Assessment of depression and anxiety in patients with chronic liver disease

Procena depresije i anksioznosti kod bolesnika sa hroničnim bolestima jetre

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Abstract

Background/Aim. In recent years mental health of patients including those with chronic liver disease (CLD), has become interesting because its disturbance leads to reduced quality of life, that is associated with worsening of clinical outcome, reduced compliance and increased mortality. The aim of the study was to determinate the frequency and severity of depression and frequency of anxiety in patients with CLD and to assess the contribution of selected socio-demographic, clinical and laboratory risk factors for depression and anxiety. **Methods.** In this cross-sectional study, we used the Hamilton depression rating scale (HDRS) and Hamilton anxiety rating scale (HARS) in patients with CLD. **Results.** The study included 54 male and 43 female patients. Depression was present in 62.9%, and anxiety in 13.4% of the patients. A higher HDRS was noted in the patients older than 50 years ($p = 0.022$) and unemployed patients ($p = 0.043$). The patients with at least one episode of gastrointestinal bleeding had a significantly higher frequency of anxiety than those without bleeding ($p = 0.018$). A higher HARS score was present in the women ($p = 0.011$), unemployed patients ($p = 0.008$) and those with non-alcoholic liver disease ($p = 0.007$). There was a significant correlation between the mean corpuscular volume (MCV) and the value of the HDRS score, and between serum potassium and sodium levels and HDRS score. **Conclusion.** Age and the mean corpuscular volume have significant influence on the HDRS score while unemployment, gastrointestinal bleeding, serum potassium and serum sodium have predictive value for HARS score.

Ključne reči:
liver diseases; chronic disease; depression; anxiety; questionnaires.

Apstrakt

Uvod/Cilj. U poslednje vreme raste interesovanje za mentalno zdravlje bolesnika sa hroničnim bolestima jetre (HBJ), zbog toga što poremećaj mentalnog zdravlja redukuje kvalitet života i udružen je sa pogoršanjem kliničkog ishoda, smanjenjem komplijanse i povećanjem mortaliteta. Cilj ove studije bio je određivanje učestalosti i težine depresije i anksioznosti kod bolesnika sa HBJ, kao i procena uticaja različitih faktora na skorove depresije i anksioznosti. **Metode.** U studiji preseka, na uzorku bolesnika sa HBJ, korišćeni su Hamiltonova skala depresije (HDRS) i Hamiltonova skala anksioznosti (HARS). **Rezultati.** U studiju je bilo uključeno 54 muškarca i 43 žene obolelih od HBJ. Depresija je bila prisutna kod 62.9%, a anksioznost kod 13.4% bolesnika. Veći HDRS skor imali su bolesnici stariji od 50 godina ($p = 0.022$) i nezaposleni bolesnici ($p = 0.043$). Bolesnici sa barem jednom epizodom gastrointestinalnog krvarenja imali su značajno veću učestalost anksioznosti od bolesnika bez epizode krvarenja ($p = 0.018$). Viši HARS skor bio je prisutan kod žena ($p = 0.011$), nezaposlenih bolesnika ($p = 0.008$) i bolesnika sa nealkoholnom bolešću jetre ($p = 0.007$). HDRS skor značajno je korelirao sa prosečnom zapreminom eritrocita (MCV), a HARS skor sa koncentracijom serumskog kalijuma i natrijuma. **Zaključak.** Starost i prosečna zapremina eritrocita imaju prediktivni značaj za HDRS skor dok su nezaposlenost, gastrointestinalno krvarenje, vrednost serumskog kalijuma i natrijuma prediktori HARS skora.

Key words:
jetra, bolesti; hronična bolest; depresija; anksioznost; upitnici.

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Introduction

Chronic liver disease (CLD) encompasses a wide spectrum of diseases, ranging from liver steatosis (alcoholic and non-alcoholic), hepatitis B and C virus infection, cirrhosis and other less common conditions [1]. Due to the high frequency of occurrence and its consequences, this group of diseases is becoming an increasingly important public health issue worldwide. Depression is one of the leading causes of disability in the adult population and expected to become the second leading cause of disability in all age groups by 2020 [1]. Furthermore, it has been pointed out that this illness is as one of the most common clinical manifestations in a broad range of different diseases [2]. Additionally, results from numerous studies have shown that CLD are often associated with psychiatric comorbidity, particularly mood disorders (depression and anxiety), personality, sleep and other behavior and cognitive deficits [2–6]. The evidence about the presence of these symptoms in CLD patients is important because they have an adverse effect upon the course of illness in the form of amplification of physical symptoms, functional impairment, reduced treatment compliance, and decreased quality of life [2, 6–13].

Most of the previous studies have been focused on depression in CLD [4, 6, 7, 12, 14–17], while only a few have been devoted to anxiety in these patients [6, 14, 16, 17]. Published studies data were heterogenic, both in terms of study population, different diagnostic criteria and assessment instruments that were used for the diagnosis of depression and anxiety.

The aim of the study was to determinate the frequency and severity of depression and frequency of anxiety in patients with CLD and to assess the contribution of selected socio-demographic, clinical and laboratory risk factors for depression and anxiety.

Methods

Data were collected on a sample of patients in the Chronic Liver Disease Questionnaire (CLDQ) validation study, and detailed methodology was previously published [18]. The study was conducted at the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia, Belgrade, in the period of one year. Consecutive outpatients and inpatients with chronic liver disease were evaluated for inclusion and exclusion criteria. Inclusion criteria was CLD (chronic hepatitis and liver cirrhosis), while exclusion criteria were: age < 18 years, psychiatric disorders (psychosis or dementia), acute complications of CLD, hepatic encephalopathy (grade > 2), liver transplantation and patients undergoing antiretroviral therapy [18].

The severity of liver disease was quantified using modified Child-Pugh classification into three groups – A, B and C class – to determinate the stage of liver insufficiency [19]. The patients were stratified into the two groups: no cirrhosis/early cirrhosis (Child A) and advanced cirrhosis (Child B/Child C).

According to the etiology, the patients were stratified on alcoholic and non-alcoholic liver disease. The group of patients with non-alcoholic etiology included: viral (hepatitis B and C), autoimmune (primary biliary cirrhosis, primary sclerosing cholangitis and autoimmune hepatitis), non-alcoholic steatohepatitis, Morbus Wilson and cryptogenic CLD.

Assessment of the presence and the level of depression was based on the Hamilton depression rating scale (HDRS) [20]. It is clinician-administrated depression estimation scale conducted using semi-structured interview in which 21 signs and symptoms of depression were evaluated. Most of the items were rated on the 0 to 4 scale, reflecting the severity of symptom manifestation, while others were rated on the 0 to 2 scale reflecting the absence, probable, or the definite existence of the symptom. HDRS can have values from 0 to 64, with the values higher than 8 labeled as abnormal (clinically meaningful depression). In relation to the value of the HDRS score, severity of depression was classified to: mild depression, 9–17; moderate depression, 18–24; severe depression, higher than 24 [20].

For estimation of anxiety, we used the Hamilton anxiety rating scale (HARS), which includes evaluation of 14 symptoms and signs. The presence of these symptoms is graded from 0 (not present) to 4 (severe). HARS score can range from 0 to 56, with the values higher than 17 as pathological (clinically significant anxiety) [21].

Testing with the scales HDRS and HARS was conducted by clinicians.

In addition, the socio-demographic, clinical and psychometric data were collected, as well as the following laboratory parameters: hematological, biochemical and viral hepatitis profiles. Data were collected using a questionnaire, based on medical records and anamnesis. Data were collected by clinicians.

This study was approved by the Ethics Committee of the Faculty of Medicine, University of Belgrade (Decision No. 29/I-2). All the subjects gave written consent to participate in the study.

Statistical analysis

The methods of descriptive and analytical statistics were applied. The continuous variables were presented as mean value ± standard deviation, while the categorical ones as proportions (percentages). For statistical analysis, we used parametric and non-parametric tests and correlation tests. A p value < 0.05 was marked statistically significant.

Hierarchical multiple regression analysis was conducted to identify predictors of depression and anxiety. The analysis was conducted separately for HDRS and HARS as outcome variables. The predictor variables were separated into three blocks (models). Selected socio-demographic characteristics were entered in the first block, clinical characteristics comprised the second block followed by laboratory parameters in the third block. After adjustment for potential confounding factor, we determined final models for HDRS and HARS scores.

Results

The study included 103 patients with CLD. The depression and anxiety scale were completed by 97 (94.1%) of the patients, and only they were analysed. Men were 54 (55.7%). The average age was 53.5 ± 12.8 years. Clinically meaningful depression was present in 61 (62.9%) of the patients, with the average HDRS score 13.4 ± 9.4. Mild depression was present in 33 (34.0%) of the patients, moderate in 16 (16.5%), and severe in 12 (12.4%) of the patients. Clinically significant anxiety was present in 13 (13.4%) of the patients. The average value of the HARS score was 10.0 ± 6.4.

The distribution of the selected socio-demographic and clinical characteristics according to the presence and category of depression measured by the HDRS score was presented in Table 1 and Table 2. There were no statistically significant differences in the frequency of varying severity of depression between the patients with different socio-demographic and clinical characteristics.

Analysis of differences in the average HDRS score, indicated that the patients older than 50 years had a significantly higher HDRS score than the patients ≤ 50 years $(15.2 \pm 9.7\ vs\ 10.6 \pm 8.3)$, $(z = 2.290, p = 0.022)$. Additionally, the unemployed patients had a significantly higher HDRS score than the employed patients $(14.6 \pm 9.4\ vs\ 10.5 \pm 8.9)$, $(z = 2.024, p = 0.043)$. For the other investigated socio-demographic and clinical characteristics, statistically significant difference was not obtained (data not shown). Furthermore, correlation analysis between the level of investigated laboratory parameters and depression status showed that only the mean corpuscular volume (MCV) significantly correlated with HDRS scores $(r = 0.215, p = 0.034)$.

Hierarchical regression analysis showed that socio-demographic variables (age, employment) explained 6.9% of the variance $(p = 0.036)$ of the HDRS as outcome measure. Addition of the variables "ascites" and "gastrointestinal

Table 1

The distribution of selected socio-demographic characteristics according to the Hamilton depression rating scale (HDRS) degree of depression severity

Socio-demographic characteristics	The HDRS degree of depression severity				*p*-value
	no depression	mild	moderate	severe	
Gender, n (%)					
male	25 (46.3)	14 (25.9)	10 (18.5)	5 (9.3)	0.095
female	11 (25.6)	19 (44.2)	6 (14.0)	7 (16.3)	
Age, n (%)					
≤ 50 years	18 (47.4)	12 (31.6)	6 (15.8)	2 (5.3)	0.217
> 50 years	18 (30.5)	21 (35.6)	10 (16.9)	10 (16.9)	
Education, n (%)					
≤ 12 years	24 (38.1)	19 (30.2)	11 (17.5)	9 (14.3)	0.609
>12 years	12 (36.4)	14 (42.4)	4 (12.1)	3 (9.1)	
Employment, n (%)					
employed	14 (48.3)	8 (27.6)	5 (17.2)	2 (6.9)	0.406
unemployed	22 (32.4)	25 (36.8)	11 (16.2)	10 (14.7)	
Marrital staus, n (%)					
single	8 (28.6)	12 (42.9)	2 (7.1)	6 (21.4)	0.103
married	26 (39.4)	20 (30.3)	14 (21.2)	6 (9.1)	
Children, n (%)					
yes	29 (36.7)	25 (31.6)	14 (17.7)	11 (13.9)	0.584
no	7 (38.9)	8 (44.4)	2 (11.1)	1 (5.6)	
Smoking, n (%)					
yes	8 (25.8)	14 (45.2)	5 (16.1)	4 (12.9)	0.355
no	28 (42.4)	19 (28.8)	11 (16.7)	8 (12.1)	

Table 2

The distribution of the selected clinical characteristics according to the Hamilton depression rating scale (HDRS) degree of depression severity

Clinical characteristics	The HDRS degree of depression severity				*p*
	no depression	mild	moderate	severe	
Disease severity, n (%)					
no cirrhosis	12 (27.3)	17 (38.6)	9 (20.5)	6 (13.6)	0.324
Child's B/ C	24 (45.3)	16 (30.2)	7 (13.2)	6 (11.3)	
Etiology, n (%)					
alcoholic	17 (47.2)	9 (25.0)	6 (16.7)	4 (11.1)	0.389
non-alcoholic	19 (31.1)	24 (39.3)	10 (16.4)	8 (13.1)	
Ascites, n (%)					
yes	16 (47.1)	10 (29.4)	5 (14.7)	3 (8.8)	0.502
no	20 (31.7)	23 (36.5)	11 (17.5)	9 (14.3)	
Gastrointestinal bleeding, n (%)					
yes	6 (27.3)	7 (31.8)	5 (22.7)	4 (18.2)	0.457
no	30 (40.5)	26 (35.1)	11 (14.9)	7 (9.5)	

bleeding", in the second model caused an increase by 5.4% in variance ($p = 0.067$). Furthermore, after adding the MCV in the third block an additional 5.4% of the variance was explained in HDRS ($p = 0.018$). The final model showed that age, employment, ascites, gastrointestinal bleeding and MCV accounted for 17.6% of the variance in HDRS (Table 3).

The patients with at least one episode of gastrointestinal bleeding had a significantly higher frequency of clinically meaningful anxiety than the patients without bleeding ($\chi^2 = 5.561$, $p = 0.018$). For the other socio-demographic and clinical characteristics, a difference in clinically significant anxiety was not found. Analysis of distribution of anxiety

With HARS as dependent variable, the first model in hierarchical regression analysis (consisting of the selected socio-demographic variables), accounted for 9.3% of the variance in the outcome variable. Moreover, "gastrointestinal bleeding", "ascites" and "etiology of CLD" explained additional 8.7% in the total change in HARS, in this analysis. Concentration of serum sodium and potassium, in the third model, accounted an additional 23.5% of the variance in HARS ($p < 0.01$). Therefore, the final model (employment, gastrointestinal bleeding, serum potassium and serum sodium) explained 41.5% of the variance in HARS ($p < 0.01$) (Table 4).

Table 3

The results of hierarchical multiple regression analysis for the Hamilton depression rating scale (HDRS) as the dependent variable

Variable	Model I			Model II			Model III		
	B	SE(B)	β	B	SE(B)	β	B	SE(B)	β
Age	3.63	2.10	0.18	3.80	2.07	0.19	4.09	2.02	0.21*
Employment	-2.53	2.24	-0.12	-2.36	2.20	-0.11	-1.83	2.15	-0.09
Ascites				-3.27	1.94	-0.16	-3.67	1.90	-0.18
GIT bleeding				3.68	2.20	0.16	3.91	2.14	0.17
MCV							0.18	0.07	0.23*
R²		0.069*			0.123			0.176*	
F for change in R²		3.448*			3.185*			3.856**	

GIT– gastrointestinal; MCV – mean corpuscular volume of erythrocytes.
* $p < 0.05$; ** $p < 0.01$.

Table 4

The results of hierarchical multiple regression analysis for the Anxe depression rating scale (HARS) as the dependent variable

Variable	Model I			Model II			Model III		
	B	SE (B)	β	B	SE (B)	β	B	SE (B)	β
Gender	-2.30	1.31	-0.18	-1.71	1.51	-0.13	-1.6	1.30	-0.13
Employment	-3.06	1.42	-0.21*	-2.95	1.38	-0.21*	-2.68	1.18	0.19*
Etiology				-1.29	1.47	-0.10	-0.71	1.27	-0.05
Ascites				-1.45	1.51	-0.10	-0.15	1.34	-0.01
GIT bleeding				3.83	1.51	0.25*	6.64	1.53	0.43**
S-Potassium							0.51	0.12	1.16**
S-Sodium							0.42	0.14	0.73**
R²		0.093*			0.181*			0.415**	
F for change in R²		4.639*			3.838**			8.629**	

GIT – gastrointestinal; S – serum; * $p < 0.05$; ** $p < 0.01$.

according to the selected demographic variables indicated that women had a significantly higher average HARS score compared to the males (11.6 ± 6.6 *vs* 8.8 ± 6.0), ($z = 2.546$, $p = 0.011$), as well as the unemployed patients had a significantly higher HARS score than the employed patients (11.0 ± 6.7 *vs* 7.5 ± 5.0), ($z = 2.659$, $p = 0.008$). Moreover, the patients with non-alcoholic liver disease had a significantly higher HARS score than the patients with alcoholic liver disease (11.2 ± 6.6 *vs* 8.0 ± 5.5), ($z = 2.688$, $p = 0.007$). For the other investigated socio-demographic and clinical characteristics, a statistically significant difference was not obtained (data not shown). Furthermore, investigation of the association between anxiety and the level of laboratory parameters showed that HARS scores significantly correlated with the value of serum potassium ($r = 0.443$, $p < 0.001$) and serum sodium ($r = -0.363$, $p < 0.001$).

Discussion

The correlation between depression and anxiety with CLD has been known for a long time [6], as well as the fact that patients with CLD had a significantly higher incidence of depression compared to healthy population [5, 12, 22–24]. Pathogenesis of depression in patients with CLD is insufficiently clarified. Neuropsychological deficits in this group of patients usually include cognitive impairment and depression [5]. These disorders occur as a consequence of accumulation neuropathogenic molecules and toxins in blood due to the inadequate clearance in a damaged liver [25]. Also, in patients with end stage liver disease, immunological mechanisms can lead to the development of depression [26]. However, it remains unclear why up to 50% of patients with noncirrhotic CLD have these disorders long before the occurrence of cirrhosis [25].

Although this psychiatric comorbidity is common in all CLD, most of the published studies are based on an estimate of depression and anxiety in liver transplant candidate or patients after liver transplatation [7, 29, 14, 15, 27], and patients with chronic viral hepatitis [28–30]. As reported in the literature, there is no difference in the level of depression and anxiety among candidates for liver transplantation and patients with liver disease who are not on the list for transplantation [24], and therefore we estimate that the scores for depression and anxiety between these two groups of patients are comparable [15].

In our study 62.9% of patients with CLD had depression, while 13.4% of patients had anxiety which was in accordance with previous findings [4, 6, 15]. Namely, in the patient with CLD, incidence of depression ranged from 20% to 70.6% [4, 6, 7, 12, 14–17], and anxiety from 13% to 71.6% [6, 14, 17]. Similar data were obtained in the group of patients with chronic hepatitis C [27, 31–34] and in patients with alcoholic cirrhosis [18]. The analysis of the severity of depression, in our patients, have revealed that 34% of patients had mild, 16.5% moderate, and 12.4% severe stage of this disorders. Similar data were obtained by Bianchi et al. [4]. Besides neuropathogenic impact of CLD [1, 5, 25], such a high frequency of this mental disturbances might be explained by the fact that a majority of these patients belonging to a high risk population for developing psychiatric disorders (alcoholism, drug addiction, etc.) [17].

The results of our study show that women and man do not differ in severity of depression, which is consistent with previous communications [14, 17]. However, although the frequency of anxiety did not differ between the genders, we confirmed a higher average HARS score in women, which is also described in other studies [35–37]. The reason for this difference may be in different biological and social factors between men and women [35, 38], respectively in greater responsibility to the health of women and the importance of their health on families and children.

The results from numerous studies demonstrated that age had no influence to the severity of depression, which is consistent with our result [14, 15, 17, 22]. However, in our sample of CLD patient, it was found that patients > 50 years old have a significantly higher mean HDRS score, than younger patients. The effect of age on depression in CLD is described by Kraus et al. [22], and Theofilou [36], which suggest that older patients have higher levels of depression.

Our study showed that employed and unemployed patients did not differ in the frequency and severity of depression and frequency of anxiety, as described by other authors [7, 22]. We also obtained the results in favor of it, that unemployed patients have a significantly higher HDRS and HARS score than employed patients. The reason for these results might be the fact that unemployment can be stressful factor because patients are exposed to existential problems, and lack of professional activity, which could at least partially occupy the patient, and turn his attention to the somatic state.

Our results indicate that patients with different disease severity have no differences in depression and anxiety. There are divided opinions about the way of liver disease severity affects the levels of depression and anxiety. Some authors

state that the Child-Pugh and Model for end-stage liver disease (MELD) score does not affect depression [3, 4, 7, 39]. However, another studies suggest that the severity of liver assessed by Child-Pugh score directly affects depression and anxiety [14, 40].

Patients with at least one episode of gastrointestinal hemorrhage had significantly higher rates of anxiety. Dramatic clinical presentation of bleeding and awareness of the possibility of recurrence, mortality and treatment methods have a negative impact on the patient's mental status and favor the development of anxiety. Certainly it should not be forgotten that bleeding usually occurs in more advanced CLD. As obtained in our research, and based on the literature data [7], it is not confirmed that gastrointestinal bleeding has influence on the level of depression.

In our study, patients with alcoholic and non-alcoholic etiology of CLD did not differ in depression and anxiety. Our results confirm previously published data, indicating that if we exclude overall psychiatric comorbidity (neuroses, affective disorders, and anti-social personality), which is more common in patients with alcoholic liver disease than in patients with non-alcoholic liver disease [41, 42], these two groups will not differ in depression and anxiety [15, 39, 43]. However, in patients with non-alcoholic etiology of the disease significantly higher HARS score was confirmed than in patients with alcoholic CLD. Besides the anxiolytic effects of alcohol, based on the modulation of neurotransmission predominantly via gamma-amynobuteric acid (GABA-A) [44, 45], the reason for the lower HARS score in patients with alcoholic liver disease may be unrealistic in their relation to health, causing CLD experience less severely than patients with non-alcoholic liver disease. In determining the differences between patients of different gender, age, employment status, and etiology of the disease, it was found that they do not differ in depression and anxiety. However, if we analyze the average HDRS or/and HARS scores a statistically significant difference in these scores is registered for some categories. The reason for this phenomenon may be that the cut-off values for determining the presence of depression and anxiety, arbitrary, cover a relatively wide range of values of these psychometric tests, and that significant changes in the absolute values of scores are not sufficient to lead to a change in category (presence/absence of disorder).

Nonmegaloblasic (normoblastic), macrocytic anemia and macrocytosis without anemia is common in chronic liver diseases [46]. The pathogenesis is not fully known. It is believed that in patients with alcoholic cirrhosis, it is a result of direct toxic effects of alcohol on red blood cells, which affects the modification of lipid components of the erythrocyte membrane [46, 47]. Also, macrocytic anemia occurs as the result of vitamin B12 and/or folic acid deficit. In the recent literature, it is described that these micronutrients deficit is associated with depression [48–50]. Also, the use of vitamin B12 with a selective serotonin reuptake inhibitor, significantly improved the symptoms of depression [51]. Our study established a positive correlation between depression score and MCV. In previous study no correlation between HDRS score and MCV was found [52]. However, Alves de Rezende et al. [53], de-

scribe a positive correlation between depression score and MCV in women. In order to investigate the association between MCV and HDRS score among CLD patients included in our study, we performed the hierarchical regression analysis.

In our study, it was found that serum potassium correlated positively with HARS score, and serum sodium negatively with the score of anxiety. More complex pictures of these correlations are obtained by hierarchical regression analysis. Namely, after controlling for potential confounding factors (gender, employment, etiology, ascites and gastrointestinal bleeding), final model showed that serum potassium and serum sodium have significant influence on the development of anxiety. For potassium, a possible explanation is based on the GABA effect. In fact, a study conducted on the experimental animals in 2012, confirmed that the use of loop diuretics, which reduce the concentration of potassium, lead to anxiolytic effect based on the modulation of GABA-A receptors, through antagonism of cation-chloride cotransporters [54]. Also, sodium imbalance is important in patients with advanced cirrhosis, which is associated with developing of numerous complications [55, 56] and even better predictor of mortality than MELD score [57]. The study of Solà et al. [58], from 2012 concluded that the concentration of serum sodium is a predictor of mental components of quality of life in CLD patients, as a result of the effect of hyponatremia on central nervous system. Based on our results, measuring MCV, serum potassium and serum sodium, could have a significance in detection of patients with CLD, which should be further examined to diagnose depression and/or anxiety.

Conclusion

In this study 62.9% of the patients with chronic liver disease had depression, while 13.4% of the patients had anxiety. The women and the patients ≤ 50 years old, had a significantly lower the HDRS score. The unemployed patients had a significantly higher HDRS and HARS score than the employed patients. The patients with different disease severity and different etiology of chronic liver disease did not differ in depression and anxiety. Of all the studied characteristics, it was concluded that only age and mean corpuscular volume had a predictive value in the development of depression, while employment, gastrointestinal bleeding, serum potassium and sodium levels had a significant influence on anxiety score.

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