier	233 (33.5)	3 (6.0)	17 (17.7)	1 (100)	19 (17.6)	5 (6.0)	< 0.001
Chronic hepatitis[1]	313 (45.0)	25 (50.0)	41 (42.7)	0	39 (36.1)	35 (42.2)	
Liver cirrhosis	115 (16.5)	22 (44.0)	30 (31.3)	0	43 (39.8)	39 (47.0)	
HCC	34 (4.9)	0	8 (8.3)	0	7 (6.5)	4 (4.8)	
ALT (× ULN) (median, IQR)	1.0 (1.0-1.8)	2.2 (1.1-4.8)	1.4 (1.0-2.1)	1.5 (1.1-1.8)	1.1 (1.0-2.1)	1.8 (1.0-2.9)	< 0.001
BMI (kg/m^2)	25.0 ± 3.4	25.5 ± 5.0	24.8 ± 3.1	22.8 ± 2.0	26.1 ± 3.5	25.6 ± 4.1	0.006
Years of schooling							< 0.001
< 6	239 (26.3)	9 (16.4)	46 (36.5)	1 (16.7)	62 (46.3)	31 (28.7)	
6-13	369 (40.7)	31 (56.4)	53 (42.1)	1 (16.7)	53 (39.5)	60 (55.6)	
> 13	299 (33.0)	15 (27.2)	27 (21.4)	4 (66.6)	19 (14.2)	17 (15.7)	
HBeAg positive	116 (12.6)	9 (15.3)	10 (7.7)	4 (66.7)	10 (7.2)	15 (13.8)	< 0.001
HBeAg negative	808 (87.4)	50 (84.7)	120 (92.3)	2 (33.3)	128 (92.8)	94 (86.2)	

[1]Only subjects with liver biopsy. HBsAg: Hepatitis B surface antigen; HDV: Hepatitis D virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase; × ULN: Times the upper limit of the normal; IQR: Interquartile range; BMI: Body mass index; HBeAg: Hepatitis B e antigen.

Comparison according to the severity of liver cirrhosis

The Child-Pugh Score was calculated for 229 (92.0%) of the 249 patients with cirrhosis: 104 cases in group CF, 43 cases in group HBV/Alcohol, 19 cases in group HBV/HDV, 30 cases in group HBV/HCV and 33 cases in the HBV/two or more cofactors group. The prevalence of patients in the Child-Pugh Classes B or C was lower in group CF (31.7%), than in group HBV/Alcohol (44.2%), in group HBV/HCV (43.3%) and in the HBV/two or more cofactors group (75.8%, $P < 0.001$) (Table 3).

DISCUSSION

This study is based on three strong points: the first, a large sample size, the second, the validity of the random selection including both tertiary and peripheral hospitals all over the country, which may have avoided the selection of "difficult-to-treat" patients, and lastly, the homogeneity of each single cofactor group and of the comparative CF group, making this study the first to investigate the clinical presentation of CF HBsAg positive chronic hepatitis and the influence of each single cofactor (HDV, HCV and alcohol intake).

Excluding the 442 patients with one or more cofactors enabled us to examine a group of almost a thousand patients with HBsAg positive chronic hepatitis and no cofactor. Most of these patients showed a mild clinical presentation and only a minority of them had liver cirrhosis (12.4%), prevalently in the Child A stage. The low prevalence of HCC (3.9%) refers to HCC at the time of diagnosis. No information is available on the risk of occurrence of HCC, death or orthotopic liver transplantation over time, since the present study is cross-sectional and no evaluation of the clinical outcomes was made.

Despite the decreasing endemicity levels, HDV infection maintains its geographical distribution in our country, i.e., more frequent in southern Italy and on the two main islands, as previously described[15-17]. Compared with those in group CF, patients in group HBV/HDV showed a more severe clinical presentation: they were younger, more frequently hospitalised and with evidence of cirrhosis. In accordance with the low prevalence of patients with HCC in previous studies[5], no patient in our HBV/HDV group showed HCC, most probably reflecting a more severe course of the illness with a rapid transition to death or to the need for liver transplantation before HCC becomes evident[23]. On the other hand, patients in group HBV/HCV were older than those in group CF, more frequently had liver cirrhosis and showed an almost double prevalence of HCC. These differences, although not statistically significant, may suggest that subjects with long-lasting HBV/HCV dual infection are at a higher risk of developing liver cirrhosis with or without liver cancer[24-26].

Most patients in group HBV/Alcohol were males with a low educational level, a combination more frequently associated with a high risk of alcohol abuse. The prevalence of patients with cirrhosis was 2.5 times higher in group HBV/alcohol than in group CF, a dif-

Table 2 Risk factors associated with cirrhosis in hepatitis B surface antigen positive patients *n* (%)

Variable	Chronic hepatitis	Cirrhosis	Crude OR (95% CI)	Adjusted OR (95% CI)	*P* value
Age (mean ± SD, yr)	44.9 ± 12.0	56.2 ± 11.6	1.06 (1.05-1.07)	1.10 (1.08-1.11)	< 0.001
Gender					
Male	371 (81.9)	192 (77.1)	1		
Female	82 (18.1)	57 (22.9)	1.34 (0.92-1.97)		
HBeAg					
Negative	387 (85.4)	225 (90.4)	1		
Positive	66 (14.6)	24 (9.6)	0.63 (0.38-1.03)		
Anti-HCV					
Negative	382 (84.3)	187 (75.1)	1	1	0.300
Positive	71 (15.7)	62 (24.9)	1.78 (1.22-2.62)	1.23 (0.84-1.80)	
HCV-RNA					
Negative	382 (86.2)	187 (77.3)	1	1	0.200
Positive	61 (13.8)	55 (22.7)	1.84 (1.23-2.76)	1.44 (0.65-1.72)	
Anti-HDV					
Negative	410 (90.5)	207 (83.1)	1	1	< 0.001
Positive	43 (9.5)	42 (16.9)	1.94 (1.23-3.06)	2.68 (1.56-4.61)	
Anti-HIV					
Negative	449 (99.1)	241 (96.8)	1	1	0.010
Positive	4 (0.9)	8 (3.2)	3.73 (1.11-12.50)	5.78 (1.50-22.27)	
Alcohol (drinks/d)					
0	247 (54.5)	117 (47.0)	1	1	
< 4	143 (31.6)	56 (22.4)	0.83 (0.57-1.21)	0.69 (0.48-1.07)	0.080
4-8	35 (7.7)	37 (14.9)	2.23 (1.34-3.72)	2.30 (1.29-4.01)	0.005
> 8	28 (6.2)	39 (15.7)	2.94 (1.73-5.01)	2.42 (1.31-4.46)	0.005
BMI (kg/m^2)					
< 25	247 (54.5)	121 (48.6)	1		
25-30	173 (38.2)	107 (43.0)	1.26 (0.91-1.75)		
> 30	33 (7.3)	21 (8.4)	1.30 (0.72-2.34)		

Crude and adjusted odds ratios (OR) deriving from multiple logistic regression analysis. Patients with HCC were excluded from the analysis. HCC: Hepatocellular carcinoma; HDV: Hepatitis D virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; BMI: Body mass index.

Table 3 Percentages of cases in different child-pugh classes in 229 of the 249 patients with liver cirrhosis, by aetiology *n* (%)

Child-pugh class	CF group (*n* = 104)	HBV/alcohol group (*n* = 43)	HBV/HDV group (*n* = 19)	HBV/HCV group (*n* = 30)	HBV/ two or more cofactors group (*n* = 33)
A	71 (68.3)	24 (55.8)	13 (68.4)	17 (56.7)	8 (24.2)
B + C	33 (31.7)[b]	19 (44.2)	6 (31.6)	13 (43.3)	25 (75.8)[b]

[b]$P < 0.001$ *vs* hepatitis B virus (HBV)/two or more cofactors. Patients with hepatocellular carcinoma are not included. CF: Cofactor-free; HCV: Hepatitis C virus; HDV: Hepatitis D virus.

ference most probably due to alcohol intake rather than to the association of the two aetiological factors, since, as described in a previous paper[4], 41.8% of 761 patients showing alcohol abuse as the only aetiological factor had liver cirrhosis. The group of patients with two or more cofactors is a miscellany of 4 subgroups that are too small to be analysed or compared with group CF or with the other cofactor groups. This miscellaneous group with more than one cofactor may be more frequently exposed to the aetiological agents of liver disease and to a higher risk of developing liver cirrhosis and/or HCC.

As observed in previous Italian studies[4,17,18], the majority of HBsAg positive patients in this study were found to be HBeAg negative. Patients with HBV/HCV dual infection and those with HBV plus alcohol abuse showed a lower prevalence of HBeAg positive cases than those in the other aetiological groups, probably because they were older and HBeAg loss is, at least in part, a time-dependent phenomenon.

In conclusion, HBV chronic infection was frequently associated with a mild or moderate clinical condition. Liver cirrhosis and HCC were detected in less than one sixth of cases, and viral and metabolic cofactors unfavourably influenced the clinical course in patients with chronic HBV infection since their presence was associated with an increased risk of cirrhosis, an association proven by multivariate logistic regression analysis for HDV infection and alcohol abuse.

COMMENTS

Background

Many cofactors play a substantial role in the progression of hepatitis B surface antigen positive chronic hepatitis to more severe clinical forms.

Research frontiers

The study aimed to evaluate the clinical relevance of each cofactor on the severity of the clinical presentation of chronic hepatitis B.

Innovations and breakthroughs

Older age, hepatitis D virus co-infection and alcohol abuse are the major determinants of severe liver disease in chronic hepatitis B virus (HBV) infection. Conversely, hepatitis C virus replication plays a lesser role in the severity of hepatic damage.

Applications

Removal of some risk factors may hamper the progression of chronic HBV-related liver disease in many patients.

Peer review

This is a large-size, multicentre study showing the importance of comorbidities in exacerbating hepatocellular necroinflammation and playing a substantial role in the progression to a more advanced stage of liver disease.

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