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Liver damage in patients hospitalized with acute decompensated heart failure, depending on the degree of glucose metabolism disorder

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ABSTRACT

Aim. To study the frequency of cardiohepatic syndrome and steatosis by the value of controlled attenuation parameter (CAP), fibrosis, and their combination, depending on the degree of glucose metabolism disorder in patients with acute decompensated heart failure (ADHF).

Materials and methods. The study included 280 patients (53% men, average age 70.1 ± 10.8 years) with ADHF: 72.5% of patients had a history of arterial hypertension, 60% of patients had coronary heart disease. The HbA1c test was performed in all patients to assess the status of glucose metabolism. The patients were divided into groups depending on the results obtained: at HbA1c values < 5.7%, patients were included in the group without glucose metabolism disorders, at HbA1c 5.7–6.4% – in the prediabetes group, at HbA1c ≥ 6.5% – in the type 2 diabetes group. All patients underwent a standard physical examination at admission and at discharge. Clinical and comprehensive assessments of congestion were performed – NT-proBNP, lung ultrasound, liver fibroscan with CAP, and bioelectrical impedance analysis of body composition.

Results. The frequency of glucose metabolism disorders in patients hospitalized with ADHF was 57.5% ($n = 161$), while prediabetes was detected in 17.1% ($n = 48$) and type 2 diabetes – in 40.4% ($n = 113$) of patients. We revealed significantly higher incidence of steatosis by CAP value (69 vs. 42%, $p < 0.001$), fibrosis (80 vs. 64%, $p < 0.001$), and their combination (59 vs. 30%, $p < 0.001$), as well as cardiohepatic syndrome (87 vs. 61%, $p < 0.001$) in patients with ADHF and glucose metabolism disorders compared to individuals with ADHF without glucose metabolism disorders, respectively. The group of ADHF patients with glucose metabolism disorders and a combination of steatosis / fibrosis was characterized by more pronounced manifestations of metabolic syndrome, impaired kidney and liver function, and more pronounced manifestations (both clinical and laboratory) of congestion.

Conclusion. In patients with ADHF with glucose metabolism disorders, liver function test and liver fibroscan with CAP allow for identifying the most severe group of patients with a combination of steatosis/fibrosis and pronounced congestion.

Keywords: heart failure, liver fibroscan, steatosis, fibrosis, glucose metabolism disorder

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at the Institute of Medicine, RUDN University (Protocol No. 28 of 15.04.2021).

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Поражение печени у пациентов, госпитализированных с острой декомпенсацией хронической сердечной недостаточности, в зависимости от степени нарушения углеводного обмена

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РЕЗЮМЕ

Цель: изучить частоту стеатоза по значению контролируемого параметра ослабления (CAP), фиброза и их сочетания, а также сердечно-печеночных синдромов в зависимости от степени нарушения углеводного обмена (НУО) у пациентов с острой декомпенсацией хронической сердечной недостаточности (ОДХСН).

Материал и методы. В исследование были включены 280 пациентов (53% мужчин, средний возраст 70,1 ± 10,8 лет) с ОДХСН. Артериальную гипертонию в анамнезе имели 72,5%, ишемическую болезнь сердца – 60% пациентов. Всем пациентам для оценки статуса углеводного обмена определяли уровень гликированного гемоглобина (HbA1c). Пациенты были разделены на группы в зависимости от полученных результатов: при значениях HbA1c < 5,7% – в группу без НУО; 5,7–6,4% – в группу предиабета; ≥6,5% – в группу сахарного диабета (СД) 2-го типа.

Пациентам проводили стандартное физическое обследование при поступлении и при выписке, а также клиническую и комплексную оценку застоя – исследования NT-proBNP, ультразвуковое исследование легких, фибросканирование печени, включая контролируемый параметр ослабления CAP, биоимпедансный анализ состава тела.

Результаты. Частота НУО у пациентов, госпитализированных с ОДХСН, составляет 57,5% (n = 161), при этом предиабет был выявлен в 17,1% (n = 48), СД 2-го типа – в 40,4% (n = 113) случаев. Выявлена достоверно более высокая частота стеатоза по значению CAP (69 против 42%, p < 0,001), фиброза (80 против 64%, p < 0,001) и их сочетания (59 против 30%, p < 0,001), а также сердечно-печеночного синдрома (87 против 61%, p < 0,001) у пациентов ОДХСН и НУО в отличие от пациентов ОДХСН без НУО соответственно. Группа пациентов ОДХСН с НУО и сочетанием стеатоза (фиброза) была наиболее тяжелой, характеризовалась более выраженными проявлениями метаболического синдрома, нарушениями функции почек, печени, более выраженными проявлениями застоя, как клиническими, так лабораторно-инструментальными.

Заключение. У пациентов ОДХСН с НУО определение уровня печеночных ферментов, а также проведение фибросканирования печени и определение CAP позволит выделить наиболее тяжелую группу пациентов с сочетанием стеатоза (фиброза) и выраженными явлениями застоя.

Ключевые слова: сердечная недостаточность, фибросканирование печени, стеатоз, фиброз, нарушение углеводного обмена

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом Медицинского института РУДН (протокол № 28 от 15.04.2021).

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INTRODUCTION

The problem of heart failure (HF) remains one of the most urgent in cardiology, and dysfunction of peripheral target organs makes a significant contribution to HF development. Carbohydrate metabolism disorders (CMD), such as type 2 diabetes mellitus (DM) and prediabetes, are common in patients hospitalized with acute decompensated heart failure (ADHF). Prolonged systemic congestion in HF contributes to the development of liver damage in patients with CMD and is associated with a poor prognosis and the formation of fibrosis and then liver fibrosis [1].

Non-alcoholic fatty liver disease (NAFLD), which is often detected in this group of patients, also contributes to this pathology to a certain extent. The presence of a combined pathology leads to significant deterioration in the prognosis, as well as an increased risk of death from cirrhosis. The overall prevalence of NAFLD in patients with type 2 DM is 55.5%, which is more than two times higher than in the general population [2]. The relationship between the presence of NAFLD and metabolic syndrome is beyond doubt, while insulin resistance, which is the main characteristic of metabolic syndrome, is a key factor in this relationship. There are few studies devoted to the assessment of structural liver disorders using elastography in patients with stable HF, ADHF, and CMD. The most common indices for the diagnosis of steatosis are the Fatty Liver Index (FLI) and the Hepatic Steatosis Index (HSI).

It has been shown that the severity of NAFLD is associated with HSI in patients with metabolic syndrome who had dyslipidemia and CMD regardless of the presence of obesity and insulin resistance [3]. It has been demonstrated that patients with ischemic heart disease and type 2 DM are characterized by the presence of pronounced structural and functional changes in the liver, which are manifested by elevated levels of liver enzymes and high values of liver HSI and fibrosis index compared to patients with HF without type 2 DM [4]. At the same time, data on the frequency of steatosis and liver fibrosis in patients with HF and prediabetes are not presented in the literature. To identify and measure steatosis, controlled attenuation parameter (CAP), a new parameter developed based on the ultrasonic properties of radiofrequency back-propagated signals received via elastography, is used.

In this regard, the aim of this research was to study the frequency of steatosis by the value of CAP as well as to study the frequency of fibrosis, their combination, and cardiohepatic syndrome depending on the degree of CMD in patients with ADHF.

MATERIALS AND METHODS

A prospective, observational study included 280 people hospitalized with ADHF. The main criteria for the diagnosis of ADHF were considered to be rapid deterioration of symptoms and signs of HF, requiring emergency hospitalization of the patient and intensive care in the presence of objective signs of heart damage, which included systolic and/or diastolic dysfunction, left ventricular hypertrophy, left atrial dilation according to echocardiography, and increased levels of NT-proBNP.

The exclusion criteria were the following: the presence of acute coronary syndrome, end-stage renal disease, liver failure, known hepatitis (cirrhosis), non-cardiogenic edema, active cancer, lung damage due to exacerbation of obstructive lung disease, bronchial asthma, pneumonia, COVID-19 or COVID-19 contact patients, type 1 diabetes mellitus, immobilization, and severe cognitive deficit.

To assess the status of carbohydrate metabolism, we determined the level of glycated hemoglobin (HbA1c). The patients were divided into groups depending on the results obtained: at HbA1c values < 5.7%, the patients were included in the group without CMD, at HbA1c 5.7–6.4% – in the prediabetes group, at HbA1c ≥ 6.5% – in the type 2 DM group [5].

Upon admission and discharge, a standard physical examination and routine laboratory and instrumental studies were performed, which included lung ultrasound, determination of NT-proBNP, liver fibroscan with CAP, and bioelectrical impedance vector analysis (BIVA) of body composition (Fig. 1).

All patients signed an informed consent to participate in the study. The study was approved by the Ethics Committee at RUDN Medical Institute (Protocol No. 28 of 15.04.2021). The clinical and demographic characteristics of the patients are presented in Table 1.

Table 1

Clinical and demographic characteristics of patients included in the study, *n* = 280

Parameter	Value
Gender (male / female), *n* (%)	148 (53%) / 132 (47%)
Age, years, *M* ± *SD*	70.1 ± 10.8

Table 1 (continued)

Parameter	Value
Body mass index, kg / m^2, *M* ± *SD*	32.1 ± 5.7
HF functional class, NYHA, *n* (%) II III IV	 90 (32%) 123 (44%) 67 (24%)
Left ventricular ejection fraction, %, *M* ± *SD*	45.1 ± 11.9
Left ventricular ejection fraction, *n* (%): <40% 40–49% ≥50%	 84 (30%) 71 (25%) 125 (45%)
Arterial hypertension, *n* (%)	203 (72.5%)
History of stroke, *n* (%)	36 (13%)
Coronary heart disease, *n* (%)	167 (60%)
History of myocardial infarction, *n* (%)	106 (38%)
Atrial fibrillation / flutter, *n* (%)	185 (66%)
Chronic kidney disease, *n* (%)	73 (26%)
Chronic obstructive pulmonary disease (bronchial asthma), *n* (%)	47 (17%)

The composite congestion score (CCS) was used to assess clinical congestion. Orthopnea, swelling of the cervical veins, and peripheral edema were evaluated in points. Each clinical symptom and sign were evaluated at admission and at discharge. The total score ≥ 1 was considered as clinical congestion at admission and as residual congestion with clinical manifestations at discharge. The results on the assessment of the hydration status in patients hospitalized with ADHF, depending on the degree of CMD, were published earlier [5].

The level of NT-proBNP was determined by the enzyme-linked immunosorbent assay (ELISA) using the NT-proBNP-ELISA-BEST test systems and the A-9102 set of reagents (Vector-Best, Russia). Lung ultrasound was performed in 8 chest zones with the calculation of the sum of B-lines on the VIVID iq ultrasound system (GE Healthcare, USA). Indirect liver elastography (ILE) was performed using the FibroScan 502 Touch device (Echosens, France) according to the standard procedure. BIVA was performed using the Russian serial bioelectrical impedance analyzer ABC-01 Medass [5].

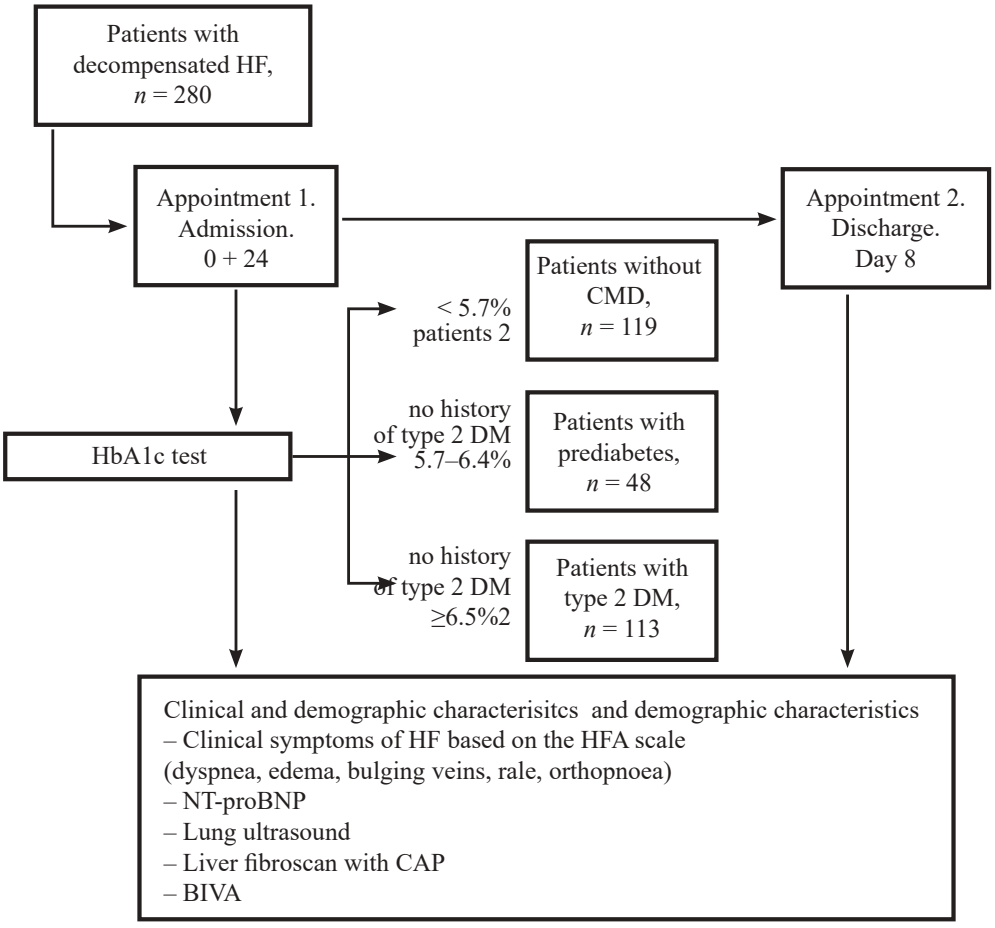

Fig. 1. Study design

If there was a deviation of at least one hepatic parameter from reference values, the patient was considered to have cardiohepatic syndrome. With an increase in markers of cytolysis syndrome (alanine transaminase (ALT), aspartate transaminase (AST)), the patient was diagnosed with hepatocellular cardiohepatic syndrome, with an increase in markers of cholestasis (alkaline phosphatase (ALP), total bilirubin) – with cholestatic cardiohepatic syndrome. A combined increase in markers of cytolysis and cholestasis and an increase in total bilirubin were designated as mixed cardiohepatic syndrome.

STATISTICAL ANALYSIS

Statistical data were processed using the MedCalc version 19.0 and IBM SPSS Statistics version 26.0 software tools. Quantitative variables were described as the arithmetic mean and the standard deviation of the mean (*M ± SD)* when the distribution was normal or as the median and the interquartile range (*Me; IQR*) in case of non-normal distribution. The nature of the data distribution was determined by the Kolmogorov – Smirnov test. With normal distribution of data, the statistical significance of the differences was assessed using the Student's *t*-test for related and unrelated samples. When the data distribution was not normal, the significance of the differences was analyzed using the Mann – Whitney test for unrelated samples and the Wilcoxon test for related samples. The differences were considered statistically significant at $p < 0.05$ (with account of the Bonferroni correction).

RESULTS

The frequency of CMDs in patients hospitalized with ADHF was 57.5% (*n* = 161), while prediabetes was detected in 17.1% (*n* = 48) and type 2 DM – in 40.4% (*n* = 113) of cases [**5**].

The incidence of steatosis in patients without CMDs was 42% (*n* = 50), while in patients with CMDs, it accounted for 69% (*n* = 111) of cases ($p < 0.001$). The incidence of fibrosis (F1–F4 > 5.8 kPa) was 64% (*n* = 77) in patients without CMDs and 80% (*n* = 129) in patients with CMDs ($p < 0.001$). The number of patients with a combination of steatosis / fibrosis among patients with ADHF and CMD was maximum and amounted to 59% (*n* = 95), which was 2 times greater than in the group of ADHF patients without CMDs – 30% (*n* = 36) (Fig. 2).

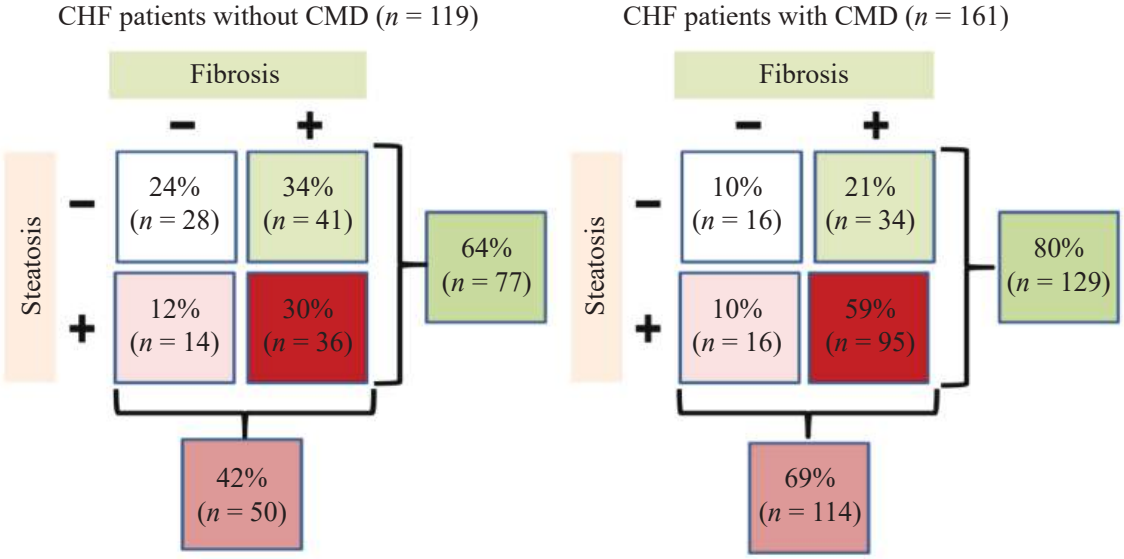

Fig. 2. The frequency of steatosis and fibrosis in patients with ADHF, depending on CMD, *n* = 280

The group of ADHF patients with CMDs and a combination of steatosis/fibrosis had the most severe course of the disease, characterized by high incidence of comorbid pathology, namely arterial hypertension, coronary heart disease, atrial fibrillation, and chronic kidney disease in the medical history, pronounced manifestations of metabolic syndrome, impaired renal and liver functions, manifestations of congestion, which were detected both in the clinical presentation and test results, the lowest values of the left ventricular ejection fraction and the 6-minute walk test (6MWT), and higher clinical rating scales (CRS).

The correlations were studied of CAP (Table 2) and liver density values (Table 3) with clinical (laboratory) parameters in patients with ADHF, depending on the degree of CMD. Significant positive correlations were found between CAP and liver enzymes (bilirubin, ALT, AST, lactate dehydrogenase (LDH)). Significant moderate positive correlations were determined between CAP and HSI, glycemic status parameters (Triglyceride – Glucose Index (TyG)), lipid metabolism parameters (total cholesterol, low-density lipoproteins (LDL), triglycerides (TG)), body mass index (BMI), waist circumference, and the frequency of coronary heart disease (CHD) in the medical history. Negative correlations were found between CAP and 6MWT and HDL in all groups of patients, regardless of the status of carbohydrate metabolism. At the same time, positive correlations of CAP with HbA1c and liver density were observed in patients with CMDs (prediabetes and type 2 DM) (Table 2).

Positive correlations were revealed between liver density index and CRS index, the level of NT-proBNP, and the content of creatinine. Negative correlations were found between liver density and glomerular filtration rate (GFR), LV ejection fraction (LVEF), and 6MWT, regardless of the status of carbohydrate metabolism (Table 3).

Table 2

Correlations of the CAP index with clinical and laboratory parameters in patients with ADHF depending on the degree of carbohydrate metabolism disorder, *r/p*

Parameter	ADHF without carbohydrate metabolism disorder, *n* = 119	ADHF and prediabetes, *n* = 48	ADHF and type 2 diabetes mellitus, *n* = 113
Clinical and demographic parameters			
BMI	0.21/ 0.02	0.40/ 0.004	0.34/ <0.001
Waist circumference	0.24/ 0.006	0.57/ <0.001	0.40/ <0.001
CHD	0.37/ <0.001	0.34/ 0.01	0.25/<0.001
6MWT	–0.23/ 0.009	–0.41/ 0.003	–0.37/ <0.001
Glycemic status			
Glucose	0.37/ <0.001	0.41/ 0.003	0.38/ <0.001
HbA1c	–	0.47/ <0.001	0.24/ 0.001
TyG	0.39/ <0.001	0.46/ <0.001	0.43/ <0.001
Lipid metabolism			
Cholesterol	0.27/ 0.002	0.42/ 0.002	0.28/ <0.001
LDL	0.30/ <0.001	0.41/ 0.003	0.31/ <0.001
HDL	–0.29/ <0.001	–0.34/ 0.01	–0.40/ <0.001
TG	0.32/ <0.001	0.45/ 0.001	0.30/ <0.001
Liver parameters			
Total bilirubin	0.59/ <0.001	0.62/ <0.001	0.54/ <0.001
ALT	0.57/ <0.001	0.56/ <0.001	0.74/ <0.001
AST	0.57/ <0.001	0.64/ <0.001	0.76/ <0.001
LDH	0.51/ <0.001	0.36/ =0.01	0.52/ <0.001
ALP	0.55/ <0.001	0.23/ <0.001	0.27/ <0.001
HSI index	0.31/ <0.001	0.33/ 0.02	0.37/ <0.001
Liver density	–	0.46/ <0.001	0.17/ 0.02

Table 3

Correlations of liver density with functional (laboratory) parameters in patients with ADHF depending on the degree of carbohydrate metabolism disorder, *r/p*

Parameter	ADHF without carbohydrate metabolism disorder, *n* = 119	ADHF and prediabetes, *n* = 48	ADHF and type 2 diabetes mellitus, *n* = 113
Functional status			
6MWT	–	–0.18/ 0.03	–0.18/ 0.04
CRS	0.22/ 0.01	0.28/ 0.005	0.26/ 0.005
Laboratory parameters			
LVEF	–0.29/ 0.001	–0.19/ 0.01	–0.40/ <0.001
NT-proBNP	0.31/ 0.001	0.26/ 0.04	0.32/ 0.002
Functional state of the kidneys			
Creatinine	0.29/ 0.001	0.45/ 0.001	0.35/ 0.001
GFR	–0.17/ 0.05	–0.21/ 0.05	–0.23/ 0.003

The frequency of cardiohepatic syndrome in patients was studied depending on the degree of CMD. The incidence of cardiohepatic syndrome in patients without CMDs was 61% (n = 72) and in patients with CMDs – 87% (n = 140) ($p < 0.001$). At the same time, the frequency of hepatocellular and cholestatic syndromes was comparable between the groups, and in ADHF patients with CMD, the frequency of the mixed type prevailed and was two times higher than in CHF patients without CMD (60% (n = 97) vs. 37% (n = 43), $p < 0.001$, respectively) (Fig. 3).

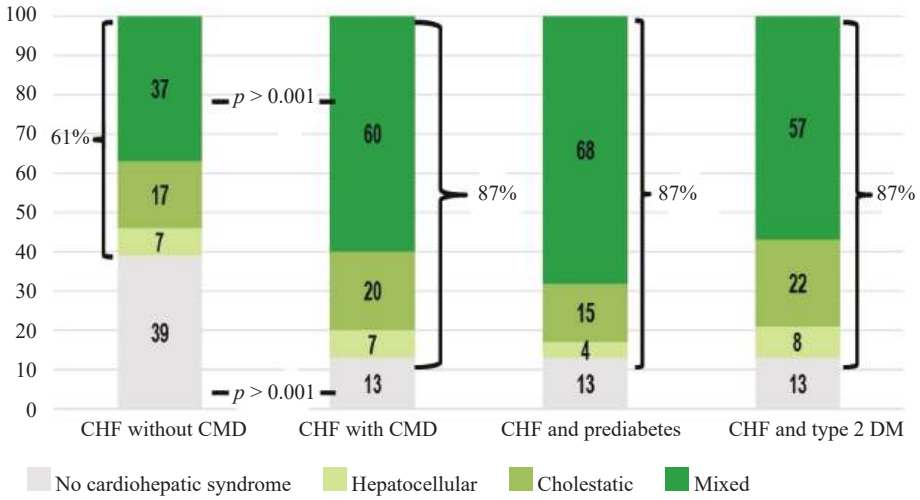

Fig. 3. The frequency of cardiohepatic syndromes in patients with ADHF depending on CMDs, n = 280

Significantly higher values of fasting glucose, total cholesterol, liver enzymes, liver density, and CAP were found in patients with ADHF and cardiohepatic syndromes, regardless of the degree of CMD.

DISCUSSION

Liver damage caused by a combined pathology, namely ADHF and CMD, was observed in a fairly large number of cases. Inflammation and fibrosis are the main factors determining the progression of liver damage. Fibrosis in patients with NAFLD is associated not only with the risk of morbidity and mortality from liver pathology, but also with the cardiovascular risk. It has been shown that an increase in liver enzymes can be observed with initial manifestations of HF caused by hemodynamic mechanisms [6]. Liver enzymes are associated with the class of HF, while the level of bilirubin according to the CHARM study [7] is the most important predictor of hospitalizations for ADHF and cardiovascular mortality. Venous congestion, decreased cardiac output, and arterial hypoxemia also play an important role in ischemic hepatitis [8]. At the same time, fibrosis has been shown to be the most critical factor in the progression of liver disease [9–12].

Given high prevalence of steatosis, its mainly benign course, and a lack of a clear association with changes in liver enzymes, it is important to use non-invasive methods to identify and quantify steatosis. CAP is a new parameter developed based on the ultrasonic properties of radiofrequency back-propagated signals receive via elastography to identify and measure steatosis. Based on CAP, the study established high frequency of steatosis (69 vs. 42%, $p < 0.001$), fibrosis (80 vs. 64%, $p < 0.001$), their combination (59 vs. 30%, $p < 0.001$), and cardiohepatic syndrome (87 vs. 61%, $p < 0.001$) in patients with ADHF and CMD, as opposed to ADHF patients without CMD, respectively. At the same time, the frequency of hepatocellular and cholestatic syndromes was comparable.

In a multicenter study involving 4,228 patients, more than 40% of patients hospitalized with acute heart failure had abnormal liver enzyme values. The multivariate analysis showed that only an increase in total bilirubin was independently associated with deterioration in clinical outcomes after both 30 and 180 days and may represent an important prognostic marker [13].

A retrospective study involving 1,032 patients with CHF of Caucasian origin demonstrated high incidence of liver dysfunction, which was characterized by a

predominant increase in cholestasis enzymes (total bilirubin, gamma-glutamyltransferase (GGT), and ALP). The frequency of elevated cholestasis enzymes was 19.2%, the frequency of elevated transaminases was 8.3% [14]. In our study, the incidence of cholestatic syndrome was 20% in patients with ADHF and CMD and 17% in ADHF patients without CMD. Hepatocellular syndrome and cardiohepatic syndrome were detected in 7 and 7% of cases, respectively.

Patients with ADHF and cardiohepatic syndrome, regardless of the degree of CMD, had higher values of BMI, waist circumference, glycemia, total cholesterol, liver enzymes, liver density, and CAP. In addition, patients with prediabetes and type 2 DM and cardiohepatic syndrome had significantly higher HSI values, a history of coronary heart disease and arterial hypertension, lower HDL values, as well as unreliably lower 6MWT results, which confirms the presence of more pronounced metabolic disorders in these patients.

The work by M.E. Statsenko et al. showed that patients with ischemic HF and type 2 DM had more pronounced structural and functional changes in the liver, manifested by high incidence of GGT, AST, and ALT, high HSI and liver fibrosis index compared to HF patients without type 2 DM [4].

In our work, the group of ADHF patients with CMD and a combination of steatosis/fibrosis was characterized by the most severe manifestations of congestion, lower values of LVEF, more pronounced functional disorders of the kidneys and liver, as well as glycemic and lipid profiles, which were detected both in the clinical presentation and test results, compared to all other groups.

Significant positive correlations of CAP with liver enzymes (bilirubin, ALT, AST, LDH) and negative correlations of CAP with 6MWT results were revealed in all groups of patients, regardless of the status of carbohydrate metabolism. At the same time, positive correlations were revealed between CAP and HbA1c and liver density in patients with CMD (prediabetes and type 2 DM). The literature also describes a strong correlation between CAP and the HOMA-IR insulin resistance index [15]. Our work also revealed the relationship between CAP and TyG index, regardless of the presence of CMD.

In our work, positive correlations were revealed between CAP and all parameters of lipid metabolism, regardless of the presence of CMD in patients with ADHF, which is consistent with the literature data [1, 3, 16]. In addition, positive correlations were noted between liver density and the values of CRS, NT-proBNP level, and creatinine; negative correlations were identified between liver density and GFR, LVEF, and 6MWT results, regardless of the status of carbohydrate metabolism. Inflammation and fibrosis are the main factors determining the progression of liver disease. Fibrosis in patients with NAFLD is associated not only with the risk of morbidity and mortality from liver pathology, but also with the cardiovascular risk.

CONCLUSION

Taking into account the presence of positive correlations between CAP and liver enzymes in all groups of CHF patients, regardless of the status of carbohydrate metabolism, on the one hand, and positive correlations between CAP and HbA1c and liver density in patients with ADHF and CMD, on the other hand, determining the level of liver enzymes and CAP and performing liver fibroscan testing will allow to identify a group of patients with a combination of steatosis/fibrosis and pronounced congestion.

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Kobalava Zh.D., Tolkacheva V. V. – conception and design. Tolkacheva V.V., Cabello Montoya F.E. – analysis of the data obtained, drafting of the manuscript. Diane M.L., Khutsishvili N.I., Misan I.A., Nazarov I.S., Smirnov I.P. – collection and processing of the material.

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