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Original Article

Impact of the Association of Alcohol Abuse and Chronic Hepatitis C Virus Infection on the Clinical and Biochemical Presentation of Liver Cirrhosis - ə

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Abstract

Aims: Evaluate the impact of alcohol abuse and chronic hepatitis C virus (HCV) infection on the clinical and biochemical presentation of liver cirrhosis at the first visit to the outpatient clinic of advanced liver disease at Federal University of São Paulo (UNIFESP), using as a parameter of comparison patients with cirrhosis of alcoholic or viral etiology exclusively.

Methods: Retrospective medical records review. Patients attending for the first time at the outpatient clinic of advanced liver disease of the UNIFESP with diagnosis of liver cirrhosis whose etiology alcohol and/or chronic HCV infection. Age, gender, presence of clinical, the presence of comorbidities and biochemical tests were evaluated.

Results: 246 patients with liver cirrhosis of alcoholic etiology, 107 with cirrhosis due to chronic HCV infection and 58 with concomitant etiologies were analyzed. There was a significant predominance of male patients in alcohol abusive. Although the HCV group presented a higher frequency of comorbidities, it presented lower number of clinical hepatic decompensation prior to the first visit. Patients with alcohol abuse also showed a significant greater impairment of liver function both by indirect tests and by the Model for End-Stage Liver Disease (MELD) score and such differences persisted even after gender adjustment.

Conclusion: Patients with cirrhosis due to hepatitis C associated with alcohol abuse have a higher frequency of previous episodes of hepatic decompensation and a significantly greater functional liver impairment than those with viral infection alone in the first consultation in a referral clinic for advanced liver diseases. These results support the hypothesis that alcohol and hepatitis C virus act synergistically for the progression of liver disease.

Keywords: Liver cirrhosis; Alcoholic liver disease; Hepatitis c; Chronic hepatitis C; Portal hypertension

INTRODUCTION

In 2010, the age-adjusted death rate due to liver cirrhosis for both sexes in Brazil was 13-17 deaths per 100,000 population [1]. Alcoholic liver disease is the main etiology of liver cirrhosis in the country, causing almost 10 deaths per 100,000 population [2], followed by chronic hepatitis C, which is also the leading cause of chronic liver disease associated with Hepatocellular Carcinoma (HCC) and Liver Transplantation (LTx) in the country [3-5]. A comparative analysis of causes of death indicated a significant increase in cases of cirrhosis attributable to hepatitis C and harmful use of alcohol in Brazil between 1990 and 2016 [6].

Only 35% of heavy drinkers develop advanced Alcoholic Liver Disease (ALD), which suggests that factors other than alcohol toxicity *per se* may influence the risk of ALD development and progression, including gender, ethnicity, and genetic factors, in addition to other risk factors such as obesity, malnutrition, iron overload and concomitant viral hepatitis [7-11].

According to a systematic review by Novo-Veleiro, et al. [13], the prevalence of chronic hepatitis C among alcoholic patients is around 16%. A similar prevalence is observed in Latin America, ranging from 12.2% to 27.7% [14].

There is substantial evidence showing that alcohol and the Hepatitis C Virus (HCV) combine synergistically to promote the development and progression of liver damage, resulting in more advanced liver disease when co-occurring than in chronic liver disease of either etiology alone, with disease decompensation at a younger age, more severe histological characteristics, faster disease progression, and significantly reduced survival [7,15-20].

The vast majority of studies on clinical presentation, however, were carried out in hospitalized patients. In this study, we set out to assess the impact of co-occurring alcohol abuse and chronic hepatitis C infection on the clinical and biochemical profile of patients with liver cirrhosis presenting for their first visit at a referral clinic for advanced liver disease and compare it to the clinical and laboratory profile of patients with cirrhosis of exclusively alcoholic or viral (HCV) etiology treated at the same clinic.

MATERIALS AND METHODS

Retrospective chart-review study of patients diagnosed with liver cirrhosis. The criteria for inclusion were liver biopsy findings consistent with stage 4 fibrosis on the METAVIR [21,22] classification; or, indirect diagnosis of cirrhosis by clinical and laboratory findings consistent with chronic liver disease and evidence of portal hypertension on imaging and endoscopy [23,24]; or, in the most recent cases, FibroScan® transient elastography values above 12.5 kPa associated with clinical and biochemical alterations compatible with chronic hepatic disease [23,25].

The diagnosis of hepatitis C was established by detection of anti-HCV antibodies and confirmed by detection of circulating HCV-RNA through RT-PCR (Amplicor-HCV, Roche Diagnostics®). Alcoholic liver disease was diagnosed in patients with an ethanol intake >20 g/day for women or >40 g/day for men over a period of more than 10 years [26]. After review of medical records, patients whose etiological investigation was incomplete or who had another concomitant liver disease (such as Hepatitis B Virus [HBV] infection, hepatic schistosomiasis, autoimmune hepatitis, or Nonalcoholic Fatty Liver Disease [NASH]) were excluded.

Data were collected on demographic variables; clinical decompensation, defined by the presence of one or more of the following signs or symptoms: ascites, variceal bleeding, encephalopathy, or jaundice [23]; and presence of comorbidities, divided into two groups: metabolic (hypertension, type 2 diabetes mellitus, dyslipidemia) and non-metabolic (chronic renal failure, chronic pulmonary failure, hypothyroidism).

The data refer to the first outpatient visit. Blood chemistry tests were performed by automated kinetic methods at a central laboratory, no later than 3 months after the first outpatient visit and compared to pre-established reference ranges.

The Model for End-stage Liver Disease (MELD) score was calculated using total bilirubin, serum creatinine, and the international normalized ratio (INR) as follows: MELD = 3.78 × Ln[serum bilirubin (mg/dL)] + 11.2 × Ln[INR] + 9.57 × Ln[serum creatinine (mg/dL)] + 6.43 [27].

All statistical analyses were performed in the IBM SPSS Statistics for Windows, Version 20.0 software environment (Armonk, NY: IBM Corp).

The normality of distribution of continuous variables was analyzed by skewness, kurtosis, and the Kolmogorov–Smirnov test. For between-group comparison of continuous variables, analysis of variance (ANOVA) with Dunnett's multiple comparisons was performed. For comparison of categorical variables, the chi-squared test with a supplemental partition of chi-squared approach or Fisher's exact test were used as appropriate. *p*-values <0.05 were deemed significant.

The study protocol followed the ethical principles of the Declaration of Helsinki, and was approved by the Federal University of São Paulo (UNIFESP) Research Ethics Committee with opinion number 2,156,861.

RESULTS

After application of the inclusion criteria, 689 medical records of patients treated consecutively at the outpatient advanced liver disease clinic at the UNIFESP in the 5 years preceding the study were selected.

Of these, 278 were excluded: 85 due to lack of sufficient data for analysis and 193 due to other diagnoses (69 with NASH, 21 with HBV cirrhosis, 30 with hepatosplenic schistosomiasis, and 73 with cirrhosis of other etiologies) (Figure 1).

Thus, the medical records of 411 patients were selected: 246 with ALD, 107 with chronic hepatitis C, and 58 (14% of total) with co-occurring ALD and chronic hepatitis C. All patients with ALD (alone or with comorbid HCV infection) had a history of alcohol intake >50 g/day for over 10 years.

The mean age was 53 years, with no significant differences in age distribution between groups. Conversely, the sex distribution of the sample differed significantly between groups, with a higher frequency of women in the HCV group (51.4%) than in the ALD groups (12.6% in the ALD alone group and 24.1% in the comorbid ALD+HCV group) [12].

Regarding the presence or absence of comorbid illnesses, almost 60% of patients in the HCV group had some comorbidity, versus only 45.5% of the patients in the ALD group and 41.4% in the ALD+HCV group. Although the ALD and HCV groups differed significantly from each other ($\chi^2 = 4.406$; $p = 0.036$), the difference between the ALD and ALD+HCV groups did not reach statistical significance. However, when comorbidities were categorized, both groups of patients with hepatitis C were found to have significantly more frequent metabolic comorbidities than the ALD group (Table 1).

Decompensation of liver disease (current or in the 6 months preceding inclusion in the study, reported, or observed at the time of the first outpatient visit) occurred in about 74% of patients in the ALD and ALD/HCV groups, a significantly higher frequency than in the group of patients with HCV alone (43.9%). It is worth noting that patients with multiple decompensations (i.e., those who had already experienced more than one clinical manifestation of decompensation at the evaluation time) were more frequently represented in the two groups of harmful alcohol users (Table 1).

In the two groups in which HCV was involved in the etiology of liver disease, aminotransferases were higher than in the non-HCV group, whereas in the latter group (patients with ALD alone), the mean GGT levels were more than twice higher than in the HCV groups and this difference reached statistical significance (Tables 2 & 3).

Tests of liver function (total bilirubin, INR, albumin) were worse in the groups with ALD, indirectly reflecting greater hepatic

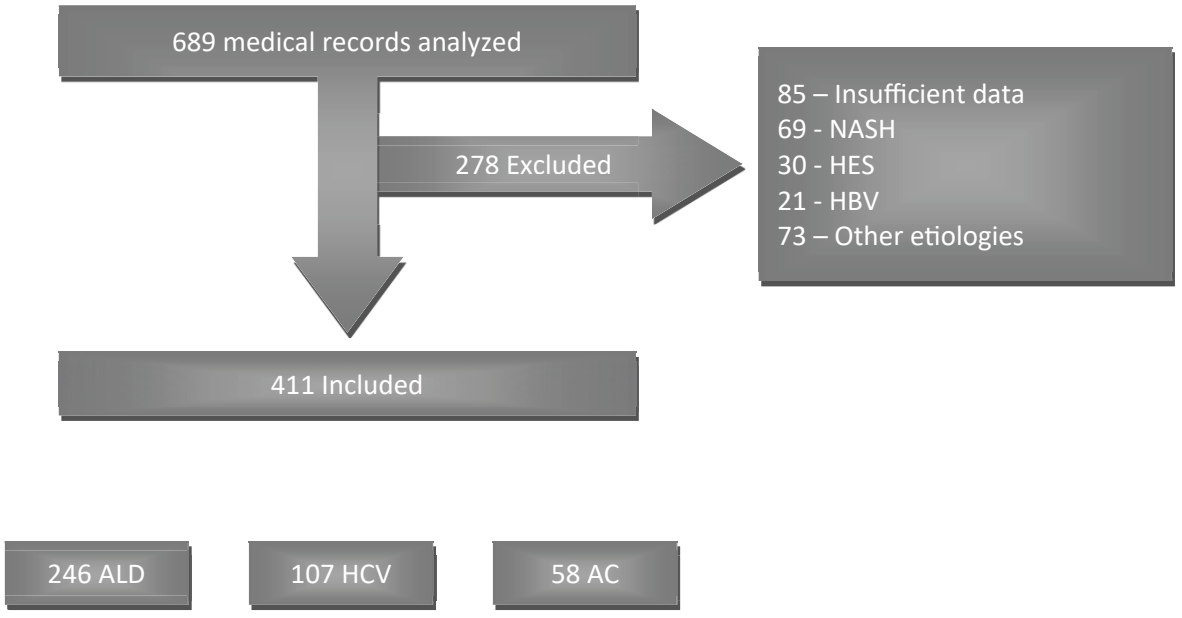

Figure 1: Flow diagram of eligible patients attending for the first time an outpatient clinic of advanced liver disease.
ALD: Alcoholic Liver Disease; HCV: Chronic Hepatitis C Virus Infection; AC: Alcoholic Liver Disease associated to chronic hepatitis C virus infection; NASH: Non-Alcoholic Steatohepatitis; HBV: Hepatitis B Vírus; HES: Hepatosplenic Schistosomiasis.

Table 1. Distribution of demographic and clinical characteristics according to etiology.

			ALD (*n* = 246)	HCV (*n* = 107)	AC (*n* = 58)	*p*
Age (mean ± SD)			52.6 (±10.0)	55.2 (±12.0)	52.6 (±10.6)	ns
Gender n (%):	Female		31 (12.6)	55 (51.4)*†	14 (24.1)	<0.001
	Male		215 (87.4)	52 (48.6)	44 (75.9)	
Comorbidities n (%):	Absent		135 (54.9)	45 (42.1)**	34 (58.6)	0.048
	Present		111 (45.1)	62 (57.9)	24 (41.4)	
		Metabolic	89 (36.2)	44 (41.1)	23 (39.7)	0.036
		Others	22 (8.9)	18 (16.8)	01 (1.7)	
Descompensation n (%):	Compensated		62 (25.2)	60 (56.1)	15 (25.9)	<0.001
	Descompensated		184 (74.8)	47 (43.9)*†	43 (74.1)	
		Ascites	48 (19.5)	16 (14.9)	20.7 (12)	
		UGB	32 (13)	13 (12.2)	8 (13.8)	
		HE	10 (4.1)	0 (0)	1 (1.7)	
		Jaundice	14 (5.7)	2 (1.9)	1 (1.7)	
		Multiple	80 (32.5)	16 (14.9)*†	21 (36.2)	

SD: Standard deviation; ALD: Alcoholic Liver Disease; HCV: Chronic Hepatitis C Virus Infection; AC: Alcoholic Liver Disease associated to chronic hepatitis C virus infection; ns: non significant; UGB: Upper Gastrointestinal Bleeding; HE: Hepatic Encephalopathy

†$p \leq 0.001$ when compared to ALD group. *$p \leq 0.001$ when compared to AC group. **p < 0.05 when compared to ALD group

Table 2: Selected laboratory values and MELD scores for the study groups (mean ± standard deviation).

	ALD (*n* = 246)	HCV (*n* = 107)	AC (*n* = 58)	*p*
AST (U/L x ULN)	1.84 (±1.72)	2.11 (± 1.98)	2.45 (±1.65)	0.051
ALT (U/L x ULN)	1.08 (±1.04)	1.95 (±2.09)	1.91 (±1.85)	<0.001
Alkaline Phosphatase (U/L x ULN)	1.16 (±3.77)	0.88 (±0.89)	0.9 (±0.46)	0.670
GGT (U/L x ULN)	7.44 (±13.78)	3.08 (±4.12)	2.96 (±2.66)	0.001
Total bilirubin (mg/dL)	2.8 (±3.6)	1.4 (±1.2)	2.66 (±4.12)	0.002
Platelets (x 10^3/L)	145.5 (±100.6)	138.7 (±80.6)	115.8 (±65.5)	0.039
Albumin (g/dL)	3.54 (±0.89)	3.66 (±0.8)	3.31 (±0.64)	<0. 001
INR	1.37 (±0.33)	1.23 (±0.22)	1.38 (±0.25)	<0.001
Creatinine (mg/dL)	0.88 (±0.23)	0.83 (±0.17)	0.87 (±0.25)	0.277
MELD	12.62 (±4.65)	10.13 (±3.21)	12.94 (±3.86)	<0.001

ALD: Alcoholic Liver Disease; HCV: Chronic Hepatitis C Virus Infection; AC: Alcoholic Liver disease associated to chronic hepatitis C virus infection; AA: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GG: Gama-Glutamyl transpeptidase; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease; ULN: Upper Limit of Normality.

impairment with hypoalbuminemia, hyperbilirubinemia, and enlargement of INR, which, in turn, translates into higher MELD scores (Table 3).

As the groups were heterogeneously distributed with regard to sex, a second evaluation, excluding all female patients from the analysis, was carried out to prevent this variable from confounding the results. Again, there were no differences in age. The differences between the groups remained essentially as previously observed regarding the percentage of patients presenting with decompensated (Table 4).

Similar results were also observed for laboratory variables and MELD score, with significant differences for ALT, GGT, bilirubins, albumin, INR, and MELD. The following table presents multiple comparisons between the three study groups and the level of significance for each of the differences observed (Table 5).

DISCUSSION

To assess the impact of excess alcohol intake on chronic hepatitis C virus infection as compared to either one of these etiologic agents of cirrhosis alone, we conducted a retrospective chart-review study of patients referred to a tertiary outpatient clinic for advanced liver disease. Patients referred to this clinic have already been diagnosed as having chronic liver disease, usually with portal hypertension, or have already experienced one or more episodes of decompensation (ascites, jaundice, encephalopathy, or upper GI bleed).

Analysis of the factors associated with chronic liver diseases, especially in cirrhotic patients, shows that, with the exception of most Asian countries, where hepatitis B is highly prevalent, alcohol abuse and HCV infection are the leading etiologies [28-30].

In this study, we found no significant differences in mean age across groups, with an overall average age of 52 years (52,6 years old in the ALD group, 55,2 years in the HCV group and 52,6 years in the AC group, with p >0,05). In terms of gender distribution, however, there was a significant difference in the prevalence of women between the HCV group (51%) and the ALD groups (13% and 24%). This age distribution and the lower frequency of women among patients with alcohol abuse are consistent with previous Brazilian and international studies [12,31-33].

When assessing for presence of comorbidities, almost 58% of patients in the group with HCV alone had some other chronic non-

communicable disease, compared to only 45% in the ALD group and 41% in the ALD+HCV group, especially those related to metabolic syndrome (such as hypertension, diabetes, and dyslipidemia), which is consistent with the concept that hepatitis C represents a systemic disease with an important metabolic component, mainly represented by a higher frequency of insulin resistance and type 2 diabetes mellitus, even in patients with cirrhosis [34-38]. The resolution of insulin resistance and reduced rate of progression to diabetes in patients with sustained virological response attest to the relationship between the virus and development of these comorbidities [37,38].

Despite the higher frequency of comorbidities in the HCV group, when assessing clinical presentation, signs of hepatocellular decompensation and complications of portal hypertension were more frequent in patients with ALD or comorbid ALD+HCV (approximately 75% in both groups) than in those with cirrhosis attributable to HCV alone (43.9%). In addition, these patients more often presented with multiple manifestations of decompensated cirrhosis, demonstrating greater clinical severity when alcohol is involved in the etiology of chronic liver disease. These clinical findings were corroborated by laboratory tests of indirect markers of liver function, such as bilirubin, INR, and albumin, as well as by the MELD, which integrates several of these parameters and is known to be predictive of survival in these patients [23,27,39].

On the other hand, there were interesting between-group differences in the pattern of cellular and cholestatic liver enzymes, with a more significant increase in aminotransferase levels (especially ALT) in the HCV groups, whereas cholestatic enzymes, especially GGT and bilirubins, were significantly more altered in the ALD groups; this is consistent with the known higher frequency of cholestatic lesions in alcoholic cirrhosis (18,32,40), as well as with the effect of alcohol as a GGT inducer [41].

Table 3: Analysis of Variance (ANOVA) of laboratory variables.

Variáveis	z	*p*
AST	2.998	0.051*
ALT	36.543	<0.001*
Alkaline Phosphatase	0.402	0.670
GGT	7.745	0.001*
Total bilirrubins	6.191	0.002*
Platelets	2.473	0.086
Albumin	3.265	0.039*
INR	8.781	<0. 001*
Creatinine	1.290	0.277
MELD	13.988	<0.001*

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gama-Glutamyltranspeptidase; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease. (*) $p < 0.05$

As women were markedly underrepresented among patients in the ALD groups than in those diagnosed with viral hepatitis, we conducted a subgroup analysis of clinical and biochemical parameters in male subjects alone to exclude this potential bias from the analysis. Even after excluding women from the analysis, we still found a statistically significant between-group difference in presence of decompensation, which was more prevalent in the ALD and ALD+HCV groups. Furthermore, markers of hepatic function status (total bilirubin, INR, and MELD score) were significantly more compromised in the ALD and ALD+HCV groups than in the HCV-alone group, which is consistent with the literature [33,40,42].

Whether this reflects true synergism between HCV and alcohol, leading to a more precipitous and more severe progression of chronic liver disease with development of cirrhosis in a shorter time than in patients with "pure" chronic hepatitis C, remains to be assessed. The presence of alcoholism may interfere with care-seeking by these patients. A study comparing alcoholic patients who seek medical treatment with dependents who do not seek care found a greater degree of personality changes, alcohol use, and elevated liver enzymes in patients who sought medical attention [43], which may suggest that alcoholic patients delay the search for care as a way of denying their disease, to avoid prejudice or stigma, or to avoid having to discontinue alcohol intake. In addition, the fragility of public policies capable of modifying the alcohol consumption behavior of these patients at the primary and secondary levels of care must be taken into account [44-46].

However, other studies provide further evidence of synergism between the two diseases. The rate of fibrosis, hepatocellular carcinoma, and early death is lower in patients with chronic hepatitis C than in those with viral hepatitides and alcoholism [47-49]. Hospitalized patients with alcoholism experience longer hospital stays and are at higher risk of death if they are positive for hepatitis C [50]. Patients with HCV who also abuse alcohol are also at a higher risk of death [51]. Patients with cirrhosis of both etiologies are more likely to be hospitalized than patients with alcoholic cirrhosis alone [40]. Patients admitted with alcoholic hepatitis and HCV are more likely to experience variceal bleeding and hepatic encephalopathy,

Table 4: Distribution of demographic and clinical characteristics according to etiology in male patients.

		ALD (*n* = 215)	HCV (*n* = 52)	AC (*n* = 44)	*p*
Age (mean + SD)		52.4 + 10.1	54.5 + 10.0	51.3 + 10.3	ns
Comorbidities n (%):	Absent Present	121 (56.3) 94 (43.7)	27 (51.9) 25 (48.9)	27 (61.3) 17 (38.7)	ns
Descompensation n (%):	Compensated Descompensated	56 (26) 159 (74)	31 (59.6) 21 (40.4)	11 (25) 33 (75)	<0.001
	Ascites	39 (18.1)	6 (11.5)	8 (18.2)	
	UGB	27 (12.6)	9 (17.4)	6 (13..6)	
	HE	8 (3.7)	0 (0)	0 (0)	
	Jaundice	14 (6.6)	2 (3.8)	1 (2.3)	
	Multiple	71 (33)	4 (7.7)*†	18 (40.9)	

SD: Standard Deviation; ALD: Alcoholic Liver Disease; HCV: Chronic Hepatitis C Virus Infection; AC: Alcoholic Liver Disease associated to chronic hepatitis C virus infection; ns: non significant; UGB: Upper Gastrointestinal Bleeding; HE: Hepatic Encephalopathy

†$p \leq 0.001$ when compared to ALD group. *$p \leq 0.001$ when compared to AC group

Table 5: Analysis of variance (ANOVA) of laboratory variables in male patients.

Variable	Z	*p*
AST	2.793	0.063
ALT	13.245	<0.001*cc
Alkaline Phosphatase	0.286	0.cc752
GGT	4.698	0.010*
Total bilirubin	3.433	0.034*
Platelets	2.858	0.059
Albumin	5.252	0.006*
INR	5.327	0.005*
Creatinine	1.668	0.190
MELD	11.253	<0.001*

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; GGT: Gama-Glutamyl Transpeptidase; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease. (*) $p < 0.05$

which are associated with in-hospital mortality, than patients admitted with alcoholic hepatitis alone [52,53]. Alcohol use disorders continue to be the main factor in the progression of liver disease, liver transplantation, and premature liver-related mortality in individuals living with chronic HCV infection in Europe [53,54].

In another study, Mankal, et al. [55] estimated the relative influence of alcohol intake and presence of chronic hepatitis C infection on decompensation in patients with chronic liver disease and observed that, in patients with cirrhosis, excess alcohol consumption is associated with a significantly higher risk of decompensation than that posed by HCV infection.

Experimental evidence supports the hypothesis that alcohol and the hepatitis C virus may have additive negative effects on the function of various liver cell types, including hepatocytes, immune cells, and stem cells, thus affecting antiviral immunity, hepatocyte survival, liver regeneration, and oncogenesis in a manner that favors HCV "survival" and replication [56]. On the other hand, ethanol has been shown to potentiate the suppressive effects of HCV on innate immunity. This dysregulation of immune response impairs elimination of HCV-infected cells, facilitating viral persistence and leading to progressive liver damage and chronic infection, which account for the worse outcomes of chronic hepatitis C in patients who make harmful use of alcohol [57].

The limitations of the study are essentially due to its retrospective design. In addition, the fact that patients in Brazil are sent to specialized referral centers for the diagnosis and treatment of hepatitis C may have reduced the case frequency and selected for more severe cases referred to our clinic. The fact that ours is a public clinic also leads to economic selection of the patient population; it is skewed toward patients with alcoholic liver disease, who generally experience greater socioeconomic hardship [58].

In summary, among the patient sample of a tertiary referral clinic for chronic liver disease, HCV patients who make harmful use of alcohol present for their first outpatient visit with a higher frequency of previous episodes of liver decompensation and with significantly greater functional impairment compared to patients living HCV who abstain from alcohol intake or drink only small amounts. These findings, as well as the extensive literature on the theme, support the hypothesis that alcohol and the hepatitis C virus act synergistically to promote progression of liver disease and greater functional liver impairment.

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