

# PECULIARITIES OF THE FUNCTIONAL STATE OF THE LIVER IN PATIENTS WITH CHRONIC HEPATITIS C IN THE PRESENCE OF CHRONIC PANCREATITIS

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## ABSTRACT

**The aim:** To study the features of the functional state of the liver in patients with chronic hepatitis C (CHC) in the presence of CP, depending on the enzymatic activity of the pancreas.

**Materials and methods:** 72 patients were under observation: 52 with CHC and CP with exocrine secretory insufficiency (EI) of the pancreas and 20 - with CHC and CP without EI. In all patients, the degree of liver fibrosis, levels of aminotransferases, total bilirubin, gamma-glutamyltransferase, albumin, stool coproscopy and pancreatic fecal elastase-1 (FE-1) were determined.

**Results:** It was revealed that in patients with CHC combined with CP+EI of the pancreas, higher activity of the necroinflammatory process and deeper stages of liver fibrosis is more often noted than in patients with preserved exocrine function of the pancreas. A statistically significant association was established between the degree of liver fibrosis and the presence of EI of the pancreas ( $p=0.03$ ), namely, in patients with CHC and CP with EI of the pancreas, the degree of fibrosis F2-4 was 2.8 times more frequent. Also, higher levels of aminotransferases and lower levels of albumin were noted in this group of patients than in patients with CHC and CP with preserved exocrine function of the pancreatic gland.

**Conclusions:** In patients with CHC combined with CP+EI of the pancreas, higher levels of fibrosis and necroinflammatory activity of the liver are more often detected, as well as a tendency to lower albumin levels, than in patients with CHC and CP without EI.

**KEY WORDS:** chronic hepatitis C, chronic pancreatitis, exocrine insufficiency, liver fibrosis, fecal elastase-1

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## INTRODUCTION

Chronic hepatitis C (CHC) and chronic pancreatitis (CP) are extremely relevant medical problems today. According to the 2021 WHO report, about 1.5 million new cases of CHC are registered every year, and 58 million people live with this diagnosis [1,2]. Spontaneous elimination of HCV in chronically infected patients occurs only in  $\approx 0.02\%$  of patients per year, almost 70% of patients have one or more extrahepatic manifestations of HCV, and about 290,000 people die annually from the consequences of HCV [3,4]. As for CP, it is a disease that actually causes irreversible changes in the morphology and function of the pancreas. Its long-term consequences are type II diabetes (DM) and pancreatic cancer. The incidence of CP in European countries varies from 5 to 10 per 100 thousand population [3-6].

The pancreas and the liver are anatomically in close proximity [7]. Thus, diseases of the pancreas that affect the outflow of bile can lead to concomitant liver damage. However, whether liver disease affects the function of

the pancreas is currently not clearly established. Some studies have shown that patients with a diagnosis of acute or fulminant hepatitis also suffer from acute pancreatitis [8-10]. The features of the simultaneous course of CHC and CP and their mutual influence remain unclear. In separate studies, the possibility of replication of the hepatitis C virus in  $\beta$ -cells of the pancreas with subsequent development of diabetes and CP has been demonstrated [11]. Also, CP, both with normal and with impaired excretory function of the pancreatic gland, is considered as a possible extrahepatic manifestation of CHC [12-15]. Therefore, the combination of these diseases and their mutual influence requires further research.

## THE AIM

To study the features of the functional state of the liver in patients with chronic hepatitis C in the presence of chronic pancreatitis depending on the enzymatic activity of the pancreas.

## MATERIALS AND METHODS

We included in the study 72 patients with CHC with concomitant CP, who were divided into 2 groups, depending on the presence or absence of exocrine insufficiency (EI) of the pancreas. The first group consisted of 52 patients with an existing EI (1st group n=52), and the second group included 20 patients without EI of pancreatic gland (2nd group n=20). All patients were between the ages of 18 and 70 and signed an informed consent to conduct research, the structure of which corresponded to the officially agreed, and the research itself - to the requirements of the Declaration of Helsinki (1975) as amended, the International Code of Medical Ethics (1983) and the relevant laws of Ukraine and WHO regulations. The study was approved by the local ethics commission of the State University "Uzhhorod National University" (protocol No. 6/2 dated September 7, 2021).

The scientific research was carried out within the departmental theme "Combined pathology and correction of homeostasis disorders of residents of the Carpathian region, taking into account adverse factors", state registration number 0121U110808 of the department of faculty therapy of the State University "Uzhhorod National University".

The diagnosis of CHC was made in accordance with the International Classification of Diseases of the 10th revision and verified by the detection of total antibodies of the IgG class to the structural and non-structural proteins of HCV (antiHCV IgG +) by the serological method of ELISA, as well as by the indication HCV RNA + in the blood of the investigated by the PCR method with the determination of the viral load and genotyping. Testing was performed on a thermal cycler with a real-time PCR product detection system "iQ 5", Vio-Rad, USA. General clinical, biochemical, serological, and molecular genetic studies were conducted in certified laboratories of the central city clinical hospital of Uzhhorod, communal non-commercial enterprise "Regional Clinical Infectious Disease Hospital" of the Transcarpathian Regional Council, and commercial laboratories ("Dila" and "Astra-Dia"). Indicators of biochemical blood analysis - total bilirubin and its fractions, total protein and fractions, activity of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase (LF) and  $\gamma$ -glutamyl transpeptidase (GGT) were determined using an automatic biochemical analyzer and original ChemWell reagents. Awareness Technology INC (USA).

The degree of activity of the pathological process was determined by the level of increased activity of ALT, according to the international classification of liver diseases (Los Angeles, 1994). The degree of fibrosis and the activity of the necroinflammatory process in the liver were determined using a non-invasive diagnostic

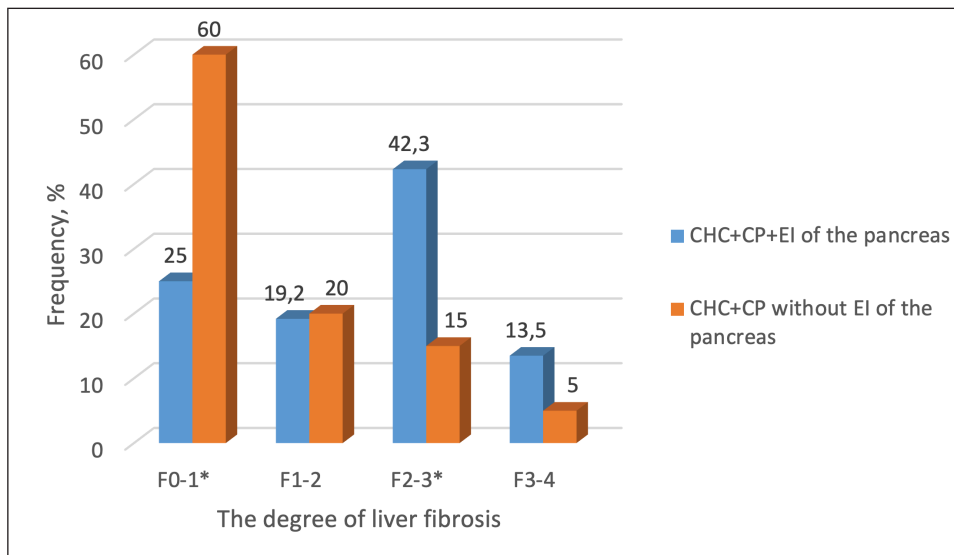
method - FibroMax, which includes: FibroTest, ActiTest, SteatoTest, AshTest, NashTest and is carried out by the company BioPredictive (Paris, France). The patients also underwent an ultrasound examination of the abdominal organs according to the generally accepted method. All patients underwent stool coproscopy, where the appearance of a small amount of neutral fat, altered muscle fibers and extracellular starch made it possible to suspect a violation of the exocrine function of the pancreas and the formation of chronic pancreatitis.

The diagnosis of CP was established in accordance with the Marseille-Rome criteria (1989) with additions and clarifications of the International Classification of Diseases of the 10th revision, as well as in accordance with the Order of the Ministry of Health of Ukraine dated September 10, 2014 No. 638 "On the approval and implementation of medical and technological documents on the standardization of medical of help in chronic pancreatitis" [16]. The exocrine function of the pancreas was evaluated based on the results of fecal coproscopy and pancreatic fecal elastase-1 (FE-1), which was studied by means of ELISA, using the test systems of ScheBo® Biotech AG (Germany). The interpretation of the results was carried out according to the following gradation: the level of FE-1 in feces is more than 200  $\mu\text{g/g}$  of feces - the exocrine secretory function of the pancreatic gland is preserved; 150–200  $\mu\text{g/g}$  of feces - a mild degree of exocrine insufficiency; 100–150  $\text{mcg/g}$  of stool - moderate EI; less than 100  $\text{mcg/g}$  of feces - severe EI.

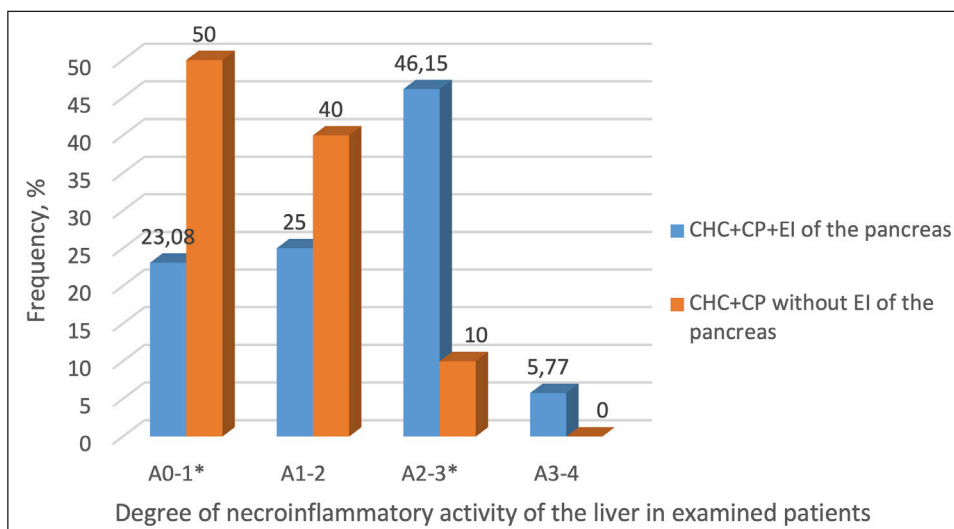
The analysis and processing of the results of the examination of patients was carried out using the computer program Jamovi 2.3.21, Microsoft Excel 2016, Statistics for Windows v.7.0 (StatSoft Inc, USA) using parametric and non-parametric methods of evaluating the obtained results. The difference was considered statistically significant at  $p < 0.05$ .

## RESULTS

When analyzing the obtained data, it was possible to establish that, in contrast to patients with CHC and CP with a preserved exocrine function of the pancreatic gland, defecation disorders are more often noted in patients with CHC in combination with CP with EI. The proportion of patients with defecation disorders (diarrhea, constipation or their alternation) was 2 times higher in 1 group, compared to the group of patients without EI of pancreas (78.8% (41/52) versus 40% (8/20) people). In particular, diarrhea was detected in 21.2% (11/52) in the first group and in 5.0% (1/20) in the second, constipation - in 30.8% (16/52) and 25% (5/20) respectively, and alternating diarrhea and constipation in 26.9% (14/52) in the first group and in 10.0% (2/20) in the second ( $p=0.016$ ). Also, patients of the first



**Fig.1.** Degree of liver fibrosis in examined patients  
Note: \* the difference is statistically significant when comparing patients of groups 1 and 2,  $p < 0.05$



**Fig. 2.** Degree of necroinflammatory activity of the liver in examined patients  
Note: \* the difference is statistically significant when comparing patients of groups 1 and 2,  $p < 0.05$

group complained more often of abdominal bloating and flatulence - 82.7% (43/52) versus 55.0% (11/20) in the second group ( $p=0.015$ ). Abdominal pain credibly bothered the patients of the first group - 63.5% (33/52) versus 35% (7/20) in the second group ( $p=0.03$ ).

During the analysis of the research results, it was found that in patients with CHC with combined CP EI of pancreatic gland, higher activity of the necroinflammatory process and deeper stages of fibrosis of the liver were more often noted than in patients with preserved exocrine function of the pancreas. The statistical significance of the association between the degree of fibrosis of the disease and the presence of EI was established ( $p=0.03$ ). also, the stage of fibrosis F2-3 (42.3% (22/52) vs. 15% (3/20)) was detected 2.8 times more often in patients with CHC+CP with EI and F0 was 2.4 times less often - 1 (25% (13/52) vs. 60% (12/20)) (Fig. 1).

It was found that in patients with CHC, comorbid with chronic pancreatitis, LUTS is associated with liver fibrosis: with a higher degree of fibrosis, the probability

of secretory insufficiency of the liver is higher ( $p=0.03$ ).

According to the results of ActiTest, which reflects the level of necroinflammatory activity of the liver, stage A2-3 was detected in patients of group 1 4.6 times more often than in patients of group 2, namely 46.15% (24/52) versus 10% (2/20), and 2.2 times less often – stage A0-1, respectively 23.08% (12/52) versus 50% (10/20) (Fig. 2).

It was established that in patients of the first group, the average level of ALT and AST was  $69.0 \pm 25.2$  IU/l and  $57.0 \pm 22.3$  IU/l, respectively, against  $42.1 \pm 18.0$  IU/l and  $33,7 \pm 16.2$  IU/l in patients of the second group ( $p < 0.001$ ).

Pigment function was unchanged or little changed in both groups. The average level of total bilirubin was  $16.7 \pm 4.5$  mmol/l in the group of CHC+CP+EI and  $12.7 \pm 4.24$  mmol/l in the group of CHC+CP without EI of the pancreatic gland ( $p < 0.001$ ).

Protein synthetic function was evaluated by albumin level. Although its average level was within the normal range in both groups, it was lower in the group of CH-

**Table 1.** Indicators of the functional state of the liver in the examined personsNote: \* the difference is statistically significant when comparing patients of groups 1 and 2,  $p < 0.05$ 

Indicator, unit of measurement	Patients groups	
	1 group, n=52 CHC+CP+EI of the pancreas	2 group, n=20 CHC+CP without EI of the pancreas
Albumin, g/l *	38,2 ± 5,14	45,2 ± 4,45
Total bilirubin, mmol/l *	16,7 ± 4,5	12,7 ± 4,24
ALP, IU/l	234 ± 58,3	226 ± 55,0
GGT, IU/l	44 ± 12,6	39,2 ± 8,0
ALT, IU/l *	69,0 ± 25,2	42,1 ± 18,0
AST, IU/l *	57,0 ± 22,3	33,7 ± 16,2

Note: \* the difference is statistically significant when comparing patients of groups 1 and 2,  $p < 0.05$ 

C+CP+SSNPs than in the group of CHS+CP without SSNPs ( $p < 0.001$ ), namely  $38.2 \pm 5.14$  g/l against  $45.2 \pm 4.45$  g/l.

When examining individual markers of cholestasis (LF and GGT) in the examined patients of both groups, a slight difference in mean values was found, but it was not statistically significant (Table 1).

It was found that the level of viral load in CHC is associated with the presence of EI. It was established that patients with impaired exocrine function of the pancreas had a high viral load 4.2 times more often - 42.3% (22/52) against 10% (2/20) in the second group ( $p = 0.002$ ).

## DISCUSSION

When evaluating the clinical features of the course of CHC with concomitant CP, we found that dyspeptic symptoms such as defecation disorders, flatulence, flatulence, and abdominal pain are more often detected with reduced enzymatic activity of pancreatic gland. This demonstrates the aggravating effect of the presence of EI on the clinical course of CHC and complements the data obtained by other authors (Babinets et al., 2019) [17]. However, in the presence of stool disorders, we did not establish a clear difference between the frequency of constipation, diarrhea, and unstable stools.

The data obtained by us regarding low levels of albumin in 1 group of patients may be due to insufficient intake of protein from food, as a result of the malabsorption syndrome, which is characteristic of EI. Our data are consistent with the data obtained by Fujita et al. (2019), Diéguez-Castillo et al. (2020), who proved that trophic insufficiency due to malabsorption syndrome often occurs in patients with CP with EI [18,19].

The results obtained by us about the aggravating interaction of a high viral load and inflammatory activity in the liver on the exocrine function of the pancreas are confirmed by the data obtained by other scientists. Thus, such researchers as Jain et al., (2007) and Panic et al. (2020) [8,20]. Blackard (2017) proved the impact of HCV on the endocrine function

of the pancreatic gland and suggested the possibility of viral replication in  $\beta$ -cells [11]. It is also known that DM is a frequent extrahepatic manifestation of CHC (Mazzaro 2021; Svegliati-Baroni 2020) [1,21]. When analyzing the obtained data, we found that among patients with a combined course of CHC and CP, a high viral load is more often found in 1 group (patients with CHC and CP with the presence of EI), which may indicate the presence of hepatitis C virus replication in the PC. Previously, Yan et al. (2000) HCV RNA was detected in pancreatic tissue obtained at autopsy [13]. Other scientists, such as Arafa et al. (2020), Fiorino et al. (2019) found that infection with the hepatitis C virus is correlated with the incidence of pancreatic cancer and this may indirectly indicate the previous presence of CP, which, however, was not diagnosed in time [13, 22, 23]. But the exact mechanism of the connection between HCV infection and the development of pancreatic cancer and CP has not been fully understood. It has been suggested that the anatomical proximity of the liver to the pancreas, as well as the sharing of blood vessels and ducts between the two organs, may make the pancreas a potential reservoir for hepatitis C virus, which can travel through the bloodstream and deposit in tissues unrelated to the liver [23].

## CONCLUSIONS

High degrees of fibrosis (higher than F2-4) were detected 2.8 times more often in patients with CHC combined with CP + EI than in patients without EI of the pancreas. At the same time, the frequency of detection and the severity of EI are directly correlated with the levels of aminotransferases and viral load. The higher the degree of inflammatory activity of the liver and the viral load, the more often patients are diagnosed with EI of the pancreatic gland.

In patients with CHC comorbid with CP and presence of the EI, a tendency to lower levels of albumin was registered, while its values were normal in patients with CHC with preserved enzymatic function of pancreatic gland.

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**Conflict of interest:**

*The Authors declare no conflict of interest.*

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