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Clinical and laboratory associations of liver fibrosis indexes in patients with decompensated Chronic Heart Failure II-IV Functional Classes

Aim — To study clinical and laboratory associations of hepatic fibrosis indexes in patients with decompensated NYHA functional class II–IV chronic heart failure (CHF).

Material and methods — The study included 128 patients admitted to the cardiological or therapeutic department of the University Clinical Hospital #4 at the I. M. Sechenov First Moscow State Medical University (Sechenov University) with symptoms of CHF associated with ischemic heart disease (IHD) and/or arterial hypertension (AH). All patients had signs of liver disease (liver enlargement on physical examination ± diffuse changes in hepatic tissue according to ultrasound data). Mean age was 70.59±10.71 years. Along with general clinical examination, severity of hepatic fibrosis was evaluated by calculated indexes, FIB-4, APRI, MELD–XI, and BARD. All calculations were based on laboratory data obtained within the first two days of hospitalization for decompensated CHF, at the onset of active therapy with intravenous diuretics. Statistical analyses were performed with the R programming language (3.6.1).

Results — In patients with NYHA FC II–IV CHF, the FIB-4 index significantly increased with the increase in NYHA FC ($p<0.05$). Also, the high liver density by most fibrosis indexes correlated with the probability of LV EF decrease to <40% (FIB-4: RR, 1.32 at 95% CI from 0.53 to 3.28, p=0.079; MELD–XI: RR, 1.62 at 95% CI from 1.19 to 2.20, p=0.004; BARD: median LV EF, 42.5% vs. 56%, p=0.019), and a tendency to heart rhythm disorders was observed (FIB-4: RR, 1.92 at 95% CI from 0.75 to 4.90, p=0.218; BARD: RR, 1.09 at 95% CI from 0.97 to 1.22, p=0.174; MELD–XI: RR, 1.34 at 95% CI from 0.94 to 1.90, p=0.101). Increases in liver fibrosis indexes correlated with other multiorgan disorders in CHF patients evident as a decrease in platelet count (FIB-4: $p<0.01$; APRI: p=0.045) and a tendency to a decrease in hemoglobin (FIB-4: 127 g/l vs. 137 g/l, p=0.249; APRI: 127 g/l vs. 136 g/l, p=0.749). Patients with a high liver density more frequently had cardiorenal syndrome diagnosed by reduced glomerular filtration rate (GFR) estimated by CKD-EPI to less than 60 ml/min/1.73 m^2 (FIB-4: $p<0.03$; MELD–XI: p=0.0001; BARD: p=0.005). In comparing liver fibrosis indexes in subgroups of CHF patients with preserved and reduced left ventricular ejection fraction (LV EF), significant differences were found only for MELD–XI (12.08 vs. 9.32, p=0.001).

Conclusions — For all studied indexes, correlations were observed with LV EF, decreases in hemoglobin, and incidence of heart rhythm disorders. For the BARD, FIB-4, and MELD–XI indexes, high results of calculations correlated with the presence of other predictors for unfavorable prognosis and disease severity (LV EF, NYHA FC, presence of type 2 diabetes mellitus, chronic kidney disease, and lower GFR). Liver fibrosis indexes are a new and promising but understudied instrument for evaluation of prognosis in CHF patients, which requires further study to determine most appropriate prognostic formulas.

Keywords — Heart failure; cardiohepatic syndrome; fibrosis index

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Chronic heart failure (CHF) is one of the most pressing problems of modern healthcare due to the inevitably growing spread of the disease around the world, unfavorable prognosis for patients, and high treatment costs [1]. CHF progression leads to damage of internal organs due to hypoperfusion and systemic congestion, i.e., CHF is a multiple organ pathology [2]. Today, much attention is given to

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the major issue of concomitant CHF and hepatic dysfunction, referred to as cardiohepatic syndrome (CHS) [3]. Similar to the cardiorenal syndrome, CHS can be categorized into five types [3, 4]. In patients with heart failure (HF) and without a history of liver disease, CHS can become evident due to development and progression of type 2 liver failure in the form of incremental substitution of hepatocytes with fibrous tissue in the setting of chronic congestion and hypoxia caused by hypoperfusion, and gradual worsening of dysfunction. In patients with acute CHF, CHS manifests as acute type 1 liver failure with rapidly increasing levels of liver enzymes and coagulopathy; acute liver failure with reduced levels of consciousness, i.e., hepatic encephalopathy, is less common [5].

However, this categorization is hypothetical. 75% of patients with CHF have at least one, and 55% have five or more non-cardiac co-morbidities with a hepatic component involved in the pathogenesis [6]. Type 2 diabetes mellitus (DM), obesity, anemia, and chronic kidney disease are the most common co-morbidities [7]. Medication used by patients to treat cardiovascular diseases, e.g., statins and anti-arrhythmic agents, and certain exogenous factors, e.g., low quality of life, use of alcohol and its surrogates, diet rich in easily digestible carbs and transfats, contribute to the development of liver damage [8]. Thus, the relationship between the heart and the liver in a typical comorbid patient with CHF is a vicious cycle.

Irrespective of its origin, liver damage always develops in the same sequence, called the «hepatic continuum:" steatosis, steatohepatitis, fibrosis, cirrhosis, hepatocellular carcinoma [8]. Every step of this continuum differs from the previous one by the degree of severity of histological alterations in liver tissue and is followed by gradual worsening of liver function [9].

Biopsy is the gold standard in liver disease diagnosis and a method of assessing the nature and degree of alterations in liver tissue. However, it is associated with some difficulties, i.e., high variability of the results due to the small volume of the examined tissue, risk of complications, and the subjective assessment of morphological changes. At present, liver elastometry is becoming more common than biopsy [10–12].

Diagnostic significance of indirect liver elastometry is actively studied in patients with liver damage of various origins. Solovyeva et al. (2018) showed in a prospective study of patients with acute decompensated CHF (ADCHF), that increased liver density confirmed by indirect liver elastometry was associated with the rate of re-hospitalizations, all-cause mortality, and worsening of long-term prognosis [13]. Patients with higher liver density had a longer history and greater severity of CHF, as well as a higher rate of co-morbidities [14, 15]. However, elastometry is limited in patients with ADCHF by the fact that the increased liver density can be caused not only by fibrosis but also by parenchymal congestion due to venous hyperemia in liver sinusoids, as well as by edema and/or ascites [16]. This method is also poorly informative in the early stages of fibrosis, in cases of severe obesity, local hepatic lesions, cholestatic or cytolytic syndrome, severe posture defects, and narrow intercostal spaces, as well as during systematic inflammatory reactions common for patients with CHF [17]. Increasingly researchers are focusing on a search for informative, non-invasive methods of screening for hepatic dysfunction, and on developing a score to permit indirect estimation of the severity of histological changes in liver tissue.

In addition to instrumental methods of histological and functional assessment of the liver, certain liver fibrosis indexes (LFIs) have been developed, based on clinical data or changes in indicators that directly or indirectly show fibrotic liver tissue damage. Over the past 10 years, many new LFIs have appeared, some of which are used in the clinical setting, predominantly in patients with viral liver diseases and non-alcoholic fatty liver disease. APRI, Fibrotest, Hepascore, FibroMeterNAFLD, FibroMeterV2G, and FIB-4 are the most well-known LDIs. BARD, Bonacini, Pohl-Score, BAAT score, Wai, GUCI, HALT-C, MELD, and its modifications (MELD–XI, MELD-Na), ALBI are less common indices. [18, 19].

Numerous clinical studies showed that there are statistically significant correlations of the LFIs with stages of fibrosis, as diagnosed by morphological criteria [19]. However, a new concept for interpreting laboratory and clinical tests for liver fibrosis is being studied: test results do not only serve as surrogate markers reflecting the histological stage of fibrosis but also serve as a tool used to assess the prognosis and to choose further management. Non-invasive fibrosis tests are of high predictive significance in terms of mortality resulting from various extrahepatic disorders [17, 19], and thus serving as potential predictors of adverse outcomes in patients with CHF. However, their role in the estimation of severity and prognosis in patients with cardiac diseases is not yet sufficiently identified nor well known.

We have analyzed the literature describing changes of LFIs in different pathologies to find more accessible and straightforward, but sensitive and specific, formulas to be used by any specialist as screening methods for the assessment of liver damage. The four most straightforward and most accessible LFIs were selected: APRI, BARD, FIB-4, MELD–XI, for which only indirect serum markers of liver damage are used. Thus, the objective of this study was to investigate clinical laboratory associations of LFIs in patients with New York Heart Association (NYHA) functional class (FC) II–IV CHF.

Material and Methods

The study included 128 patients with CHF and coronary artery disease and/or hypertensive heart disease who were admitted for decompensated CHF requiring intravenous administration of diuretics in the Cardiology or Therapeutics Departments of University Clinical Hospital No. 4, I. M Sechenov First Moscow State Medical University. The study population included 88 female and 40 male patients, age 40 to 90 years (mean age 71.5 ± 10.7 years). The inclusion criteria were FC II–IV CHF for at least six months, age more than 18 years, and signed informed consent to participate in the study. All patients had percussion and palpation signs of hepatomegaly and also liver enlargement and diffuse alterations according to ultrasonography. The exclusion criteria were: 1) primary liver pathology (viral, toxic, or any other known origin, including alcohol abuse), accumulation diseases (hemochromatosis, Wilson-Konovalov disease, etc.) and biliary tract diseases; 2) malignancies including lymphatic and myeloproliferative disorders; 3) severe or uncontrolled active acute or chronic infection; 4) kidney failure requiring hemodialysis.

All patients underwent standard examinations including complete blood counts and biochemical analyses, urinalyses, coagulation profile, electrocardiography, abdominal and kidney ultrasonography, chest and X-ray examinations, echocardiography, and 24-hour Holter monitoring to establish the presence and nature of arrhythmias. Clinical characteristics of patients are provided in Table 1

In addition to the general clinical examination, for all patients the severity of hepatic fibrosis was assessed according to the LFIs: APRI, BARD, FIB-4, MELD–XI. Due to an uncertain role of LFIs in patients with CHF, we suggest using the following terms to simplify understanding and terminology of results: «high risk of fibrosis,» «low risk of fibrosis,» and «gray zone,» if applicable.

All calculations were made based on the laboratory findings received during the first two days of hospitalization and before the beginning of active diuretic therapy with parenteral agents. Taking into account the possibility of iatrogenic influences on LFIs, we analyzed the pre-hospital treatment of patients (Table 2).

Most patients took medicines affecting the activity of the renin-angiotensin-aldosterone system,

Table 1. Clinical characteristics of the study subjects

Parameter	Value
Age, years	71.5±10.7
Sex, n (%)	female 88 (69) male 40 (31)
BMI, kg/m^2	31.7 [26.8; 36.4]
GFR*,ml/min/1.73 m^2	55.3±16.8
GFR (CKD-EPI), <60 ml/min/1,73 м^2, n (%)	Yes: 92 (71.9) No: 36 (28.1)
LVEF, n %	54.5 [40.0; 63.8]
	HFpEF 63 (49.2)** HFmrEF 32 (25) HFrEF 33 (25.8)
NYHA FC, n (%) • II • III • IV	 24 (19) 74 (58) 30 (23)
Type 2 DM, n (%) Impaired glucose tolerance, n (%)	44 (34) 4 (3)
Anemia***, n (%)	Yes: 37 (28.9) No: 91 (71.1)
Rhythm disorders****, n (%)	Yes: 80 (62.5) No: 48 (37.5)

*GFR, rate of glomerular filtration calculated using the CKD-EPI formula. ** Following the clinical guidelines of the Russian Society of Heart Failure Specialists (OSSN), Russian Society of Cardiology (RKO), and Russian Scientific Medical Society of Primary Care Physicians (RNMOT). Heart failure: chronic (CHF) and acute decompensated (ADCHF). Diagnosis, prevention, treatment, 2019. *** Anemia was determined under the WHO criteria: Hb<130 g/l in males and <120 g/L in females. **** Rhythm disorders (atrial fibrillation or flutter, high-grade ventricular extrasystoles, sick sinus syndrome), diagnosed by 24-hour Holter monitoring. BMI, body mass index; LVEF, left ventricular ejection fraction; HFpEF, heart failure with preserved left ventricular ejection fraction; HFmrEF, heart failure with mid-range left ventricular ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; NYHA FC, functional class according to the New York Heart Association (NYHA) classification, type 2 DM, type 2 diabetes mellitus.

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Table 2. Pre-hospital treatment of patients

Group of drugs	Number of patients treated, n (%)
Angiotensin-converting enzyme inhibitors	111 (86.7)
Angiotensin II receptor blockers	10 (7.8)
Beta-blockers	104 (81.3)
Mineralocorticoid receptor antagonists	77 (60.2)
Loop diuretics	98 (76.5)
Thiazide and thiazide-like diuretics	11 (8.6)
Cardiac glycosides (digoxin)	30 (23.4)
Statins	44 (34.4)
Amiodarone	16 (12.5)
Nitrates	26 (20.3)
Antiplatelet drugs (aspirin)	49 (38.3)
Indirect oral anticoagulants	38 (29.6)
Calcium channel blockers	19 (14.8)

i.e., angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, mineralocorticoid receptor antagonists, and diuretics. There is no evidence of adverse effects on liver function of these medicines, or of beta-blockers, nitrates, and other pharmaceutical agents used in the therapy of CHF [20]. Only statins and amiodarone are known to have potential hepatotoxic effects. Therefore they were considered in the analysis of findings.

LFIs were calculated using the following formulas:

$$\text{APRI (aspartate aminotransferase to platelet ratio index)} = \text{AST (aspartate aminotransferase)} \times 100 / (\text{[AST upper limit]} \times n_{platelets}\ [109/l])\ [21].$$

APRI >1.0 corresponded to high risk of severe fibrosis; and APRI <0.5 to the low risk of severe fibrosis.

BARD is the sum of 3 indicators:

AST / ALT (alanine transaminase) ratio>0.8= 2 points; BMI (body mass index) ≥28 kg / m^2= 1 point; the presence of type II diabetes mellitus=1 point.

Total score 0–1 is likely to indicate the absence of a high risk of severe liver fibrosis, and 2–4 points correspond to a high risk of severe fibrosis [22].

$$\text{FIB-4 (Fibrosis-4)} = \text{age (years)} \times \text{AST} / [(n_{platelets}\ (109\ l) \times \sqrt{\text{[ALT]}})].$$

FIB-4 <1.45 indicates the absence of a high risk of fibrosis, and values >3.25 are likely to indicate the presence of severe fibrosis [23].

$$\text{MELD–XI (Model for End-Stage Liver Disease)} = 5.11\ (\ln\ [\text{total bilirubin}],\ \mu\text{mol}/l) + 11.76\ (\ln\ [\text{creatinine}],\ \mu\text{mol}/l) + 9.44\ [24].$$

MELD–XI >10.4 shows a high risk of liver fibrosis.

Statistical analyses of data were carried out using the R programming language (3.6.1). The Shapiro-Wilk test was used to verify the normality of continuous variables. The median and quartiles were determined for quantitative and continuous variables. The categorical data were expressed as significance, absolute number, and the percentage in the group. Significance of differences was verified by Fisher's or Kruskal – Wallis tests. If more than two groups with normal distributions were compared, ANOVA was used. The correlation coefficient was determined by Spearman's method. The intergroup differences were considered statistically significant at $p<0.05$.

Results and Discussion

Higher LFIs were observed in patients with NYHA FC II–IV CHF as the FC increased (Table 3). Moreover, there was a clear correlation between high risk of severe liver fibrosis as shown by several LFIs and reduced left ventricular ejection fraction (LVEF) <40%. The odds ratio [OR] of LVEF <40% in the FIB-4 high- and low-risk groups was 1.32 with 95% confidence interval (CI) 0.53–3.28, p=0.079. For MELD–XI the OR was 1.62 with 95% CI 1.19–2.20; p=0.004. For BARD the median LVEF was 42.5% versus 56% in the groups of high and low risk of severe fibrosis, respectively, p=0.019. OR of the presence of serious heart rhythm disturbances in the groups of high and low risks of severe fibrosis were, respectively: APRI, OR was 2.4 with 95% CI 0.28–20.85, p=0.65; FIB-4, OR was 1.92 with 95% CI 0.75–4.90, p=0.218; BARD, OR was 1.09 with 95% CI 0.97–1.22, p=0.174).

APRI

APRI >1 showed a high probability of severe fibrosis only in 5 (3.9%) patients. 25 (19.5%) patients were in a «gray zone.» The other 98 (76.6%) patients had APRI<0.5, which placed them in the

Table 3. The values of liver fibrosis indexes in different NYHA FCs

Fibrosis index	NYHA FC II	NYHA FC III	$p_{FCII-FCIII}$	NYHA FC IV	$p_{FCIII-FCIV}$
APRI (median, [Q1; Q3])	0.32 [0.25; 0.46]	0.39 [0.29; 0.50]	> 0.05	0.32 [0.27; 0.45]	> 0.05
BARD (n of patients; percentage)					
0 points	0	2; 0.03	> 0.05	0	> 0.05
1 point	3; 0.13	4; 0.05		1; 0.03	
2 points	4; 0.17	22; 0.29		9; 0.3	
3 points	8; 0.35	30; 0.4		9; 0.3	
4 points	8; 0.35	17; 0.23		11; 0.37	
MELD-XI (median, [Q1; Q3])	8.83 [7.22; 11.74]	10.92 [8.55; 14.09]	>0.05	11.45 [7.32; 13.35]	>0.05

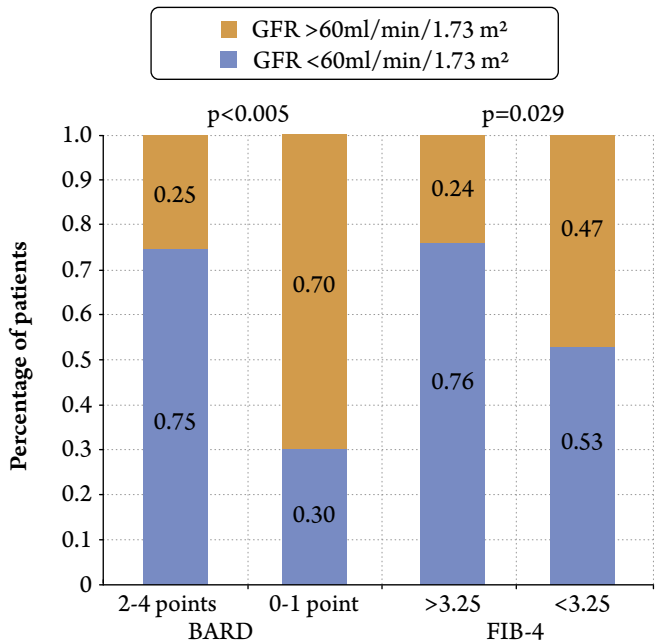
NYHA FC, functional class according to the New York Heart Association (NYHA) classification, APRI, aspartate aminotranseferase to platelet ratio index, FIB-4, Fibrosis-4, BARD – BMI (Body Mass Index) ≥28=1 point, AAR (AST/ALT ratio) ≥0.8=2 points, DM (diabetes mellitus)=1 point, MELD-XI, Model for End-Stage Liver Disease.

group with low risk of severe liver fibrosis. Notably, an increase in APRI was associated with a decrease in LVEF (median: 57%; 45%; 42%), though differences were insignificant due to the small number of patients in the subgroups. The increase in APRI correlated not only with the degree of intracardiac hemodynamic disturbances but also with other disorders, including hematic homeostasis, particularly in the case of decreased levels of immunoglobulin to 127 [126;157] g/l in the high-risk group versus 136 [120; 147] g/l in the low-risk and gray zone groups (p>0.05). There were no statically significant correlations between APRI and kidney dysfunctions in terms of a decrease in the GFR levels at admission (p>0.05).

BARD

High risk of severe fibrosis determined by the increase in BARD ≥2 was identified in 118 (92.2%) patients, which is significantly higher than for the APRI index. The percentage of patients at low risk of liver fibrosis, according to BARD, was only 7.8%. The large number of patients with high risk of severe fibrosis, according to BARD, was related the significant percentage of patients with type 2 DM and BMI>28 kg/m^2. This corresponds to 2 points on this scale and puts these patients in the group of high-risk of liver fibrosis. Thus, as expected, all patients showing a high risk of severe fibrosis (2–4 points) most often had type 2 DM (p=0.018). Moreover, a high BARD score was associated with reduced glomerular filtration rate (GFR according to CKD-EPI <60 ml/min/1.73 m^2) (Figure 2). The OR was 1.20 with 95% CI 1.02–1.42 (p=0.005). More severe kidney dysfunction in patients with high risk of liver fibrosis may be attributed to specific clinical characteristics of this subgroup, in particular, a high prevalence of patients with type 2 DM and diabetic nephropathy. Notably, LVEF in the group with a high

Figure 1. The percentage of patients with reduced GFR (CKD-EPI)<60ml/min/1.73m2 in patients exposed to high and low risk of liver fibrosis as measured by BARD and FIB-4



risk of liver fibrosis was higher than that in the group of low risk of liver fibrosis (p=0.019) (Figure 2), which may be related to the compromised myocardial relaxation and HF with preserved EF (HFpEF) typical of patients with DM [23].

FIB-4

FIB-4>3.25, corresponding to a high risk of severe liver fibrosis, was detected in 21 (17.8%) patients (Table 4). Table 4 shows that FIB-4, like APRI, has a gray zone, i.e., values making it impossible to describe with reliable probability the presence or absence of severe liver fibrosis. FIB-4 was initially developed for patients with viral liver diseases and HIV, 1/3 of whom usually are in the gray zone [25]. However, more than 55% of the patients were in the gray zone in our study, which might be associated with the

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Table 4. FIB-4 scores in patients with FC II-IV CHF

FIB-4 values	Number of patients, n (%)	Interpretation of results
<1.45	32 (25)	Low probability of severe fibrosis
1.45-3.25	77 (57.2)	Gray zone
>3.25	21 (17.8)	High probability of severe fibrosis

Figure 2. Left ventricular ejection fraction in patients exposed to high and low risks of severe liver fibrosis

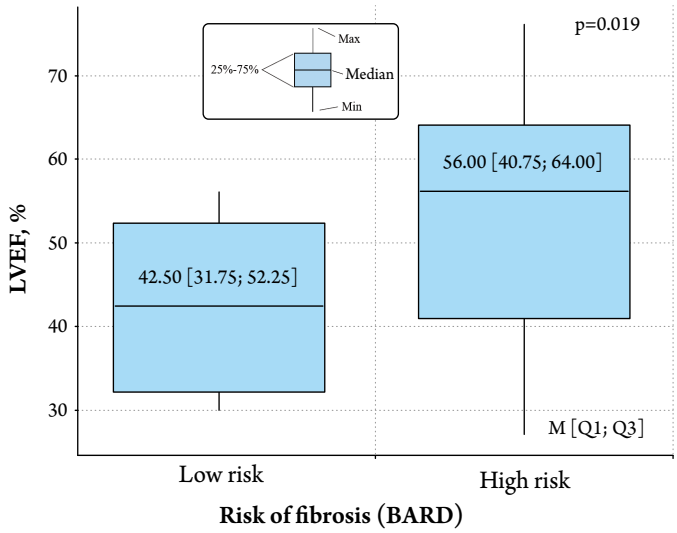
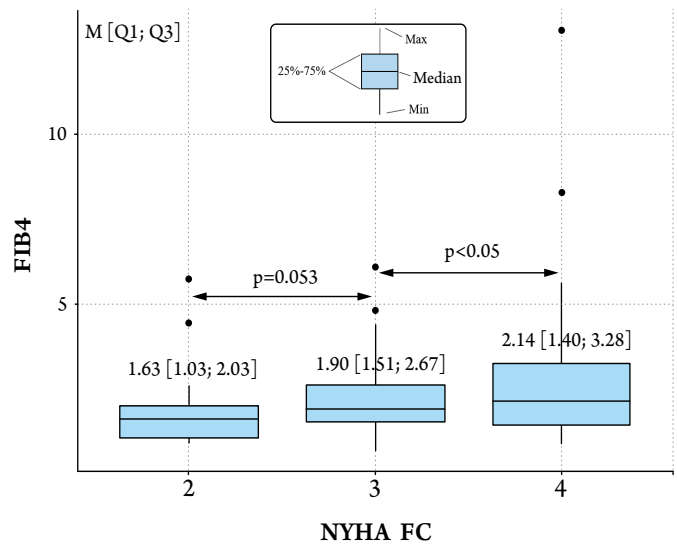


Figure 3. FIB-4 scores in patients with NYHA FC II-IV CHF



pathogenesis of the cardiohepatic syndrome, and, in particular, a significant contribution of hemodynamic factors.

Patients with CHF and a higher NYHA FC tended to have a higher FIB-4 fibrosis index ($p<0.05$) (Figure 3). Moreover, there were more patients with NYHA FC III–IV (OR 2.78, 95% CI 0.75–10.27; $p=0.192$) among those who had a high risk of fibrosis than those who did not. These patients also tended to have a higher risk of serious heart rhythm disturbances (OR 1.92 with 95% CI 0.75–4.90, $p=0.218$). LVEF did not differ between the groups. Patients with FIB-4 >3.25 also had more evident signs of multiple organ disorders, such as lower hemoglobin levels (127 [120;143] g/l and 137 [120;148] g/l, $p=0.249$). Reduced GFR (according to CKD-EPI) <60ml/min/1.73 m^2 was more common in patients with high risk of severe liver fibrosis and cardiohepatic syndrome (OR 1.25 with 95% CI 0.50–3.16; $p=0.029$) (Figure 2).

It should be mentioned once more that most patients (75, 58.6%) in our study had gray-zone FBI-4 values. Further study is required, as this index was not a reliable tool for assessing the risk of liver fibrosis in patients with CHF. Our findings differ from those of Sato et al., who showed in a group of 1058 patients with CHF, the presence of statistically significant correlations of FIB-4, not only with the severity of clinical laboratory alterations (severity of CHF, levels of N-terminal pro-brain natriuretic peptide and GFR), but also with markers of liver fibrosis (type IV collagen, type III procollagen peptide, hyaluronic acid) [26]. Higher values of FIB-4 were associated with both risk of higher all-cause-mortality and a higher risk of CHF incidence [27].

MELD–XI

MELD–XI is quite easy to calculate, yet potentially significant. Its formula includes creatinine and total serum bilirubin, which makes it possible to assess liver and kidney dysfunction/failure. This is relevant for the interpretation of CHF as a multi-organ syndrome. MELD–XI is a modification of the MELD score that excludes the international normalized ratio. This allows using it with high predictive value for patients taking anticoagulant agents, including for the treatment of non-valvular atrial fibrillation. Previous studies revealed the presence of a negative inverse relationship between this index and survival rate of patients with liver cirrhosis and of those with ADCHF [25–27]. An increase of its value >11 for patients with liver cirrhosis of viral origin is a sign of decompensation and a predictor of poor prognosis. At the same time, a value >10.4 for patients with CHF is associated with higher levels of N-terminal

Table 5. Evaluation of the treatment effect on LFI in patients with CHF

Liver fibrosis index	Total per group, n=128	Statins subgroup, n= 44	p value	Amiodarone subgroup, n= 16	p value
APRI	0.35 [0.28; 0.47]	0.35 [0.28; 0.50]	>0.05	0.33 [0.26; 0.47]	>0.05
FIB-4	1.88 [1.46; 2.75]	1.84 [1.49; 2.63]	>0.05	1.38 [1.01; 1.63]	>0.05
MELD-XI	10.69 [7.88; 13.52]	10.71 [8.27; 14.16]	>0.05	12.4 [8.02; 15.35]	>0.05

CHF, chronic heart failure; LFI, liver fibrosis indexes,
APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4; MELD-XI, Model For End-Stage Liver Disease.

pro-brain natriuretic peptide (NT-proBNP), systolic hypotension, low LVEF, and increased risk of death within six months [26, 27].

In our study, MELD–XI >10.4, corresponding to high risk of severe fibrosis and poor prognosis, was found in 71 (55.5%) patients, and MELD–XI <10.4 was found in 57 (44.5%) patients. There was a tendency for higher MELD–XI with increased FC (p=0.195). Moreover, there was a correlation between higher MELD–XI and the severity of CHF. MELD–XI >10.4 was associated with a decrease in LVEF to 44% [37; 61] [51; 66] in patients with low risk of fibrosis (p=0.001), versus 61%. Patients with clinical manifestations of more severe CHF prevailed among patients with MELD–XI >10.4. Most patients had NYHA FC III–IV (p=0.023), LVEF <40% (p=0.004), and a higher prevalence of serious rhythm disturbances (OR 1.34, 95% CI 0.94–1.90; p=0.101).

The MELD–XI calculation formula includes total bilirubin and creatinine, which is why the significant differences between the groups of MELD–XI>10.4 and MELD–XI <10.4 were associated with GFR (p<0.001) and with its rate of decrease<60 ml/min/1.73 m² (p<0.001) (Figure 4). In addition to the decrease in GFR, patients with CHF and MELD–XI >10.4 had also increased blood urea nitrogen, up to 9.1 [6.95; 11.45] versus 6.9 [5.10; 8.62] mmol/l (p=0.012), which is indicative of a relationship between liver and kidney dysfunction [28].

Thus, MELD–XI is an integral indicator necessary for an adequate evaluation of the general condition of patients with CHF and multiple-organ disorders. MELD–XI has been used in real-world cardiological practice for the longest time and has proven to be sustainable, as is supported by our study. For example, several international studies showed that this index significantly correlated with the risk of cardiovascular complications, in-hospital mortality, and it predicted

Figure 4. GFR in patients with FC II-IV CHF exposed to low and high risks (MELD-XI <10.4 and >10.4, respectively)

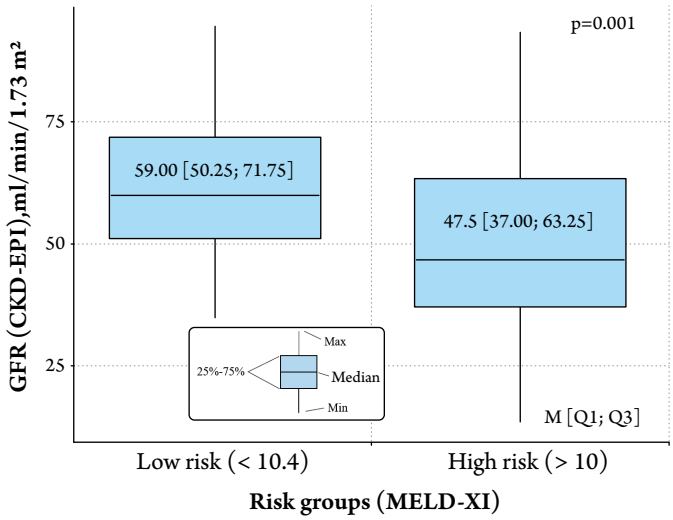
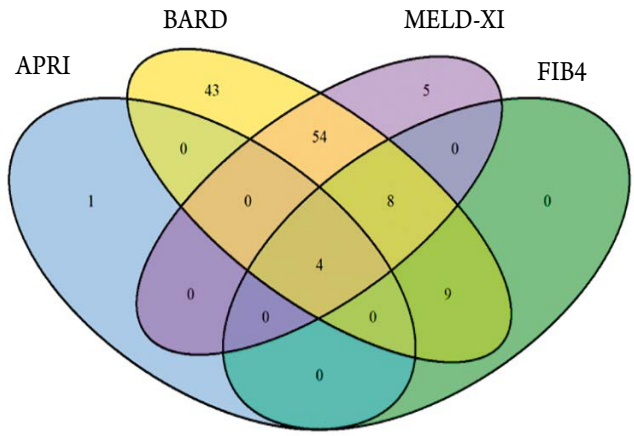


Figure 5. Venn diagram the number of patients with a positive set of scores



all-cause deaths in patients with ADHF [29,30]. This allowed the authors to suggest using MELD–XI as a risk stratification score for patients with HF [26, 30, 31].

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The comparative analysis revealed no statistically significant differences of any LFI in subgroups of patients using medicines with hepatotoxic effect, i.e., statins and amiodarone, and those who did not receive such therapy (Table 5). There were only tendencies (p>0.05).toward an increase in FBI-4 for patients who received statins or in MELD–XI for those who took amiodarone.

The calculations of LFIs for each patient included in the study are based on the premise of a required, complex evaluation of multi-organ dysfunction in CHF. Only four patients were had high risk of liver fibrosis as shown by all four scores (Figure 5). All of these patients had type 2 DM, had signs of NYHA FC III–IV CHF with reduced LVEF <40%, and biochemical alterations in blood typical of cardiohepaic syndrome, i.e., an increase in one or more measurements of AST, ALT, gamma-glutamyl transpeptidase, and total bilirubin. Three patients had serious heart rhythm disturbances.

Conclusion

Our study found associations between traditional markers of poor prognosis in patients with CHF and LFIs, such as APRI, BARD, FIB-4, and MELD–XI. An apparent increase in the probability of liver fibrosis was particularly shown by FBI-4 and MELD–XI with higher CHF FC. On the contrary, the higher values the BARD LFI occurred in patients with preserved LV function, owing to the high prevalence of obesity and diabetes in this group. All LFIs found highly significant relationships between heart rhythm disturbances identified by 24-hour Holter monitoring and extracardiac multiple organ disturbances.

A relationship between all LFIs and changes in hematologic parameters was established, in particular for decreased levels of immunoglobulin and platelets. The mechanisms of the identified disorders, e.g., the role of liver dysfunction in the pathogenesis of anemia in patients with CHF, should be studied further.

Reduced GFRs were mostly found in patients exposed to high risk of severe fibrosis, as shown by the BARD, FIB-4, and MELD–XI scores. Thus, the significance of interorgan interactions owing to both general neurohumoral regulatory factors and generalized microcirculation failures in patients with CHF is underscored.

Given these points, LFIs are a new and prospective tool, though rather understudied, and can be used to objectify the severity of disease and to estimate the prognosis in patients with decompensated CHF. LFIs require further investigation to determine the most appropriate formulas.

Limitations of the study

Most of the patients were female. The LFI was calculated at the beginning of active diuretic therapy with parenteral agents without the evaluation of liver density over time. LFIs are not yet officially validated to evaluate liver density in CHF. It is possible that other threshold values, which differ from the values characteristic of liver diseases, should be evaluated in order to produce more accurate and reliable results. We were not able to compare the LFI values with findings of the elastometry examinations. The low number of patients in the subgroups affected the level of significance. More extensive studies should be carried out even though most of the revealed tendencies are generally consistent with other large-scale studies.

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