UNIVERSITY OF MEDICINE AND PHARMACY
„CAROL DAVILA", BUCHAREST
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Extrahepatic manifestations in patients diagnosed with chronic hepatitis C virus

PhD THESIS SUMMARY

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SUMMARY

SUMMARY OF THE DOCTORAL THESIS

Extrahepatic manifestations in patients diagnosed with chronic hepatitis C virus

The doctoral thesis "Extrahepatic manifestations in patients diagnosed with chronic hepatitis C virus" is structured in two parts: a general part, which has 2 chapters, in which I presented a synthesis of the current state of knowledge regarding hepatitis C virus and extrahepatic manifestations; a part of personal research structured in 4 chapters, in which the motivation, objectives, methodology and results of the research carried out throughout the doctoral studies are presented.

GENERAL PART

Epidemiological data

According to the World Health Organization, in 2015 there were 71 million people (1% of the population) with HCV globally. Also 2.3 million people diagnosed with HIV were also co-infected with the hepatitis C virus. In the same year, there were 1.34 million deaths caused by viral hepatitis, an increase of 22% compared to the year 2000 when the number of deaths was 1.10 millions. In 2015, 30% of deaths were caused by complications of HCV infection [6].

In 2016, 33,860 new cases were reported in Europe, representing a decrease of 6.1% compared to the previous year. The infection rate was 7.4 per 100,000 inhabitants. Regarding the gender distribution, a ratio of B:F = 1.9:1 was recorded. The most affected age group was 35-44 years for men (20 cases per 100,000 inhabitants) and 25-34 years for women (9.9 cases per 100,000 inhabitants) [7].

More recent data report a number of approximately 50 million people diagnosed with chronic hepatitis C virus globally and 1 million new cases diagnosed annually [8] .

The genetic heterogeneity of the hepatitis C virus, with the formation of quasispecies, requires the determination of the viral genotype prior to the start of treatment. Genotype 1 (with subclasses 1a and 1b) is predominant in North America and Europe (49.1%) [9]. Genotype 3 ranks second in global prevalence (17.9%) [10]. Genotype 4 is mainly associated with the African region, being found mostly in Egypt, and genotype 5 predominates in South Africa [10].

Genotype 1 of HCV predominates in Romania, being the most resistant to treatment among the 6 described genotypes. Genotype 1 is the most widespread in Romania, being acquired through blood transfusions. Before 1990, blood donors were not screened for virus C. The presence of this genotype was almost exclusive for a period of time [11]. With the increase in the number of intravenous drug users, more than 80% of whom are co-infected with HCV, and due to the intense circulation after Romania's admission to the European Union, new genotypes were observed, indicating a link between them and intravenous drugs [12].

Natural evolution is influenced by host, virus and environmental factors [17].

Hepatitis C virus is transmitted parenterally. Following exposure, approximately 20% of people will develop an acute form of the disease. Most cases of acute hepatitis are asymptomatic, and a percentage of 20-40% of people will recover spontaneously in the first 6 months. The other infected people will develop the chronic form of the disease. This can have several evolutionary forms [17].

Chronic hepatitis C virus rarely heals spontaneously. It can have a slow evolution towards fibrosis, but also towards cirrhosis during 25-30 years, up to 20-30% of cases [18]. Among patients diagnosed with cirrhosis, approximately 25% will develop hepatocellular carcinoma [17].

A peculiarity of the hepatitis C virus is the fact that, during the course of the disease, patients can develop extrahepatic manifestations. Lymphotropism of the virus, molecular mimicry, cryoglobulinemia and non-cryoglobulinemic autoimmune phenomena are considered to be the main factors involved in the pathogenesis [5].

The hepatitis C virus affects other tissues besides the liver tissue, with the appearance of extrahepatic manifestations. Approximately 74% of patients with chronic hepatitis C virus develop at least one extrahepatic manifestation during the natural course of the disease. HCV

infection is currently considered a systemic infection, due to the ability of the virus to enter and multiply in the cells of other systems [19].

Also, hepatitis C virus has the ability to replicate in certain anatomical sites (bone marrow, pancreas, thyroid, spleen, lymphoid organs) and in certain cells (macrophages, B lymphocytes, T lymphocytes, endothelial cells) [20, 21] .

PERSONAL CONTRIBUTIONS

Objectives

In the case of patients with chronic hepatitis C virus, studies frequently focus on the somatic condition, the psychological part being less investigated. During the asymptomatic evolution of the disease, extrahepatic manifestations, including those of a psychiatric nature, appear, but are often not diagnosed in time.

The present study aims to follow the influence of demographic, epidemiological, clinical, paraclinical variables on patients diagnosed with chronic hepatitis C virus, who also developed extra-hepatic manifestations during the course of the disease, especially psychiatric ones. Moreover, the present study aims to find a correlation between the level of depression and the degree of fibrosis.

Also, the COVID-19 Pandemic has influenced medicine and public health and produced previously unknown effects. Based on this premise, we conducted a study to observe the interrelationship between COVID-19 and chronic hepatitis C virus.

Material and Methods

Prospective study, longitudinal surveillance of patients diagnosed with chronic hepatitis C virus, treated and monitored in the Clinic of Infectious and Tropical Diseases of the Hospital ``Dr. Victor Babeș", Bucharest.

Inclusion criteria:

– Patients over 18 years of age diagnosed with chronic hepatitis C virus

– Patients naïve to antiviral treatment

– Patients should be able to understand and sign an informed consent regarding the procedures to be performed

Exclusion criteria:

– Patients diagnosed with co-infection with HBV or HIV

– Patients pretreated with Interferon and Ribavirin or with direct acting antivirals

- Patients diagnosed with hepatocellular carcinoma and other malignant pathologies

- The pregnancy in progress at the time of enrollment in the study or during it

Data analysis

An ANOVA (analysis of variance) with repeated measures ("Repeated Measures ANOVA" - RM-ANOVA) was used, both raw (without any factor, only the time of measurement) and with the degree of depression as a factor.

JASP 0.18.3 R © JASP Team (2024) was used for statistical analysis.

JASP (Version 0.18.3) [Computer software].

Binomial logistic regression with logit link function was used to assess the importance of predictors in the outcome of interest, including HCV status (deceased or survivor) or severity of COVID-19 (severe versus non-severe).

For statistical analysis, R, program version 4.4.0 Copyright (C) 2024 The R Foundation for Statistical Computing, R Core Team (2024). A: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org. I additionally used the "gtsummary" package for R.

For all statistical tests, the α cut-off level was 0.05, all p-values below 0.05 were considered significant.

Correlations between the level of depression in patients diagnosed with chronic hepatitis C virus and the degree of fibrosis, prior to direct-acting antiviral therapy

The main objective was to reproduce the evolution of depression (quantified with the help of the HAM-D questionnaire), and to investigate whether the degree of fibrosis is associated with this evolution.

The evaluation of the degree of fibrosis was done using the Fibroscan test in all patients, prior to treatment. The Fibroscan test is an imaging method through which the level of stiffness of the liver is evaluated. This corresponds to scar tissue, transposed into areas of fibrosis.). The degree of fibrosis was quantified as follows: normal value (1.6-5.5 kPa), grade F1 (7-7.1 kPa), grade F2 (7.2-9.5 kPa), grade F3 (9.6-12.5 kPa), grade F4 or cirrhosis (> 12.5 kPa).

The Hamilton depression scale was applied to all patients. The Hamilton Depression Rating Scale is a self-assessment tool for the severity of depressive symptoms. Initially, Hamilton identified 21 assessment items, but stopped at only 17. Obsessional symptoms, paranoid symptoms, derealization, and diurnal variation in mood are the excluded items because they are too rarely present in the depressive syndrome or do not measure depression or its intensity.

Eleven items are rated on a 0-4 scale and the remaining items on a 0-2 scale. A score of 7-17 means mild depression, 18-24 represents moderate depression, and above 25 severe depression.

The studied group included 75 patients. Of these, 45 (61%) were female, and 29 (39%) were male.

The descriptive statistical analysis of the observed studied variables can be found in table 1.

Table 1.1. Descriptive analysis of the studied variables

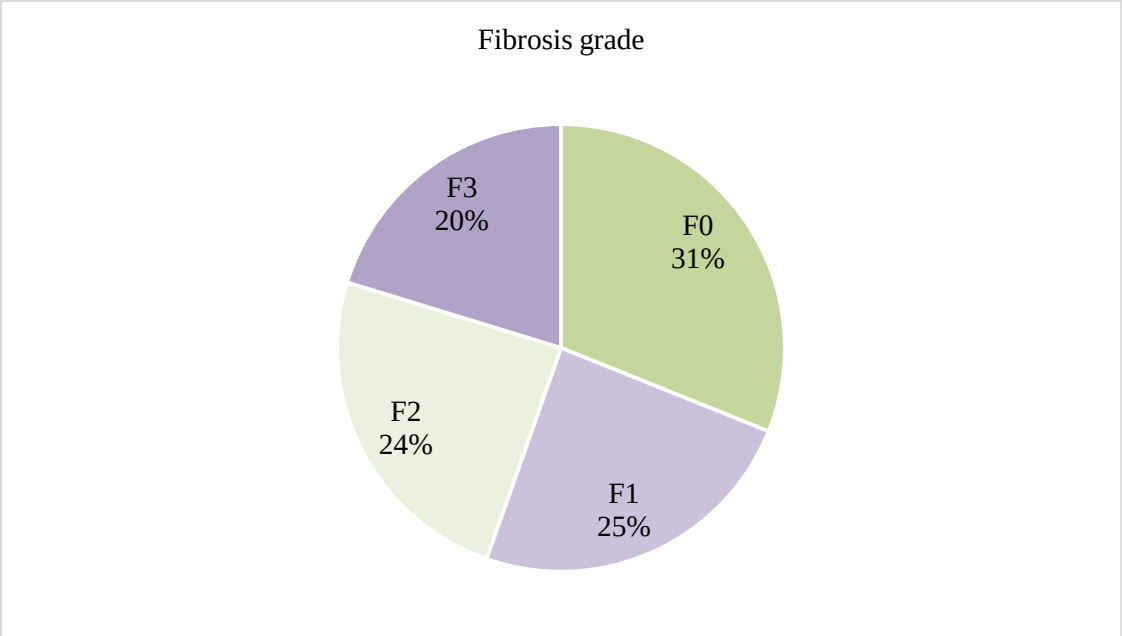
Variabile	N = 74
Age, Average (SD)	49 (14)
Gender, n (%)	
Female	45 (61)
Male	29 (39)

Variabile	N = 74
BMI, Average (SD)	26.3 (5.5)
Area, n (%)	
Rural	17 (23)
Urban	57 (77)
Education, n (%)	
Primary school	19 (14)
High school	42 (66)
University degree	13 (20)
Profession, n (%)	
Household	13 (21)
Active worker	37 (59)
Retired	13 (21)
Tattoo, n (%)	
Yes	18 (28)
No	46 (72)
N/A	10
Surgical interventions, n (%)	
Yes	32 (43)
No	42 (57)
Dental interventions, n (%)	
Yes	74 (100)

Variabile	N = 74
Blood transfusions, n (%)	
Yes	18 (25)
No	56 (75)
Drug use, n (%)	
Yes	15 (21)
No	59 (79)
Oncological conditions, n (%)	
Yes	5 (7)
No	69 (93)
Viremia Pre-treatment (UI/mL), Medie (SD)	5.85 (0.84)
Fibrosis grade, n (%)	
0	23 (31)
1	18 (24)
2	18 (24)
3	15 (20)
Psychiatric disorders n (%)	
Yes	9 (12)
No	65 (88)
High blood pressure, n (%)	
Yes	21 (29)
No	52 (71)

Variabile	N = 74
Diabetes mellitus, n (%)	
Yes	12 (17)
No	62 (83)
Endocrine disorders, n (%)	
Yes	1 (1)
No	73 (99)
Thyroid disorders, n (%)	
Yes	6 (8.3)
No	68 (92)
Kidney diseases, n (%)	
Yes	1 (1)
No	73 (99)

The evaluation of the degree of fibrosis was done using the Fibroscan test in all patients, prior to treatment. Fibrosis grades ranged from F0 to F3. 18 patients had fibrosis grade F2 (24%), 15 patients (20%) had fibrosis grade F3. F0 was present in 23 patients (31%), and 18 patients had F1 (24%).



Graph 1.1. Distribution of degrees of fibrosis

After analyzing the responses to the Hamilton questionnaire, 51 of the patients scored in the category of mild depression. The score corresponding to a moderate degree of depression was registered in 10 cases, and 6 patients had a score correlated with a severe degree of depression.

Of the 51 patients, 32 (63%) women experienced a mild level of depression compared to 19 (37%) men.

Among patients who obtained a score corresponding to the category of mild depression, 5 (10%) were known to have mental disorders and were under medical treatment, prior to the diagnosis of chronic hepatitis C virus, 4 (8%) patients were known to have diabetes , 15 (30%) with hypertension, and another 3 (6%) patients were diagnosed with thyroid conditions. Malignancies were present in 4 (8%) patients.

Regarding the degree of fibrosis, 15 (29%) patients had F0, 17 (33%) patients had F1, 14 (27%) patients had F2, and 5 (11%) patients had F3.

And in the case of the 10 patients who obtained a score corresponding to moderate depression, it was recorded in a higher percentage in women (6 women versus 4 men, 60% versus 40%).

From this category, 2 (20%) patients were known to have previously diagnosed mental illnesses. Diabetes mellitus was present in half of the patients (5), and hypertension in 2 cases (20%). Thyroid disorders were also present in 2 (20%) cases, and 1 (10%) patient was known to have oncological pathology.

Half of the patients had a fibrosis grade of F3, 3 (30%) patients had F2, and 2 (20%) patients had F0.

Regarding patients who scored a severe degree of depression, the gender ratio was 1:1 (3 women, 3 men). 3 (50%) patients were known to have both hypertension and diabetes, and another 2 (33%) patients were known to have psychiatric illness.

All patients had a fibrosis grade of F3.

Multivariate regression was used to analyze whether the degree of fibrosis is an independent predictor of Hamilton scale values.

Table 1.2. Multivariate regression of coefficients and their significance.

	B *	Beta**	t***	p-value****
Age	-.030	-.066	-.343	.736
BMI	.306	.264	1.390	.183
Gender	1.277	.114	.522	.609
Fibrosis	3.115	.581	3.075	.007

*Unstandardized regression coefficients.

**Standardized regression coefficients.

***t statistic (t-test).

****Statistical significance of the test

Fibrosis was the only factor with statistical significance associated with a higher value of the Hamilton scale (t-test=3.075, p=0.007).

Extrahepatic manifestations in patients diagnosed with chronic hepatitis C virus

The analyzed batch included 55 women and 37 men, totaling 92 patients.

Regarding the evolution of depression, the Hamilton questionnaire was applied to all patients, at the initiation of the direct-acting antiviral treatment, but also 3 months after the completion of the treatment.

53 of the patients obtained a score corresponding to a mild degree of depression. On re-evaluation, all patients obtained a score below the minimum corresponding to a mild degree of depression (below 7 points).

10 of the patients obtained a score corresponding to a moderate degree of depression. Upon re-evaluation, following treatment, 8 patients obtained a score corresponding to a mild degree of depression, and 2 patients obtained a score below the minimum corresponding to a mild degree of depression (below 7 points).

6 patients obtained a score corresponding to a severe degree of depression. At re-evaluation, following treatment, 3 patients obtained a score corresponding to a mild degree of depression, and 3 patients patients obtained a score corresponding to a moderate degree of depression

Thus, an improvement in the level of depression was observed in all patients, following the treatment.

Of the 92 patients, 13 were known to have diabetes. Of these, 10 were diagnosed at a distance from the diagnosis of chronic hepatitis C virus

RM-ANOVA

Cases	Sum of Squares	df	Mean Square	F	p
Total Score HAM-D	4016.493	1	4016.493	418.261	< .001
Residuals	701.007	73	9.603		

The interrelationship between chronic hepatitis C virus and SARS-Cov-2 infection

The main objective of the study was to investigate the influence of chronic hepatitis C virus infection on mortality and the form of COVID-19 (severe / non-severe) in the sample of patients.

The secondary objective of the study was to identify other predictors in the category of demographic, clinical and paraclinical parameters, with influences on mortality and forms of COVID in the patients in the sample.

Another secondary objective was to investigate the association of newly discovered type II diabetes and its influence on chronic hepatitis C virus infection.

The study analyzes the potential association between clinical presentation, laboratory tests, and outcomes of patients admitted to the Clinical Hospital for Infectious and Tropical Diseases "Dr. Victor Babeş", known to have chronic hepatitis C virus (HCV) infection and diagnosed with COVID-19. It also aims to analyze the course of SARS-CoV-2 infection in these patients, including the progression of symptoms, the severity of the disease.

Patients were divided into several subgroups/cohorts according to their HCV treatment status:

- 1 experimental group (patients who received treatment with Interferon or direct-acting antivirals (DAA)),

- 1 naive group (patients who have not been treated)

- 1 batch with cirrhosis (previously treated or untreated).

Also, the influence of the presence of HCV infection on the evolution of COVID-19 was studied. In this sense, the risk factors of severe evolution for COVID-19 known in the literature (obesity, hypertension, diabetes) were accumulated, assigned one point each and integrated into a risk factor score (FR score).

In Table 2, the importance of demographic and clinical factors in the severity of SARS-CoV2 infection was evaluated

Table 2. Univariate logistic regression on the significance of demographic and clinical variables in the severe form of COVID19

Predictor	**N**	**Severe Form (N)**	**OR (95% CI)*1***	**P value**
Gender				
Female	63	28	—	
Male	26	13	1.25 (0.50 la 3.15)	0.633
Age	89	41	1.04 (1.01 la 1.08)	**0.036**
Area				
Rural	18	5	—	
Urban	71	36	2.67 (0.90 la 9.06)	0.088
BMI	50	24	1.07 (0.98 la 1.18)	0.136
Fever				
Yes	49	27	—	
No	40	14	0.44 (0.18 la 1.03)	0.060
Cough				
Yes	48	26	—	
No	41	15	0.49 (0.20 la 1.13)	0.099
Cephalea				
Yes	23	14	—	
No	66	27	0.45 (0.16 la 1.16)	0.102

Predictor	**N**	**Severe Form (N)**	**OR (95% CI)*1***	**P value**
Year				
2020	35	12	—	
2021	43	27	3.23 (1.29 la 8.44)	**0.014**
2022	11	2	0.43 (0.06 la 2.00)	0.320
Anosmia				
Yes	12	3	—	
No	77	38	2.92 (0.80 la 13.9)	0.128
Ageusya				
Yes	9	3	—	
No	80	38	1.81 (0.44 la 9.04)	0.424
Digestive manifestations				
Yes	26	10	—	
No	63	31	1.55 (0.62 to 4.03)	0.357
Vomiting				
Yes	9	5	—	
No	80	36	0.65 (0.15 to 2.65)	0.549
Oxygen saturation	89	41	0.58 (0.45 la 0.71)	**<0.001**
RF score	89	27	1.72(1.06-2.79)	**0.027**
Psychiatric affections				

Predictor	**N**	**Severe Form (N)**	**OR (95% CI)*1***	**P value**
Yes	8	4	—	
No	81	37	0.84 (0.19 la 3.78)	0.815
Kidney diseases				
Yes	13	5	—	
No	76	36	1.44 (0.44 la 5.14)	0.553
Oncological diseases				
Yes	10	5	—	
No	79	36	0.84 (0.22 la 3.23)	0.791
Thyroid disorders				
Yes	14	10	—	
No	75	31	0.28 (0.07 la 0.93)	0.047

Patients who had a higher RF score were 72% more likely to present a severe form of COVID-19 than patients with lower score values.

Table 3. Influence of HCV on COVID-19

	Undetected viremia, n=37	Detected viremia, n=26 (without cirrhotics)	p
Age (mean)	62.81 (58.63-6699)	66.96 (61.76-72.17)	0.206
Gender			0.305
Male	13(35.1%)	6(23.1%)	
Female	24(64.9%)	20(76.9%)	
Clinical form of COVID-19			<0.001
Severe	28(75.7%)	32(88.9%)	
Moderate/Mild	9(87.5%)	4(11.1%)	
RF score (mean)	0.81 (0.51-1.12)	0.96 (0.65-1.27)	0.503
Number of hospitalization days (mean)	13.46 (10.5-16.42)	14.69 (11.95-17.43)	0.213
Pulmonar changes			0.339
No change or interstitial accentuation	9(25.%)	4(15%)	
Infiltrates or gound-glass	26(75%)	22(85%)	
Laboratory findings			
LDH (U/L) (mean)	284.5 (244.2-324.7)	381.9 (291.5-472.2)	0.033

ALT (U/L) (mean)	33.28 (26.43-40.13)	35.71 (28.9-42.5))	0.623
Platelets (mean) (valx10^9)	188 (157.4-219.9)	229 (187.5-271.0)	0.110
Ferritin (ng/ml) (mean)	586.61 (308.0-865-12)	952.17 (609.4-1294-8))	0.052
Leukopenia(yes, %)	14(37.8%)	6(26.1%)	0.348
Treatment			
Corticosteroid(yes)	24(64.9%)	23(88.5%)	0.034
Immunomodulators(yes)	8(21.6%)	14(53.8%)	0.008
Outcome (n, %)			0.086
Favorable	35(94.6%)	21(80.8%)	
Unfavorably (deceased)	2(5.4%)	5(19.2%)	

From the above table it was found that LDH and ferritin value were important severity factors. The FR score had no significant influence on the two subgroups of patients.

Of the 26 non-cirrhotic patients with detectable viremia, 12 were known to have diabetes. Of the 14 patients, 12 (8 women and 4 men) were diagnosed with newly discovered diabetes during hospitalization. All patients presented severe form of the disease.

Patients with known diabetes had a risk of severe form of the disease approximately 6 times higher compared to patients without diabetes.

Conclusions and personal contributions

The analysis of the level of depression demonstrated a significant correlation between the stage of liver fibrosis and the presence of depression in patients with chronic hepatitis C virus. The prevalence rate of depression is consistent with the specialized literature, but the data from Romania remain insufficient.

Fibrosis was the only factor with statistical significance associated with a higher value of the Hamilton scale, patients with a higher degree of fibrosis having higher evolving HAM-D scores, and thus more severe degrees of depression.

Patients with higher education had lower depression scores.

Early diagnosis and appropriate treatment of depression have a favorable effect both on the quality of life and on the evolution of liver disease.

Treatment with direct-acting antivirals has an effect on extrahepatic manifestations.

Chronic hepatitis C virus (HCV) existing before COVID-19 can worsen the effects of the SARS-CoV-2 virus, leading to a more severe form of the disease. This appears to be true regardless of other medical conditions the patient may have, initial blood test results, or any liver damage caused by COVID-19 itself. Findings from the present study suggest that chronic hepatitis C may exacerbate the severity of COVID-19 infection.

Older age is a risk factor for the occurrence of a severe form of COVID-19, an increase of 1 year being associated with a 4% increase in the odds of severe forms (OR=1.04, 95% CI [1.01, 1.08], p=0.036).

Decreased oxygen saturation is also a risk factor for the occurrence of a severe form (OR=0.58, 95% CI [0.45, 0.71], p<0.001).

Patients with DM had a risk of severe forms of the disease approximately 6 times higher than patients without DM (OR=0.16, 95% CI [0.05, 0.47], p=0.001).

The existence of a thyroid pathology was also a risk factor, patients with known thyroid conditions had a 4 times higher risk of developing the severe form of the disease (OR=0.28, 95% CI [0.07, 0 .93], p=0.046).

From an imaging point of view, computed tomography with abnormal results (with the presence of ground-glass opacities), also an important risk factor, people who presented with these abnormalities had an almost 8-fold higher risk of severe form (OR =0.13, 95% CI[0.03 to 0.44], p=0.003).

Compared to patients from 2020, patients from 2021 had a 3.2 times higher risk of severe forms (OR=3.23, 95% CI [1.29,8.44], p=0.014).

These findings underscore the urgent need for specific management strategies tailored to this vulnerable patient population. By implementing such strategies, healthcare professionals can potentially improve outcomes and reduce the risks associated with COVID-19 infection in people with chronic hepatitis C. This research adds to the growing knowledge of the complex interaction between pre-existing medical conditions and COVID-19. She emphasizes the importance of continuing research in this area to develop effective preventive and therapeutic approaches for high-risk groups. Patients with neuropsychiatric conditions should be tested for hepatitis C virus.

Personal contributions

By investigating the association between depression and the degree of fibrosis, the study contributes to the current literature and uses a depression quantification tool.

The present study shows a direct causal relationship between depression and the severity of fibrosis in patients with chronic hepatitis C virus, an aspect that is not frequently investigated.

In the future, more studies should be performed, on larger groups with a role in the analysis of psychiatric conditions. Moreover, more tests should be used to quantify other neuropsychiatric manifestations as well.

In the study, we compiled a risk factor score (FR score) in which the risk factors of severe evolution for COVID-19 known in the literature (obesity, hypertension, diabetes) were accumulated. Patients who had a higher FR score are 72% more likely to have a severe form of COVID than patients with lower score values. Thus, this score can be used in future research.

These contributions can present a solid basis for future studies related to both extrahepatic manifestations, especially neuropsychiatric ones, and the evolution of SARS-CoV2 infection

in this population. Future multidisciplinary and multicenter studies could lead to maximizing the efficiency of care for patients with chronic hepatitis C virus.

3 articles from the doctoral research were published in journals indexed in international databases. Also, presentations were made at National Conferences, the abstracts of which were published in national magazines and supplements.

Limitation

The studies present as a limitation the small group of patients. However, patient characteristics/grade of fibrosis are comparable to results from other studies in the literature.

The current data cannot conclusively establish a direct causal relationship between depression and the severity of fibrosis in patients with chronic hepatitis C virus. Our study deepens this complex interaction, exploring the possibility of a reciprocal influence, in which depression could exacerbate the progression of fibrosis.

The third study exclusively included patients with chronic hepatitis C virus (HCV) infection (with or without prior antiviral treatment), which inherently predisposes them to a greater risk of liver function deterioration compared to the general population . We cannot definitively dissociate the independent effects of preexisting chronic hepatitis C and SARS-CoV-2 infection on liver injury and mortality in co-infected individuals. Future prospective studies with larger cohorts are needed. Another limitation is the small size of the patient group.

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List of published scientific papers

1. **Stoenescu A**, Popescu C, Florescu S, et al. (June 23, 2024) The Prevalence of Depression and Its Potential Link to Liver Fibrosis in Patients Diagnosed With Chronic Hepatitis C Virus Infection Prior to the Initiation of Direct-Acting Antiviral Treatment. Cureus 16(6): e62970. doi:10.7759/cureus.62970

2. Extrahepatic Manifestations of Chronic Hepatitis C Virus: Review of the Literature **Andreea Florentina STOENESCU**, Simin Aysel FLORESCU, Corneliu POPESCU, Stefan LAZAR, Geta VANCEA, Emanoil CEAUSU, Petre CALISTRU. MAEDICA – a Journal of Clinical Medicine https://doi.org/10.26574/maedica.2024.19.2.365

3. Lazar S D**, Stoenescu A F**, Popescu C, et al. (August 11, 2024) The Interplay of Chronic Hepatitis C and COVID-19: Implications for Prognosis and Treatment. Cureus 16(8): e66639. doi:10.7759/cureus.66639