

# Clinical and Biochemical Considerations Regarding Stress and Arrhythmic Risk in Patients with Chronic Viral Liver Diseases

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*The prevalence of depression and anxiety is higher at the patients diagnosed with viral liver disease. The correlation between stress and chronic liver disease is a natural, implicit one, but still insufficiently studied. The study has the objective of finding out the clinical and also biochemical correlations between stress and chronic viral diseases. Our research was realized on a group of 78 patients with chronic viral liver disease, who underwent an evaluation of the stress level, both from a subjective point of view and based on concrete methods like questionnaires. The patients were asked to express their state more or less affected by stress, and, subsequently, they were subjected to a questionnaire that was analyzed, followed by establishing the necessary correlations. Our patients were also evaluated by cardiological, psychological and psychiatric examinations. After the first evaluation we had these results: 38 patients (49.19%) consider that they have an average stress level, 18 patients (22.58%) have a high stress level. Only 22 patients (28.22%) declared stress was at a low level. We divided the patients in two groups, function of Qt (questionnaire total score) results and we observed that a number of 38 patients (49.19%) registered  $\leq Qt 20$  and 40 patients (50.81%) had  $Qt \geq 20$ , 63 patients (50.81%). We found a strong correlation between the patients' subjective evaluation of the stress level and the objective evaluation of stress level according to the used questionnaire, which confirms the objectivity of our study. We found a direct correlation, with a morphological, biochemical and functional support between stress and the arrhythmia risk in the evolution of chronic liver disease. We consider very important a complex examination psychiatrically, psychologically and cardiological of the patients diagnosed with viral liver disease in order to help them and to prevent arrhythmic events, depression, anxiety and other mood disorders.*

**Keywords:** chronic hepatitis, psychiatric disease, stress, arrhythmia risk

Worldwide, there are more than 550 millions people infected by hepatitis viruses and from these around 350-400 millions people are infected by hepatitis virus B, 170-180 millions by hepatitis virus C and 15 millions people by hepatitis virus D. On the other hand, hepatitis viruses are presented in 60% cases of cirrhosis and in 80% cases of hepatocellular carcinoma [1].

More than that, it is wellknown that in hepatic cirrhosis evolution the prolongation of is frequently and it increases the arrhythmic risk [2].

The hepatitis treatment was improved during the time, first with alpha interferone and than with nucleoside analogues but a perfect treatment with no side effect hasn't appeared, yet [3].

We can define the psychological stress being a condition which influences and alters the internal balance or the *psychological homeostasis* of the people [4].

It is very important to find and to diagnose, as early as possible, the psychiatric symptoms during the evolution of the liver diseases, especially at the patients who are using interferone.

Depressive symptoms are presented between 22 to 59% at the people infected with viral hepatitis C and the depression ration is higher in viral hepatitis B [5].

The number of people with chronic hepatitis C and depressive disorder increased between 1995-2005 from 18 to 35% [5].

The main objectives of our research were to establish certain from medical and biochemical point of view between viral liver diseases and psycho stress factors, to evaluate the level at which stress affects the evolution of the liver disease, and also the life quality of the patient suffering from viral liver disease. We want to prove that stress factors are involved in the alteration of biochemical balance.

## Experimental part

### Material and methods

The studied group included 78 patients hospitalized to the Clinic of Internal Medicine of Clinical County Emergency Hospital of Craiova.

The research study was performed between April 1st and December 30th 2017.

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The subjects included in our study underwent a complex examination, both clinically and paraclinically, with a complex biochemical examination in order to establish the diagnosis of chronic viral hepatitis, according to the present diagnosis criteria.

The subjects were asked to complete a questionnaire of 10 items regarding the stress felt every day and their activities in the last period of time, activities like: spending free time, eating, working, sleeping etc.. The patients were asked to answer by giving scores from 0 to 4 to every question. More than that, the subjects were evaluated using The Holmes and Rahe Stress Scale.

The patients were asked to answer by giving scores from 0 to 4 to every question. They were encouraged to answer honestly. We guaranteed the confidentiality of the questionnaire.

Also, the patients were asked to specify the main reasons that generated the stress, and also to self-evaluate their stress level (low, average or high) and their standard of living (low, average, good, very good).

In order to find if the psychological factors are taken account in addition to the physical disease, we evaluated the biochemical parameters like: haemoglobin, creatinine, leucocyte number, erythrocytes number etc.

## Results and discussions

### The stress level declared by the patient

The stress level of the subjects was at first evaluated subjectively by them, the patients being asked to choose one of the following versions: low, average or high stress level.

A number of 35 patients (28.22%) considered that they presented a low stress level, 61 (49.19%) an average stress level, while 28 (22.58%) presented a high stress level.

Level of felt stress	Low	Medium	High	Total
Cases	22	38	18	78
Percentages	28.23%	49.19%	22.58%	100.00%

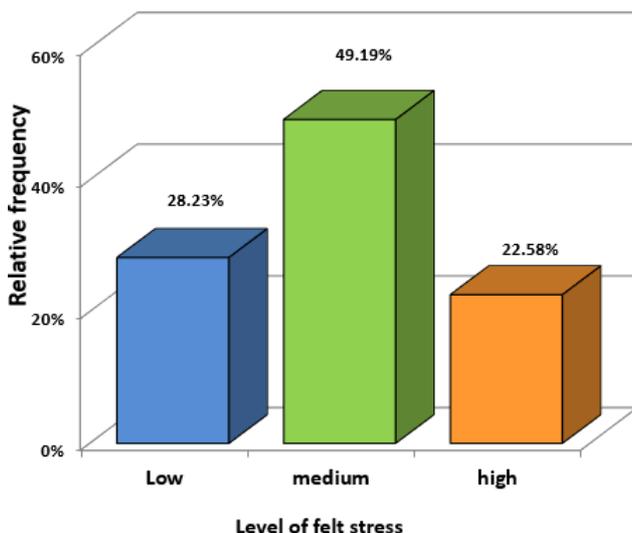


Fig. 1. Table and chart presenting the distribution of the stress level declared by patients

### Evaluation of stress level

In order to quantify the stress level, the patients were asked to answer the 10 items in the questionnaire, giving scores from 0 to 4.

Subsequently, the patients' answers were statistically processed, and after the analysis we obtained the following results:

-3 patients presented scores between 0 and 10

-35 patients presented scores between 11 and 20

-38 patients presented scores between 21 and 30

-2 patients recorded a score between 31 and 40.

The obtained results highlighted the fact that extreme profiles, expressing either a high stress level or an extremely low stress level, were not very frequent, their balance being recorded by those with an average stress level (mild to average and average to severe).

Qt= 0-10, 3 patients

Qt=11-20, 35 patients

Qt=21-30, 38 patients

Qt=31-40, 2 patients

We considered useful a distribution of patients in two groups:

Qt ≤ 20, 38 patients (49.19%)

Qt ≥ 20, 40 patients (50.81%)

Total Q	Cases	Percentages
Total Q ≤20	38	49.19%
Total Q >20	40	50.81%
Total	78	100.00%

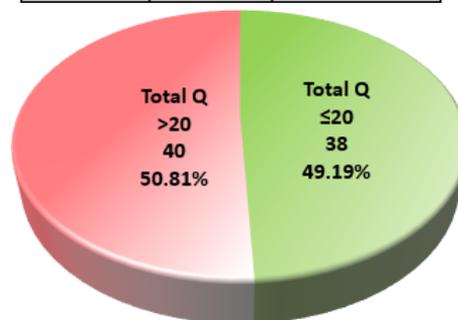


Fig. 2. Table and chart presenting the distribution of stress level evaluated according to the questionnaire

### Correlations between the stress level declared by the patient and the one evaluated based on the questionnaire

We wished to perform a correlation between the stress level declared by the patient and the stress level that emerged after completing the questionnaire.

Surprisingly, although there was a tendency that patients declaring a low stress level to have a stress score lower than 20 (60%), and that patients declaring a high stress level to have a stress score higher than 20 (60.71%), the differences recorded between the three stress categories were not statistically significant (Chi square  $p = 0.246 > 0.05$ ).

In our study, we also included a subjective opinion of the patients regarding stress in general and the one caused by a disease.

According to the study results, 38 patients (49.19%) consider that they have an average stress level, while 18 patients (22.58%) have a high stress level. Only 22 patients (28.22%) declared stress was at a low level.

There is no doubt that these patients are expected to state the presence of certain significant psycho stress factors that may generate mental changes in the context of a chronic liver disease.

This evaluation is a subjective one. It is difficult to objectivize and evaluate stress based on subjective criteria, nevertheless the fact that there were significant percentages of patients declaring low to high stress levels makes us rely on this evaluation.

With no preconceived ideas and in order to determine a high level of objectivity, we first recorded and then processed the present results.

Level of felt stress	Low	Medium	High	Total
Total Q ≤20	20 (60.00%)	16(47.54%)	2(39.29%)	38 (49.19%)
Total Q >20	10(40.00%)	24 (52.46%)	6(60.71%)	40 (50.81%)
Total	30(100.00%)	40(100.00%)	8(100.00%)	78(100.00%)
Chi square p	0.2463842	NS		

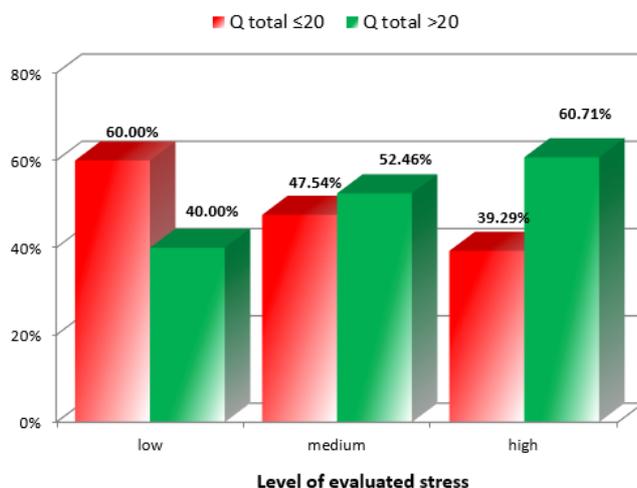


Fig. 3. Table and chart presenting the distribution of the stress level declared by the patient and the one evaluated in the questionnaire

We did not try to find out at what extent this parameter is present in the studied group, we studied the group and, subsequently, we reached the final conclusions.

#### *The stress level felt by the patient and the evaluated stress level*

Regarding the association between the stress level felt by the patient and the stress level evaluated according to the questionnaire, we found the following observations:

-there is a correlation between stating the low stress level and the questionnaire evaluation that confirmed this low stress level (60%)

-in the group of patients that mentioned an average stress level, our study based on the test confirms the same thing, the ratio between the ones with low stress level and the ones with high stress level being 47.54%/52.46%.

-the ones that mentioned a high stress level caused by liver disease also presented a confirmation, our study revealing that the majority is represented by the ones with a high stress level, with a percentage of 60.71%

This correlation highlights the fact that there is a similarity between the patients' subjective evaluation of the stress level and the objective evaluation of stress level according to the used questionnaire, which confirms the objectivity of our study.

The uncertainty regarding the disease is according to Mishel: the inability to determine the course of events correlated with the disease and that are produced in the case when the patient cannot structure a framework in which he/she may place those events, due to lack of clues, in order to make the experience valuable or anticipate the result [6].

The uncertainty is because of unpredictable and inconsistent experiences, a poor life perspective in the context of the disease and/ or the permanent questions regarding the possibility of an acute relapse or wasting complications of the disease [6,7].

The four characteristics of uncertainty are represented by: ambiguity, complexity, inconsistency and unpredictability [6].

The correlations between the severity of chronic C hepatitis and cancer incidence and mortality were proved by Grossarth-Maticek by using the method of questionnaires [8].

A group of patients completed a number of questionnaires, such as stress inventory, a self-report questionnaire for evaluating the psycho-social stress and personality, and they were classified into three groups, according to the severity of hepatitis:

- group A, chronic C hepatitis, with a normal level of serum alanine aminotransferase;
- group B, chronic C hepatitis, with a high level of serum alanine aminotransferase;
- group C, liver cirrhosis.

Each of the questionnaire items was significantly correlated with the level of hepatitis severity. The result of the study revealed that psycho-social stress may influence the progression of chronic C hepatitis [8].

In order to quantify the stress level of the patients, there were proposed other questionnaires and scales used in psychiatric practice, and not only. The American Institute of Stress uses a questionnaire called *The Holmes-Rahe Life Stress Inventory* [9].

The questionnaire comprises 42 psycho-stress situations, every situation having a score according to the emotional and psycho stress level generated by the respective situation. In the questionnaire, there are included various psycho stress situations, such as the death of a family member, divorce, marriage problems, home change, law problems, etc. [9].

The subjects are required to choose from given situations the ones that have been present in their lives for the past year. After completing the questionnaire, there will be performed a total score, resulted from the value of the cumulated scores. A result up to 150 points suggests a low stress level [9].

The values comprised between 150 and 300 show an average risk of developing a stress generator situation, while values cumulating up to 300 points indicate a high level of stress for the emergence of an emotional disorder [9].

The stress questionnaire of ISMA (International Stress Management Association) is a questionnaire made of 25 items regarding current activities. The subjects included in the study were asked to tick *Yes* or *No* for every statement. For every affirmative answer, the participant receives one point. In the end, there is calculated the total sum. A score under 4 shows a low stress level. The subjects with scores between 5 and 13 present a high stress level, with a risk for developing mental or somatic disorders caused by stress, while a value over 14 suggests a high stress level correlated with a high risk for a mental disorder. In this case, the most indicated is to recommend the subject to consult a psychiatrist, for a complex evaluation and for receiving an adequate treatment, respectively [10].

QOLS (Quality of Life Scale) is a useful scale in medical practice and scientific research. The original version has 15 questions on various life areas: mental and physical wellness, relationships with other people, social activities, personal development and leisure activities. The version

used today also comprises a 6th field related to the person's independence.

The idea of adding a field to evaluate the independence level proved to be extremely useful, due to the use of the present scale in the patients with chronic diseases where the autonomy and independence level is often affected [11].

The Beck depression scale is one of the diagnosis and prognosis means frequently used in psychiatric practice. The Beck scale is composed of 21 items related to symptoms of depression, such as sadness, feelings of guilt, low resistance to frustration, irritability, anhedonic tendencies, social isolation tendency or autolytic ideation. To every question the patient is asked to give a score between 0 (representing the absence of the symptom) and 3 (representing a maximum level of the depressive feeling). The severity level of depression will be calculated according to this scale, according to the individual score. Thus, scores 0-13 suggest a low level of depression, results 14-19 show mild depression, scores 20-28 indicate a moderate depression, while values between 29 and 63 raise the suspicion of severe depression [12].

The Hamilton depression scale is a useful instrument for evaluating the intensity and severity of the depressive symptoms. The Hamilton scale evaluates the depressive symptoms, such as: sadness, hypnic disorders, fatigue, anhedonia, depressive ideation of social ruin and existential failure, general somatic symptoms, suicidal behavior and ideation, etc. [12].

#### *Liver disease and the stress level*

Our study regarding the correlation between chronic viral liver disease and the stress level shows that the most stressed ones are the patients diagnosed with cirrhosis (65% of them presented a high level of stress), in comparison to those diagnosed with chronic viral hepatitis that recorded a percentage of 44.05%. These results were predictable, as cirrhosis is a more serious disease, with a long progression, sometimes with an unfavourable prognosis, with significant complications, this leading to a high stress level in these patients.

The definition of mental stress is *a state in which homeostasis is threatened or altered*, homeostasis referring to the complex and dynamic balance between all the systems that work in a living organism [3].

The definition above does not include the mental disorders that may influence the individual's integration abilities. The idea that psycho stressor situations may affect the man's health and the stage of disease progression has been postulated for a long time now, but only recent progress in psycho neuroimmunology led to a new perspective upon this matter [13].

In the last decades, studies from specialized literature highlighted numerous correlations between the neuroendocrine systems, such as hypothalamic-hypophyseal-adrenal axis (HPA) and the sympathetic nervous system (SNS), as well as various pathologies [13].

Studies on human subjects and laboratory animals indicate that liver disease is strongly influenced by chronic mental stress [4].

At present, it is well-known the fact that there is a central stress mechanism, made up of distinct brain structures, such as the lateral prefrontal cortex and medial prefrontal structures, which, in their turn, are connected to the amygdale and paraventricular nucleus (PVN) in the hypothalamus. The neurosecretions in these structures are projected on pontomedullary nuclei and pituitary gland. The signals from this central system are transmitted to the

components of the sympathetic nervous system, regulated by neuromediators, such as norepinephrine and epinephrine [4].

Although, sometimes, a low or moderate stress level may be useful, helping in taking accurate decisions, stress becomes malignant when psycho stressor daily activities get out of hand [14].

The effects of chronic viral hepatitis upon the liver parenchyma are scientifically proven, but the idea that real life events, independent from the disease itself, may influence the progression of this disease, is still under study at present [4, 15].

The patients diagnosed with chronic C hepatitis and depressive symptoms have high levels of uncertainty and suspiciousness regarding the disease and the correlations are related more to the personality characteristics or to neuropsychiatric symptoms, than to the acknowledgement and progression of present disease [6,16].

There is data in literature showing that patients with chronic C hepatitis who present cognitive disorders (concentration, memory, attention) also present abnormalities of the brain metabolism. It is considered that there is a direct viral effect of C hepatitis virus that generates cognitive related symptoms [6].

A regular control of the hepatic function can prevent a future depressive episode, especially at the people suffering of others somatic disorders like diabetes [17].

The evolution of depression can lead to sleep problems and these problems can be complicated with abnormal hormonal secretions and alteration in circadian sleep-wake cycles [18].

Were found many and significant correlations between prolongation of QT interval and sudden death [19].

#### **Conclusions**

The present study showed that stress represents an extremely important element for the analysis of correlations between chronic viral liver diseases and human psychic.

We consider that there is a strong correlation between stress, arrhythmias, psychiatric diseases and chronic viral liver diseases [20].

The psychiatrically symptoms associated with chronic viral hepatitis are well known, but the influence of the stress over the liver and over cerebral metabolism is still unknown.

Although, the idea that the stress events can influence the quality of the patient's life and the evolution of the liver disease is also accepted, we suggest a more complex psychiatric and psychological evaluation of the people diagnosed with liver disease.

In this paper, we tried to underline the importance of the correlation stress-psychiatric disease-chronic liver disease of viral ethiology.

#### **References**

- 1.LEMOINE M., THURSZ M., NJIE R., DUSHEIKOG.: Forgotten, not Neglected: Viral Hepatitis in Resource-limited Settings, Recall for Action, Liver International. 2014;34(1):12-15.
- 2.ROBERT DANIEL NEGRU, DOINA-CLEMENTINA COJOCARU\*, MAURA FELEA, ANCA TRIFAN: QT interval parameters and ventricular arrhythmic events in liver cirrhosis correlation with severity and etiology Biomedical Research 2017; 28 (3): 1130-1134.
- 3.RAMONA GABRIELA URUSU, CATALINA MIHAELA LUCA, ANDREI STEFAN LUCA, ELENA TOADER, LAURENTIU SIMION, LUMINITA SMARANDA IANCU: Laboratory diagnosis for optimize therapy of b hepatitis virus infection by using biochemical and molecular biology method, Chemistry Magazine, volumel 2016, december .

4. VERE CC, STREBA CT, ROGOVEANU I, IONESCU AG, STREBA LAM: Psychosocial Stress and Chronic Viral Hepatitis. Posted on July 13, 2012, The Link Between Stress, Emotions and Cytokine-Related Diseases
5. QURESHI M.O., KHOKHARN., FARZANA SHAFQAT: Severity of Depression in Hepatitis B and Hepatitis C Journal of the College of Physicians and Surgeons Pakistan 2012, Vol. 22 (10):632-634
6. COLAGRECO J. P., BAILEY D. E., FITZPATRICK J. J., MUSIL C. M., AFDHAL N. H., LAI M.: Watchful Waiting: Role of Disease Progression on Uncertainty and Depressive Symptoms in Patients With Chronic Hepatitis C, *J Viral Hepat.* 2014;21(10):727-733
7. YOUNOSSE Z., BROWN A., BUTI M., FAGIUOLI S., MAUSS S., ROSENBERG W., SERFATY L., SRIVASTAVA A., SMITH N., STEPANOVA M., BECKERMAN R. : Impact of Eradicating Hepatitis C Virus on the Work Productivity of Chronic Hepatitis C (CH-C) Patients. An Economic Model From Five European Countries *J Viral Hepat.* 2016;23(3):217-226.
8. NAGANO J, NAGASE S, SUDO N, KUBO C. Psychosocial stress, personality, and the severity of chronic hepatitis C. *Psychosomatics.* 2004 Mar-Apr;45(2):100-6
- 9.\*\*\* <http://www.stress.org/holmes-rahe-stress-inventory>
- 10.\*\*\* <http://isma.org.uk/wp-content/uploads/2013/08/Stress-Questionnaire.pdf>
11. BURCKHARDT C.S., KATHRYN L ANDERSON: The Quality of Life Scale (QOLS): Reliability, Validity, and Utilization, *Health Qual Life Outcomes.* 2003; 1: 60. Published online 2003 Oct 23. doi: 10.1186/1477-7525-1-60
12. PRELIPCEANU D., *Psihiatrie Clinica, Ed. Medicala, Bucuresti, 2013* Pag. 683, 641-684, 809-810.
13. CHIDA Y, SUDO N, KUBO C Does stress exacerbate liver diseases? *J Gastroenterol Hepatol.* 2006 Jan;21(1 Pt 2):202-8.
14. JARET PETER, M.A. Hepatitis C and Stress Last Updated: Jan 20, 2016 Hepatitis C Health Library Copyright ©2016 LimeHealth. All Rights Reserved.
15. JARET PETER: Hepatitis C and Stress Last Updated: Jan 20, 2016 Hepatitis C Health Library Copyright ©2016 LimeHealth. All Rights Reserved.
16. YENYCE NECATI, KALYON SEMIH, ATILGAN ÜNAL, KUTODLU KEMAL, ARICAN NURTEN, ÇAKIR ÜLKÜ : Evaluation of Depression in Hepatitis C or B Patients Under Antiviral Therapy (Antiviral Tedavi Altındaki Hepatit B ve C Hastalarında Depresyonun Değerlendirilmesi), *Türkiye Klinikleri J Gastroenterohepatol* 2010;17(2):71-5
17. GROZDAN, A.M., GHIURU, R., DUCEAC, L.D., BODESCU, M.M., *Rev Chim. (Bucharest),* **67**, no.12, 2016, p.2658
18. NECHITA, F., PIRLOG, M.C., CHIRITA, AL. Circadian malfunctions in depression - neurobiological and psychosocial approaches, *Rom J Morphol Embryol.* 2015;56(3):949-55
19. MAURO BERNARDI, SALVATORE CALANDRA, ALESSANDRA COLANTONI, FRANCO TREVISANI, MARIA L. RAIMONDO, GIUSEPPE SICA, FILIPPO SCHEPIS, MARINA MANDINI, PATRIZIA SIMONI, MANUELA CONTIN, GIOVANNI RAIMONDO: Q-T Interval Prolongation in Cirrhosis: Prevalence, Relationship With Severity, and Etiology of the Disease and Possible Pathogenetic Factors, *HEPATOLOGY* 1998;27:28-34.
20. CALBOREAN, V., GHEORMAN, V., AL NAMAT, R., CAZACU, I. M., VARJU, P., GEDE, N., STREBA, C.T., VERE, C.C., GHEONEA, D.I., GHEORMAN, V., LUNGULESCU, C., LUNGULESCU, C.V., *Rev Chim. (Bucharest),* **68**, no.12, 2017, p.3011

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