Hepatitis C pretreatment profile and gender differences: Cognition and disease severity effects

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Abstract

BACKGROUND The hepatitis C virus (HCV) is known to infect the brain, however findings on associated neuropsychiatric syndrome are controversial and the association itself remains unclear. Gender research in HCV infection is limited, failing to integrate the role of gender in neurocognitive syndrome. This study aimed to characterize psychological and neurocognitive profiles in HCV-infected patients before treatment and to describe gender differences in those profiles as well as the impact of disease severity. METHODS A total of 86 patients diagnosed with chronic hepatitis C were selected in the context of a multidisciplinary out-patient clinic. A semistructured interview was performed to collect social-demographic data and clinical characterization. Assessment was performed using the Hamilton anxiety scale (HAM-A), Hamilton depression scale (HAM-D), Beck depression inventory and a neuropsychological battery to measure attention, concentration, memory and executive functions components validated for the Portuguese population, before starting treatment. To identify the disease severity, platelet ratio index and FibroScan® were used. RESULTS A statistically significant gender effect was found on HAM-A (B = 0.64, confidence interval (CI): 0.17-1.11) and HAM-D, with women scoring higher (B = 0.62, CI: 0.14-1.09) compared to men. Regarding neuropsychological scores, significant differences between gender were identified in executive functions Trails Making Test (TMT)-B (B = 0.48, CI: 0.02-0.97), TMT B-A (B = 0.26, CI: -39.2 to -3.7) and in digit span total (B = -0.52, CI: -1.0 to -0.04), with women performing worse than men. Controlling for years of substance dependence, Digit Span Total was no longer significant; however, TMT-B and TMT B-A continued showing gender differences. Regarding the presence or absence of substance dependence, only HAM-A and HAM-D remained significant. For categorial variables, Digit Span Total was also influenced by gender, with women being more likely to be impaired (odds ratio (OR) = 7.07, CI: 2.04-24.45), and a trend was observed for Digit Span Backward (OR = 3.57, CI: 1.31-9.75). No significant differences were found between disease severity and neurocognitive performance. CONCLUSION Data suggest that gender has an influence on depression, anxiety and cognitive functions independently of the stage of infection. This effect seems influenced by substance dependence.

Introduction

Hepatitis C virus (HCV) is one of the most important infections worldwide, with 71 million people infected [1]. Despite the advent of HCV therapies and high rates of cure, if not treated HCV acute infection tends to progress to chronic state, hepatic cirrhosis (10% to 40%) and hepatocellular carcinoma, which frequently serves as a clinical indication for liver transplant (1% to 5% per year) [2].

HCV patients frequently present neuropsychiatric symptoms, including fatigue, anxiety, depression and neurocognitive impairment, that have been associated with negative treatment outcomes [2–4]. Several studies have demonstrated that HCV-associated neuropsychological impairments are independent of liver disease stage (excluding cirrhosis) [2,4], suggesting that in chronic patients HCV infection itself might directly cause cerebral dysfunction, contributing to deficits in patients [5]. Therefore, the neurocognitive profile of these patients before treatment needs to be addressed, due to the possible implications on the treatment course (*e.g.* nonadherence-like behavior due to cognitive abnormalities).

Additionally, it is important to address other risk factors that can have a negative impact on cognition. The high rate of substance abuse and the prevalence of psychiatric disorders among HCV-infected patients are important factors associated with cognitive impairment that triggers poor adherence and treatment efficacy [6].

Despite being physically asymptomatic, most of the patients with HCV consistently report a significant reduction in health-related quality of life, in comparison with healthy controls [7]. The psychiatric symptomatology in chronic hepatitis C, in particular depression, is twice as high as in the general population, and it is probably one of the major factors for decreasing quality of life, treatment discontinuation and/or negative treatment outcomes [2].

According to several studies, it has been hypothesized that depression and cognitive impairment might be associated with HCV neurotoxicity [8]. Recent studies with interferon-free treatment showed that HCV patients presented neuropsychiatric symptoms like fatigue, insomnia, anxiety, depression and cognitive dysfunction [9–11], supporting the HCV neurotoxicity hypothesis.

In untreated HCV patients, emotional distress and depressive disorders suggest the role of HCV itself in the onset of these neuropsychiatric manifestations [12]. In a recent review, the hepatitis C brain syndrome was identified as being composed of cognitive impairment, fatigue, and depression. This syndrome is probably generated by peripheral immune responses affecting the central nervous system (CNS), by a neuroinflammatory response associated with CNS HCV infection and also by negative life events and other psychogenic stressors [4].

Neurocognitive impairment, one of the most common extrahepatic manifestations of HCV, can lead to subtle changes in processing speed, memory, and cognitive performance (attention, concentration, psychomotor speed, and verbal fluency), and up to 50% of HCV-infected patients can develop clinical or subclinical manifestations of this dysfunction [13,14]. Cognitive impairments were previously thought to be associated with the development of hepatic encephalopathy [15]. However, their presence was demonstrated in the absence of advanced liver disease as well as in the absence of human immunodeficiency virus (HIV) coinfection, depression or substance dependence [4,16,17]. HCV is known to infect the brain; however, findings from studies on associated neurocognitive changes are controversial and it remains unclear if HCV eradication improves neurocognitive performance [16].

Regarding gender differences, women with HCV seem to experience stigma, concerns about confidentiality, treatment side effects and lack of engagement with health services more than men [18]. However, the gender differences research in symptoms profile as well as in treatment response and treatment adherence is scarce, albeit crucial to improving medical- and psychological-integrated interventions.

The aims of this study were to characterize psychological and neurocognitive profiles in HCV-infected patients, before treatment, and to describe gender differences as well as the impact of disease severity in those profiles.

Materials And Methods

This research is part of a larger longitudinal protocol including two assessment times, before and after HCV direct action antiviral medication. It was submitted to and approved by the Centro Hospitalar Lisboa Norte ethics committee (Ref. 0536) and by the Portuguese Data Protection Authority (No. 6331/2012).

If eligible, subjects were informed about the nature of the study and their voluntary cooperation. After confidentiality assurance, a written informed consent was obtained.

Recruitment of participants

A total of 86 patients diagnosed with chronic hepatitis C were selected through a convenience procedure, in the context of a multidisciplinary outpatient clinic (Viral Hepatitis at the Hospital de Santa Maria, Lisbon).

The inclusion criteria were: minimum formal schooling completed with success (at least 4 years education or fluency in reading and writing); ages between 18 and 65 years-old; diagnosis of hepatitis C for at least 6 months. The exclusion criteria were: presence of neurological or psychiatric disorders that may induce cognitive deficits; major depression according to DSM-V; consumption of opiates, cocaine and/or other recreational drugs in the 6 months prior to the beginning of the assessment; use of medication that may interfere with the study objectives; history of neurological, infectious or tumoural pathology or systemic illness with impact at CNS level; a Mini-Mental State Examination (MMSE) score below the cut-off for dementia in the Portuguese population; or, severe physical deterioration incompatible with the psychologic and neuropsychologic assessments.

Assessment and evaluation

A semistructured interview was performed to collect social-demographic data and clinical characterization. Sociodemographic variables included age, time since diagnosis (in years), gender, civil status, education (in years), employment status, psychiatric antecedents, drug consumption, length of psychoactive substances dependence (in years), alcohol and tobacco use.

Psychiatric evaluation

Depression

Depressive symptoms were assessed using a patient-rated questionnaire and a clinician administrated one, to control for the bias of self-reporting.

Hamilton depression scale (HAM-D)

Depression was assessed using the 17-item HAM-D [19]. The Hamilton scale was developed for patients diagnosed with depression, with the purpose of measuring its intensity and to identify depressive symptoms profiles. The HAM-D is a standardized questionnaire. We used the cut-off scores validated for

the Portuguese population [20], in which mild depression was scored 10-12, moderate depression was 13-17 and severe depression was >17 [21].

Beck depression inventory (BDI)

Beck *et al* [22] published the "Inventory for Measuring Depression" in 1961, representing the first self-assessment questionnaire for the study of depression. The inventory comprises 21 symptoms that cover multiple aspects of depressive manifestations, not only affective but also cognitive, motivational and behavioral. The answers are classified into four categoriesnonexistent, mild, moderate and severe, with scores from 0 to 3. The sum of these scores allows for the determination of a total score. This structure is in accordance with the authors' own views on depressive illness and was based on the clinical observation that affective symptoms may not be apparent in the depressed patients, especially when depression has a mild or moderate intensity. In this study, the translated and validated Portuguese version was used [20].

Anxiety

Hamilton anxiety scale (HAM-A)

Anxiety was assessed using the 14-item HAM-A [23]. The Hamilton scale for anxiety comprises 14 symptoms covering the most characteristic manifestations of the anxious syndrome, both in terms of "psychic" (items 1 to 6) and "somatic" (items 6 to 14) symptoms. The rating is determined by scoring on a 5-point Likert scalefrom 0 (not present) to 4 (very severe). Scores range from 0 to 56.

This scale is an instrument that has long been validated by several studies and measured for different Portuguese populations [20].

Neuropsychological evaluation

MMSE

The MMSE is one of the most widely used brief instruments for the clinical evaluation of global cognitive state in adults [24]. The MMSE is used for a brief evaluation of the mental state and screening of dementia. It is a 30-point questionnaire, measuring the following areas of cognitive function: time orientation, spatial orientation, registration, attention and calculation, recall, language, repetition, and visual construction. The maximum score is 30. The normative cut-off values for the Portuguese population adjusted to education were used. Participants should score above 22 if they had $\leq$ 11 years of education, or above 27 if they had > 11 years of education [25].

Trails Making Test (TMT)

The TMT is an instrument that measures executive functions [26]. It consists of two parts. In Part A, the subject is instructed to connect a set of 25 numbers as fast as possible, while still maintaining accuracy. In Part B, the subject is instructed to connect numbers sequentially with letters. Scoring is expressed in

terms of the time (in sec) for Part A and Part B of the test. The TMT B-A score (calculated as the difference between TMT-B and TMT-A, to remove the individual motor speed element from the task and the composite) is considered a measure of cognitive flexibility relatively independent of manual dexterity [27]. The Portuguese-validated version was used [28].

The Battery of Lisbon for the Assessment of Dementia (BLAD)

The BLAD is a comprehensive neuropsychological battery evaluating multiple cognitive domains and validated for the Portuguese population [29]. Tests of interest for the present study were Digit Span (DS) and Logical Memory (immediate and delayed recall). DS is a test that evaluates immediate memory (Digit Span Forward), working memory (Digit Span Backward), and attention and concentration (Digit Span Total). Logical Memory (immediate or delayed recall) evaluates verbal memory and learning. The participants below education and age-adjusted values for the Portuguese population (1 standard deviation) were considered impaired. A cut-off value of 1 standard deviation was adopted considering that use of the cut-off value of 1.5 standard deviations [30] could exclude subjects that, from a clinical point of view, suffered from mild cognitive impairment [31,32].

Disease severity

Aspartate aminotransferase (AST) to platelet ratio index (APRI)

This APRI is among the best-validated methods for predicting HCV progression [33]. In a meta-analysis of 40 studies, investigators concluded that an APRI score > 1.0 had a sensitivity of 76% and specificity of 72% for predicting cirrhosis. In addition, they concluded that APRI score > 0.7 had a sensitivity of 77% and specificity of 72% for predicting significant hepatic fibrosis. The lower the APRI score (< 0.5), the greater is its negative predictive value (and ability to rule out cirrhosis); the higher the value (> 1.5), the greater the positive predictive value (and ability to rule in cirrhosis). The APRI alone is likely not sufficiently sensitive to rule out the significant disease. Some evidence suggests that the use of multiple indices in combination (such as APRI plus findings on transient hepatic elastography, or an algorithmic approach, may result in higher diagnostic accuracy than using APRI alone [34].

Transient hepatic elastography -TE

Liver stiffness measurement by TE was performed according to published recommendations, using the M probe of FibroScan. The results were expressed in kPa. Only procedures with at least 10 validated measurements and > 60% success rate and an interquartile range inferior to 25% of the median value were considered reliable [35]. The standard 12.5 kPa for the diagnosis of cirrhosis and 7.1 kPa for F2, F3, and F4 were used [36].

Statistical analysis

Results were analyzed using descriptive statistics, including percentages to describe categorical variables and means and standard deviations for continuous ones.

Demographic, clinical, psychological and neuropsychological data were analyzed using independent *t*-tests or linear regression models for dependent continuous variables, as normality was achieved in every distribution. The continuous variables were all standardized to the mean and standard deviation (Z score), and the reported B values represent the standardized coefficients or the dimension of the effect. Every B value between 0.2 and 0.5 was considered as presenting a relevant effect, and above 0.5 were considered of medium dimension. Although the significance (*P*-value) is presented and the significance value was established at a two-tailed threshold of <0.05, all interpretation is based on the concomitant values of the coefficient B and the *P*-value, following recent discussion on the interpretation bias caused by the sole interpretation of the latter [37,38].

For categorical analysis, chi-squared tests (with the report of Cochran's and Mantel-Haenszel statistics (odds ratio (OR)) when just one independent variable was being tested or logistic regression models when there was more than one independent variable) were developed. The values reported for this analysis are the ORs, with a reference neutral value of 1. Once again, a balanced analysis between the odds and the respective *P*-value was reported. Odds superior to 1.5 or inferior to 0.75 were considered as relevant. All the neuropsychological tests were categorized with the value of 1 for defect and 0 for the absence of defect, and women were categorized as 1 and men as 0.

The variables related to disease severity (APRI and FibroScan values) are both continuous. Patients with a level of APRI and FibroScan value superior to 2.5 standard deviations of the respective mean were excluded from the sample, as their level of disease severity was found to be compromising the normality of the analysis. Three males fell under this condition.

Statistical analyses were performed using IBM SPSS Statistics 23 for Windows (2016; IBM Corp, Armonk, NY, United States). The statistical methods of this study were reviewed by Isabel Flores, senior trainer, and consultant in biostatistics.

Results

Demographic and clinic characterization data

The sample consisted of 86 HCV-infected patients, 63 men and 23 women with a mean age of 48 ± 9 24-67 years-old, submitted to psychological and neuropsychological assessments. Group comparisons for continuous variables were obtained through a *t*-test for independent samples and for categorical variables through a Pearson chi-squared test.

There were no statistically significant differences between genders related to age, diagnosis time, civil status, education, employment, psychiatric antecedents, years of substance dependence, alcohol use or smoking. There were statistical differences in substance dependence (89.5% for men and 50% for women, $P < 0.001$) (INSERT HERE Table 1).

Differences in psychological and neuropsychological tests by gender

There were two levels of analyses: the effect of gender on the continuous variables, and the effect of gender on each neuropsychological indicator classified in two categorieswith or without cognitive defect (Tables 2 and 3). A linear regression model was used to calculate gender differences on psychological and neuropsychological performance (INSERT HERE Table 2).

Results are presented controlling for years of substance dependence (A.Beta1) and for the presence or absence of previous illicit drugs consumption (A.Beta2), as a statistically significant difference between males and females was found. Beta (B) scores represent the influence of the gender over the psychological or neuropsychological measures and the respective standard deviations for a significance at 95%. Beta values higher than 0.20 represent an effect at the sample level.

Regarding gender, it was possible to identify significant effects on HAM-A (B = 0.64, confidence interval (CI): 0.17–1.11), with women having higher scores on anxiety. The same type of effect was found on HAM-D, with women obtaining a higher significance (B = 0.62, CI: 0.14-1.09) in depression. No difference between genders was found on the BDI.

In neuropsychological tests, we found significant differences between gender in executive functions measured by TMT-B (B = 0.48, CI: 0.02–0.97) and in TMT B-A (B = 0.25, CI: -39.2 to -3.7), with women performing worse.

Digit Span Total was also influenced by gender (B = -0.52, CI: -1.0 to -0.04), with women having a lower score. Controlling for years of substance dependence, Digit Span Total was no longer significant; however, TMT-B and TMT B-A continued showing gender differences. Controlling for the presence or absence of substance abuse, only HAM-A and HAM-D remained significant.

To describe categorical variables analysis, logistic regression models were used (INSERT HERE Table 3). The reported values are ORs and adjusted ORs for the number of years of substance dependence (A.ORs) and for the presence or absence of illicit drugs consumption (A.OR1); a confidence interval of 95% was established.

In terms of odds, Digit Span Total shows a very relevant result, with women having a 7-times higher possibility of scoring at an abnormal level in this indicator than men (ORs = 7.07, CI: 2.04-24.45). After adjustment, the ORs remained significant and with a relevant dimension (A.ORs = 6.86, CI: 1.88–24.96; A.OR1 = 5.77, CI: 1.53–21.88). For Digit Span Backward, a gender effect was significant only in ORs (ORs = 3.57, CI: 1.31–9.75), but was lost after adjustments.

Another relevant difference was found in Logical Memory (immediate recall) OR adjusted for years of substance dependence, where women showed a higher percentage of normal results, presenting a lower possibility of verbal memory and learning defect (A.ORs = 0.28, CI: 0.09-0.83). All the other indicators showed no relevant differences between genders.

Although not reaching a significant level, ORs in TMT-B and Digit Span Forward showed a trend to a worse performance in women, with a probability up to 2.5-times higher for a defect, facing men.

Disease severity, gender, psychological and neuropsychological measures

The possibility of a defect was assessed using as predictors gender, APRI, and FibroScan values, as measures of disease severity. For psychological dimensions, results were obtained following a multivariable linear regression model and the values reported are the standardized coefficients of the variables (Beta); the $R2$ represents a measure of goodness of fit. For neuropsychological ones, the indicators were codified as 'with defect' (1) and 'without defect' (0), and a multiple logistic binary regression was performed (INSERT HERE Table 4).

Results showed that disease severity has no relevant effect in any score and only gender had a small predictive capacity for HAM-A (B = 0.62, CI: 0.12–1.09; $R2$ = 0.13) and for HAM-D (B = 0.56, CI: 0.09–1.06; $R2$ = 0.12), confirming what had already been reported from the previous analysis.

Digit Span Total provided the most relevant result (Nagelkerke $R2$ = 0.23) fully explained by gender, and once again disease severity seemed to have no influence on this score. The OR of 8.01 showed that women have a possibility of about 8 times higher for being classified as with defect on this indicator. In the presence of disease severity, the Digit Span Backward had a 3.6 higher chance of being classified as a defect (Nagelkerke $R2$ = 0.10), in the same line of what had been described before.

Discussion

Gender research in HCV infection is limited, failing to integrate the role of gender in neurocognitive syndrome. To the best of our knowledge, our study is the first to explore the gender effect in pre-treatment HCV-infected patients.

According to our results using clinician rated instruments (HAM-A and HAM-D), women presented mild levels of anxiety and depression and men showed only mild levels of anxiety. In the self-evaluation questionnaire (BDI), men and women scored below the cut-off level for the diagnosis of clinical depression, ultimately due to a devaluation in emotional self-report.

On neuropsychological performance in pretreatment HCV-infected patients, the gender effect was even more evident. Domains such as attention, concentration, and memory (short-term and working memory), the ability to shift strategy, executive functions and visual-spatial working memory showed significant differences with women being more impaired than men. Additionally, when participants were categorized as with or without defect, women performed poorly in short-term and working memory and attention. This gender effect for executive functions was lost when controlling for substance dependence but was maintained and stood out as significant for attention, concentration and working memory.

These results can be explained due to the gender impact of the disease. Previous findings suggest a significantly higher impact on quality of life and also a higher burden of the hepatitis C diagnosis in women [39]. In fact, in the general population the prevalence of depressive disorders is higher in women

[40], with a greater burden of mood and anxiety disorders and a lifetime prevalence around 21% compared to 13% in men [41].

The impact of psychosocial factors associated with these disorders are also higher in women, and the risk of developing mood disorders associated to adverse life events imply several contributing factors, such as family, work, environmental-related stressors, poor social support or childhood abuse [42]. Biological sex-related variables are also a major determinant of risk for depression [41] and facing a chronic disease, such as hepatitis C. Those factors may, perhaps, enhance vulnerability to the neurotoxic effects of the virus as well as to the burden of the disease [43]. In subsequent analysis, our data replicated previous findings of gender effect, with women presenting higher scores in depression and anxiety, even when controlling for drug use and years of substance dependence. Years of dependence seems to be important for verbal memory and learning, with men scoring worse than women. Although these results highlighted the impact of several years of drug use, they do not fully explain the impairment in cognitive functions in our sample. So, these results can be in agreement with several literature reports that have highlighted the CNS toxicity of HCV [44].

Disease severity does not seem to influence gender effect, or the profile displayed by patients, perhaps due to the low variability of disease severity in our sample.

The psychological and neurocognitive characterizations of these patients before treatment assume particular significance. The importance of preventing and treating psychological comorbidities, such as depression and anxiety, can lead to a better quality of life and better overall functioning during treatment. Impairments due to psychological or neurocognitive symptoms are likely to interfere with the way patients experience treatment, in a more or less psychological adjusted way [45]. The use of a personalized and patient-centered approach for these patients, promoting a deeper understanding of disease state and needs, is also desirable [39,46].

Moreover, factors like gender, depression, psychiatric diagnosis in general, illicit drug use, HIV coinfection, treatment regimen, and hemoglobin levels are variables identified as significantly and consistently associated with adherence/nonadherence [47]. According to the review by Mathes *et al* [48], there is a tendency for males with HCV to be more adherent than females. Although inconclusive, this tendency is consistent with recent findings in the wider chronic illness population. In addition, women were reported as less likely to receive long-term medical treatment and to engage in clinically recommended monitoring [49]. These factors are equally relevant in the new treatment landscape because they are independent of treatment duration.

Furthermore, HCV-related morbidity and mortality impose a great burden on societies and public health services and these insights may allow the design of targeted interventions being aware of personal variables linked to the HCV patient profile before treatment, helping to maximize intervention efficacy and behavior modification in order to prevent nonadherence and treatment failure. Additionally, psychological and neurocognitive factors are also important for more complex combinations of HCV enzyme inhibitors,

becoming increasingly important to achieving treatment success as resistant mutations may develop [11].

Research suggests that depression in HCV-infected patients may be under-diagnosed, thereby increasing the risk of treatment discontinuation and depression severity, being that HCV itself is a risk factor for depression [50].

The research presented herein has several limitations. The convenience sampling method and the relatively small sample sizes, particularly for women, is a major limitation. Time-since-diagnoses in a wide range and the nonexistence of a matched control group are also relevant limitations. However, being part of a longitudinal protocol, first evaluation results will be analysed in future research using an intra subjects design, allowing a comprehensive discussion of therapy effects in psychological and neurocognitive functions. These results will require verification in larger samples, and our findings must be interpreted with caution and are not generalizable to all HCV-infected patients.

Despite these limitations, this study has important strengths as well. In contrast to the many studies that have relied solely on self-reported symptoms scales, this study used both when assessing the severity of depressive symptoms. The clinician administrated instruments were applied by a single trained clinical psychologist, preventing bias on assessment. In addition, this study also used culturally adapted and validated measures for assessing psychological and neuropsychological symptoms, and all patients were followed in a single center. Lastly, the results of this study might also have important implications for clinical practice. These findings are also important to encourage mental health professionals to take an active role in HCV treatment in the post-interferon era [9].

In conclusion, chronic HCV infection is known to be associated with neuropsychiatric dysfunction. Recognition of neurocognitive symptoms is important before and during the treatment of these patients, but it is noteworthy that neurocognitive and neuropsychiatric symptoms (depression, anxiety, and cognitive disorders) may be associated with direct HCV neurotoxicity.

According to our investigation, gender seems to have an influence on depression, anxiety and some of the indicators of cognitive functions, and this effect is not influenced by disease severity nor substance dependence.

Declarations

Ethics approval and consent to participate

This research protocol was submitted to and approved by the Centro Hospitalar Lisboa Norte ethics committee (Ref. 0536) and by the Portuguese Data Protection Authority (No. 6331/2012)

Consent for publication

Not applicable

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests associated with this study.

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Authors' contributions

David Pires Barreira, Renata Fialho and Sílvia Ouakinin conceived of the study, participated in the design and coordination. Rui Tato Marinho, Manuel Bicho and Silvia Ouakinin reviewed this manuscript. Isabel Flores analyzed the data. All authors read and approved the final draft of the manuscript.

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Tables

Table 1 Demographic and personal characterization with gender comparison

	Females, *n* = 23	Males, *n* = 63	*P*
Age	48.0 ± 8.8	47.7 ± 9.9	0.87
Time diagnosis, in yr	9.9 ± 8.6	7.5 ± 7.3	0.24
Education, in yr	9.9 ± 3.3	9.6 ± 4	0.78
Civil status			0.9
Single	18.2%	18.3%	
Married	50%	53.3%	
Divorced/separated	27.3%	26.7%	
Widowed	4.5%	1.7%	
Employment			0.83
Employed	54.5%	53.3%	
Unemployed	31.8%	38.3%	
Medical leave	4.5%	1.7%	
Retired	9.1%	6.7%	
Psychiatric antecedents	27.3%	11.7%	0.08
Substance dependence	50%	89.5%	0.001a
Years of substance dependence	17.0 ± 9.1	17.2 ± 10.7	0.97
Alcohol			0.41
No	86.4%	78.3%	
< 10 g/day	13.6%	20%	
≥ 10 g/day	4.5%	3.3%	
Smoking			0.55
No	45.5%	33.3%	
< 10 cigarettes/day	31.8%	43.3%	
≥ 10 cigarettes/day	22.7%	23.3%	

a$P < 0.01$.

30

Table 2 Gender effect in psychological and neuropsychological evaluations

	Females, *n* = 23	Males, *n* = 63	Beta (95%CI)	A.Beta1 (95%CI)	A.Beta2 (95%CI)
HAM-A	14.3 ± 5.2	10.5 ± 6.0	0.64b (0.17-1.11)	0.81b (0.35-1.29)	0.72b (0.22-1.24)
HAM-D	10.2 ± 4.2	7.3 ± 4.6	0.62a (0.14-1.09)	0.74b (0.26-1.24)	0.65a (0.13-1.16)
BDI	8.7 ± 8.1	7.8 ± 8.4	0.11 (-0.38-0.60)	0.12 (-0.39-0.63)	0.23 (-3.0-0.77)
TMT-A	50.3 ± 6.6	44.6 ± 13.6	0.39 (-0.36-0.15)	0.36 (-0.16-0.88)	0.24 (-0.28-0.77)
TMT-B	134.6 ± 49.8	111.1 ± 49.8	0.48 a (0.02-0.97)	0.53a (0.02-1.05)	0.31 (-0.20-0.83)
TMT B-A	84.3 ± 35.2	62.8 ± 35.9	0.26a (-39.2 to -3.7)	0.2a (-39.9 to -2.6)	0.17 (-33.2-4.28)
Digit Span Forward	5.3 ± 1.4	5.9 ± 1.2	-0.44 (-0.92-0.04)	-0.45 (-0.96-0.05)	-0.21 (-0.72-0.30)
Digit Span Backward	3.2 ± 0.9	3.7 ± 1.1	-0.44 (-0.92-0.04)	-0.28 (-0.78-0.21)	-0.25 (-0.77-0.27)
Digit Span Total	8.6 ± 2.0	9.7 ± 2.1	-0.52a (-1.0 to -0.04)	-0.44 (-0.94-0.06)	-0.27 (-0.77-0.23)
Logical Memory (immediate recall)	7.5 ± 2.6	6.8 ± 2.6	0.24 (-0.25-0.73)	0.33 (-0.18-0.85)	0.31 (-0.22-0.84)
Logical Memory (delayed recall)	6.6 ± 2.1	5.9 ± 2.4	0.03 (-0.52-0.46)	0.05 (-0.20-0.25)	-0.08 (-0.63-0.45)

Data is presented as mean ± standard deviation, unless otherwise indicated. a$P < 0.005$; b$P < 0.001$. BDI: Beck depression inventory; CI: Confidence interval; HAM-A: Hamilton anxiety scale; HAM-D: Hamilton depression scale; TMT: Trails Making Test.

Table 3 Association between gender and neuropsychological results, categorised as with or without defect

		Males (0), *n* = 63	Females (1), *n* = 23	ORs (95%CI)	A.ORs (95%CI)	A.OR1 (95%CI)
TMT-A	No defect (0)	83.3%	83%	1.05 (0.94-3.76)	0.96 (0.25-3.63)	1.07 (0.26-4.27)
	Defect (1)	16.7%	17%			
TMT-B	No defect (0)	73.3%	52.2%	2.5 (0.92-6.84)	2.48 (0.87-7.07)	1.98 (0.67-5.88)
	Defect (1)	26.7%	47.8%			
Digit Span Forward	No defect (0)	88.3%	73.9%	2.7 (0.78-9.04)	2.35 (0.65-8.44)	2.05 (0.54-7.86)
	Defect (1)	11.7%	26.1%			
Digit Span Backward	No defect (0)	73.3%	43.5%	3.57a (1.31-9.75)	2.49 (0.85-7.27)	2.82 (9.62-8.31)
	Defect (1)	26.7%	56.5%			
Digit Span Total	No defect (0)	91.7%	60.9%	7.07b (2.04-24.45)	6.86b (1.88-24.96)	5.77b (1.53-21.88)
	Defect (1)	9.3%	29.1%			
Logical Memory (immediate recall)	No defect (0)	26.7 %	47.8%	0.39 (0.14-1.07)	0.28a (0.09-0.83)	0.39 (0.13-1.16)
	Defect (1)	73.3%	51.2%			

Logical Memory (delayed recall)	No defect (0)	35%	39%	0.84 (0.31-2.25)	0.720 (0.95-1.02)	0.66 (0.22-1.20)
	Defect (1)	65%	61%			

a$P < 0.005$; b$P < 0.001$. OR: Odds ratio; TMT: Trails Making Test.

Table 4 Association between gender, psychological and categorized neuropsychological results, controlling for disease severity

Psychological	Sexo	APRI	FibroScan	*R*2
	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	
HAM-A	0.62a	-0.33	0.05	0.13
	(0.12-1.09)	(-6.79-0.13)	(-0.17-3.44)	
HAM-D	0.56a	-0.23	0.07	0.12
	(0.09-1.06)	(-0.64-0.51)	(-0.23-2.8)	
BDI	0.21	-0.25	0.01	0.04
	(-0.26-6.94)	(-0.59-0.09)	(-0.27-2.35)	
Neuropsychological	**Sexo**	**APRI**	**FibroScan**	**Nagelkerke**
	OR	**OR**	**OR**	**(*R*2)**
TMT-A	0.83	0.39	1.20	0.05
	(0.19-3.59)	(0.09-1.56)	(0.56-2.58)	
TMT-B	3.04	0.68	0.51	0.15
	(0.99-9.38)	(0.27-1.72)	(0.24-1.72)	
Digit Span Forward	3.62	0.86	1.46	0.96
	(0.95-13.75)	(0.27-2.72)	(0.58-2.51)	
Digit Span Backward	3.60a	1.0	1.1	0.10
	(1.24-10.49)	(0.44-2.23)	(0.57-1.84)	
Digit Span Total	8.01b	0.81	0.95	0.23
	(2.01-31.97)	(2.36-2.78)	(0.24-1.52)	
Logical Memory (immediate recall)	0.39	0.82	1.04	0.05
	(0.13-1.13)	(0.37-1.80)	(0.58-1.87)	
Logical Memory (delayed recall)	0.91	1.48	0.90	0.02
	(0.31-2.63)	(0.65-3.37)	(0.51-1.59)	

a$P < 0.005$; b$P < 0.001$. CI: Confidence interval.