fibrinogen <296 mg / dl (OR 0.55 [95% CI 0.31-1.00], p = 0.03). In our study based on regression analysis was significant (p = 0.03) positive nonlinear association of fibrinogen level and the duration of the disease in patients with DRP and especially during the first 10 years from the onset of diabetes. Therefore, our results complement VADT study on role fibrinogen in the progression of DRP.

CONCLUSIONS

1. With the progression of DRP from non-proliferative to proliferative stage with type 2 diabetes as a component of MS occurs significant increase in concentration fibrinogen in the blood.

2. Identified reliable positive nonlinear association of blood fibrinogen concentration and duration of type 2 diabetes, especially throughout the first 10 years from the onset of the disease.

3. A modifying effect on blood fibrinogen concentration in patients with type 2 diabetes type only for the proliferative stage of DRP such factors like older patients, degree compensation for carbohydrate metabolism in severe trends in the participation of diabetes duration factor.

Authors declare no conflict interests.

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MARKERS OF LIVER DAMAGE IN COMORBIDITY OF NON-ALCOHOLIC LIVER DISEASE AND HYPERTENSION

Summary. Objective: to study the features of liver damage and to study the main factors of influence on this process with comorbidity between non-alcoholic fatty liver disease and essential hypertension or renoparenchymal arterial hypertension.

Materials and methods. The object of the study was 269 patients, included in three groups: group 1 - patients with non-alcoholic fatty liver disease (60 patients), group 2 - patients with comorbidity of non-alcoholic fatty liver disease and essential hypertension (121 patients), group 3 - patients with comorbidity of non-alcoholic fatty liver disease and renoparenchymal arterial hypertension (88 patients). The control group consisted of 20 healthy individuals of the same age and gender categories. Clinical examination of patients included an assessment of the parameters of an objective examination: in particular, anthropometric data and blood pressure according to standard methods. We studied both laboratory and instrumental markers of liver damage. To diagnose the

condition of the liver and blood vessels in all patients, an ultrasound method was used. Some patients (212 people) underwent the Fibromax test. To assess the severity of insulin resistance, the HOMA index was calculated. Glomerular filtration rate was determined by the formula CKD-EPI. The level of cytokeratin-18 in blood plasma was determined by ELISA.

Results and its discussion. A highly significant difference was found for most indicators between the groups of patients and the control group. The greatest difference was found in levels of transaminases (ALT and AST), gamma-glutamyl transpeptidase, as well as cytokeratin-18 ($p < 0.001$). The most pronounced increase in transaminases was observed in patients of group 3. The levels of gamma-glutamyltranspeptidase in patients of all three groups significantly exceeded the corresponding parameters of the control group, were the highest in group 3 - 68.10 ± 33.31 U/l. Moreover, this the indicator did not significantly differ between groups 2 and 3 ($p > 0.05$). Cytokeratin-18 was significantly increased in patients with non-alcoholic fatty liver disease, and was significantly different between all groups.

Fewer patients with no hepatic fibrosis were recorded in group 1. We found significant correlation between the duration of non-alcoholic fatty liver disease and all markers of liver damage in group 1. Also, markers of liver damage positively correlated with body mass index, which indicates an important role obesity in the pathogenesis of non-alcoholic fatty liver disease. Given the correlations with the indicators of adiponectin, malondialdehyde, tumor necrosis factor-alpha, HOMA, we can state the important role of inflammation, oxidative stress, insulin resistance in the pathogenesis and development of non-alcoholic fatty liver disease. A strong negative correlation between cytokeratin-18 and glomerular filtration rate of - 0.402 ($p < 0.001$) was also found. Important in our opinion were the positive relationships between indicators of hepatic damage and blood pressure in groups 2 and 3, which may indicate a relationship within comorbidity. In general, the largest number of strong correlation bonds were found for cytokeratin-18, and the smallest for gamma-glutamyltranspeptidase. The profile of the correlation between the main indicators did not differ much from group 2. Using ANOVA dispersion analysis, we found a close relationship between the degree of liver steatosis and the main markers of liver damage ALT, AST, GGT, cytokeratin-18, fibrotest, and actitest. The highest Fisher coefficient was recorded for cytokeratin-18 - $F = 118.58$ ($p < 0.001$), actitest - $F = 102.18$ ($p < 0.001$), fibrotest - $F = 95.03$ ($p < 0.001$), gamma-glutamyltranspeptidase - $F = 26.6$ ($p < 0.001$). Such data indicate a close relationship between the processes of fat accumulation, inflammation, and apoptosis in the liver with non-alcoholic fatty liver disease in the presence or absence of comorbidity with essential hypertension or renoparenchymal arterial hypertension.

Conclusions. For patients with non-alcoholic fatty liver disease, in the presence of its comorbidity with essential hypertension or renoparenchymal arterial hypertension, a more pronounced increase in gamma-glutamyl transpeptidase, cytokeratin-18 and actitest was characteristic, which may indicate the presence of more active processes of inflammation and hepatic apoptosis. A negative effect of comorbidity with essential hypertension or renoparenchymal arterial hypertension on liver fibrosis was also found. Markers of liver damage are associated with the duration of non-alcoholic fatty liver disease activity, body mass index, adiponectin, markers of inflammation and oxidative stress, kidney function. The degree and list of correlation relationships differ with non-alcoholic fatty liver disease depending on the presence or absence of comorbidity with essential hypertension or renoparenchymal arterial hypertension. Severe liver steatosis strongly affects the processes of hepatic inflammation, fibrosis and apoptosis with the comorbidity of non-alcoholic fatty liver disease with essential hypertension or renoparenchymal arterial hypertension.

Keywords: liver lesions, cytokeratin-18, non-alcoholic fatty liver disease, hypertension

Introduction. The problem of comorbidity is very topical in medicine, and separately in patients with liver disease. One of the most common chronic diseases in hepatology is non-alcoholic fatty liver disease (NAFLD), which is now regarded as a multidisciplinary problem [3, 5]. In the vast majority of patients, NAFLD is associated with various endocrine abnormalities, renal dysfunction and vascular disorders, in particular essential arterial hypertension (EAH) [1, 8]. In the management of patients with NAFLD, markers of hepatic lesions: inflammation, fibrosis, apoptosis, etc. should be monitored [2, 7]. It is known that NAFLD can be presented as a hepatic continuum, the initial stage of which is liver steatosis, and the end stage is cirrhosis with or without hepatocellular carcinoma [5, 7]. The main task of the physicianis to create conditions for maximum inhibition and possibly regression of existing liver disorders. It is well-known that there is a close link between the increase in liver parameters and the severity of some parameters of the metabolic syndrome (MS), in particular obesity, dyslipidemia, etc. [3, 4, 6].

Meanwhile, the peculiarities of liver lesions in comorbidity between NAFLD and EAH or renoparenchymal arterial hypertension (RPAH) remain unknown.

Aim of the study: To investigate the peculiarities of liver lesions and to investigate the main factors influencing this process in comorbidity between NAFLD and EAH or RPAH.

Research materials and methods

Our research was conducted on the basis of the Department of Gastroenterology and Therapy, as well as the polyclinics of the Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical Sciences of Ukraine".

Clinical and biochemical laboratory studies were carried out in the clinical and diagnostic laboratory of the Government Institution "L.T.Malaya Therapy National Institute of the National Academy of Medical

Sciences of Ukraine" and «Alfa Labservice Laboratory». Functional studies were performed in the department of functional and ultrasound diagnostics.

There were 269 patients, which were were included in the study group: group I - patients with NAFLD (60 patients), group II - patients with comorbidity of NAFLD and EAH stage II, grade 2 (121 patients), group III - patients with comorbidity NAFLD and RPAH stage 2, grade 2 (88 patients) undergoing inpatient and outpatient treatment. The age of patients ranged from 18 to 66 years. The mean age of the patients was 48.07 ± 10.81 years. Of these, 53.9% were men and 46.1% were women. The distribution of patients by gender was uniform.

All patients with RPAH were diagnosed with chronic pyelonephritis, which was in remission at the time of the study. Also, these patients did not have a significant reduction in the rate of glomerular filtration, the degree of chronic kidney disease (CKD) was I-III.

The study did not include patients with diabetes mellitus, coronary heart disease, CHF stage II B - III.

The control group consisted of 20 healthy individuals of similar age and sex.

Clinical examination of patients included assessment of objective examination parameters, including anthropometric data and blood pressure (BP) by standard methods.

Both laboratory and instrumental markers of liver damage (MLD) have been studied.

All patients were diagnosed with non-alcoholic steatosis using an ultrasound examination method on the ultrasound diagnostic system "GE", USA. Cranio-caudal dimensions of the right and left parts of the liver, the length and width of the gallbladder, the length and width of the spleen were determined. Determined 3 degrees of liver steatosis. The degree of liver steatosis was established according to ultrasound: degree I - a slight increase in echogenicity of the liver parenchyma, normal visualization of intrahepatic vessels and diaphragms; grade II - moderate diffuse increase in echogenicity of the liver parenchyma, slight impaired visualization of intrahepatic vessels and diaphragm; grade III - marked increase in echogenicity of the liver parenchyma, visualization of intrahepatic vessels, diaphragm and back of the right lobe is significantly impaired or absent.

Several patients: 46 from the first group, 89 from the second group and 77 from group 3 were tested by "Fibromax". Patients with NAFLD were screened for liver fibrosis (LF) and a study of serum biomarkers of the Fibrotest from the kit "Fibromax", Biopredictive (France) was performed. Fibromax test includes 5 diagnostic blocks, of which we used 4 - Fibrotest (determination of stage of liver fibrosis), Steatotest (determination of degree of steatosis), Actitest (determination of activity of inflammatory process of liver), Nashtest (determination of presence of non-alcoholic steatohepatitis). The algorithm of the Fibromax panel is based on the determination of the following serum parameters: alanine aminotransferase (ALT) and aspartate aminotransferase (AST), gamma-glutamyltranspeptidase (GGT), total cholesterol (TC), triglycerides (TG), blood glucose, total bilirubin, α2-macroglobulin, apolipoprotein A1, haptoglobin, and also includes general information about age, gender and BMI. There were no patients with F4 in our study. To determine the degree of LF, all patients were divided into five subgroups, depending on the Fibrotest scale from 0 to 1. Subgroup F0 - the range of indicators of the scale 0.00-0.21; F 0-1 - the range of indicators of the scale 0,22-0,31; F1-2 - range of indicators of scale 0,32-0,48; F2-3 - scale of indicators of scale 0,49-0,58; F3 - the range of indicators of the scale 0,59-0,72. To determine the degree of inflammation in the liver, all patients were divided into five subgroups, depending on the score of the Actitest scale from 0 to 1. Subgroup A0 - a range of indicators of the scale 0.00-0.17; And 0-1 - the range of indicators of the scale 0,18-0,29; And 1-2 - the range of indicators of the scale 0,30-0,52; And 2-3 - the range of indicators of the scale 0,53-0,62; And 3 - the range of indicators of the scale of 0.63-1.00.

To determine endothelium-dependent vasodilation (EDVD), a test with reactive hyperemia was performed according to the method of Celermajer D.S. in the modification of Ivanova O.V.

Blood biochemical parameters were determined by standard conventional methods, determined the levels of: AST, ALT, GGT, alkaline phosphatase (AF), thymol test (TT), total bilirubin and its fractions; TG, insulin. To quantify the severity of insulin resistance (IR), a mathematical model of homeostasis (HOMA) was used to determine the HOMA index.

GFR was determined by the formula CKD-EPI.

The level of cytokeratin-18 (CK-18) in blood plasma was determined by enzyme-linked immunosorbent assay using the CK-18 (M65) Human ELISA Kit manufactured by Biotech (China). Avi Bion Human Adiponectin (Acrp30) Elisa Kit test system (Ani Biotech Oy Orgenium Laboratories Busines Unit, Finland) was used to determine adiponectin levels. The enzyme-linked immunosorbent assay using Vector-Best (Russia) kits was determined by the concentration of TNF-α. Determined prooxidant indicator malonic dialdehyde (MDA) when conducting spectrophotometry on a spectrophotometer Hitachi U-1900 (Japan).

Statistical processing of the results was performed using Microsoft Excel and STATISTICA computer programs using standard variational statistics methods. The t - Student test (M ± σ) was used to assess the significance of the difference in paired changes in indicators. The difference was considered statistically significant at $p < 0.05$.

Results and Discussion

From the beginning, the difference between the major biochemical parameters and the marker of hepatic apoptosis CK-18 was analyzed in three groups of patients. A highly significant difference was found in most indicators between the patient groups and the control group. The largest differences were found in transaminases (ALT and AST), GGT, and CK-18 ($p < 0.001$).

There were no laboratory signs of liver injury in the control group (Table 1).

The highest levels of transaminases were observed in patients of group 3. Thus, the average AST in this group was 51.33 ± 31.79 U/l, and significantly exceeded the corresponding indicator in the control group 21.15 ± 4.97 U/l (p <0.001). However, when there was a tendency to increase, there was no significant difference between the indicators of group 1 and groups 2 and 3 in relation to the ALT level (p> 0.05). The GGT levels in the patients of all three groups significantly exceeded the corresponding values of the control group of 22.20 ± 7.12 U/l and were at the level of 49.64 ± 32.97 U/l in group 1; 62.70 ± 44.76 U/l in group 2 and 68.10 ± 33.31U/l in group 3. However, this indicator did not differ significantly between groups 2 and 3 (p> 0.05). It should be noted that there is no significant difference between the total bilirubin and its fractions between the individual patient groups and the difference between the patients and the control group (p> 0.05). The same trend was observed for AF. TT was significantly different between control subjects 1.67 ± 0.59 and patients in group 3 - 2.47 ± 1.77 (p <0.05).

Table 1

The main markers of liver damage in the studied patients

Indicators	Group 1 (n=60)	Group 2 (n=121)	Group 3 (n=88)	Control group (n=20)
ALT, U/l	42,80±24,49 к) 3)	48,45±27,71 к)	60,87±43,70 к)	24,80±5,59
AST, U/l	35,22±19,42 к) 3)	40,13±21,25 к)	51,33±31,79 к)	21,15±4,97
AP, U/l	1552,82±311,00	1641,28±334,20	1597,15±351,89	1600,70±303,80
GGT, U/l	49,64±32,97 к) 2)3)	62,70±44,76 к)	68,10±33,31 к)	22,20±7,12
Bilirubin total, μmol / l	12,54±6,52	11,73±5,47	13,74±6,21	10,91±3,14
Bilirubin direct, μmol / l	3,34±1,54	3,21±1,43	3,75±1,56	3,04±0,99
Bilirubin indirect, μmol / l	9,19±5,25	8,53±4,36	10,00±5,09	7,87±2,38
TT	2,01±1,40	2,16±1,15	2,47±1,77 к)	1,67±0,59
CK-18, U/l	261,74±61,14 к) 2)3)	282,26±50,12 к)3)	316,06±52,79 к)	133,22±27,09

Note: k) - the difference is significant when compared with the control group. 2) - the difference is significant when compared with the indicators of group 2. 3) - the difference is significant when compared with the indicators of group 3.

According to recent data, CK-18 (M65) is considered to be a more specific marker of non-alcoholic steatohepatitis (NASH) because of its significant positive predictive value. In addition, CK-18 has some additional advantage over other biomarkers - it reflects the degree of hepatocellular apoptosis, which is one of the main characteristics of NASH. CK-18 was significantly elevated in patients with NAFLD. Thus, in the control group it was 133.22 ± 27.09 U/l, which was significantly lower than in all groups of patients (p <0.001). The levels of this indicator also depended on the presence of comorbidity with EAH or RPAG. In group 1 it was 261.74 ± 61.14 U/l and was significantly higher than in group 2 - 282.26 ± 50.12 U/l (p <0.05). In group 3, the CK-18 level was 316.06 ± 52.79 U/l and was significantly higher than in group 1 (p <0.001) and group 2 (p <0.001).

Most of the patients studied showed signs of liver fibrosis according to Fibromax (Table 2). In group 1, there were significantly more patients with F0 - 41.3%, which was significantly higher than group 2 and 3 - 20.22% (p <0.01) and 15.58% (p <0.01). There were significantly fewer patients in group 1 with F3 - 6.52% versus 17.98% in group 2 (p <0.05) and 15.58% in group 3 (p <0.05).

Table 2

Fibrotest and Actitest indicators in the studied patients

Indicators	Group 1 n = 46	Group 2 n = 89	Group 3 n = 77
F0	19 (41,3%)2)3)	18 (20,22)%	12 (15,58)%
F0-F1	5 (10,86)%	14 (15,73)%	10 (12,98)%
F1-F2	10 (21,73)%	20 (22,47)%	20 (22,73)%
F2-F3	9 (19,56)%	21 (23,6)%	23 (29,87)%
F3	3 (6,52)%2)3)	16 (17,98)%	12 (15,58)%
A0	3 (6,52%)	4 (4,49%)	1 (1,3%)
A0-A1	19 (41,3%)3)	25 (28,09%)	11 (14,28%)
A1-A2	8 (17,39%)3)	33 (37,08%)	25 (32,47%)
A2-A3	10 (21,74%)	20 (22,47%)	25 (32,47%)
A3	6 (13,04%)	7 (7,86%)	15 (19,48%)

Regarding the Actitest scale, differences were also found that indicate a higher level of liver inflammation in patients with NAFLD with comorbidity of RPAH. There was no significant difference between Actitest

scores between groups 1 and 2 and groups 2 and 3 (p> 0.05).

In order to identify possible features in the course and progression of NAFLD in various variants of comorbidity with hypertension, the correlation between the most significant biochemical indicators of liver damage (ALT, GGT, CK-18) on the one hand and the main clinical parameters on the other was studied. Relationships with: duration of nosology, BMI, BP, GFR, carbohydrate and lipid metabolism, MDA, adiponectin, TNF-α were studied. We analyzed all indicators individually in three groups of our patients. Tables 3-5 present a pair of only significantly correlated indicators.

We found significant correlations between the duration of NAFLD and all markers of liver injury in group 1 (Table 3). Thus, a positive correlation between ALT and NAFLD duration of +0.393 (p <0.01) was found in the mean strength. Also, markers of liver lesions were positively correlated with BMI, indicating the important role of obesity in the pathogenesis of NAFLD. Considering the correlated relationships found in adiponectin, MDA, TNF-α, HOMA, we can state the important role of inflammation, oxidative stress, IP in the pathogenesis and development of NAFLD. A strong negative correlation was also found between CK-18 and GFR -0.402 (p <0.001). An interesting finding is that, despite the existence of a link between the MLD and the EDVD across all indicators, no correlation was found with the BP indicators.

Table 3

Correlations of major markers of liver injury with major clinical and biochemical parameters in patients with NAFLD (group I)

Indicators	ALT	IL	GGT	IL	CK-18	IL
NAFLD duration	0,393	p<0,01	0,356	p<0,01	0,421	p<0,01
BMI	0,348	p<0,01	0,526	p<0,001	0,532	p<0,001
SBP	nsc	-	nsc	-	nsc	-
DBP	nsc	-	nsc	-	nsc	-
EDVD	-0,378	p<0,01	-0,341	p<0,01	-0,491	p<0,001
MDA	0,579	p<0,001	0,456	p<0,001	0,664	p<0,001
TG	0,328	p<0,05	nsc	-	nsc	-
HOMA	0,353	p<0,001	0,466	p<0,001	0,577	p<0,001
Adipinectin	-0,502	p<0,001	-0,548	p<0,001	-0,516	p<0,001
TNF-α	0,383	p<0,01	0,394	p<0,01	0,732	p<0,001
GFR	nsc	-	-0,314	p<0,05	-0,402	p<0,001

Note: - IL – importance level; - nsc – not significant correlations

Then conducts a similar analysis in group 2 (table 4). NAFLD duration was associated with CK-18 and a strong correlation + 0.322 was found between these indicators (p <0.001). When considering ALT and GGT indicators no significant relationships were found (unlike group 1). A positive association with weight gain was observed for GGT and CK-18. Important in our view is the positive association between liver injury and blood pressure, which may indicate a correlation within comorbidity. So CK-18 was associated with both SBP and DBP (p <0.001). ALT was positively correlated only with DBP + 0.230 (p <0.05). With regard to GGT, no such relationship has been identified. In general, the highest number of strong correlation relationships was found for CK -18 and the lowest for GGT. In this group, only MDA was moderately or strongly correlated with all three indicators, emphasizing the significant role of oxidative stress in the comorbidity of NAFLD and EAH: with ALT + 0.292 (p <0.01), with GGT + 0.249 (p <0.01), with CK-18 +0.405 (p <0.001).

Table 4

Correlation between the main indicators in group 2

Indicators	ALT	IL	GGT	IL	CK-18	IL
NAFLD duration	nsc	-	nsc	-	0,322	p<0,001
BMI	nsc	-	0,326	p<0,05	0,448	p<0,001
SBP	nsc	-	nsc	-	0,475	p<0,001
DBP	0,230	p<0,05	nsc	-	0,327	p<0,001
EDVD	nsc	-	nsc	-	-0,411	p<0,001
MDA	0,292	p<0,01	0,249	p<0,01	0,405	p<0,001
TG	0,328	p<0,05	nsc	-	nsc	-
HOMA	0,353	p<0,001	nsc	-	0,577	p<0,001
Adipinectin	-0,502	p<0,001	nsc	-	-0,385	p<0,001
TNF-α	0,246	p<0,01	nsc	-	0,490	p<0,001
GFR	nsc	-	nsc	-	-0,358	p<0,001

Note: - IL – importance level; - nsc – not significant correlations

We also examined the correlation relationships in group 3 (Table 5). The profile of correlation relationships between MLD and NAFLD duration, BMI, SMP and DSP, MDA, TG was almost indistinguishable from group 2. Negative correlations between CK-18 and GFR indices were found to be 0.358 (p <0.001), and also between GGT and GFR - 0.282 (p <0.01).

Table 5

Correlation between the main indicators in group 3

Indicators	ALT	IL	GGT	IL	CK-18	IL
NAFLD duration	nsc	-	nsc	-	0,358	p<0,001
BMI	nsc	-	0,314	p<0,05	0,375	p<0,001
SBP	nsc	-	nsc	-	0,487	p<0,001
DBP	0,224	p<0,05	nsc	-	0,418	p<0,001
EDVD	-0,280	p<0,01	-0,293	p<0,01	-0,531	p<0,001
MDA	0,293	p<0,01	0,279	p<0,01	0,434	p<0,001
TG	0,221	p<0,05	nsc	-	nsc	-
HOMA	0,571	p<0,001	nsc	-	0,577	p<0,001
Adipinectin	nsc	-	-0,252	p<0,05	-0,492	p<0,001
TNF-α	0,303	p<0,01	0,500	p<0,001	0,504	p<0,001
GFR	nsc	-	-0,282	p<0,01	-0,341	p<0,01

Note: - IL – importance level; - nsc – not significant correlations

After evaluating the correlation relationships in the entire patient sample, the extent of the effect of liver steatosis on other MLD was determined using a ANOVA dispersion analysis (Table 6). Determined the Fisher coefficient - F.

Table 6

Indicators of ANOVA dispersion analysis in the studied patients with NAFLD

Indicators	The degree of steatosis Таблиця 4. Кореляційні зв'язки між основними показниками у групі 2	
	F	IL
ALT	F=18,63	p<0,001
AST	F=21,25	p<0,001
AP	F=2,34	p>0,05
GGT	F=26,6	p<0,001
TS	F=0,28	p>0,05
CK-18	F=118,58	p<0,001
fibrotest	F=95,03	p<0,001
actitest	F=102,18	p<0,001

We have found a close relationship between the degree of liver steatosis and the main MLD: ALT, AST, GGT, CK-18, fibrotest, actitest. The highest Fisher coefficient was recorded for SC-18 - F = 118.58 (p <0.001), actitest - F = 102.18 (p <0.001), fibrotest - F = 95.03 (p <0.001), GGT - F = 26.6 (p <0.001). Such data indicate a close relationship between fat accumulation, inflammation, and apoptosis in the liver with NAFLD in the presence or absence of comorbidity with EAH / RPAH.

Conclusions

1. For patients with NAFLD, in the presence of its comorbidity with EAH or RPAH, more significant increase of GGT, CK-18 and Aktitest indicators is more characteristic, which may indicate the presence of more active processes of inflammation and hepatic apoptosis. A negative effect of comorbidity with EAH or RPAH on liver fibrosis was also found.

2. MLD are closely related to indicators of NAFLD duration, BMI, adiponectin, markers of inflammation and oxidative stress by renal function. The degree and the list of correlation relationships are different for NAFLD depending on the presence or absence of comorbidity with EAH or RPAH.

3. The severity of liver steatosis strongly affects the processes of hepatic inflammation, fibrosis and apoptosis in comorbidity of NAFLD with EAH or RPAH.

Thus, we investigated the peculiarities of changes in laboratory markers of liver lesions that contribute to the formation, manifestation, and progression of NAFLD in comorbidity with EAH or RPAH and in its absence.

The prospects for further research are the development and implementation of integrated treatment regimens to effectively influence all processes of hepatic lesion in conditions of comorbidity.

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RELATIONSHIP OF THE DEGREE OF NEOPLASIA AND VEGF, TNF-A AND TNF-B MOLECULAR MARKERS IN PATIENTS WITH BLADDER CANCER IN STAGE T3N0M0

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СВЯЗЬ СТЕПЕНИ НЕОПЛАЗИИ И МОЛЕКУЛЯРНЫХ МАРКЕРОВ VEGF, TNF-A И TNF-B У БОЛЬНЫХ РАКОМ МОЧЕВОГО ПУЗЫРЯ СТАДИИ $T_3N_0M_0$

Abstract. The purpose of the study was to determine the molecular markers of VEGF, TNF-α and TNF-β in the urine of patients with bladder cancer stage T3N0M0 and to establish their relation to the degree of G neoplasia. The study included 47 patients with bladder cancer stage T3N0M0 (main group). Clinical data from 30 healthy individuals were used as control group data. The determination of the molecular markers of VEGF, TNF-α and TNF-β in the urine of patients with bladder cancer in stage T3N0M0 may serve the basis for the development of new methods for early diagnosis of the disease, as well as predicting the course and evaluating the effectiveness of treatment.

Аннотация. Целью исследования стало определение молекулярных маркеров VEGF, TNF-α и TNF-β в моче больных раком мочевого пузыря стадии $T_3N_0M_0$ и установления их связи со степенью неоплазии G. В работу было включено 47 больных с раком мочевого пузыря стадии $T_3N_0M_0$ (основная группа). В качестве контроля были использованы клинические данные 30 здоровых людей. Определение содержания молекулярных маркеров VEGF, TNF-α и TNF-β в моче больных с раком мочевого пузыря в стадии $T_3N_0M_0$ может быть основанием для разработки новых методов ранней диагностики заболеваний, а также прогнозирования течения и оценки эффективности лечения.

Ключевые слова: рак мочевого пузыря, фактор роста эндотелия сосудов, фактор некроза опухоли, полиморфизм.

Несмотря на современные достижения в диагностической и лечебной тактике больных раком мочевого пузыря (РМП), актуальность этой онкоурологической проблемы остается насущной и до сих пор. Согласно данных Украинского национального канцер-регистра, в 2018 году показатель заболеваемости раком мочевого пузыря составлял 11,4 человек на 100 тыс. населения. Из числа впервые выявленных 14,7% больных имели стадию Т3, а показатель смертности достигал 8 на 100 тыс. мужчин и 1,3 - женщин [1].

Одним из основных факторов развития и распространения опухолевых клеток является ангиогенез. К настоящему времени полностью