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FEATURES OF LIPID METABOLISM AND LIVER STEATOSIS INDICES IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE WITH COMORBID COMMUNITY-ACQUIRED PNEUMONIA

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Aim of the study *– to determine the features of lipid metabolism, biochemical markers of liver injury, and the degree of hepatic steatosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) with obesity in the presence of comorbid community-acquired pneumonia (CAP) associated with coronavirus disease.*

Material and methods. *A total of 125 patients with MASLD and class I obesity were examined: 90 patients with metabolic dysfunction-associated steatohepatitis (MASH) and comorbid CAP, 35 patients with MASH without pneumonia, and 35 patients with moderate CAP. The assessment included lipid profile parameters, atherogenic index, activities of cytolytic and cholestatic enzymes, protein-synthesizing function of the liver, ultrasonographic characteristics, hepatic steatosis indices (HSI, LFS), and the NAFLD Fibrosis Score.*

Results. *Patients with MASLD and CAP exhibited the most pronounced dyslipidemia, including increased levels of total lipids, cholesterol, triglycerides, LDL-C, and elevated atherogenic index, along with a reduction in HDL-C. Comorbidity with CAP was associated with a significant intensification of cytolysis, cholestasis, mesenchymal inflammation, decreased protein synthesis, and more pronounced hepatomegaly. The HSI, LFS, and NAFLD FS indices indicated a higher degree of hepatic steatosis and fibrosis in the MASLD+CAP group compared to isolated MASLD.*

Conclusions. *Community-acquired pneumonia is associated with a substantial enhancement of lipid distress syndrome, progression of hepatic steatosis and fibrosis, and deterioration of liver functional state in patients with MASLD and obesity. The comorbid course forms an unfavorable metabolic profile and requires therapeutic strategies that consider liver injury.*

ОСОБЛИВОСТІ ЛІПІДНОГО МЕТАБОЛІЗМУ ТА ІНДЕКСІВ СТЕАТОЗУ ПЕЧІНКИ У ХВОРИХ НА СТЕАТОТИЧНУ ХВОРОБУ ПЕЧІНКИ, АСОЦІЙОВАНУ З МЕТАБОЛІЧНОЮ ДИСФУНКЦІЄЮ, ЗА КОМОРБІДНОСТІ З НЕГОСПІТАЛЬНОЮ ПНЕВМОНІЄЮ

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Ключові слова: *метаболічно-асоційована стеатотична хвороба печінки, стеатогепатит, негоспітальна пневмонія, COVID-19, дисліпідемія, стеатоз, фіброз печінки.*

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Мета роботи *– встановити особливості ліпідного метаболізму, системи біохімічних маркерів пошкодження печінки та ступеня стеатозу у хворих на метаболічно-асоційовану стеатотичну хворобу печінки (СХП МД) з ожирінням, за коморбідності з негоспітальною пневмонією, асоційованою з коронавірусною хворобою.*

Матеріал і методи. *Обстежено 125 пацієнтів із СХП МД та ожирінням І ступеня: 90 пацієнтів із МА-СГ та коморбідною НГП, 35 пацієнтів із МА-СГ без пневмонії та 35 хворих на НГП середньої тяжкості. Оцінювали показники ліпідограми, індекс атерогенності, активність цитолітичних і холестатичних ферментів, білоксинтезувальну функцію печінки, ультрасонографічні характеристики, індекси стеатозу (HSI, LFS) та NAFLD Fibrosis Score.*

Результати. *У хворих на СХП МД із НГП встановлено максимальну інтенсивність дисліпідемії: зростання рівнів загальних ліпідів, холестеролу, триацилгліцеролів, ХС ЛПНЩ і підвищення індексу атерогенності разом зі зниженням ХС ЛПВЩ. Коморбідність із НГП супроводжувалася суттєвим посиленням цитолізу, холестазу,*

мезенхімального запалення, зниженням білоксинтезу та більш вираженою гепатомегалією. Індекси HSI, LFS та NAFLD FS продемонстрували вищий ступінь стеатозу та фіброзу печінки у групі СХП МД із НГП порівняно з ізольованим перебігом.

Висновки. *Негоспітальна пневмонія асоціюється з істотним посиленням ліпідного дистрес-синдрому, прогресуванням стеатозу й фіброзу печінки та поглибленням порушень функціонального стану печінки у хворих на СХП МД з ожирінням. Коморбідний перебіг формує несприятливий метаболічний профіль і потребує корекції з урахуванням ураження печінки.*

The relevance of studying lipid metabolism in the context of previously experienced community-acquired pneumonia associated with coronavirus disease (COVID-19) remains exceptionally high [1, 2, 4]. This is due to the ability of SARS-CoV-2 to affect lipid metabolism, trigger lipid distress syndrome, induce obesity, accelerate the early development of atherosclerosis, and contribute to inflammatory damage of the liver and pancreas. It may also promote the progression of metabolic dysfunction–associated steatotic liver disease (MASLD) [3], liver fibrosis, and its transformation into liver cirrhosis.

The issue of hyperlipidemia and dyslipidemia is especially pressing in patients with MASLD that develops alongside excess body weight and obesity, driven by a cascade of mutually aggravating mechanisms characteristic of insulin resistance (IR). Despite the fact that researchers around the world are actively studying the progression of MASLD, the prevalence of this condition and its complications continues to rise. In industrially developed countries, 25–40% of the population is affected by MASLD [5]. According to the NHANES III (Third National Health and Nutritional Examination Survey), the prevalence of MASLD reaches up to 16% in individuals with normal body weight and up to 76% in patients with obesity.

MASLD is a dynamic condition that may regress to isolated steatosis with a relatively stable level of activity, or it may progress toward advancing fibrosis that ultimately results in liver cirrhosis (F4 fibrosis stage). Steatohepatitis (MASH) develops in about 25% of patients with MASLD, and among them, 25% subsequently develop liver cirrhosis [6-8].

At present, the pathogenic mechanisms underlying the mutual aggravation of MASLD and community-acquired pneumonia associated with COVID-19 remain unclear. In particular, there is insufficient understanding of the functional state and markers of liver injury in relation to blood lipid profile parameters, the atherogenic index, and indicators of hepatic steatosis in patients with MASLD who have obesity and pneumonia [9-11].

The aim of the study was to determine the characteristics of liver functional status and markers of liver injury in relation to blood lipid profile components, the atherogenic index, and hepatic steatosis indices in patients with metabolic dysfunction–associated steatotic liver disease (MASLD) and obesity in the presence of comorbid community-acquired pneumonia (CAP) associated with coronavirus disease.

Materials and Methods. A total of 125 patients with MASLD and class I obesity were examined: 90 patients with MASH and class I obesity with comorbid moderate community-acquired pneumonia (Group 1), and 35 patients with MASH and class I obesity (Group 2). The control group consisted of 35 patients with moderate community-acquired pneumonia (Group 3). To assess the dependence of MASLD progression on the presence of pneumonia, the groups were randomized by age and degree of obesity. The mean age of the patients was 53.8 ± 3.34 years.

The diagnosis of MASLD was established according to the unified clinical protocol approved by Order No. 826 of the Ministry of Health of Ukraine (06.11.2014) (“Non-alcoholic fatty liver disease”), based on the exclusion of chronic diffuse liver diseases of viral, hereditary, autoimmune, or drug-induced origin as causes of cytolytic or cholestatic syndromes, as well as according to ultrasonography with shear-wave elastography and the SteatoTest (Synevo). Diagnosis and treatment of CAP were performed in accordance with the “Community-Acquired Pneumonia in Adults: Etiology, Pathogenesis, Classification, Diagnosis, Antimicrobial Therapy, and Prevention” evidence-based clinical guideline (2019).

All patients underwent anthropometric assessment. The waist-to-hip ratio (WHR) was used as an additional criterion to characterize the pattern of adipose tissue distribution and was calculated using the formula: WHR = waist circumference / hip circumference. Abdominal obesity was diagnosed at WHR values > 0.9 in men and > 0.85 in women.

Upon hospital admission, liver functional status was assessed using the standard panel of enzyme activities, markers of pigment and nitrogen metabolism, proteinogram, lipid profile, and calculation of the De Ritis ratio. Lipid metabolism parameters—total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), and triacylglycerols—were measured using standard diagnostic kits manufactured by “Danush Ltd” (Lviv). The atherogenic index (AI) was calculated according to formula (1)

$$AI = (TC - HDL\text{-}C) / HDL\text{-}C \quad (1),$$

where TC is total cholesterol in blood, and HDL-C is high-density lipoprotein cholesterol.

The hepatic steatosis index (HSI) was calculated according to formula (2):

$$HSI = 8 \times ALT/AST + BMI + 2 \text{ (if diabetes is present)} + 2 \text{ (if female)} \quad (2),$$

A value of HSI > 36 was considered indicative of hepatic steatosis.

The liver fat score (LFS) was calculated using formula (3):

LFS = 1.18 × metabolic syndrome + 0.45 × diabetes (2 = yes; 0 = no) + 0.15 × fasting insulin (mU/L) + 0.04 × AST (U/L) − 0.94 × (AST/ALT) − 2.89 (3).

The MASLD fibrosis score was calculated according to formula (4):

MASLD fibrosis score = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m²) + 1.13 × serum insulin / diabetes (yes = 1, no = 0) + 0.99 × AST/ALT − 0.013 × platelet count (×10⁹/L) − 0.66 × albumin (g/dL) (4).

To identify structural changes in the liver parenchyma, abdominal ultrasonography was performed. For quantitative assessment of liver echogenicity, echodensitometry was used with calculation of the hepatic reflectivity index (HRI) (Webb M. et al., 2009). Echodensitometry was carried out after overnight fasting using the Ultima PA system ("Radmir", State Enterprise JSC NDIRET, Kharkiv, Ukraine) with a convex transducer (3–5 MHz), followed by digital histogram analysis of the ultrasound images.

HRI was obtained using the formula by Webb M. et al. (2009): HRI = MNA / MNB.

All patients underwent anthropometric measurements including body mass index (BMI), waist circumference (WC), hip circumference (HC), and their ratio, the waist-to-hip index (WHR = WC/HC).

Statistical analysis of the results was performed according to the study design and the type of numerical data obtained. The normality of distribution was assessed using the Lilliefors test, Shapiro–Wilk test, and visual inspection of histogram plots. Quantitative variables with a normal distribution were presented as mean (M) ± standard deviation (SD). For non-parametric data, results were expressed as median (Me) as the measure of central tendency, and upper (Q75) and lower quartiles (Q25) as measures of dispersion. Discrete variables were presented as absolute and relative frequencies (percentage of total observations).

For comparisons of normally distributed data, parametric tests were applied, including Student's t-test and Fisher's F-test. In cases of non-normal distribution, the median test and Mann–Whitney U-test were used; for multiple comparisons of dependent samples, the Wilcoxon T-test was applied. Statistical and graphical analyses were performed using Statistica for Windows version 8.0 (StatSoft Inc., USA) and Microsoft Excel 2007 (Microsoft, USA).

Results.

Analysis of lipid profile parameters in patients with MASH and obesity indicates the presence of lipid metabolism disorders (Table 1).

Table 1

Lipid profile parameters in patients with MASH and obesity, CAP, and in comorbid MASH with CAP, as well as in practically healthy individuals (M±m)

Indicators, unit	Healthy, n=20	Patient groups		
		NASH, n=35	NASH + CAP, n=90	CAP, n=35
Total lipids, mmol/L	5,83±0,11	7,95±0,12 */#	8,71±0,14 */**/#	6,43±0,15 */**
Total Cholesterol, mmol/L	4,26 ± 0,10	6,23±0,11 */#	6,92 ± 0,12 */**/#	5,38±0,13 */**
Triglycerides, mmol/L	1,05 ± 0,04	2,85±0,05 */#	3,18 ± 0,07 */**/#	1,78±0,03 */**
LDL-C, mmol/L	2,59±0,02	5,09±0,05 */#	5,93 ± 0,06 */**/#	4,20±0,08 */**
HDL-C, mmol/L	1,67 ± 0,05	1,14±0,04 *	0,99 ± 0,05 *	1,18±0,07 */**
Atherogenic Index	1,55 ± 0,03	4,46±0,02*	5,99±0,03*/**/#	3,56±0,04 */**
Notes: * − statistically significant difference compared with the value in healthy individuals ($p < 0.05$); ** − statistically significant difference compared with the value in patients with NASH ($p < 0.05$); # − statistically significant difference compared with the value in patients with CAP ($p < 0.05$).				

Though, the mean blood levels of total lipids exceeded those of the PHG by 1.4-times ($p<0.05$), total cholesterol by 1.5-times ($p<0.05$), triglycerides by 2.7-times ($p<0.05$), LDL-C by 1.9-times ($p<0.05$), while HDL-C levels were 1.5 times lower than in the PHG ($p<0.05$). These findings indicate that patients with MASH have markedly impaired lipid metabolism, creating metabolic prerequisites for the progression of MASLD.

The study of the blood lipid spectrum in patients with MASH and CAP revealed several similar changes (see Table 1), differing in the degree of metabolic disturbance. Total lipid levels in Group 2 patients exceeded normal values by 1.5-times ($p<0.05$), with a statistically significant difference between Groups 1 and 2 ($p<0.05$). Total cholesterol was also significantly elevated compared to the PHG: 1.6-times in Group 2 ($p<0.05$) vs. 1.5-times in Group 1 ($p<0.05$) (see Table 1).

Triglyceride levels in Group 2 were also significantly increased—3.0-times vs. 2.7-times in Group 1 ($p<0.05$) (see Table 1). Thus, TG levels in the comorbid course of CAP and MASLD were significantly higher than in isolated MASH.

The analysis of pro-atherogenic lipoprotein fractions revealed several significant changes: LDL-C in Group 2 patients was 2.3 times higher than in the control group ($p<0,05$), whereas in Group 1 it was increased 1.9-times ($p<0.05$), with a statistically significant difference between the groups ($p<0.05$). Meanwhile, HDL-C levels were markedly lower than in the PHG—1.5-times in Group 1 and 1.7-times in Group 2 ($p<0.05$), without significant differences between these two groups (see Table 1).

This metabolic profile resulted in a substantial increase in the atherogenic index across all comparison groups (see Table 1). In Group 1, AI exceeded PHG values by 2.9-times ($p<0.05$). The highest AI was observed in Group 2, exceeding PHG levels by 3.9-times ($p<0.05$). A combination of high TG, low HDL-C, and increased AI may be viewed as an essential component of metabolic syndrome and a pathogenic basis for developing MASLD and atherosclerosis.

Lipidogram analysis in Group 3 (CAP associated with COVID-19) also indicated dyslipidemic disruptions. Total lipid levels exceeded PHG by 10.3% ($p<0.05$), total cholesterol by 1.3-times ($p<0.05$), triglycerides by 1.7-times ($p<0.05$), LDL-C by 1.6-times ($p<0.05$), while HDL-C levels were 1.4 times lower ($p<0.05$). AI exceeded PHG values by 2.3-times ($p<0.05$). These results suggest that patients with CAP associated with COVID-19 exhibit impaired lipid metabolism, creating conditions for the development and progression of MASLD.

Thus, both in patients with MASH and obesity and in those with comorbid MASH and CAP, hyperlipidemia and dyslipidemia were detected, increasing proportionally to the number of metabolic comorbidities. In patients with MASLD and obesity with CAP, a decompensated lipid distress syndrome was confirmed, contributing to the progression of MASLD. Patients with CAP associated with COVID-19 demonstrated significant dyslipidemia, which may contribute to the development of both MASLD and atherosclerosis.

The analysis of non–organ-specific biochemical markers of liver injury (Table 2) showed that MASH without CAP was accompanied by active hepatocellular cytolysis: AST levels were 2.0-times and ALT levels 2.9-times higher ($p<0.05$). In MASLD with CAP, AST exceeded PHG values 3.0-times and ALT 3.8-times ($p<0.05$) (see Table 2). The de Ritis ratio was reduced by 1.2–1.4 times compared to the PHG ($p<0.05$), indicating MASLD progression depending on the presence of CAP ($p<0.05$).

Table 2

Biochemical markers of liver injury and functional liver status in patients with steatotic liver disease and PHG, depending on the presence of community-acquired pneumonia

Indicator, unit	Healthy, n=20	NASH + CAP, n=90	NASH, n=35
Total Bilirubin, μmol/L	19,20± 1,15	45,27± 2,23 *	33,10± 2,29 */**
Conjugated Bilirubin, μmol/L	4,51± 0,27	17,87± 1,25*	9,54± 1,30 */**
Unconjugated Bilirubin, μmol/L	14,69± 0,43	27,40± 1,37*	23,56± 1,25*
AST, U/L	25,33 ± 1,53	78,25± 1,47*	51,63 ± 1,23 */**
ALT, U/L	22,71 ±1,48	85,44 ± 2,53*	67,12 ± 2,31 */**
De Ritis Ratio	1,11± 0,01	0,92± 0,01*	0,77± 0,01*/**
GGT, U/L	34,52 ± 5,27	132,75 ± 7,17 *	103,63 ± 5,88 */**
ALP, U/L	58,52 ± 4,36	108,53 ± 5,39 *	72,15 ± 4,46 */**
Thymol Test, units	2,50± 0,17	6,27 ± 0,17*	3,97 ± 0,23 */**
Total Protein, g/L	75,53 ± 4,35	54,38 ± 2,42*	65,22 ± 2,31**
Albumin, g/L	43,22 ± 2,65	29,38 ± 1,34*	37,51 ± 1,45 **
Notes: 1.* - statistically significant difference compared with the value in healthy individuals ($p<0,05$); 2.** - statistically significant difference compared with the value in patients with steatohepatitis and CAP ($p<0,05$)			

In patients with MASH without CAP, a significant hyperbilirubinemia was recorded: total bilirubin levels exceeded those of the PHG by 1.7-times ($p<0.05$). Conjugated bilirubin exceeded normal values 2.1-times ($p<0.05$), and unconjugated bilirubin — 1.6-times ($p<0.05$).

In the presence of CAP, patients with MASH showed even higher elevations: total, direct, and indirect bilirubin exceeded PHG levels by 2.4-times, 3.9-times, and 1.9-times, respectively ($p<0.05$). However, these values differed from those in the MASH-only group only for total and direct bilirubin ($p<0.05$) (see Table 2). These changes indicate the development of a mild cytolytic syndrome in patients with MASH, and a moderately active steatohepatitis in those with MASH and CAP.

The analysis of biochemical markers of cholestasis shows that ALP activity was elevated 1.2-times in patients with MASH and 1.9-times in those with MASH and CAP ($p<0.05$) (see Table 2). GGT activity was increased 3.0-times and 3.8-times, respectively ($p<0.05$). Thus, clinical signs of cholestasis in MASH were confirmed by biochemical markers — elevated ALP and GGT, as well as direct hyperbilirubinemia, which was higher in the presence of CAP (3.9-times vs. 2.1-times) ($p<0.05$) (see Table 2).

Both groups demonstrated a mesenchymal inflammatory syndrome, but the most pronounced manifestations were observed in the MASH+CAP group. The thymol test exceeded PHG values 1.6-times in MASH and 2.5-times in MASH+CAP ($p<0.05$), with a statistically significant difference between the groups ($p<0.05$) (see Table 2).

A slight trend toward decreased protein-synthesizing liver function was noted in the MASH group (a 1.2-times reduction in total protein and a 1.2-times reduction in serum albumin) ($p>0.05$). Patients with MASH+CAP demonstrated a more pronounced decrease in total protein and albumin — 1.4-times and 1.5-times, respectively ($p<0.05$) (see Table 2).

Ultrasound examination of the liver in both groups of patients with steatotic liver disease revealed a significant degree of hepatomegaly (100.0% of patients), medium-granular structural transformation, and heterogeneous parenchymal densification (“patchiness,” hyperechogenicity) with dorsal attenuation of the ultrasound signal due to diffuse fatty infiltration, as well as a substantial degree of hepatic steatosis. Liver echotexture was altered in all patients, with diffuse heterogeneity of both lobes predominating (Table 3).

The degree of hepatomegaly differed slightly between groups. In patients with MASH, the sizes of the right and left liver lobes exceeded PHG values 1.5-times and 1.4-times, respectively ($p<0.05$). In the presence of CAP, a higher degree of hepatomegaly was recorded — a 1.6-times enlargement of both right and left lobes ($p<0.05$), with significant differences between the groups ($p<0.05$).

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Table 3

Results of liver ultrasonography in patients with steatohepatitis depending on the presence of comorbid community-acquired pneumonia (M ± m)

Indicator, unit	Healthy, n=20	NASH + CAP, n=90	NASH, n=35
Right liver lobe size, mm	112,1 ± 2,4	178,2 ± 2,3 *	167,9 ± 2,5 */**
Left liver lobe size, mm	74,7 ± 1,3	116,5 ± 1,6 *	106,8 ± 1,5 */**
Hepatorenal Index	1,15 ± 0,07	2,47 ± 0,01 *	1,82 ± 0,02 */**
Notes: 1.* - statistically significant difference compared with the value in healthy individuals (p<0,05); 2.** - statistically significant difference compared with the value in patients with steatohepatitis and CAP (p<0,05)			

Characteristic ultrasonographic changes of the hepato-renal index were also identified. In patients with MASH and those with MASH combined with CAP, this index exceeded the PHG value by 2.1-times and 1.6-times, respectively (p<0.05), indicating a higher degree of hepatocyte steatosis in the presence of comorbid CAP.

Examination of patients using the integrated Steato-test yielded the following results (Table 4). In patients with MASH, S1 grade hepatic steatosis was detected in 57.1% of cases. However, in patients with MASH and CAP, the number of S1 cases was 2.1 times lower (p<0.05).

S2 grade steatosis in MASH with CAP occurred 1.7 times more frequently than in MASH alone (p<0.05), while S3 grade steatosis in MASH with CAP exceeded its frequency in MASH by 1.8-times (p<0.05).

The obtained results indicate a significantly higher degree of hepatic steatosis in patients with MASH when it is comorbid with community-acquired pneumonia. The highest S3 grade of steatosis predominated in cases of MASH combined with CAP.

Calculation of biochemical indices approved by hepatology associations for detecting hepatocyte steatosis and liver fibrosis (Table 5) demonstrates the presence of hepatocellular steatosis in patients of Group 1, since the HSI value exceeded that of the PHG group by 2.0-times (p<0.05), indicating mild-to-moderate hepatocyte steatosis. This finding is consistent with the increase in LFS, which surpassed reference values by 7.8-times (p<0.05).

Analyzing these data, we concluded that obesity contributes to the development of lipid distress syndrome and to the onset and progression of metabolic-associated steatotic liver disease (MASLD).

Evaluation of the liver fibrosis index shows a significant increase in Group 1 patients, corresponding to F2 stage liver fibrosis (see Table 5).

Table 4

Distribution of patients with steatohepatitis by degree of hepatic steatosis (based on Steato-test results) depending on the presence of comorbid community-acquired pneumonia (n, %)

Steatosis degree	NASH + CAP, n=90	NASH, n=35
S0	0	0
S1	24/26,7	20/57,1*
S2	39/43,3	9/25,7*
S3	27/30,0	6/17,1*

Table 5

Biochemical indices of hepatic steatosis in patients with MASH and MASH with CAP compared with practically healthy individuals (M±m)

Indicator, unit	Healthy, n=20	Patient groups	
		NASH, n=35	NASH + CAP, n=90
HSI	23,32±1,19	47,35±1,34 */**	54,71±1,13 */**/***
LFS	-0,32± 0,01	2,51± 0,02*/**	4,18±0,03 */**/***
NAFLD FS	-1,16± 0,01	0,49± 0,01 */**	0,68±0,01 */**/***
Notes: * − statistically significant difference compared with the value in healthy individuals (p < 0.05); ** − statistically significant difference compared with the value in patients with NASH (p < 0.05);			

In patients of Group 2, the HSI value exceeded that of the PHG group by 2.3-times (p<0.05) (see Table 5), indicating severe hepatocyte steatosis, which is confirmed by the LFS, exceeding reference values by 13.1-times (p<0.05). Analyzing these data, we concluded that CAP and underlying obesity contribute to severe lipid distress syndrome and the progression of metabolic-associated steatotic liver disease (MASLD). Changes in the liver fibrosis index indicate a significant increase in Group 3 patients, corresponding to F3–F4 stage liver fibrosis (see Table 5).

Discussion of study results. The clinical course of metabolically associated steatohepatitis with comorbid pneumonia is characterized by a higher frequency and intensity of biochemical syndromes of MASH. The pulmonary inflammatory focus generates a high degree of endogenous intoxication syndrome, introducing a large amount of toxins, pro-inflammatory cytokines, and inflammatory mediators into systemic circulation, promoting the development of metabolic acidosis. The liver provides the primary metabolic load for detoxifying endo- and exotoxins.

In the presence of MASH with obesity, the damaged liver has a limited capacity to neutralize toxic metabolites, bacterial endotoxins, and their metabolic products and is further affected by antibacterial agents used to eliminate

the CAP pathogen, most of which possess hepatotoxic properties. Consequently, comorbidity of MASH with CAP increases the intensity of mesenchymal-inflammatory syndrome, as low-grade inflammation in MASH is supplemented by a cytokine storm and infiltration of polymorphonuclear leukocytes into pulmonary tissue, forming extensive inflammatory foci and enhanced circulation of pro-inflammatory agents in the systemic bloodstream [12, 13].

This leads to impaired liver function in bile secretion, formation of pathologically altered bile lacking sufficient bile acids required for digestion and activation of pancreatic proteolytic and lipolytic enzymes. Our study demonstrated an increased degree of hepatomegaly (by the sizes of the right and left liver lobes) in MASLD patients with comorbid CAP, likely due to an increased number of circulating active leukocytes and lymphocytes, which, in addition to the pulmonary inflammatory focus, infiltrate the liver parenchyma, damage steatotically altered hepatocytes, cause hepatocyte necrosis, and contribute to the intensification of cytolytic and mesenchymal inflammation syndromes. These processes promote activation of connective tissue, formation of liver fibrosis, compression of sinusoids, and the development of early portal hypertension. Focal inflammatory infiltrates and fibrous septa within the liver parenchyma compress intrahepatic bile ducts, contributing to cholestasis, which may also be initiated by loss of hepatocyte polarity and pathological transport of bile micelles from the cholangiolar to the sinusoidal side, releasing bile components into systemic circulation.

It should be noted that most antibiotics recommended for empirical CAP therapy may induce both hepatocyte cytolysis and cholestasis through various mechanisms, exacerbating the clinical manifestations of MASLD.

Elevated blood lipid levels in CAP, particularly when associated with MASLD, may be regarded as a result of the complex systemic response to inflammation, cytokinemia, and endogenous intoxication. Acute pulmonary inflammation activates the “stress–metabolic adaptation” axis, releasing catecholamines, glucocorticoids, and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6). These mediators stimulate lipolysis in adipose tissue and enhance the influx of free fatty acids into the liver. In the context of pre-existing insulin resistance in MASH and obesity, the liver loses the ability to efficiently β-oxidize fatty acids, promoting their re-esterification into triacylglycerols and the synthesis of pro-atherogenic lipoprotein fractions. Simultaneously, cytokine-induced suppression of lipoprotein lipase activity impairs lipid clearance from the blood, leading to hypertriglyceridemia [14].

During pneumonia, the immune system’s demand for structural lipids (for membrane and surfactant synthesis) further stimulates hepatocellular lipogenesis. SARS-CoV-2, in particular, can interfere with lipid metabolism, disrupt microsomal oxidation systems, induce steatosis, and increase expression of de novo lipogenesis genes. Collectively, these mechanisms generate lipid distress syndrome, the severity of which, as shown in our study, increases when MASH is combined with pneumonia compared to isolated MASH. This metabolic remodeling creates conditions for steatosis progression, fibrosis, and deterioration of liver function.

The comorbid course of MASH with CAP is characterized by a higher degree of hepatic steatosis ($p<0.05$). This phenomenon can be explained by increased cytolytic and inflammatory load under the influence of endogenous intoxication, inflammation, antibiotic exposure, etc., with greater functional mitochondrial insufficiency, specifically inhibition of hepatocyte β-oxidation and deposition of neutral fats (macro- or microvesicular steatosis). These processes are likely aggravated by increased insulin resistance induced by the pro-oxidative and toxic effects of comorbid pneumonia, as confirmed by our research and multiple literature sources. The observed lipid distress syndrome intensifies in the presence of CAP with MASH compared to isolated MASH, potentially contributing to both disease progression and fibrosis or cirrhosis development [15].

Conclusions

The blood lipid profile in patients with metabolic-associated steatotic liver disease and obesity is characterized by significant increases in total lipids, total cholesterol ($p<0.05$), LDL-cholesterol ($p<0.05$), and triacylglycerols ($p<0.05$) compared with practically healthy individuals. Patients with MASLD and CAP demonstrated the highest intensity of lipid distress syndrome among comparison groups ($p<0.05$) and the greatest increase in the atherogenic index (3.9-times, $p<0.05$), predisposing them to MASLD and atherosclerosis.

Biochemical indices (HSI, LFS) reflecting hepatocyte steatosis, and indices indicating liver fibrosis (NAFLD FS) reveal hepatocyte steatosis in MASH patients with obesity: HSI and LFS indicate mild-to-moderate steatosis with manifest lipid distress syndrome and progressive increase in the liver fibrosis index corresponding to F2 stage fibrosis. In patients with MASH, obesity, and CAP, severe hepatocyte steatosis is observed, confirmed by increases in HSI and LFS (13.1-times, $p<0.05$), associated with severe lipid distress syndrome and elevated liver fibrosis index corresponding to F3–F4 stage fibrosis.

The comorbid course of MASH with CAP is associated with a higher degree of hepatic steatosis (HRI, 1.4-times) compared with patients with isolated MASH ($p<0.05$). The frequency of S3 grade hepatic steatosis predominated in MASH patients with CAP by 1.8-times ($p<0.05$) compared with isolated MASH.

Future research should focus on elucidating the pathogenetic mechanisms of mutual aggravation between steatotic liver disease and community-acquired pneumonia in comorbid conditions.

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