Research, Society and Development, v. 9, n. 11, e52291110075, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i11.10075

Depressive symptoms are independently associated with cirrhosis in untreated subjects with Chronic Hepatitis C infection

Sintomas depressivos estão independentemente associados à cirrose em indivíduos não tratados com hepatite C crônica

Síntomas depresivos se asocian de forma independiente con la cirrosis en sujetos no tratados con hepatitis C crónica

Received: 11/10/2020 | Reviewed: 11/16/2020 | Accept: 11/19/2020 | Published: 11/25/2020

Henrique Pott-Junior
ORCID: https://orcid.org/0000-0003-3126-2946
Universidade Federal de São Carlos, Brasil
henriquepott@ufscar.br
Eveline Tonelotto Barbosa Pott
ORCID: https://orcid.org/0000-0001-8263-6093
Universidade Paulista, Brasil
evelinebarbosaa@gmail.com
Rita Moretto
ORCID: https://orcid.org/0000-0003-0445-933X
Universidade Federal de São Paulo, Brazil
ritmoretto@gmail.com
Jorge Figueiredo Senise
ORCID: https://orcid.org/0000-0003-4624-912X
Universidade Federal de São Paulo, Brazil
senise.jorge@gmail.com
Adauto Castelo
ORCID: https://orcid.org/0000-0001-8009-4577
Universidade Federal de São Paulo, Brazil
acastelof42@gmail.com

Abstract

Objectives: Depression has shown to be a major public health problem, and is often reported in people with chronic hepatitis C infection. However, little is known about the role of liver fibrosis in predicting depressive symptoms among untreated patients. This study aimed to

assess depressive symptoms among HCV-untreated patients, and to explore its association with liver fibrosis. **Methods:** A propensity score matched cross-sectional study was conducted on 154 subjects with CHC infection. Depression was defined as a score greater than 11 points to depression symptomatology in the Beck Depression Inventory-II. **Results:** The prevalence of depressive symptoms was 42.9%, and affected predominantly females, aged ≥ 45 years, who had an overall lower education level, without a history of current or previous use of antidepressants or anxiolytics. Median BDI-II score was 6 (IQR, 3 – 16) and 12 (IQR, 6 – 19) for the non-cirrhotic and cirrhotic group, respectively. Depressive symptoms were more frequent in compensated cirrhotic subjects than non-cirrhotic subjects, despite controlling for a range of demographic variables and comorbid conditions. **Conclusions:** HCV-untreated subjects have an elevated prevalence of depressive symptoms. This is especially relevant among those with cirrhosis, and should raise the awareness of this condition to health professionals.

Keywords: Hepatitis C; Depression; Depressive disorder; Cross-sectional studies.

Resumo

Objetivos: A depressão tem se mostrado um importante problema de saúde pública e é frequentemente relatada em pessoas com hepatite C crônica (HCC). No entanto, pouco se sabe sobre o papel da fibrose hepática na predição de sintomas depressivos em pacientes não tratados. Este estudo teve como objetivo avaliar os sintomas depressivos entre pacientes não tratados com HCV e explorar sua associação com a fibrose hepática. **Métodos:** Um estudo transversal com escore de propensão combinado foi conduzido em 154 indivíduos com HCC. A depressão foi definida como uma pontuação maior que 11 pontos para a sintomatologia da depressão no Inventário de Depressão de Beck-II. **Resultados:** A prevalência global de sintomas depressivos foi de 42,9%, afetando predominantemente indivíduos do sexo feminino, com idade ≥ 45 anos, que apresentavam menor escolaridade geral, e sem história de uso atual ou prévio de antidepressivos ou ansiolíticos. A pontuação média do BDI-II foi 6 (IQR, 3 - 16) e 12 (IQR, 6 - 19) para o grupo não cirrótico e cirrótico, respectivamente. Os sintomas depressivos foram mais frequentes em indivíduos cirróticos compensados do que em indivíduos não cirróticos, apesar do controle de uma série de variáveis demográficas e condições associadas. **Conclusões:** Indivíduos não tratados com HCV apresentam elevada prevalência de sintomas depressivos. Isso é especialmente relevante entre aqueles com cirrose e deve aumentar a conscientização sobre essa condição para os profissionais de saúde.

Palavras-chave: Hepatite C; Depressão; Distúrbio depressivo; Estudos transversais.

Resumen

Objetivos: La depresión ha demostrado ser un problema importante de salud pública y, a menudo, se informa en personas con infección crónica por hepatitis C. Sin embargo, se sabe poco sobre el papel de la fibrosis hepática en la predicción de síntomas depresivos en pacientes no tratados. Este estudio tuvo como objetivo evaluar los síntomas depresivos entre pacientes no tratados con el VHC y explorar su asociación con la fibrosis hepática. **Métodos:** Se realizó un estudio transversal emparejado por puntuación de propensión en 154 sujetos con infección por HCC. La depresión se definió como una puntuación superior a 11 puntos en la sintomatología de la depresión en el Inventario de Depresión de Beck-II. **Resultados:** La prevalência global de síntomas depresivos fue del 42,9%, y afectó predominantemente a mujeres, ≥ 45 años, que tenían un nivel educativo general más bajo, sin antecedentes de uso actual o previo de antidepresivos o ansiolíticos. La mediana de la puntuación BDI-II fue 6 (IQR, 3 - 16) y 12 (IQR, 6 - 19) para el grupo no cirrótico y cirrótico, respectivamente. Los síntomas depresivos fueron más frecuentes en los sujetos cirróticos compensados que en los no cirróticos, a pesar de controlar una variedad de variables demográficas y condiciones comórbidas. **Conclusiones:** Los sujetos no tratados con VHC tienen una elevada prevalencia de síntomas depresivos. Esto es especialmente relevante entre las personas con cirrosis y debería sensibilizar a los profesionales de la salud sobre esta condición.

Palabras clave: Hepatitis C; Depresión; Desorden depresivo; Estudios transversales.

1. Introduction

Depression has shown to be a major public health problem, and is often reported in people with chronic illnesses. This is particularly evident among those with chronic hepatitis C (CHC) infection, for which the prevalence of depression has been estimated to be up to 4 times higher than that observed in the general population. (Adinolfi et al., 2017; Nelligan et al., 2008) Therefore, and as the global prevalence of CHC infection increases, the impact of this condition can be even more substantial.

However, although there is a consistent evidence about the association between CHC infection and depression, its true prevalence remains an unresolved issue, and may actually be underestimated due to concomitant disorders and individual sociocultural background. (Adinolfi et al., 2017) Therefore, efforts should be made to identify those at high-risk of having depressive symptoms, in order to early diagnosis and provide individualized care.

Previous studies reported that having a history of depression was significantly associated with the ocurrence of depressive symptoms during antiviral treatment with interferon alfa plus ribavirin. (Raison et al., 2005) More recently, being treated with new interferon-free direct-acting antivirals had no impact on the occurence of anxiety or depression, even in high-risk patients with major psychiatric disorders. (Gallach et al., 2018) However, until now, little is known about the factors associated with depressive symptoms among untreated patients. Specifically, there is conflicting data on the role of liver fibrosis in predicting the ocurrence of depressive symptoms among those patients.

Therefore, this study was designed to assess the prevalence and severity of depressive symptoms in untreated patients with CHC infection, and also to explore the association between depressive symptoms and severity of liver fibrosis, using propensity score matching analysis.

2. Methods

2.1 Study design

This was a prospective cross-sectional study to assess the the prevalence and severity of depressive symptoms in untreated patients with CHC infection, and also to explore the association between depressive symptoms and severity of liver fibrosis, using propensity score matching analysis.

2.2 Study population

Eligible subjects were prospectively recruited at two sites: The Viral Hepatitis Outpatient Clinic at the Universidade Federal de São Paulo, and the Center for Prevention and Assistance to Infectious Diseases in São Caetano do Sul.

Subjects were enrolled if they satisfied all of the following inclusion criteria: ≥18 years of age; with chronic hepatitis C infection; and absence of Child-Pugh B or C liver cirrhosis. Key exclusion criteria included chronic liver disease unrelated to HCV infection; coinfection with human immunodeficiency virus or hepatitis B virus; and history of previous HCV treatment with interferon, pegylated interferon, and/or ribavirin; neurological disorders (in the subject or first-degree relatives); traumatic brain injury; or a major current psychiatric disorder.

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Universidade Federal de São Paulo Research Ethics Committee. Written informed consent was obtained from all subjects.

2.3 Measurements

The following data was gathered from those meeting inclusion criteria: age (years); sex (male / female); education level (high school diploma or less / undergraduate / postgraduate); marital status (single / married / divorced / widowed); current or previous use of antidepressants or anxiolytics, alcohol and drugs (yes / no); weight (kilogram, kg), height (meters, m), and body mass index (kilogram per square meter, kg/m^2); and severity of liver fibrosis (no fibrosis / mild fibrosis / moderate fibrosis / severe fibrosis / cirrhosis). The presence of cirrhosis was defined as a Metavir score of F4 on liver biopsy up to 12 months after first consultation and/or a liver stiffness value higher than 12.5 kPa. In case of conflicting fibrosis results according to these methods, biopsy data took precedence. If biopsy data were not available, the FibroScan result was considered. All patients enrolled in the study also completed the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) (Bush, 1998), and the Beck Depression Inventory (BDI-II) (Beck, 1961). Biochemical parameters including HCV genotype and HCV RNA viral load were also assessed by commercial laboratory methods.

2.3.1 Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)

The AUDIT-C is a three-item scale used to identify persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence). (Bush, 1998) Each item has five answer choices and is scored from 0 to 4. A cumulative score is determined by adding the scores of the individual items. Generally, the higher the score, the more likely it is that the patient's drinking is affecting his or her safety. A score of >3 (females) or >4 (males) indicated persons who are hazardous drinkers or have active alcohol use disorders.

2.3.2 Beck Depression Inventory-II (BDI-II)

The BDI-II is a 21-item self-report scale that assesses the severity of depressive symptoms. (Beck, 1961) Each item has four answer choices and is scored from 0 to 3. A cumulative score is determined by adding the scores of the individual items. Cutoff scores were determined by using the guidelines set forth in the Brazilian version of the BDI-II. (Gomes-Oliveira et al., 2012; Wang & Gorenstein, 2013) Scores are summed so that a BDI-II total score of ⩽11 indicated minimal depressive symptoms (no depression) and a BDI-II total score of >12 indicated mild-to-severe depressive symptoms. (Gomes-Oliveira et al., 2012)

2.3.3 Biochemical determinations

HCV genotype or subtype was determined using the a RealTime HCV Genotype II assay (Abbott Molecular, Abbott Park, IL, USA). Plasma HCV RNA levels were assessed using the HCV COBAS TaqMan Test (version 2.0; Roche Molecular Systems, Pleasanton, CA, USA) with a lower limit of quantitation of 12 IU/mL.

2.4 Sample size

Based on previous findings on the prevalence of mood disorders in Brazilian HCV-infected patients, we assumed that the prevalence of depression in this population would be around 15 percent. (Batista-Neves et al., 2008) Therefore, we calculated a required sample size of 196 patients with an allowable error margin of 5% and a 95% confidence level.

2.5 Statistical methods

As one of the objectives was to explore the association between depressive symptoms and severity of liver fibrosis, subjects where divided into two subgroups, with and without liver cirrhosis. In order to address the imbalance between cirrhotic and non-cirrhotic groups, we matched the baseline conditions using logistic regression estimated propensity scores. In this model the following variables have been chosen as covariates: sex (1= female, 2= male), age range (1= “18 - 24 years", 2= "25 - 34 years", 3= "35 - 44 years", 4= "45 - 54 years", 5= "55 - 64 years", 6= "> 65 years"), education level (1= "≤ high school diploma", 2= "Undergraduate", 3= "Postgraduate"), marital status (1= "Single", 2= "Maried", 3=

"Divorced", 4= "Widowed"), and hazardous drinkers or have active alcohol use disorders (1= “Normal”, 2= “Misuse”). Once the propensity scores were estimated, nearest neighbour was used to match the baseline conditions after adjusting to the differences between the two groups. After matching, absolute standardized mean differences were used as a summary measure of balance between the two groups.

Continuous data are presented as mean (standard deviation) or median [interquartile range] according to the Shapiro-Wilk test of normality. Categorical variables are presented as counts and percentages. Comparisons between groups were performed using Wilcoxon-Mann-Whitney test for continuous variables, and Pearson's Chi-squared test with Yates' continuity correction for categorical variables. Statistical significance was assessed at a two-sided p value < 0.05. All analyses were conducted using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria) in R-studio 1.1.463 (RStudio Inc., Boston, USA).

3. Results

Demographic and clinical features

Of all 206 recruited subjects, 154 remained after matching. The general characteristics of the studied population are presented in Table 1. Overall, the majority of the subjects were males (82/154, 53.2%) with a mean age of 55.3 ± 7.91 years, had an educational level of a high school diploma or less (138/154, 89.6%), and were married (98/154, 63.6%). Seventy-four percent reported having no history of current or previous use of antidepressants or anxiolytics, whereas the prevalence of substance or alcohol misuse was 16.2% and 10,4%, respectively. The genotype 1 was the most prevalent genotype (66.2%), followed by genotype 3 (27.3%).

Table 1: Characteristics of the study population.

Variable	Overall (N=154)	Non-cirrhotic (n=77)	Cirrhotic (n=77)	p	SMD
Sex				0.8	0.05
Female	72 (46.8)	35 (45.5)	37 (48.1)		
Male	82 (53.2)	42 (54.5)	40 (51.9)		
Age, y	55.32 (7.91)	54.88 (7.77)	55.75 (8.06)	0.6	0.1
Age range				0.5	0.2

35 - 44 years	12 (7.8)	6 (7.8)	6 (7.8)		
45 - 54 years	53 (34.4)	23 (29.9)	30 (39.0)		
55 - 64 years	72 (46.8)	40 (51.9)	32 (41.6)		
> 65	17 (11.0)	8 (10.4)	9 (11.7)		
Education level				0.4	0.2
≤ high school diploma	138 (89.6)	68 (88.3)	70 (90.9)		
Undergraduate	1 (0.6)	0 (0.0)	1 (1.3)		
Postgraduate	15 (9.7)	9 (11.7)	6 (7.8)		
Marital status				0.7	0.1
Single	10 (6.5)	5 (6.5)	5 (6.5)		
Divorced	29 (18.8)	13 (16.9)	16 (20.8)		
Maried	98 (63.6)	52 (67.5)	46 (59.7)		
Widowed	17 (11.0)	7 (9.1)	10 (13.0)		
History of use of antidepressants or anxiolytics				0.7	
No	115 (74.7)	56 (72.7)	59 (76.6)		0.09
Yes	39 (25.3)	21 (27.3)	18 (23.4)		
History of use of intravenous or inhaled substances				1	0.03
No	129 (83.8)	64 (83.1)	65 (84.4)		
Yes	25 (16.2)	13 (16.9)	12 (15.6)		
Alcohol misuse by the AUDIT-C				0.4	0.1
Normal consuption	138 (89.6)	71 (92.2)	67 (87.0)		
Misuse	16 (10.4)	6 (7.8)	10 (13.0)		
Beck Depression Inventory-II				0.05	0.4
Minimal	88 (57.1)	52 (67.5)	36 (46.8)		
Mild	34 (22.1)	12 (15.6)	22 (28.6)		
Moderate	28 (18.2)	12 (15.6)	16 (20.8)		
Severe	4 (2.6)	1 (1.3)	3 (3.9)		
Overall score	11.83 (10.02)	10.03 (9.86)	13.64 (9.92)	0.01	0.3
Anthropometric measurements					
Body weight, kg	70.45 [63.00, 81.00]	70.40 [63.00, 82.00]	70.50 [63.00, 81.00]	0.8	0.01
Height, m	1.65 (0.10)	1.65 (0.10)	1.65 (0.10)	0.7	0.03
Body mass index, kg/m2	26.26 [23.39, 29.51]	26.30 [23.42, 29.72]	25.78 [23.14, 29.05]	0.7	0.01

Liver fibrosis				<0.001	12.3
No fibrosis	1 (0.6)	1 (1.3)	0 (0.0)		
Mild fibrosis	32 (20.8)	32 (41.6)	0 (0.0)		
Moderate fibrosis	23 (14.9)	23 (29.9)	0 (0.0)		
Severe fibrosis	21 (13.6)	21 (27.3)	0 (0.0)		
Cirrhosis	77 (50.0)	0 (0.0)	77 (100.0)		
Viral parameters					
HCV Genotype				0.5	0.2
1	102 (66.2)	54 (70.1)	48 (62.3)		
2	9 (5.8)	4 (5.2)	5 (6.5)		
3	42 (27.3)	18 (23.4)	24 (31.2)		
4	1 (0.6)	1 (1.3)	0 (0.0)		
HCV viral load, logUI/mL	5.96 [5.58, 6.39]	6.06 [5.62, 6.52]	5.93 [5.48, 6.32]	0.06	0.3

Data are presented as n (%), mean (standard deviation) or median [interquartile range]. SMD, Standardized Mean Difference; AUDIT-C, Alcohol Use Disorders Identification Test-Consumption; BDI-II, Beck Depression Inventory-II; HCV, Hepatitis C virus.

Source: Authors.

Prevalence of depressive symptoms

The median BDI-II score was 9 (Interquartile Range [IQR], 4 – 18), and the percentage of subjects classified as having minimal depressive symptoms (0 – 11) was 57.1% (88/154), while 42.9% (95% Confidence Interval [95% CI], 35% - 50.7%) of subjects were classified as having at least mild depressive symptoms (22.1% as mild, 18.2% as moderate, and 2.6% as severe).

These subjects were predominantly females (60.6%; p = 0.004), aged ≥ 45 years (92.4%; p = 1.0), and had an overall lower education level (90.9%; p = 0.3), without a history of current or previous use of antidepressants or anxiolytics (60.6%; p = 0.001), whereas the prevalence of substance or alchool misuse was 12.1% and 10,6%, respectively. (Table 2)

Table 2: Characteristics of subjects with depressive symptoms, according to the BDI-II classification.

Variable	No depression (N=88)	Depression (n=66)	p	Depression			p
				Mild (n=34)	Moderate (n=28)	Severe (n=4)	
Sex			0.004				0.02
Female	32 (36.4)	40 (60.6)		20 (58.8)	17 (60.7)	3 (75.0)	
Male	56 (63.6)	26 (39.4)		14 (41.2)	11 (39.3)	1 (25.0)	
Age, years	55.76 (8.38)	54.73 (7.25)	0.3	57.18 (6.86)	51.50 (6.55)	56.50 (8.19)	0.01
Age range			0.9				0.3
35 - 44 years	7 (8.0)	5 (7.6)		2 (5.9)	3 (10.7)	0 (0.0)	
45 - 54 years	29 (33.0)	24 (36.4)		8 (23.5)	14 (50.0)	2 (50.0)	
55 - 64 years	41 (46.6)	31 (47.0)		19 (55.9)	11 (39.3)	1 (25.0)	
> 65	11 (12.5)	6 (9.1)		5 (14.7)	0 (0.0)	1 (25.0)	
Education level			0.3				0.4
≤ high school diploma	78 (88.6)	60 (90.9)		32 (94.1)	24 (85.7)	4 (100.0)	
Undergraduate	0 (0.0)	1 (1.5)		0 (0.0)	1 (3.6)	0 (0.0)	
Postgraduate	10 (11.4)	5 (7.6)		2 (5.9)	3 (10.7)	0 (0.0)	
Marital status			0.1				0.6
Single	3 (3.4)	7 (10.6)		4 (11.8)	3 (10.7)	0 (0.0)	
Divorced	16 (18.2)	13 (19.7)		6 (17.6)	6 (21.4)	1 (25.0)	
Maried	61 (69.3)	37 (56.1)		20 (58.8)	15 (53.6)	2 (50.0)	
Widowed	8 (9.1)	9 (13.6)		4 (11.8)	4 (14.3)	1 (25.0)	
History of use of antidepressants or anxiolytics			0.001				0.002
No	75 (85.2)	40 (60.6)		23 (67.6)	14 (50.0)	3 (75.0)	
Yes	13 (14.8)	26 (39.4)		11 (32.4)	14 (50.0)	1 (25.0)	
History of use of intravenous or inhaled drugs			0.3				0.3
No	71 (80.7)	58 (87.9)		28 (82.4)	26 (92.9)	4 (100.0)	
Yes	17 (19.3)	8 (12.1)		6 (17.6)	2 (7.1)	0 (0.0)	
Alcohol misuse by the AUDIT-C			1.0				0.4

Normal	79 (89.8)	59 (89.4)	32 (94.1)	23 (82.1)	4 (100.0)
Misuse	9 (10.2)	7 (10.6)	2 (5.9)	5 (17.9)	0 (0.0)

Data are presented as n (%), or mean (standard deviation). AUDIT-C, Alcohol Use Disorders Identification Test-Consumption.

Source: Authors.

Relationship between depressive symptoms and liver cirrhosis

The median BDI-II score was 6 (IQR, 3 – 16) and 12 (IQR, 6 – 19) for non-cirrhotic and cirrhotic subjects, respectively (p = 0.007). In the non-cirrhotic group, the percentage of subjects classified as having minimal depressive symptoms (0 – 11) was higher as compared to the cirrhotic group (67.5% [95% CI; 57.1% - 78%] vs 46.8% [95% CI; 35.6% - 57.9%], respectively).

Also, among those with depressive symptoms, the distribution of subjects classified as having gradual depressive symptoms (mild, moderate, and severe) in the non-cirrhotic group was lower as compared to the cirrhotic group (p = 0.05). (Table 3) (Figure 1)

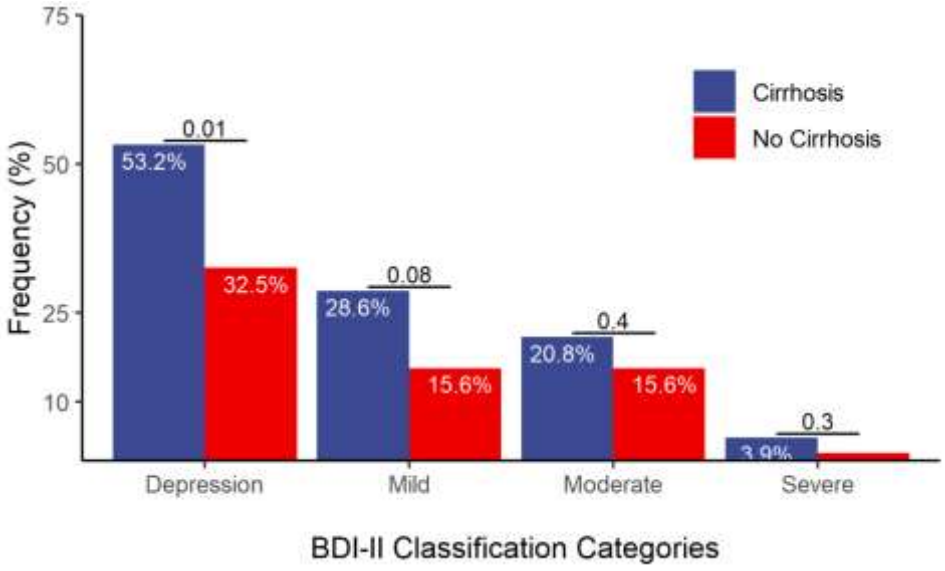
Table 3: Relationship between depressive symptoms and cirrhosis.

Variable	Non-cirrhotic (n=77)	Cirrhotic (n=77)	p
Beck Depression Inventory-II			
No Depression	52 (67.5)	36 (46.8)	0.01
Depression	25 (32.5)	41 (53.2)	
Mild	12 (15.6)	22 (28.6)	0.05
Moderate	12 (15.6)	16 (20.8)	
Severe	1 (1.3)	3 (3.9)	
Overall score	6.00 [3.00, 16.00]	12.00 [6.00, 19.00]	0.007

Data are presented as n (%), or median (interquartile range).

Source: Authors.

Figure 1: Distribution of severity of depressive symptoms according to Beck Depression Inventory II (BDI-II) score according to the fibrosis grading.



Source: Authors.

4. Discussion

In this study of subjects with untreated chronic hepatitis C virus infection living in an urban area, almost 43% had a total score of above 12 on the Beck Depression Inventory-II. Such finding differs from data previously reported in the literature, which showed a much lower prevalence in the same population. (Batista-Neves et al., 2008).

One possible explanation for this difference is the use of different questionnaires to assess depressive symptoms, each with a different sensitivity and specificity. Despite that, the overall prevalence of depressive symptoms is fairly high in this population, as opposed to general population samples, for example (Silva et al., 2014).

Although speculative at this point, there may be some explanations for our findings. Chronic diseases may confront patients with variety of stressors that challenge patients' abilities to maintain balance, and while all chronic diseases can potentially require psychosocial resources to maintain equilibrium, HCV appears to carry with its unique challenges. (Bisschop et al., 2004; Blasiole, 2006) These patients usually develop fear of interaction with others and progressive deterioration of social and familial relationships. As a result, a variety of psychosocial responses may be elicited, mainly depression. (Blasiole, 2006)

However, despite having a consistent evidence about CHC infection as a risk factor for depression, to our knowledge, there are only a few, small sampled, single-center studies that have examined the role of specific factors, such as cirrhosis in this association. In this context, as others have previously discussed the importance of sex, age, education level, marital status and alcohol consumption to the occurrence of depressive symptoms, we aimed to control for these potential confounders by using a propensity score–matching analysis.

The overall patient profile for the study population was similar to that described for those with depressive symptoms as a whole: mostly perimenopausal women of low socioeconomic status and education level, living in an urban area. Accordingly, most of these characteristics (age, sex, and educational level) have already been shown to be associated with lower mental health in patients with chronic diseases, despite not fully understood on how. (Bisschop et al., 2004)

Although these factors may be significantly involved, it also has been suggested that the virus itself can cross the blood-brain barrier, replicate in central nervous system, and thus causing a series of mental disorders. (Iriana et al., 2017) To the best of our knowledge, only a single study have shown that anxiety and depression measures did not differ between pre- and post-treatment timepoints; however, more studies are necessary to document this. (Gallach et al., 2018)

In addition, and in agreement with our results, it has also been shown that the mental health of patients with liver cirrhosis is severely compromised; this occurs both in subjects with compensated disease and, more markedly, in the presence of end stage liver disease. (Bianchi et al., 2005) However, this assumption has never been investigated solely in subjects with untreated CHC infection. This is of particular interest as mental health of these subjects can be altered only by an awareness of viral infection and liver cirrhosis, regardless of organ function. These aspects are relevant not only to identify cirrhosis as a milestone in their life, but also to highlight the burden that this condition imposes on them. To this end, and as all of our subjects had CHC infection, subjects with compensated cirrhosis (i. e., Child-Pugh A) were shown to present a higher proportion of depressive symptoms as compared to non-cirrhotic subjects, despite controlling for a range of demographic variables and comorbid conditions ($p = 0.01$). Thus, it seems that the awareness of cirrhosis has a significant impact on their mental health, regardless of liver function.

Furthermore, a remarkable proportion of the depressed subjects reported current or previous use of antidepressants or anxiolytics, compared to those without symptoms ($p = 0.001$). Of those who were currently using medication, the percentage of patients who were

presenting depressive symptoms was as many as those without symptoms (data not shown), despite adequate dose and treatment duration. These findings suggest that HCV-associated depression should be seen as a unique clinical problem that requires further studies to properly address its treatment needs.

5. Final Considerations

The results of this study should be interpreted with some limitations. First, the cross-sectional study design does not provide the evidence of a temporal relationship between depressive symptoms and the independent variables used in the analysis. On the other hand, as the study variables were assessed at the same time of measurement, bias owing to variations between independent and dependent variables within the same individual was reduced. Moreover, other confounding factors such as common social aspects, medication, drug habits and clinical characteristics were also controlled.

Notably, cultural aspects were not addressed in this study, and they may certainly play a role as a potential confounder. Despite those limitations, the study provides evidence on the importance of identifying those with liver cirrhosis as at risk for depression. The topic remains an important one and further studies should evaluate the impact of depression on HCV treatment outcomes or the impact of HCV cure on depression.

In conclusion, this study demonstrated a high prevalence of depressive symptoms among untreated chronic HCV-infected subjects. The percentage of depressive symptoms in those with liver cirrhosis was higher as compared to non-cirrhotic subjects, despite controlling for a range of demographic variables and comorbid conditions. These findings reaffirm the need to actively screen for depressive symptoms in all patients with CHC infection, but especially in those with cirrhosis.

References

Adinolfi, L. E., Nevola, R., Rinaldi, L., Romano, C., & Giordano, M. (2017). Chronic Hepatitis C Virus Infection and Depression. *Clinics in Liver Disease*, *21*(3), 517–34. https://doi.org/10.1016/j.cld.2017.03.007.

Batista-Neves, S. C., Quarantini, L. C., de Almeida, A. G., Bressan, R. A., Lacerda, A. L.,

De-Oliveira, I. R., Paraná, R., & Miranda-Scippa, Â. (2008). High frequency of unrecognized mental disorders in HCV-infected patients. *General Hospital Psychiatry*, *30*(1), 80–2. https://doi.org/10.1016/j.genhosppsych.2007.08.014.

Beck, A. T. (1961). An Inventory for Measuring Depression. *Archives of General Psychiatry*, *4*(6), 561. https://doi.org/10.1001/archpsyc.1961.01710120031004.

Bianchi, G., Marchesini, G., Nicolino, F., Graziani, R., Sgarbi, D., Loguercio, C., Abbiati, R., & Zoli, M. (2005). Psychological status and depression in patients with liver cirrhosis. *Digestive and Liver Disease*, *37*(8), 593–600. https://doi.org/10.1016/j.dld.2005.01.020.

Bisschop, M. I., Kriegsman, D. M. ., Beekman, A. T. ., & Deeg, D. J. . (2004). Chronic diseases and depression: the modifying role of psychosocial resources. *Social Science & Medicine*, *59*(4), 721–33. https://doi.org/10.1016/j.socscimed.2003.11.038.

Blasiole, J. A. (2006). Mental and physical symptoms associated with lower social support for patients with hepatitis C. *World Journal of Gastroenterology*, *12*(29), 4665. https://doi.org/10.3748/wjg.v12.i27.4665.

Bush, K. (1998). The AUDIT Alcohol Consumption Questions (AUDIT-C) - An Effective Brief Screening Test for Problem Drinking. *Archives of Internal Medicine*, *158*(16), 1789. https://doi.org/10.1001/archinte.158.16.1789.

Gallach, M., Vergara, M., da Costa, J. P., Miquel, M., Casas, M., Sanchez-Delgado, J., Dalmau, B., Rudi, N., Parra, I., Monllor, T., Sanchez-Lloansí, M., Dosal, A., Valero, O., & Calvet, X. (2018). Impact of treatment with direct-acting antivirals on anxiety and depression in chronic hepatitis C. *PLOS ONE*, *13*(12), e0208112. https://doi.org/10.1371/journal.pone.0208112.

Gomes-Oliveira, M. H., Gorenstein, C., Neto, F. L., Andrade, L. H., & Wang, Y. P. (2012). Validation of the Brazilian Portuguese Version of the Beck Depression Inventory-II in a community sample. *Revista Brasileira de Psiquiatria*, *34*(4), 38994. https://doi.org/10.1016/j.rbp.2012.03.005.

Iriana, S., Curry, M. P., & Afdhal, N. H. (2017). Neurologic Manifestations of Hepatitis C Virus Infection. *Clinics in Liver Disease*, *21*(3), 535–42. https://doi.org/10.1016/j.cld.2017.03.008.

Nelligan, J. A., Loftis, J. M., Matthews, A. M., Zucker, B. L., Linke, A. M., & Hauser, P. (2008). Depression Comorbidity and Antidepressant Use in Veterans With Chronic Hepatitis C. *The Journal of Clinical Psychiatry*, *69*(5), 810–816. https://doi.org/10.4088/JCP.v69n0514.

Raison, C. L., Borisov, A. S., Broadwell, S. D., Capuron, L., Woolwine, B. J., Jacobson, I. M., Nemeroff, C. B., & Miller, A. H. (2005). Depression During Pegylated Interferon-Alpha Plus Ribavirin Therapy. *The Journal of Clinical Psychiatry*, *66*(01), 41–8. https://doi.org/10.4088/JCP.v66n0106.

Silva, M. T., Galvao, T. F., Martins, S. S., & Pereira, M. G. (2014). Prevalence of depression morbidity among Brazilian adults: a systematic review and meta-analysis. *Revista Brasileira de Psiquiatria*, *36*(3), 262–270. https://doi.org/10.1590/1516-4446-2013-1294.

Wang, Y.-P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: a comprehensive review. *Revista Brasileira de Psiquiatria*, *35*(4), 416–31. https://doi.org/10.1590/1516-4446-2012-1048.

Percentage of contribution of each author in the manuscript

Henrique Pott-Junior – 25%

Eveline Tonelotto Barbosa Pott – 25%

Rita Moretto – 25%

Jorge Figueiredo Senise – 25%

Adauto Castelo – 25%