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Original Article

Alcoholic intake predisposes to more interface hepatitis in chronic hepatitis C

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Abstract

Progression of liver disease in chronic hepatitis C depends on several factors related to the host, virus and the environment which deserves further investigations. 120 candidates for blood donation with hepatitis C virus were divided into three groups according to alcohol intake: abstainers⁴¹, light drinkers³⁶ and heavy drinkers⁴³. Liver histopathology alterations, namely architectural staging, periportal and lobular inflammation as well as portal inflammatory infiltrate were graded from 0 to 4 and afterwards divided into light (0 to 2) and severe (3 to 4). There were more drinkers among men (83.5%) than among women (41.5%). Regarding the three groups, mild periportal inflammation was significantly related with abstainers and light drinkers groups whereas severe periportal inflammation was more predominant in heavy drinkers ($p = 0.033$). When we compared mild with severe histopathological alterations older age was significantly ($p = 0.004$) associated with severe fibrosis, periportal inflammation and portal inflammatory infiltrate. In relation to enzyme levels a significant difference in fibrosis and lobular activity was found for ALT, AST and GGT. Only AST was a marker of greater portal inflammatory infiltrate. Additionally, platelets were significantly lower in severe fibrosis and in periportal

inflammation. Logistic regression analysis identified AST and platelets as independent predictors for severe fibrosis. In conclusion, a correlation was found between alcohol consumption and periportal inflammation. Fibrosis correlated with age, high enzymes levels and low platelets. AST and platelets were the best predictors for severe fibrosis.

Key words: Hepatitis C virus, fibrosis, platelets, ethanol ingestion, blood donors.

Introduction

Hepatitis C virus (HCV) is recognized as the major cause of chronic hepatitis worldwide.¹ Once HCV infection develops, it progresses silently to chronic hepatitis in about 80% of the cases. Cirrhosis and hepatocellular carcinoma will develop in respectively 20% and 4%.² The natural history of HCV infection remains speculative, mainly due to the absence of symptoms that would require medical attention. Predictive factors for the progression of the disease continue to be a major challenge, mainly in asymptomatic patients, as candidates for blood donation. Many studies have been developed in order to try to identify which are the potential prognostic markers that could lead to the development of cirrhosis.³ Various factors of the host, the virus and the environment have been investigated, including older age, gender, age at contamination, viral load, genotype, alcohol intake and disease transmission patterns.⁴⁻⁶

The interaction between HCV infection and alcohol intake contributes to the severity of liver disease. According to many studies, excessive use of alcohol influences the progression of HCV infection.⁷⁻¹⁰ However, alcohol consumption alone may cause damage, but only 20% develop cirrhosis,¹¹ suggesting that other factors may contribute to hepatic disorders. Some investigators, examining HCV carriers with different levels of alcohol consumption, found fibrosis progression especially in obese and diabetes patients.¹²

Controversies exist concerning histological findings in chronic hepatitis C¹³ and in general, hepatic enzyme values are considered to correlate poorly with histopathological changes.¹⁴⁻¹⁶ Although the architectural alterations,

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Abbreviation used: HCV: hepatitis C virus; CHC: chronic hepatitis C; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; BMI: body mass index; HBsAg: Hepatitis B surface antigen; IgG: immunoglobulin G; IgM: immunoglobulin M.

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namely degree of fibrosis, are clinically relevant for staging chronic hepatitis C, the degree of the inflammatory process should also be considered in the natural history or the progression of the disease.

The aim of our study was to evaluate the relationship between different alcohol consumption and grading of histopathological variables.

Patients and methods

During a period of two years, 120 consecutive outpatients at the Hemocentro of São Paulo (Clinic Hospital of FM-USP) were studied. Inclusion of these candidates for blood donation was made according to the following criteria: a) Anti-HCV positive, confirmed by supplementary recombinant immunoblot assay (RIBA or LIA and HCV RNA by PCR); b) alanine aminotransferase (ALT) levels above normal; c) age ranging from 18 to 65 years for both genders; d) a written informed consent of the patients, as approved by our hospital ethics committee; e) acceptance of liver biopsy performance. In all patients the following clinical and demographic information were obtained: gender, age, Body Mass Index (BMI) (calculated as weight in kilograms divided by height in meters squared), source of HCV infection (transfusion, intravenous drug use, surgery, tattoos, acupuncture, sexual contacts), estimated duration of HCV infection (defined as the number of years since the time of the earliest exposure to an identified risk factor), laboratory data at the time of liver biopsy: serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), serum gamma glutamyl transferase (GGT), platelet number (mm^3), serum Immunoglobulin M (IgM), Immunoglobulin G (IgG). Exclusion criteria were: presence of anti-nuclear antibodies, anti-smooth muscle antibodies, anti-liver-kidney microsomes antibodies, anti-mitochondrial antibodies in titles $> 1/80$; Anti-HIV, HBsAg and hepatocellular carcinoma.

Alcohol quantification. All patients and family members were interviewed to obtain informations about the type of alcoholic drink, the amount of alcohol consumed per day, duration and complete stopping of alcoholic intake. The quantification of the daily alcohol intake was submitted to the following formula: volume in ml multiplied by 0.8 (constant) and by the alcoholic degree of the beverage, divided by 100 and express in g/day. In this study the patients were divided into three groups: Group A: abstainers; Group B: light alcohol intake as < 40 g/day for men and < 20 g/day for women and Group C: heavy alcohol intake, defined as > 40 g/day for men and > 20 g/day for women. Complete stopping was considered only after six months of abstinence. At the time of liver biopsy, complete stopping was observed in 24.3% of patients in group B and in 29.5% of patients in group C.

Liver Histology. Liver biopsy samples were obtained by percutaneous puncture ultrasound oriented. Mean length of biopsy samples was 1.8 ± 0.5 cm and they were formalin-fixed, paraffin-embedded and stained with Hematoxylin-

Eosin, Perls, Masson's trichrome and reticulin impregnation by silver salts. The mean number of portal tracts was 10 ± 4 . The histological inflammatory activity (grade) and degree of architectural derangement or fibrosis (stage) of the viral hepatitis were assessed according to the Brazilian classification of the chronic hepatitis¹⁷ as follows: the stage of fibrosis (F) or architectural alterations was assessed on a four-point scale: F0 = normal lobular architecture; F1 = fibrous portal expansion; F2 = fibrous portal expansion with portal-portal septa; F3 = partial preservation of the lobular architecture with portal-portal and portal-central septa, with occasional sketch of nodules; F4 = cirrhosis. Periportal activity (PA) was graded according to the intensity of necroinflammatory lesions: PA0 = absence of inflammation; PA1 = spill-over of inflammatory cells without interface hepatitis; PA2 = mild interface hepatitis; PA3 = moderate interface hepatitis; PA4 = severe interface hepatitis. Lobular activity (LA) was graded as following: LA0 = normal hepatocytes; LA1 = mild alterations in hepatocytes, including ballooning degeneration or acidophil body, associated with lymphocytes/histiocytes infiltrate and rare foci of necrosis; LA2 = foci necrosis of hepatocytes, numerous areas of mononuclear aggregates; LA3 = foci necrosis of hepatocytes surrounded by mononuclear aggregates in several areas, limited areas of confluent necrosis; LA4 = foci necrosis of hepatocytes surrounded by mononuclear aggregates in numerous areas, with extensive/multiple confluent necrosis. Portal Infiltrate (PI) was graded: PI0 = rare portal lymphocytes; PI1 = mild increase of the number of portal lymphocytes; PI2 = moderate increase of the number of portal lymphocytes; PI3 = marked increase of the number of portal lymphocytes; PI4 = very marked increase of the number of portal lymphocytes. Steatosis was scored as present or absent.

For statistical comparisons between groups or variables, two levels of histopathological alterations were considered: grades 0, 1 and 2 were grouped as light (absent or mild) and grades 3 and 4 as severe.

Statistical Analysis. Chi-square test was used for analysis of qualitative variables, whereas quantitative variables as age, BMI, duration of infection and platelet were assessed using analysis of variance (ANOVA). When significant, the Tukey or the Student's t-test was used to discriminate the differences. Kruskal-Wallis test, Dunn test or Wilcoxon rank-sum test were also used to analyze variables as ethanol (g/d), duration of alcohol intake, ALT, AST, GGT, IgG, IgM, and abstinence. Multiple logistic regression analysis with stepwise of selected variables was performed to correlate the degrees and stages of the histopathological alterations with other clinical and biochemical data. Odds ratios and 95% confidence intervals were calculated. Values of $p < 0.05$ were considered to be significant.

Results

This study included 120 patients, 83 (69.2%) men and 37 (30.8%) women with chronic hepatitis C divided ac-

cording to alcohol intake as follow: the group A, abstainers: n = 41; group B, light drinkers: n = 36 and group C, heavy drinkers: n = 43. Male patients were common in groups B and C (69.4% and 95.3% respectively), whereas female patients more common in group A (58.5%) ($p < 0.001$). The epidemiological, clinical and demographic data of the 120 patients at the time of the liver biopsy are shown in *table I*. The three groups were not different in terms of age, BMI, duration of infection or surgery as a contamination factor. Groups B and C were not different in terms of duration of alcohol intake and abstinence. Transfusion as a risk factor was more frequent in the abstainers ($p = 0.056$) whereas drug addiction predominated in heavy drinkers ($p < 0.001$). The three groups were not different in terms of ALT, AST, GGT and platelet count (*Table I*). AST/ALT index was also analyzed in the three groups and no differences were found ($p = 0.106$).

Histopathological Data. There was no difference between findings of liver histology concerning the degree of fibrosis, periportal inflammatory activity, lobular inflammation, portal inflammatory infiltrate and steatosis, among the three groups.

Grouping the results of these variables as light (grades 0, 1 and 2) or severe (grades 3 and 4), no differences were found in architectural alterations, lobular inflammatory activity or portal inflammatory infiltrate. Nevertheless, heavy drinkers have shown higher percentages of grades 3 and 4 of interface hepatitis when compared to abstainers and light drinkers ($p = 0.033$), as shown in *table II*.

Demographic, epidemiological and biochemical data analyzed according to the different degrees of fibrosis and periportal inflammatory activity are shown in *table III*. Among the demographic variables, older age ($p = 0.004$) and BMI ($p = 0.013$) were significantly associated with severe fibrosis. Otherwise, the gender, duration of infection and duration of alcohol intake were not associated with severe fibrosis. The serum ALT ($p < 0.001$), AST ($p < 0.001$), GGT ($p = 0.012$) and IgG ($p = 0.040$) values were significantly higher in severe fibrosis compared to no or mild fibrosis. Additionally, the platelet count was significantly lower ($p < 0.001$) in severe fibrosis compared to no or mild fibrosis. The periportal inflammatory activity was shown to be significantly more severe in older age ($p = 0.001$) and duration of alcohol intake ($p = 0.001$), compared to no or mild periportal activity. The ALT ($p = 0.031$), AST ($p < 0.001$) and GGT ($p = 0.013$) values were significantly higher in severe periportal inflammatory activity (grades 3 and 4), whereas the platelet count was significantly ($p = 0.049$) lower. On the other hand, gender, BMI, duration of infection, IgG, IgM, did not differentiate between mild and severe periportal inflammatory activity.

Demographic, epidemiological and biochemical data analyzed according to the different degrees of lobular inflammatory activity and portal inflammatory infiltrate are shown in *table IV*. There was a significant association between BMI ($P = 0.039$), higher levels of ALT ($p = 0.013$), AST ($p = 0.001$) and GGT ($p = 0.003$) and severe lobular

Table I. Comparative analysis of the demographic data, epidemiological and biochemical characterization of the patients at the time of liver biopsy

Parameters	Group A	Group B	Group C	"p"
Number of patients	41	36	43	
Gender n (M/F)****	17/24	25/11	41/2	< 0.001
Age (year)*	40.8 ± 11.8	36.7 ± 10.4	38.8 ± 9.9	0.248
Alcohol Intake (mean)				
Amount (g/d)***	0	18.1 ± 11.1	149.9 ± 119.2	< 0.001
Duration (yr)***	0	12.9 ± 9.7	15.2 ± 8.4	0.137
Abstinence (days)***	0	375.8 ± 918.6	413.3 ± 853.1	0.911
BMI (kg/m ²)*	25.3 ± 3.7	25.8 ± 3.9	26.1 ± 4.1	0.672
Contamination factors****				
Transfusion n (%)	17 (41.40)	6 (16.70)	12 (27.90)	0.056
Drug addicted n (%)	1 (2.50)	6 (16.70)	17 (39.50)	< 0.001
Surgery n (%)	24 (58.50)	17 (47.20)	29 (67.40)	0.192
Others n (%)	8 (19.50)	6 (16.70)	10 (23.30)	0.763
Duration of contamination (yr)*				
Laboratory data				
ALT (xULN)**	19.8 ± 7.9	15.9 ± 7.4	16.5 ± 7.7	0.108
AST (xULN)**	2.1 ± 1.5	2.3 ± 1.4	2.4 ± 1.4	0.751
GGT (xULN)**	1.8 ± 1.0	1.7 ± 0.8	2.2 ± 1.4	0.365
Platelet (mm ³)*	204.541 ± 57.281	197.583 ± 56.052	190.813 ± 71.173	0.333
AST/ALT (mean)**	0.8 ± 0.3	0.6 ± 0.2	0.7 ± 0.2	0.106

Abbreviations: Group A: abstainers; Group B: light drinkers; Group C: heavy drinkers.

M, male; F, female; xULN, x upper limit of normal; BMI: body mass index

Values in mean and SD

* Analysis of variance, ** Kruskal-Wallis test,

*** Wilcoxon rank-sum test, **** chi-square

Table II. Histopathological results in the three studied groups.

	Groups						Total	p*	
	Abstainers		Light drinkers		Heavy drinkers				
Fibrosis									
0/1/2	30	73.20%	27	75.00%	30	69.80%	87	72.50%	
3/4	11	26.80%	9	25.00%	13	30.20%	33	27.50%	
Periportal activity									
0/1/2	26	63.40%	26	72.20%	18	43.90%	70	59.30%	
3/4	15	36.60%	10	27.80%	23	56.10%	48	40.70%	
Portal inflammatory infiltrate									
0/1/2	27	67.50%	21	58.30%	24	60.00%	72	62.10%	
3/4	13	32.50%	15	41.70%	16	40.00%	44	37.90%	
Lobular activity									
0/1/2	31	79.50%	29	80.60%	28	70.00%	88	76.50%	
3/4	8	20.50%	7	19.40%	12	30.00%	27	23.50%	
Abstinence									
< 6 months	-	-	29	80.60%	30	69.80%	59	74.70%	
> 6 months	-	-	7	19.40%	13	30.20%	20	25.30%	

* Chi-Square of Pearson

Table III. Demographic, epidemiological and biochemical data, analyzed according to different degrees of fibrosis and periportal inflammatory activity.

Parameter Degrees	Mean	Fibrosis		p	Periportal inflammatory activity			p
		SD	p		Mean	SD	p	
Gender n (M/F)***								
0/1/2	60/27	-	0.938		51/19	-	0.234	
3/4	23/10	-	-		30/18	-	-	
Age (year)*								
0/1/2	37.2	11.3	0.004		35.4	10.6	0.001	
3/4	43.4	7.9			43.9	9.1		
BMI (kg/m²)*								
0/1/2	25.2	3.9	0.013		25.4	4.3	0.299	
3/4	27.2	3.7			26.2	3.4		
Duration of infection (yr)*								
0/1/2	17.3	7.9	0.790		16.4	7.9	0.100	
3/4	17.8	7.9			19.1	7.6		
Duration of alcohol intake (yr)**								
0/1/2	13.3	8.6	0.207		11.1	7.6	0.001	
3/4	16.6	9.8			18.2	9.5		
ALT (xULN)**								
0/1/2	2.1	1.5	< 0.001		2.1	1.5	0.031	
3/4	2.7	1.1			2.4	1.1		
AST (xULN)**								
0/1/2	1.6	0.8	< 0.001		1.6	0.9	< 0.001	
3/4	2.8	1.3			2.4	1.2		
Platelet (mm³)*								
0/1/2	209.850	49.965	< 0.001		206.800	51.607	0.049	
3/4	165.006	78.109			184.108	72.607		
GGT (xULN)**								
0/1/2	1.3	0.9	0.012		1.3	0.8	0.013	
3/4	1.9	1.2			1.7	1.1		
IgG (mg/dL)**								
0/1/2	1.539	307	0.040		1.533	314	0.078	
3/4	1.771	567			1.706	497		
IgM (mg/dL)**								
0/1/2	134	70	0.052		138	77	0.456	
3/4	176	119			156	102		

M, male, F, female; xULN, x upper limit of normal

* Student t-test

** Wilcoxon rank-sum test

*** Chi-square

inflammation. The other studied variables did not show differences between the groups. There was a significant association between older age ($p = 0.001$) and AST ($p = 0.018$) with severe portal inflammatory infiltrate. For the other variables there were no significant correlations.

Logistic regression analyses: Considering the two levels of the architectural alterations in relation to the different clinical variables, it was shown that the only independent predictive factor of severe fibrosis were AST (odds ratio = 2.734 and CI 95% 1.687–4.431) and platelet count (odds ratio = 0.862 and CI 95% 0.782–0.950). Considering these variables, the best sensitivity and specificity cut-off was reached as respectively 78.8 and 71.3 (see figure 1a). Considering the two levels of periportal inflammation activity in relation to the different clinical parameters of alcoholic groups B and C it was shown that the only independent predictive factors of severe periportal inflammation were AST (odds ratio = 2.684 and CI 95% 1.437–5.013) and duration of

alcohol intake (odds ratio 1.112 CI 95% 1.041–1.188). Considering the studied parameters, the best cut-off for the sensitivity was 75.8% and for specificity 70.5% (see figure 1b).

Considering the two levels of lobular inflammation activity in relation to the different clinical parameters, it was shown that the only independent predictive factors of severe lobular inflammation were AST (odds ratio 2.049 CI 95% 1.304–3.221) and GGT (odds ratio 1.866 CI 95% 1.134–3.069). Considering these variables, the best cut-off for sensitivity was 66.7 and specificity 70.5 as shown in figure 1c.

Considering the two levels of portal inflammatory infiltrate in relation to the different clinical parameters, it was shown that the only independent predictive factor of severe portal inflammatory infiltrate was age (odds ratio 1.071 CI 95% 1.028–1.115). Considering this variable, the best cut-off for sensitivity was 63.6 and specificity 67.6 as shown in figure 1d.

Table IV. Demographic, epidemiological and biochemical data analyzed according to different degree of lobular inflammatory activity and portal inflammatory infiltrate.

Parameter Degree	Lobular inflammatory Activity			Portal inflammatory Infiltrate		
	Mean	SD	p	Mean	SD	p
Gender n (M/F)***						
0/1/2	61/27	-	0.795	47/25	-	0.404
3/4	18/9	-	-	32/12	-	-
Age (year)*						
0/1/2	38.1	11.2	0.252	36.3	11.1	0.001
3/4	40.8	9.0		42.9	8.8	
BMI (kg/m²)*						
0/1/2	25.3	3.9	0.039	25.4	4.1	0.371
3/4	27.1	3.9		26.1	3.7	
Duration of infection (yr)*						
0/1/2	18.2	7.9	0.219	17.1	8.2	0.494
3/4	15.8	7.8		18.3	7.5	
Duration of alcohol intake (yr)*						
0/1/2	13.9	9.1	0.696	12.9	9.1	0.072
3/4	15.2	9.6		16.3	8.9	
ALT (xULN)**						
0/1/2	2.1	1.3	0.013	2.2	1.6	0.104
3/4	2.8	1.4		2.3	0.9	
AST (xULN)**						
0/1/2	1.6	0.8	0.001	1.7	1.1	0.018
3/4	2.6	1.4		2.1	1.0	
Platelet (mm³)*						
0/1/2	200.845	54.834	0.469	203.211	52.817	0.052
3/4	190.562	82.832		189.318	74.648	
GGT (xULN)**						
0/1/2	1.3	0.8	0.003	1.5	0.9	0.680
3/4	2.0	1.7		1.5	1.1	
IgG (mg/dL)**						
0/1/2	1.561	390	0.048	1.588	412	0.606
3/4	1.734	438		1.630	399	
IgM (mg/dL)**						
0/1/2	138	81	0.090	137	77	0.222
3/4	171	106		161	103	

M, male; F, Female ULN, x upper limit of normal

* Student's t-test

** Wilcoxon rank-sum test

*** Chi-square

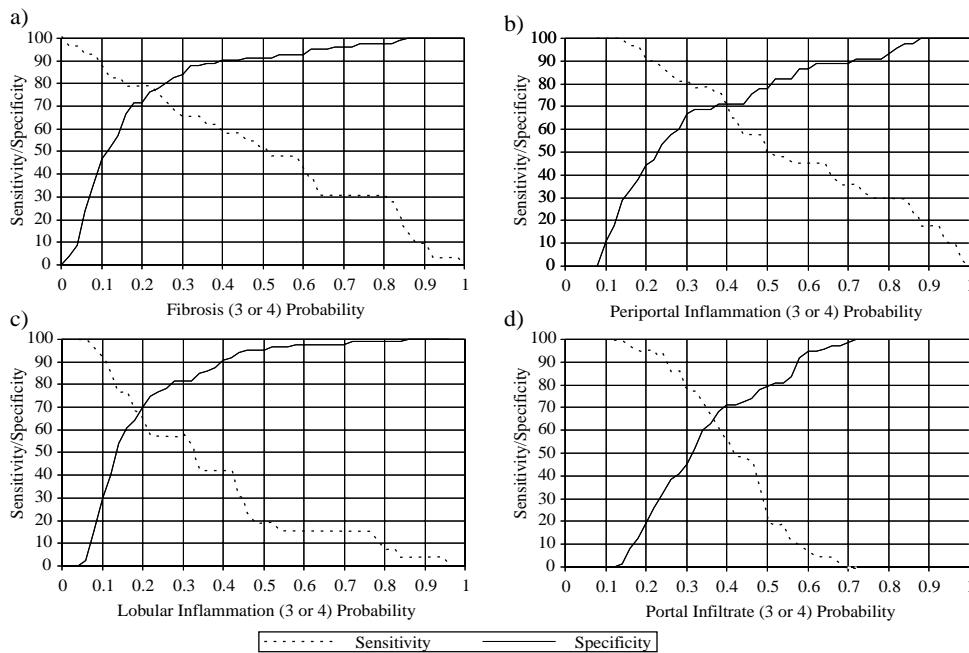


Figure 1. The cut-off values near the crossing between the sensitivity and specificity are shown in the figure above.

They correspond to the probability of grades 3 or 4 of each histopathological variable be detected, by clinic and biochemical results, according to the logistic regression analysis.

Concerning fibrosis, the sensitivity was 79.30 and specificity 76.50 for AST and platelets. Concerning periportal inflammation, the sensitivity was 69.70 and specificity 71.10 for AST and duration of alcohol intake. Concerning lobular inflammation, the sensitivity was 69.20 and specificity 64.40 for AST and GGT.

Concerning portal inflammatory infiltrate, the sensitivity was 65.10 and specificity 63.00 for age.

Discussion

This study shows that histopathological parameters like fibrosis, lobular inflammation and portal infiltrate in candidates for blood donation with hepatitis C did not differ when alcohol abstainers, light drinkers and heavy drinkers were compared. Only periportal inflammation was more severe in heavy drinkers. The most commonly used parameter to evaluate the progression of liver disease is fibrosis,¹⁸ and many studies have indicated an increased risk of progression of chronic hepatitis C with increasing levels of alcohol consumption.^{14,19} As some of these studies have included higher percentages of cirrhotic patients than ours, our results may reflect an earlier phase of disease progression.²⁰ As the inflammatory process precedes fibrosis development, it is understandable that there was a statistically significant difference for inflammation but not for fibrosis. The histopathological finding of periportal inflammation cannot be associated with isolated alcohol abuse. In fact, the most common histopathological alcoholic alterations predominate in zone 3 of the Rappaport acinus.²¹ On the other hand, we are dealing with an association of hepatitis C and alcohol, and the histopathological parameters, suggestive of alcoholic damage, are different from those of viral hepatitis.²² Another possibility which explains no differences in fibrosis, when abstainers were compared to light or heavy drinkers, is a beta error. In fact, the greater degree of histological architectural alterations was found in only 13 patients, the majority of them (61.5%) being heavy drinkers. One can speculate that, in a larger population, a significant difference would appear, as shown by other authors.^{6,14}

The comparison of demographic and clinical parameters between groups have shown interesting differences, namely, more female are abstainers (58.5%).²³ In relation to contamination factors, the two major risk factors for HCV infection were prevalent in different groups: blood transfusion was more frequently found in abstainers whereas drug addiction was significantly higher in heavy drinkers. It is uncertain why heavy drinkers are more likely to be infected with HCV, although alcoholics are more prone to have used injection drugs or have had other exposures to the virus.^{24,25} Interaction of alcohol and drugs are considered to enhance susceptibility to infections,²⁶ probably due to alterations in the immune system.²⁷

ALT is commonly used as a marker of hepatic inflammation and damage, especially in HCV infection,²⁸ although it can be more pronounced in patients with both HCV infection and alcoholic liver disease.²⁹ In contrast, some studies have found persistently normal ALT levels in alcoholic patients HCV infected with a slow progression rate of fibrosis.³⁰

Differently from other studies,³¹ we have analyzed histopathological variables separately and in relation to epidemiological and laboratory parameters. An independent risk factor associated with fibrosis is older age, as shown in several epidemiological studies.^{32,33} Like others,¹⁴ we have found older age related to fibrosis and periportal inflammation. The amount of portal inflammatory infiltrate is not usually taken into consideration in the various classifications of chronic hepatitis,^{31,34} but is considered in our classification.¹⁷ The only parameter that differentiated slight from severe portal infiltrate was age. Younger people more frequently had lower grades of portal inflammatory infiltrate. The strong relationship of age with severi-

ty of chronic hepatitis may reflect qualitative and quantitative changes in the immune response which occur with increasing age, or more likely indicate the longer disease duration.³⁵ To our knowledge this is the first report of relation between older age and greater portal infiltrate in hepatitis C.

Duration of infection is an important parameter in the progression of the disease, but it has been described in community-based studies that HCV infection may persist for decades without causing clinically apparent liver disease.^{36,37} Lack of differences regarding duration of infection in our study may be related to the blood donor population, in which a mild liver disease was more frequently found.

Elevated ALT, AST and GGT levels are associated with fibrosis^{38,39} and were correlated also with periportal and lobular inflammation in our study although only AST was an independent predictor of severe fibrosis. One of the possible reasons to explain higher AST values could be HCV-induced liver injury in the mitochondrial fraction of hepatocytes where it is present, and/or due to the presence of alcohol.⁴⁰ On the other hand, decreased platelet count has been used to non-invasively assess the severity of disease in patients with chronic liver disease.⁴¹ Platelet counts clearly separated early from late stages of fibrosis as well as the degrees of periportal inflammation. Although the hepatitis C virus by itself may be related to low platelet counts, many authors have had similar results.^{16,42,43} To amplify the opposite relationship between AST levels and platelets count in determining the stage of fibrosis, a novel index, called "AST to platelet ratio index" (APRI) has recently been proposed.⁴⁴ Our results are in keeping with this study.

Obesity has also been associated with more advanced degrees of fibrosis in CHC²⁸ and an association between BMI and fibrosis has been demonstrated.⁴⁵ In our series, 39.3% of patients presented steatosis, similarly to other histopathological studies of CHC, which have reported microvesicular and macrovesicular fatty change in 31% to 72% of patients.⁴⁶⁻⁴⁸ Lately, even low alcohol intake has been shown to play a synergistic effect on HCV infection leading to steatosis.⁴⁹

Using logistic regression analysis it was remarkable to see that AST was an independent predictor of severity not only for fibrosis and periportal inflammation but also for lobular inflammation. On the other hand, platelet was an independent predictor only for fibrosis. The levels of sensitivity varying from 65.1 up to 79.3, and specificity ranging from 63 up to 76.5, were unexpectedly high. There are no doubts about the clinical usefulness of fibrosis, recognized as the most important factor in the progression of liver disease. So, it was rewarding to find the best sensitivity and specificity levels for the detection of fibrosis, by the use of AST values and platelets counts.

In conclusion, epidemiological and biochemical data can predict both fibrosis and periportal inflammation with acceptable levels of sensitivity and specificity.

References

1. Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a bloodborne non-A, non-B Hepatitis genome. *Science* 1989; 44: 359-62.
2. Seeff LB. Natural history of chronic hepatitis C. *Hepatology* 2002; 36: S35-S46.
3. Mohsen AH. Trent HCV Study Group. The epidemiology of hepatitis C in a UK health regional population of 5.12 million. *GUT* 2001; 48: 707-13.
4. Smith BC, Chapman CE, Burt AD, Toms GL, Bassendine MF. Outcome of post-transfusion hepatitis C: disease severity in blood-component recipients and their implicated donors. *QJM* 1997; 90: 587-92.
5. Tassopoulos NC, Papatheodoridis GV, Katsoulidou A, Delladetsima JK, Sypsa V, Touloumi G, Nikandros M, et al. Factors associated with severity and disease progression in chronic hepatitis C. *Hepatogastroenterol* 1998; 45: 1678-83.
6. Pessione F, Degos F, Marcellin P, Duchatelle V, Njapoum C, Martinot-Peignoux M, Degott C, et al. Effect of alcohol consumption on serum hepatitis C virus RNA and histological lesions in chronic hepatitis C. *Hepatology* 1998; 27(6): 1717-22.
7. Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: the effect of lifetime intake and hepatitis C infections in men and women. *Am J Epidemiol* 2002; 155(4): 323-31.
8. Harris HE, Ramsay ME, Andrews N, Eldridge KP on behalf of the HCV National Register Steering Group. Clinical course of hepatitis C virus during the first decade of infection: cohort study. *BMJ* 2002; 324: 450-3.
9. Ostapowicz G, Watson KJR, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. *Hepatology* 1998; 27(6): 1730-5.
10. Corrao G, Aricò S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology* 1998; 27: 914-9.
11. Patek AJ, Toth IG, Saunders MG, Castro GAH, Emgel JI. Alcohol and dietary factors in cirrhosis. An epidemiological study of 304 alcoholic patients. *Arch Intern Med* 1975; 135: 1053-7.
12. Monto A, Alonzo J, Watson JJ, Grunfeld C, Wright TL. Steatosis in chronic hepatitis C: relative contributions of obesity, diabetes mellitus and alcohol. *Hepatology* 2002; 36(3): 729-36.
13. Marcellin P, Asselah T, Boyer N. Fibrosis and disease progression in hepatitis C. *Hepatology* 2002; 36: S47-S56.
14. Poynard T, Bedossa P, Opolon P, for the OBSVIRC, METAVIR, CLINIVIR and DOSVIRC groups. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *Lancet* 1997; 349: 825-32.
15. Alter MJ, Marcolis HS, Krawczynski K, Judson FN, Mares A, Alexander WJ, Hu PY, et al. The natural history of community-acquired hepatitis C in the United States. *N Engl J Med* 1992; 327: 1899-1905.
16. Poynard T, Bedossa P. Age and platelet count: a simple index for predicting the presence of histological lesions in patients with antibodies to hepatitis C virus. METAVIR and CLINIVIR Cooperative Study Groups. *J Viral Hepatol* 1997; 4(3): 199-208.
17. Gayotto LCC e Comitê SBP/SBH. Visão histórica e consenso nacional sobre a classificação das hepatites crônicas. Projeto do Clube de Patologia Hepática da Sociedade Brasileira de Patologia aprovado pela Sociedade Brasileira de Hepatologia. *GED* 2000; 19(3): 137-40.
18. Poynard T, Ratiu V, Benmanov Y, Martino V, Bedossa P, Opolon P. Fibrosis in patients with chronic hepatitis C: detection and significance. *Semin Liver Dis* 2000; 20(1): 47-55.
19. Peters MG, Terrault NA. Alcohol use and hepatitis C. *Hepatology* 2002; 36: S220-S5.
20. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; 28(8): 805-9.

21. Maddrey WC. Alcoholic hepatitis: clinicopathologic features and therapy. *Semin Liver Dis* 1988; 8: 91-102.
22. Hall P de la M. Alcoholic liver disease. In: *Pathology of the liver*. Mac Sween RNM, Anthony PP, Portmann BC, Burt AD, eds., 3rd ed. Churchill Livingstone, Edinburgh, 1994.
23. Strauss E, Nemoto TC, Borges GT, Cunha AA, Freitas GC, Parrado MAR, et al. Chronic alcoholism: evaluation epidemiologic clinic in 300 cases. *GED, Gastroenterol Endoscop Dig* 1998; 17: S75.
24. Mendenhall CL, Moritz T, Rouster S, Roselle G, Polito A, Quan S, Dinelle RK. Epidemiology of hepatitis C among veterans with alcoholic liver disease. The VA Cooperative Study Group 275. *Am J Gastroenterol* 1993; 88: 1022-6.
25. Verbaan H, Anderson K, Eriksson S. Intravenous drug abuse-the major route of hepatitis C virus transmission among alcohol-dependent individuals? *Scand J Gastroenterol* 1993; 28: 714-8.
26. MacGregor RR. Alcohol and immune defense. *JAMA* 1986; 256: 1474-9.
27. Cook RT. Alcohol abuse, alcoholism, and damage to the immune system-a review. *Alcohol: Clin Exp Res* 1998; 22: 1927-42.
28. Ortiz V, Berenguer M, Rayón JM, Carrasco D, Berenguer J. Contribution of obesity to hepatitis C-related fibrosis progression. *Am J Gastroenterol* 2002; 97(9): 2408-2414.
29. Fong TL, Kanel GC, Conrad A, Valinluck B, Charboneau F, Adkins RH. Clinical significance of concomitant hepatitis C infection in patients with alcoholic liver disease. *Hepatology* 1994; 19(3): 554-557.
30. Mathurin P, Moussalli J, Cadanel JF, Thibault V, Charlotte F, Dumouchel P, Cazier A, et al. Slow progression rate of fibrosis in hepatitis C virus patients with persistently normal alanine transaminase activity. *Hepatology* 1998; 27: 868-72.
31. Bedossa P, Poupon T. An algorithm for the grading of activity in chronic hepatitis C. *Hepatology* 1996; 24: 289-93.
32. Iacono OL, Decastro M, Garcia-Buey L, Garcia-Monzon C, Borque MJ, Sanz P, Garcia-Sanchez A, et al. Epidemiological risk factors and clinic-pathological presentation in chronic hepatitis C. *Hepato-Gastroenterol* 1998; 45: 1715-1721.
33. Poupon T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol* 2001; 34: 730-739.
34. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: Diagnosis, grading and staging. *Hepatology* 1994; 19: 1513-1520.
35. Delladetsima JK, Rassidakis G, Tassopoulos NC, Papatheodoridis GV, Smyrnoff T, Vafiadis I. Histopathology of chronic hepatitis C in relation to epidemiological factors. *J Hepatol* 1996; 24: 27-32.
36. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, Nolt K, et al. The natural history of hepatitis C virus infection. Host, viral, and environmental factors. *JAMA* 2000; 284(4): 450-456.
37. Rodger AJ, Roberts S, Lanigan A, Bowden S, Brown T, Crofts N. Assessment of long-term outcomes of community-acquired hepatitis C infection in a cohort with sera stored from 1971 to 1975. *Hepatology* 2000; 32: 582-587.
38. Ghany MG, Kleiner DE, Alter H, Doo E, Khokar F, Promrat K, Herion D, et al. Progression of fibrosis in chronic hepatitis C. *Gastroenterology* 2003; 124: 97-104.
39. Silva IS, Ferraz ML, Perez RM, Lanzoni VP, Figueiredo VM, Silva AE. Role of gamma-glutamyl transferase activity in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol* 2004; 19(3): 314-318.
40. Assy N, Minuk GY. Serum aspartate but not alanine aminotransferase levels help to predict the histological features of chronic hepatitis C viral infections in adults. *Am J Gastroenterol* 2000; 95(6): 1545-50.
41. Pohl A, Behling C, Oliver D, Kilani M, Monson P, Hassanein T. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. *Am J Gastroenterol* 2001; 96(11): 3142-3146.
42. Streiff MB, Mehta S, Thomas DL. Peripheral blood count abnormalities among patients with hepatitis C in the United States. *Hepatology* 2002; 35(4): 947-952.
43. Bauduer F, Marty F, Larrouy M, Ducout L. Immunologic thrombocytopenic purpura as presenting symptom of hepatitis C infection. *Am J Hematol* 1998; 57(4): 338-340.
44. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003; 38: 518-526.
45. Hourigan LF, Macdonald GA, Purdie D, Whitehall VH, Shorthouse C, Clouston A, Powell EE. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. *Hepatology* 1999; 29: 1215-9.
46. Scheuer PJ, Ashrafaeza P, Sherlock S, Brown D, Dusheiko GM. The pathology of hepatitis C. *Hepatology* 1992; 15: 567-571.
47. Bach N, Thung SN, Schaffner F. The histological features of chronic hepatitis C and autoimmune chronic hepatitis C: a comparative analysis. *Hepatology* 1992; 15: 572-577.
48. Lefkowitch JH, Schiff ER, Davis RL, Perrillo RP, Lindsay K, Bodenheimer HC Jr., Balart LA, et al. Pathological diagnosis of chronic hepatitis C: a multicenter comparative study with chronic hepatitis B. *Gastroenterology* 1993; 104: 595-603.
49. Serfaty L, Poujol-Robert A, Carbonell N, Chazouillères O, Poupon RE, Poupon R. Effect of the interaction between steatosis and alcohol intake on liver fibrosis progression in chronic hepatitis C. *Am J Gastroenterol* 2002; 97: 1807-1812.