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RESEARCH ARTICLE

Association of Arterial Hypertension with Hepatobiliary Pathology: The Occurrence of Comorbidity and Features of Metabolic Processes

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Abstract: Comorbidity of hypertension and hepatobiliary pathology has negative medical and social consequences, including an increase in the indicators of hospital admissions, disability and mortality.

***Objective*:** The aim was to study the occurrence of hypertension combined with hepatobiliary diseases depending on social status, gender and age in 2003-2017 and their influence on indicators of metabolic processes in patients with a therapeutic profile.

***Methods*:** A cross-sectional study using the inpatients' medical record database of the clinic of Federal Research Centre for Basic and Translational Medicine (Novosibirsk, Russia), which collects demographics, diagnoses (using ICD-10 codes), procedures and examinations of all inpatients from 2003-2017 was conducted. The incidence of comorbidity of hypertension and hepatobiliary pathology depending on age, gender and social status, based on the analysis of 13496 medical records was examined. A comparative analysis of biochemical parameters characterizing the main types of metabolism (lipid, protein, carbohydrate and purine) was carried out in 3 groups of patients: with hypertension; with hepatobiliary pathology, and with a combined pathology.

***Results*:** During the years 2003-2005, there was the greatest frequency of this comorbidity in workers, in women, in the age group 60 years and older. In 2009-2017, the highest incidence was observed in the male administrative staff. In patients with this comorbidity, more pronounced changes in carbohydrate, protein, lipid and purine metabolism were found in comparison with groups of patients with isolated diseases.

***Conclusion*:** The results highlight the need to improve the system of prevention and treatment of comorbidity taking into account sex, age, occupation and features of metabolism.

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1. INTRODUCTION

At the present stage, one of the most important and urgent problems of medical science and practical medicine is comorbidity (CM). CM is defined as the presence of more than one disease (disorder) coinciding in time in one patient, regardless of the activity of each of them [1, 2]. Diseases or disorders that are comorbid to a specific disease are understood to be such disorders that occur most frequently with a specific disease and have some joint etiological or pathogenetic mechanisms with it [3]. In recent years, CM has become widespread [4-7]. Over a third of the population suffers from more than one disease [3]. CM significantly influences the course and outcome of diseases. Among patients with comorbid pathology, higher rates of mortality, hospitalization and complications, a significant worsening in the prognosis of morbidity, reduced functional possibilities and quality of life are noted [8-13]. CM is associated not only with an increase in the number of patients with several diseases, but also with the difficulties of organization of diagnostics and treatment, with the severity of the condition of these patients, "masking" of various nosologies, similar syndromes, worsening of the prognosis and increasing financial

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costs for treatment [3, 9, 13-16]. Combined pathology creates a new clinical situation that requires consideration of its features in the diagnosis, treatment and prevention of diseases [17-19]. The state of CM in patients can be considered not only as a predisposing factor to the progression of separate nosological forms composing the pattern of CM, but also as a risk factor for the occurrence of new severe pathological processes: oncological diseases, strokes, myocardial infarctions, arrhythmias, autoimmune diseases [20-24].

Disorders of the cardiovascular system are of particular importance in the formation of CM. One of the most common chronic diseases of the cardiovascular system, the main risk factor for atherosclerosis, coronary heart disease, including myocardial infarction and heart failure, and the main cause of cerebrovascular diseases, including cerebral stroke, is arterial hypertension (AH), the prevalence of which in the world reaches over 40% [25-27]. According to the WHO experts, hypertension is the leading factor determining the high mortality rate of the population in modern society [25]. In the presence of AH, there is a large number of comorbidities that significantly affect the quality of life of patients [16, 28-30]. Comorbid diseases with AH can, through disturbance in the mechanisms of neuroendocrine regulation, metabolic changes, and activation of inflammatory processes, become additional factors that increase vascular stiffness, contribute to the development of endothelial dysfunction, and progression of atherosclerosis, and increase the risk of vascular complications [31].

Another "epidemic of our century" is hepatobiliary disease. In therapeutic and prognostic relation, an important example of CM is a combination of cardiovascular diseases and hepatobiliary pathology (HBP), due to the fact that these classes of diseases are among the most common causes of morbidity, disability, and mortality, and also have common pathogenetic links [32-35]. One of the actual examples of comorbidity in the presence of AH with common pathogenetic mechanisms is the combination of AH with nonalcoholic fatty liver disease (NAFLD). NAFLD, being one of the main causes of liver damage in industrialized countries and involving 20-30% of the total population is a significant public health problem [35-40]. In recent years, there is an increase in the incidence of AH, occurring in conditions of comorbidity with NAFLD and also with other diseases of the hepatobiliary system, on the base of which, stress, dyskinetic, metabolic, vascular and other mechanisms lay [41-43]. There is an opinion that CM of disease of the gastrointestinal tract, beginning with a disorder of one organ, and further transforming, leads to the development of a number of diseases of other organs and systems, including AH [44].

In clinical practice, very often one encounters a combination of AH and HBP, which are combined not only by high prevalence and, consequently, a high probability of the combination, but also by common risk factors and pathogenetic mechanisms. In the presence of such comorbidity, physicians face a number of problems, ranging from a more severe course of the disease, and ending with significant difficulties in the treatment of such patients. For effective prevention and treatment of patients with AH combined with HBP, it is necessary to reveal common risk factors and pathogenetic links of this CM formation [3]. Due to the fact that CM mostly is composed of chronic noncommunicable diseases (CNCD), which are the main causes of morbidity and mortality of population over the world [45], it is reasonable to assume the possible role of risk factors for CNCD in the formation of AH and HBP comorbidity.

It has been established that the formation of CM is influenced by many socioeconomic factors, including age, gender, social status of a person, region of residence *etc* [4, 28, 46-52]. Some studies have found that socioeconomic factors may have an even more pronounced effect on the state of human health than lifestyle [53]. One of the significant social factors is the professional status, which, to a large extent, has a strong impact on an individual's health [54]. However, in the literature, there are insufficient data highlighting the impact of the socio-economic situation on the incidence of combined diseases in patients with comorbidity of AH and HBP, taking into account sex and age. Modified hemodynamic and metabolic risk factors for CNCD, which include: high blood pressure, obesity, dyslipidemia, hyperglycemia, hyperuricemia, *etc*. [32] are of special interest for practical medicine. Such hypertension risk factors as obesity, physical inactivity, smoking, and excessive alcohol consumption are well known. It is proved that all these risk factors with the same degree can lead to metabolic liver damage and the development of NAFLD [37]. However, the role of changes in lipid, carbohydrate, purine and protein metabolism in the formation of a combined pathology, in particular, a combination of FY and HBP, is not well understood. In the world, there are only a few studies that indicate the possible connection between the formation of CM and the imbalance of these metabolic parameters [55]. The peculiarities of the formation of AH and HBP comorbidity and its relationship with biochemical indicators characterizing the metabolic processes are still not fully studied.

All of the above determines the need to study the characteristics of the occurrence of AH and HBP, depending on age, gender and professional affiliation, as well as the features of metabolic processes in this comorbidity.

1.1. Objective

To study the occurrence of hypertension combined with hepatobiliary diseases depending on social status, gender and age in 2003-2018 and its influence on indicators of metabolic processes in patients with a therapeutic profile.

2. MATERIALS AND METHODS

A cross-sectional population-based study was conducted. This cross-sectional study used the inpatients' medical record database of the clinic of Federal Research Centre for Basic and Translational Medicine (Novosibirsk, Russia), which had the data of demographics, diagnoses (using ICD-10 codes), procedures (using ICD-CM-9 codes) and examinations of all inpatients from 2003-2017.

The analysis of data from medical records of 13496 patients (6151 men and 7345 women), residents of the Asian part of the Russian Federation who were treated at the clinic, was carried out. Comorbidity of arterial hypertension with hepatobiliary pathology was identified.

2.1. Criteria for Inclusion in the Study

- men, women,
- age from 16 to 92 years,
- the presence of nosological forms (in accordance with ICD-10):
- arterial hypertension - I10-I14;
- diseases of the biliary system - K80-K87;
- non-alcoholic fatty liver disease - K76.0.

2.2. Exclusion Criteria from the Study

- acute respiratory diseases, acute surgical diseases, malignant neoplasms, type 1 diabetes mellitus, impaired cerebral circulation regardless of the timing of transient ischemic attack and stroke; heart failure 2-3 st; arachnoiditis in history; epilepsy; severe concomitant diseases of the liver, kidneys; peptic ulcer in the acute stage; the presence of other chronic diseases in the stage of decompensation or exacerbation.

The average age of patients was 46.8 ± 5.2 years, and the average experience of the disease was 6.5 ± 3.5 years. The average threefold blood pressure measurement (BP) before the start of the course of treatment was: systolic blood pressure (SBP) - 154.7 ± 15.8 mm Hg, diastolic blood pressure (DBP) - 93.3 ± 8.8 mm Hg).

Patients received basic antihypertensive drug therapy (angiotensin-converting enzyme inhibitors, angiotensin-receptor-blockers, beta-blockers, calcium antagonists, diuretics), hepatoprotectors, cholagogue, and antispasmodics.

To analyze the dynamics of CM, all the patients were divided into three groups depending on the examination period, age, gender, and the nature of work: workers, employees, and administrative personnel (AP). The division by professional affiliation was carried out in accordance with the All-Russian Classifier of Occupations of Workers, Employees' Positions and Tariff Scores OK 016-94. The absence of work was an exception to inclusion in the study. The structure of social status of the patients was as follows: working specialties - 3300 people, employees - 5406 people, AP-4790 people.

Analysis of combinations of AH and HBP was carried out in the period from 2003 to 2017, with division into 3 periods: 2003-2005; 2006-2008 and 2009-2017. With the purpose to enrich the clinical sample to comparable numerical values, the duration of the 3 periods was increased. A specially conducted analysis showed that the same individuals who were analyzed in more than one observation period were no more than 1%.

To assess comorbidity, an archival method was used, which included a statistical analysis of all the nosological forms, groups and classes of ICD-10. Calculation of the transnosological comorbidity coefficient was carried out according to the presence of diseases on the ICD-10 classification. The presence of one nosological form was taken for; the value of the transnosological comorbidity coefficient for a patient represented the total amount of nosologies.

Patients underwent complex anthropometric, clinical, laboratory and instrumental examination.

Measurement of blood pressure, height and body weight was carried out using standardized methods on certified equipment according to the Clinical recommendations of the European Society of Cardiology 2013. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

For biochemical studies, blood was taken from the cubital vein, on an empty stomach, in the morning hours, not earlier than 12 hours after the last meal. The program of biochemical studies on the automatic biochemical analyzer "Konelab 30i", Thermo Clinical Labsystems (Finland) and the automatic biochemical analyzer "AU 480" Beckman Coulter (USA), included the definition of C-reactive protein (CRP), thymol test, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gammaglutamyltranspeptidase (GGTP), alpha-amylase, bilirubin, glucose, glycosylated hemoglobin, fructosamine, uric acid, urea, creatinine, total protein, cholesterol, triglycerides, high-density lipoprotein cholesterol (HS-HDL), low-density lipoprotein cholesterol (HS-LDL), and atherogenic coefficient (CAT).

Statistical analysis of the research results was performed using the STATISTICA v.10.0 application software (StatSoft Inc., USA). To present the results, we used percentages of the volume of the corresponding patient samples and their standard error (% ± sp). For the comparative analysis, the ʒ-criterion was used, followed by a post-hoc comparison using the Bonferroni amendment. In the parametric distribution of the test trait, the evaluation of intergroup differences was performed using the Student's t-test. The methods of correlation analysis (Spearman, Pearson) were used. The level of statistical significance was assumed to be 0.05 ($p < 0.05$).

3. RESULTS

In the period 2003-2005, data from 4231 patients were analyzed. For men, the average age of workers was 47.1 ± 12.3, and of employees - 46.2 ± 14.5, AP - 49.5 ± 10.5 years; while for women, the average age of workers was 48.7 ± 10.9, and of employees - 46.1 ± 12.1, AP - 47.8 ± 9.7 years.

In the period 2006-2008, data from 4768 patients were analyzed. For men, the average age of workers was 48.8 ± 11.6 and of employees - 45.2 ± 15.2, AP - 49.9 ± 11.2 years; while among women workers, the average age was 48.8 ± 11.5, and of employees - 47.2 ± 12.9, AP - 48.3 ± 9.7 years.

In the period 2009-2017, data from 4497 patients were analyzed. For men, the average age of workers was 50.1 ± 10.2, and of employees - 48.6 ± 15.1, AP - 50.6 ± 11.4 years; while for women, the average age of workers was 51.0 ± 10.2, and of employees - 48.5 ± 12.5, AP - 50.2 ± 9.9 years.

The distribution of patients by sex, social status and hospitalization period is presented in Table **1**.

The analysis of the occurrence of AH and HBP combination, depending on the social status, sex and age of the patients at different time periods, was carried out. Data on the

Table 1. Distribution of patients by social status, gender and period of hospitalization.

Period of Hospitalization	Gender	Workers	Employees	Administrative Personnel
2003-2005.	men	799	371	917
	women	446	1100	598
2006-2008.	men	728	476	1015
	women	436	1405	708
2009-2017.	men	518	467	860
	women	373	1587	692

frequency of the combination of AH and HBP, depending on the professional status, gender and age of patients in the period from 2003 to 2017 are shown in Table **2**.

In the period 2003-2005, analysis of the occurrence of AH and HBP combination depending on the social status of patients revealed the following findings. The incidence of this comorbidity was higher in workers than in employees: for men - by 7.1%, while for women - by 6.3%. Also, the incidence of this comorbidity was higher among men being administrative and management personnel than among employees (by 6.0%). In the time period 2003-2005, gender differences in the frequency of this association of diseases were found depending on the social status and age of the patients. In the age group of 20-39 years, the frequency of this syntropia was higher in men than in women: in workers - by 12.2%, in employees - by 6.5%, and in the administrative staff- by 7.1%.

In the age group of 40–59 years, gender differences in the incidence of this comorbidity were the determining character for employees: the combination of AH with HBP was found 7.1% more often in women than in men. In the older age group (60 years and more), this comorbidity was more often detected in women than in men: among workers - by 23.3%, among employees - by 15.4%. In the time interval from 2006 to 2008. in general, in the examined cohort of patients regardless of age, in men employed in administrative and managerial work, this combined pathology was statistically significant, by 3.8%, more often than in women. In the age group of 20-39 years of men, this indicator was higher by 8.4% than in women, which indicates that this difference in the social group was mainly due to the people of this age.

In the period from 2009 to 2017 in general, this comorbidity was more common, by 6%, among men employed in the administrative and managerial departments than among men-workers. These differences were formed mainly due to the age group of 20-39 years, in which the combination of these nosologies among the administrative staff was 10.9% higher than among the workers.

In the period from 2009 to 2017, gender differences in the frequency of the combination of these nosologies were found among the employees and employees of the administrative and management department . Higher rates of occurrence of this comorbidity were observed in men compared with women. These differences were due to the age groups of 20-39 years and 40-59 years.

For the analysis of biochemical features in the presence of comorbidity, 3 groups of patients were allocated, depending on the available diagnoses of AH and HBP. The first group consisted of patients with AH I and II stages, 1-3 degrees (n =5501); the second group - patients with HBP (n=3127); the third group included patients with a combination of AH and HBP (n =3876). The average age of patients in the groups was comparable ($p > 0.05$) and was therefore equal in the first group being 58.2 ± 0.22 years, in the second group being 53.7 ± 0.33 years, and in the third group being 59.25 ± 0.23 years old.

Analysis of the calculation of the values of transnosological comorbidity coefficients showed a statistically significant increase in patients with a combination of AH and HBP (6.99 ± 0.03) compared with groups with isolated nosologies - AH (5.43 ± 0.03), HBP (4.31 ± 0.03).

A comparative analysis of anthropometric, hemodynamic and biochemical parameters in patients. with a combination of AH and HBP compared with groups with isolated nosologies - AH, HBP was conducted. Weight index was higher in patients with comorbidity by 14.5% compared with patients with isolated AH and 10.1% compared with patients with isolated HBP (Table **3**).

BMI in patients with this combined pathology (AH and HBP) was higher by 15.6% than in patients with isolated AH and by 12.7% than in patients with isolated HBP (Table **3**).

A comparative analysis of hemodynamic parameters showed the following findings. The systolic blood pressure in AH patients in combination with HBP was 16% higher than in patients with isolated HBP and was not statistically significantly different from the corresponding rate in patients with isolated AH. The diastolic blood pressure in individuals with comorbidity of AH and HBP was 2.4% higher than in patients with isolated AH and 12.3% higher than in patients with isolated HBP (Table **3**).

A comparative determination of liver enzymes in all the studied groups of patients was carried out. Patients with combined diseases - AH and HBP had statistically significantly higher levels of AST and ALT in serum compared with patients with isolated AH and HBP, which indicated a

Table 2. The dynamics of occurrence of arterial hypertension associated with hepatobiliary diseases in the period from 2003 to 2017 (%±s_p).

Period of Hospitalization	Age (Years)	Gender	1. Workers (N=3300)		2. Employees (N=5406)		3. Administrative staff (N=4790)		p Chi-square	p Amended by Bonferroni		
			%	p men-women	%	p men-women	%	p men-women		{1-2}	{1-3}	{2-3}
2003-2005.	20-39	men	14.6±2.5	**0.0028**	7.5±2.3	**0.0002**	11.7±2.5	**0.0298**	0.1448	0.1440	1.0000	0.6693
		women	2.4±1.7		1.0±0.6		4.6±1.8		**0.0486**	0.9531	1.0000	**0.0474**
	40-59	men	23.7±1.9	0.7211	14.2±2.7	**0.0383**	22.0±1.7	0.6718	**0.0335**	**0.0270**	1.0000	0.0768
		women	24.8±2.4		21.3±1.6		20.9±2.0		0.3904	0.6570	0.6354	1.0000
	60 and older	men	18.6±4.2	**<0.0001**	24.6±5.2	**0.0358**	19.5±3.5	0.1282	0.6101	1.0000	1.0000	1.0000
		women	51.9±6.9		40.0±4.8		30.4±6.8		0.0938	0.4722	0.0939	0.7830
	Generally	men	20.8±1.4	0.2195	13.7±1.8	0.0885	19.7±1.3	0.4384	**0.0137**	**0.0108**	1.0000	**0.0333**
		women	23.8±2.0		17.5±1.1		18.1±1.6		**0.0132**	**0.0135**	0.0726	1.0000
2006-2008.	20-39	men	9.1±2.3	0.2332	8.7±2.0	0.0788	10.5±2.2	**0.0026**	0.8180	1.0000	1.0000	1.0000
		women	4.8±2.4		5.0±1.1		2.1±1.2		0.3374	1.0000	0.7749	0.4179
	40-59	men	25.0±2.0	0.7989	21.3±2.9	0.7384	22.0±1.6	0.1537	0.4046	0.9114	0.6981	1.0000
		women	24.2±2.4		22.4±1.4		18.6±1.7		0.1175	1.0000	0.1692	0.2937
	60 and older	men	28.0±5.0	0.5680	32.1±5.1	0.8979	22.5±3.4	0.4817	0.2587	1.0000	1.0000	0.3228
		women	23.4±6.2		32.9±3.6		27.1±5.8		0.3834	0.6336	1.0000	1.0000
	Generally	men	22.0±1.5	0.5194	18.1±1.8	0.7710	19.8±1.3	**0.0445**	0.2379	0.3030	0.7911	1.3131
		women	20.4±1.9		18.7±1.0		16.0±1.4		0.1312	1.0000	0.1743	1.0000
2009-2017.	20-39	men	6.0±2.4	0.0689	5.1±1.8	**0.0151**	16.9±2.9	**<0.0001**	**0.0006**	1.0000	**0.0300**	**0.0024**
		women	0.0±0.0		1.5±0.6		0.9±0.9		0.6046	1.0000	1.0000	1.0000
	40-59	men	19.8±2.2	0.1153	27.9±3.2	**0.0004**	22.6±1.8	**0.0051**	0.0939	0.0933	0.9783	0.4095
		women	14.9±2.2		17.1±1.2		15.7±1.6		0.6215	1.0000	1.0000	1.0000
	60 and older	men	16.5±4.2	0.4647	32.7±4.4	0.9553	28.5±3.6	0.3556	**0.0388**	**0.0354**	0.1287	1.0000
		women	21.6±5.8		32.4±3.0		34.1±5.0		0.2603	0.3852	0.3525	1.0000
	Generally	men	16.6±1.6	0.2366	21.4±1.9	**0.0027**	22.6±1.4	**0.0008**	**0.0264**	0.1638	**0.0222**	1.0000
		women	13.7±1.8		15.5±0.9		15.8±1.4		0.6314	1.0000	1.0000	1.0000

risk of the cytolytic syndrome in patients with comorbidity (Table **3**).

The concentration of alkaline phosphatase, and GGTP in the serum of patients with combined pathology (AH and HBP) was higher by 4.5% and 29.3%, respectively, than in patients with isolated hypertension and by 10.3% and 46%, higher than in patients with isolated PBP, respectively, which indicated the possible contribution of the presence of comorbidity in the formation of cholestatic syndrome.

Indicator of thymol test in patients with combined pathology statistically significantly exceeded the corresponding indicators in patients with isolated hypertension (by 6.7%) and in patients with isolated HBP (by 6.6%). Serum CRP concentration was statistically significantly higher in patients with combined pathology than in patients with isolated diseases, which may indicate a greater degree of manifestation of an inflammatory process in the presence of comorbidity.

Analysis of lipid metabolism indicators showed the following findings. Patients with AH and comorbidity of AH and HBP had higher levels of total cholesterol and atherogenic coefficient compared with the group of patients with isolated HBP (by 25.6% and 2.1%, respectively) (Table **4**).

The serum concentration of triglycerides in patients with AH was higher than in patients with HBP and in patients

Table 3. Comparative indicators of anthropometric, hemodynamic parameters and functional liver tests in patients with arterial hypertension, hepatobiliary pathology and in patients with comorbidity (hypertension and hepatobiliary pathology) (M ± m).

-	Patients with AH (n=5501)	Patients with HBP (n=3127)	Patients with AH and HBP (n=3876)	P
Height (sm)	165.02±0.21	168.19±0.36	165.93±0.20	p1.2<0.0001 p2.3=0.0005
Weight (kg)	81.52±0.15	86.62±0.63	95.35±0.32	p1.2<0.0001 p1.3<0.0001 p2.3<0.0001
Body mass index (kg/m^2)	29.94+0.18	30.69+0.43	34.60+0.30	p1.3<0.0001 p2.3<0.0001
Blood pressure systolic (mm Hg)	146.19±1.28	126.22±0.61	146.45±0.41	p1.2<0.0001 p2.3<0.0001
Blood pressure diastolic (mm Hg)	90.29±0.13	82.31±0.95	92.46±0.26	p1.2<0.0001 p1.3<0.0001 p2.3<0.0001
Aspartate aminotransferase (AST) (U/l)	25.21±0.34	25.01±0.37	27.3±0.37	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001
Alanine aminotransferase (ALT) (U/l)	29.67±0.49	29.68±0.56	33±0.6	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001
Alkaline phosphatase (U/l)	206.4±1.96	195.64±2.27	215.89±1.91	$p_{1.3}$<0.001 $p_{2.3}$<0.0001 $p_{1.2}$<0.01
Total bilirubin (μmol/l)	15.77±0.12	16.9±0.19	16.39±0.16	$p_{1.3}$<0.0001 $p_{2.3}$<0.05 $p_{1.2}$<0.0001
Bilirubin straight (μmol/l)	7.06±0.07	8.01±0.21	7.99±0.14	$p_{1.3}$<0.01 $p_{1.2}$<0.0001
Thymol test (unit S-H)	1.78±0.03	1.77±0.03	1.9±0.04	$p_{1.3}$<0.05 $p_{2.3}$<0.05
C-reactive protein (mg/l)	7.65±0.34	6.42±0.35	7.95±0.43	$p_{1.3}$<0.05 $p_{2.3}$<0.05 $p_{1.2}$<0.05
Alpha-amylase (u/l)	55.06±0.95	61.9±2.66	56.39±0.71	$p_{2.3}$<0.05 $p_{1.2}$<0.05

Table 4. Comparative indicators of lipid, purine, carbohydrate and protein metabolism in patients with hypertension, hepatobiliary diseases and their combination (M±m).

-	Patients with AH (n=5501)	Patients with HBP (n=3127)	Patients with AH and HBP (n=3876)	P
Cholesterol (mmol/l)	5.81±0.02	5.66±0.03	5.99±0.02	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001 $p_{1.2}$<0.0001
HS-HDL (mmol/l)	1.3±0.01	1.31±0.01	1.28±0.01	$p_{1.3}$<0.05 $p_{2.3}$<0.05
Atherogenic coefficient (U)	3.75±0.03	3.62±0.04	3.94±0.03	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001 $p_{1.2}$<0.01
Triglycerides (mmol/L)	1.79±0.02	1.57±0.03	1.80±0.02	$p_{2.3}$<0.0001 $p_{1.2}$<0.0001
HS-LDL (mmol/l)	3.71±0.02	3.63±0.03	3.89±0.02	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001 $p_{1.2}$<0.05
Uric acid (μmol/L)	323.45±1.98	307.83±2.78	349.21±2.27	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001 $p_{1.2}$<0.0001
Glucose fasting capillary blood (mmol/l)	5.13±0.02	4.86±0.02	5.03±0.03	$p_{1.3}$<0.001 $p_{2.3}$<0.05 $p_{1.2}$<0.001
Glycosylated hemoglobin (%)	6.25±0.56	6.15±0.14	7.41±0.29	$p_{1.3}$<0.05 $p_{2.3}$<0.001
Fructosamine (μmol/l)	304.09±2.09	292.2±2.33	302.34±1.82	$p_{2.3}$<0.001 $p_{1.2}$<0.001
Urea (mmol/l)	6.51±0.12	5.81±0.16	6.3±0.04	$p_{2.3}$<0.0001 $p_{1.2}$<0.001
Creatinine (μmol/l)	85.55±0.32	82.55±0.32	88.78±0.59	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001 $p_{1.2}$<0.0001
Total protein (g/l)	72.41±0.08	72.43±0.09	71.86±0.1	$p_{1.3}$<0.0001 $p_{2.3}$<0.0001

with a combined pathology (by 25.6% and 2.1%, respectively). The serum concentration of HSl-LDL in patients with comorbidity (AH, combined with HBP) was statistically significantly higher than in patients with isolated hepatobiliary pathology and isolated AH (by 6.7% and 4.6%, respectively).

One of the significant risk factors for the development of metabolic syndrome and the disorders of carbohydrate and lipid metabolism is an increase in serum uric acid content. In this study, it was found that in the presence of an associated state (AH and HBP), the serum uric acid concentration was 7.4% higher than in patients with isolated AH and 11.9% higher than in patients with isolated HBP.

Analysis of carbohydrate metabolism showed that the serum glucose content in the group with combined diseases was 13% higher and fructosamine content was 3.4% higher than in the group with isolated HBP (Table **4**).

When analyzing the values of indicators characterizing protein metabolism, a statistically significant increase in serum urea and creatinine levels was found in patients with comorbid pathology compared with a group of patients with HBP only (by 7.8% and 7.1%, respectively) (Table **4**).

4. DISCUSSION

When analyzing data from histories of patients treated in a general therapeutic clinic from 2003 to 2017, the occurrence of a combination of AH with HBP was observed to depend on the social status, age of patients and had gender differences.

It is known that, according to forecasts, the incidence and prevalence of the pathology of the hepatobiliary system will increase, and its occurrence is based on stress, dyskinetic, metabolic and other mechanisms [33], which is also characteristics of circulatory diseases [32] and increase the likelihood of their pathogenetic relationship.

According to our data, in the period from 2003 to 2017, the frequency of the combination of AH with HBP in patients with a therapeutic profile had a heterogeneous structure depending on gender and professional affiliation. In the period 2003-2005, the greatest occurrence of this comorbidity was found in workers. At the age of 60 years and older (workers and employees), the frequency of this combined pathology in women was higher than that in men.

In 2009-2017, the highest incidence of this comorbid pathology was observed in male employees, over the age of 60 years and in AUP workers aged 20-39 years. The frequency of the combination of these nosologies in men aged 20–39 years occupied by administrative activities, mainly with managerial functions, was higher by 11.8% than that of employees.

The results obtained indicate that the formation of combined somatic pathology is strongly influenced by the social status and gender of patients.

Temporary changes in the influence of these factors were identified. If before 2005 the highest incidence of comorbidity of AH and HBP was observed among workers and women (in the group over 60 years old), then after 2009, it was observed in men, employees (in the group over 60 years old) and administrative personnel (in the group 20-39 years).

The data obtained may indicate an increase in the value of occupational psycho-emotional stress and a decrease in resistance to it in men in the mechanisms of the formation of comorbidity in recent years. From the literature, the important role of psychosocial factors, including occupational stress, is known for the development of AH [32, 56, 57], diseases of the digestive system [33].

The stress of the psycho-emotional sphere contributes to the increased synthesis of steroid hormones, followed by an increase of atherogenic lipoprotein fractions in the blood, an increase in the content of catecholamines with cardiotropic effect, deterioration of liver function and the development of AH. The combination of these changes provides an important etiopathogenetic link in the development of diseases of the circulatory system and the hepatobiliary system [33, 58, 59].

In patients with the combination of AH and HBP, an increase in the comorbidity index was found in comparison with groups of patients with isolated diseases (AH, HBP).

In combined pathology (AH and HBP), the severity of the inflammatory process, as well as disorders of the liver, were found to be higher than with the presence of isolated AH and HBP. Changes in carbohydrate, protein, lipid and purine metabolism were more pronounced in combined pathology (AH and HBP). These changes aggravate the course of the pathology and are risk factors for diabetes, atherosclerosis and associated diseases, which require a personalized approach to the treatment and prevention of this category of patients.

AH is one of the main risk factors for NAFLD, which, in turn, is considered to be an independent risk factor for the development and progression of cardiovascular diseases [60, 61]. Non-alcoholic fatty liver disease is considered as a manifest pathology for metabolic syndrome [62]. A number of studies have shown that risk factors for cardiovascular diseases: arterial hypertension, central obesity, hyperglycemia, low level of high-density lipoprotein cholesterol, and hypertriglyceridemia are significantly associated with NAFLD [37, 63, 64].

NAFLD is associated with the formation of a pro-atherogenic lipid profile, including an increased level of HS-LD, apolipoprotein B100 and triglycerides, a decreased level of HS-HDL in serum [37, 65]. Disorders of lipid metabolism in the form of dyslipidemia underlie the development of atherosclerosis. Atherosclerosis and endothelial dysfunction, associated with it, in its turn, lead to the progression of AH, numerous microcirculatory disorders, ischemia and impaired function of internal organs, including the liver [66]. Thus, the violation of the functional state of the liver is one of the most important factors in the formation of dyslipidemia. At the same time, the liver is a target organ in atherogenic dyslipidemia associated with AH [60].

Disturbances in carbohydrate exchange, manifested by hyperglycemia, increased levels of insulin in serum and insulin resistance are important pathogenetic links of both

NAFLD and AH. Hyperglycemia promotes lesions of vessels walls and AH progression [67].

The obtained results indicate that in the pathogenesis of the comorbidity: AH and HBP, hyperglycemia, dyslipoproteinemia and hyperuricemia may play a significant role.

The metabolic risk factors of CNCD identified in patients with AH and NAFLD are closely interacting, being simultaneously the key pathogenetic links in the formation of CM.

Together, these factors can be considered as manifestations of the metabolic syndrome, which is defined as a complex of metabolic, hormonal and clinical disorders, based on insulin resistance and compensatory hyperinsulinemia [68-70]. In this case, a key role in the disturbances of lipid, carbohydrate and purine metabolism is played by the impaired liver function, which is also a target organ in the development of this syndrome [65, 71-73].

Discussing the pathogenetic relationship of AH and HBP, it is promising to consider current data on the epigenomic regulation of the blood circulation and metabolism by RNA interference involving small RNAs. Thus myco-RNA 10b is a factor affecting the activity of PPAR-alpha in the liver, participating in the pathogenetic mechanisms of NAFLD, and is also considered as a possible pathogenetic mediator of myocardial hypertrophy and atherosclerosis [74, 75].

Patients with comorbid conditions have a poorer prognosis for the course of the disease and reduced quality of life, with more pronounced difficulties in therapy compared to patients with mononosologies of the same class [53]. In this regard, it is necessary to develop an optimal strategy for the management of patients with combined nosologies. Prevention and treatment of chronic non-communicable diseases, including polymorbid pathology, may be more effective with a multifactorial approach. Such an approach will make it possible to deviate from the mononosological strategy of helping patients in a therapeutic clinic, which was most clearly revealed when introducing medical and economic standards.

5. LIMITATIONS

The results of our study should be interpreted within the context of the limitations.

Firstly, this study used a cross-sectional study design which limits the inferences of causality between the independent and dependent variables.

Secondly, the analysis did not take into account behavioral risk factors, as it was not possible to analyze all confounding factors that could affect the study - a detailed analysis of smoking, alcohol consumption *etc*. However, we controlled confounding factors as much as possible.

Thirdly, an artificially increased 3rd time period was taken for analysis due to the small number of patients.

CONCLUSION

In general, the results determine the need to study the common pathogenic mechanisms of the formation of AH, combined with HBP, development and improvement of the system of prevention, diagnostic and treatment of combined nosologies in patients with a therapeutic profile.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Committee of Biomedical Ethic of Federal Research Center for Basic and Translational Medicine, Novosibirsk, Russia.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures followed were in accordance with the requirements of the Helsinki Declaration of the World Association “Ethical Principles of Human Medical Research with Human Involvement” (2000) (in the revision of the 59th General Assembly of the World Medical Association, Seoul, 2008).

CONSENT FOR PUBLICATION

Informed written consent was obtained from the participants.

AVAILABILITY OF DATA AND MATERIALS

Research data were obtained by archival method. The source of the data - DOCA Clinical Information System + (Number of state registration certificate: 2011610378. Date of registration: 01/11/2011) of Federal Research Centre of Basic and Translational Medicine (Novosibirsk).

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Lefèvre T, d’Ivernois JF, De Andrade V, Crozet C, Lombrail P, Gagnayre R. What do we mean by multimorbidity? An analysis of the literature on multimorbidity measures, associated factors, and impact on health services organization. Rev Epidemiol Sante Publique 2014; 62(5): 305-14. http://dx.doi.org/10.1016/j.respe.2014.09.002 PMID: 25444838

[2] Wittenberg R. The challenge of measuring multi-morbidity and its costs. Isr J Health Policy Res 2015; 4: 1. http://dx.doi.org/10.1186/2045-4015-4-1 PMID: 25949796

[3] Belialov F. Treatment of heart disease in terms of comorbidity. Irkutsk: PIO IGMAPO, 2014, p. 308.

[4] Roberts KC, Rao DP, Bennett TL, Loukine L, Jayaraman GC. Prevalence and patterns of chronic disease multimorbidity and associated determinants in Canada Health Promot Chronic Dis Prev Can 2015; 35(6): 87-94.

[5] Nikolaev YuA, Sevostyanova EV, Mitrofanov IM, Polyakov VYa, Dolgova NA. Features of polymorbidity in patients of a therapeutic clinic of the cardiological and gastroenterological profile. Therapeutic archive 2016; 1: 40-45.

[6] Oganov RG, Drapkina OM. Comorbidity: Specifics of co-development and concomitance of several diseases in one patient. Cardiovasc Ther Prev (Fidenza) 2016; 5(4): 4-9. http://dx.doi.org/10.15829/1728-8800-2016-4-4-9

[7] Ahmadi B, Alimohammadian M, Yaseri M, *et al.* Multimorbidity: Epidemiology and risk factors in the Golestan cohort study, Iran: A cross-sectional analysis. Medicine (Baltimore) 2016; 95(7): e2756. http://dx.doi.org/10.1097/MD.0000000000002756 PMID: 26886618

[8] Zygmuntowicz M, Owczarek A, Elibol A, Chudek J. Comorbidities and the quality of life in hypertensive patients. Pol Arch Med Wewn 2012; 122(7-8): 333-40. http://dx.doi.org/10.20452/pamw.1345 PMID: 22814517

[9] Nikolaev YuA, Mitrofanov IM, Polyakov VYa, Dolgova NA. Arterial hypertension associated with somatic pathology in present-day practice of internal diseases. Health 2014; 6(1): 94-8. http://dx.doi.org/10.4236/health.2014.61015

[10] Dolgova NA, Shkurupy VA, Yakimova AV, Dobrovolskaya NP. Deforming dorsopathy in patients with a combination of arterial hypertension, dyslipidemia and obesity: Possible solutions of the problem. Bull Russ Acad Med Sci 2014; 34(2): 61-5.

[11] Quiñones AR, Markwardt S, Botoseneanu A. Multimorbidity Combinations and Disability in Older Adults. J Gerontol A Biol Sci Med Sci 2016; 71(6): 823-30. http://dx.doi.org/10.1093/gerona/glw035 PMID: 26968451

[12] Nunes BP, Flores TR, Mielke GI, Thumé E, Facchini LA. Multimorbidity and mortality in older adults: A systematic review and meta-analysis. Arch Gerontol Geriatr 2016; 67: 130-8. http://dx.doi.org/10.1016/j.archger.2016.07.008 PMID: 27500661

[13] Tarlovskaya EI. Comorbidity and polymorbidity - a modern interpretation and urgent tasks facing the therapeutic community. Kardiologiia 2018; 58(Suppl. 9): 29-38. http://dx.doi.org/10.18087/cardio.2562 PMID: 30312569

[14] Onder G, Palmer K, Navickas R, *et al.* Joint Action on Chronic Diseases and Promoting Healthy Ageing across the Life Cycle (JA-CHRODIS). Time to face the challenge of multimorbidity. A European perspective from the joint action on chronic diseases and promoting healthy ageing across the life cycle (JA-CHRODIS). Eur J Intern Med 2015; 26(3): 157-9. http://dx.doi.org/10.1016/j.ejim.2015.02.020 PMID: 25797840

[15] Quinodoz A, Déruaz-Luyet A, N'Goran AA, Herzig L. Prioritization strategies in the care of multimorbid patients in family medicine. Rev Med Suisse 2016; 12(518): 928-31. PMID: 27352587

[16] Park C, Fang J, Hawkins NA, Wang G. Comorbidity status and annual total medical expenditures in U.S. hypertensive adults. Am J Prev Med 2017; 53(6S2)(Suppl. 2): S172-81. http://dx.doi.org/10.1016/j.amepre.2017.07.014 PMID: 29153118

[17] Nikolaev YuA, Mitrofanov IM, Pospelova TI, Dolgova NA, Polyakov VYa. Features of polymorbidity in the modern clinic of internal diseases. Bulletin of the SB RAMS 2014; 34(2): 44-9.

[18] Arrigo M, Nijst P, Rudiger A. Optimising heart failure therapies in the acute setting. Card Fail Rev 2018; 4(1): 38-42. http://dx.doi.org/10.15420/cfr.2017:21:1 PMID: 29892475

[19] Dorofeeva JA, Tarlovskaya EI. [The quality of treatment of patients with atrial fibrillation, depending on the index of polymorbidity, preceded hospitalization for acute coronary syndrome]. Kardiologiia 2018; 5(S5): 54-9. http://dx.doi.org/10.18087/cardio.2478 PMID: 29894677

[20] Oganov RG, Simanenkov VI, Bakulin IG, *et al.* Comorbid pathology in clinical practice. Algorithms for diagnosis and treatment. Cardiovasc Ther Prev (Fidenza) 2019; 18(1): 5-66. http://dx.doi.org/10.15829/1728-8800-2019-1-5-66

[21] Gomez-Rubio P, Rosato V, Márquez M, *et al.* PanGenEU Study Investigators. A systems approach identifies time-dependent associations of multimorbidities with pancreatic cancer risk. Ann Oncol 2017; 28(7): 1618-24. http://dx.doi.org/10.1093/annonc/mdx167 PMID: 28383714

[22] Hudson B, Walker AJ, Irving WL. Comorbidities and medications of patients with chronic hepatitis C under specialist care in the UK. J Med Virol 2017; 89(12): 2158-64. http://dx.doi.org/10.1002/jmv.24848 PMID: 28480974

[23] Mehta KY, Wu HJ, Menon SS, *et al.* Metabolomic biomarkers of pancreatic cancer: A meta-analysis study. Oncotarget 2017; 8(40): 68899-915. http://dx.doi.org/10.18632/oncotarget.20324 PMID: 28978166

[24] Marrie RA. Comorbidity in multiple sclerosis: Past, present and future. Clin Invest Med 2019; 42(1): E5-E12. http://dx.doi.org/10.25011/cim.v42i1.32383 PMID: 30904030

[25] Chazova IE, Oschepkova EV. Experience in dealing with cardiovascular diseases in Russia. Analytical Vestnik 2015; 44(597): 4-8.

[26] Mozaffarian D, Benjamin EJ, Go AS, *et al.* American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation 2015; 131(4): e29-e322. http://dx.doi.org/10.1161/CIR.0000000000000152 PMID: 25520374

[27] Park JB, Kario K, Wang JG. Systolic hypertension: an increasing clinical challenge in Asia. Hypertens Res 2015; 38(4): 227-36. http://dx.doi.org/10.1038/hr.2014.169 PMID: 25503845

[28] Liu J, Ma J, Wang J, *et al.* Comorbidity analysis according to sex and age in hypertension patients in China. Int J Med Sci 2016; 13(2): 99-107. http://dx.doi.org/10.7150/ijms.13456 PMID: 26941567

[29] Al-Tuwijri AA, Al-Rukban MO. Hypertension control and comorbidities in primary health care centers in Riyadh. Ann Saudi Med 2006; 26(4): 266-71. http://dx.doi.org/10.5144/0256-4947.2006.266 PMID: 16883084

[30] Tini G, Sarocchi M, Tocci G, *et al.* Arterial hypertension in cancer: The elephant in the room. Int J Cardiol 2019; 281: 133-9. http://dx.doi.org/10.1016/j.ijcard.2019.01.082 PMID: 30718135

[31] Asmar R. Effects of treatment on arterial stiffness and central blood pressure--points to consider. J Clin Hypertens (Greenwich) 2015; 17(2): 105-6. http://dx.doi.org/10.1111/jch.12477 PMID: 25641094

[32] Oganov RG. Arterial hypertension. Moscow: GEOTAR-Media 2008.

[33] Komarov FI, Rapoport SI. Guide to gastroenterology M. Medical Information Agency 2010.

[34] Bang KB, Cho YK. Comorbidities and Metabolic Derangement of NAFLD. J Lifestyle Med 2015; 5(1): 7-13. http://dx.doi.org/10.15280/jlm.2015.5.1.7 PMID: 26528424

[35] Mikolasevic I, Milic S, Turk Wensveen T, *et al.* Nonalcoholic fatty liver disease - A multisystem disease? World J Gastroenterol 2016; 22(43): 9488-505. http://dx.doi.org/10.3748/wjg.v22.i43.9488 PMID: 27920470

[36] Farrell GC, Wong VW-S, Chitturi S. NAFLD in Asia--as common and important as in the West. Nat Rev Gastroenterol Hepatol 2013; 10(5): 307-18. http://dx.doi.org/10.1038/nrgastro.2013.34 PMID: 23458891

[37] Fargion S, Porzio M, Fracanzani AL. Nonalcoholic fatty liver disease and vascular disease: state-of-the-art. World J Gastroenterol 2014; 20(37): 13306-24. http://dx.doi.org/10.3748/wjg.v20.i37.13306 PMID: 25309067

[38] Hassan K, Bhalla V, Regal ME. A-Kader HH. Nonalcoholic fatty liver disease: a comprehensive review of a growing epidemic. World J Gastroenterol 2014; 20: 12082–101. J Gastroenterol 2014; 20(37): 13306-24.

[39] Ivashkin VT, Mayevskaya MV, Pavlov ChS, *et al.* Clinical recommendations on the diagnosis and treatment of non-alcoholic fatty liver disease of the Russian Society for the Study of the Liver and the Russian Gastroenterological Association. Rus J Gastroenterol, hepatol, Coloproctol 2016; 26(2): 24-42.

[40] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64(1): 73-84. http://dx.doi.org/10.1002/hep.28431 PMID: 26707365

[41] Polyakov VYa, Nikolaev YuA, Obukhov IV, Gevorgyan MM. Features of clinical and functional parameters in patients with arterial hypertension combined with diseases of the hepatobiliary system in the conditions of the North. Bulletin of new medical technologies 2013; 2: 395-399.

[42] Vya P, Nikolaev YuA, Pegova SV, *et al.* Features of changes of the carotid and vertebral arteries in patients with arterial hypertension associated with the pathology of the hepatobiliary system. Clin Med (Northfield Ill) 2016; 1: 39-42.

[43] Sevostyanova EV, Polyakov VYA, Nikolaev YUA, Mitrofanov IM. Risk factors for hypertension in patients with non-alcoholic fatty liver disease clinical medicine 2018; 6: 395-399.

[44] Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: Implications for pay for performance. JAMA 2005; 294(6): 716-24. http://dx.doi.org/10.1001/jama.294.6.716 PMID: 16091574

[45] Ferretti F. Unhealthy Behaviours: An International Comparison. PLoS One 2015; 10(10): e0141834. http://dx.doi.org/10.1371/journal.pone.0141834 PMID: 26512717

[46] Caughey GE, Vitry AI, Gilbert AL, Roughead EE. Prevalence of comorbidity of chronic diseases in Australia. BMC Public Health 2008; 8: 221. http://dx.doi.org/10.1186/1471-2458-8-221 PMID: 18582390

[47] Schäfer I, Hansen H, Schön G, *et al.* The influence of age, gender and socio-economic status on multimorbidity patterns in primary care. First results from the multicare cohort study. BMC Health Serv Res 2012; 12: 89. http://dx.doi.org/10.1186/1472-6963-12-89 PMID: 22471952

[48] Lochner KA, Cox CS. Prevalence of multiple chronic conditions among Medicare beneficiaries, United States, 2010. Prev Chronic Dis 2013; 10: E61. http://dx.doi.org/10.5888/pcd10.120137 PMID: 23618541

[49] Mitrofanov IM, Nikolaev YuA, Dolgova NA, Pospelova TI. Regional features of polymorbidity in the modern clinic of internal diseases. Clin Med (Northfield Ill) 2013; 6: 26-9.

[50] Sloane PD, Oudenhoven MD, Broyles I, McNabney M. Challenges to cost-effective care of older adults with multiple chronic conditions: Perspectives of Program of All-Inclusive Care for the Elderly medical directors. J Am Geriatr Soc 2014; 62(3): 564-5. http://dx.doi.org/10.1111/jgs.12708 PMID: 24628628

[51] Sevostyanova EV, Nikolaev YuA, Mitrofanov IM, Polyakov VYa, Dolgova NA. The role of risk factors for chronic non-communicable diseases in the development of polymorbid pathology. Clin Med (Northfield Ill) 2017; 95(8): 735-41.

[52] Nizov AA, Suchkova EI, Dashkevich OV, Trunina TP. Cardiovascular comorbidity in the real clinical practice of an ambulatory physician. Comparative register research in the Ryazan region. Cardiovasc Ther Prev (Fidenza) 2019; 18(2): 70-5. http://dx.doi.org/10.15829/1728-8800-2019-2-70-75

[53] Rijken M, van Kerkhof M, Dekker J, Schellevis FG. Comorbidity of chronic diseases: Effects of disease pairs on physical and mental functioning. Qual Life Res 2005; 14(1): 45-55. http://dx.doi.org/10.1007/s11136-004-0616-2 PMID: 15789940

[54] Belialov F. Comorbidity in internal medicine. Bulletin of Contemporary Clinical Medicine. 2010; 3(2): 44-47. http://dx.doi.org/10.20969/VSKM.2010.3(2).44-47.

[55] Schöttker B, Saum KU, Jansen EH, Holleczek B, Brenner H. Associations of metabolic, inflammatory and oxidative stress markers with total morbidity and multi-morbidity in a large cohort of older German adults. Age Ageing 2016; 45(1): 127-35. http://dx.doi.org/10.1093/ageing/afv159 PMID: 26563887

[56] Cuffee Y, Ogedegbe C, Williams NJ, Ogedegbe G, Schoenthaler A. Psychosocial risk factors for hypertension: an update of the literature. Curr Hypertens Rep 2014; 16(10): 483. http://dx.doi.org/10.1007/s11906-014-0483-3 PMID: 25139781

[57] Trudel X, Brisson C, Milot A, Masse B, Vézina M. Adverse psychosocial work factors, blood pressure and hypertension incidence: repeated exposure in a 5-year prospective cohort study. J Epidemiol Community Health 2016; 70(4): 402-8. http://dx.doi.org/10.1136/jech-2014-204914 PMID: 26530810

[58] Steptoe A, Feldman PJ, Kunz S, Owen N, Willemsen G, Marmot M. Stress responsivity and socioeconomic status: A mechanism for increased cardiovascular disease risk? Eur Heart J 2002; 23(22): 1757-63. http://dx.doi.org/10.1053/euhj.2001.3233 PMID: 12419295

[59] Ermakova MA, Aftanas LI, Shpagina LA. Characteristics of psychophysiological markers of stress in patients with arterial hypertension, depending on the degree of occupational risk. Bulletin SB RAMS 2014; 4: 42-7.

[60] Balukova EV. Non-alcoholic fatty liver disease and the risk of cardiovascular events. Russ Med J 2013; 13: 737-40.

[61] Brea A, Puzo J. Non-alcoholic fatty liver disease and cardiovascular risk. Int J Cardiol 2013; 167(4): 1109-17. http://dx.doi.org/10.1016/j.ijcard.2012.09.085 PMID: 23141876

[62] Katsiki N, Perez-Martinez P, Anagnostis P, Mikhailidis DP, Karagiannis A. Is nonalcoholic fatty liver disease indeed the hepatic manifestation of metabolic syndrome. Curr Vasc Pharmacol 2018; 16(3): 219-27. http://dx.doi.org/10.2174/1570161115666170621075619 PMID: 28669328

[63] Caserta CA, Mele A, Surace P, *et al.* Association of non-alcoholic fatty liver disease and cardiometabolic risk factors with early atherosclerosis in an adult population in Southern Italy. Ann Ist Super Sanita 2017; 53(1): 77-81. PMID: 28361809

[64] Ghani RA, Saqlain M, Zafar MM, Jabeen S, Naqvi SM, Raja GK. Identification of metabolic risk phenotypes predisposing to non-alcoholic fatty liver disease in a Pakistani cohort. Pak J Med Sci 2017; 33(1): 121-6. PMID: 28367184

[65] Gastaldelli A, Kozakova M, Højlund K, *et al.* RISC Investigators. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. Hepatology 2009; 49(5): 1537-44. http://dx.doi.org/10.1002/hep.22845 PMID: 19291789

[66] Zvenigorodskaya LA, Samsonova NG, Efremov LI, Cherkashova EA, Lazebnik LB. Gastrointestinal aspects of atherosclerosis. Exp Cllin Gastroenterol 2011; 2: 31-36.

[67] Vorobyova EN, Schumacher GI, Khoreva MA, Osipova IV. Endothelial dysfunction is a key element in the pathogenesis of atherosclerosis. Russ J Cardiol 2010; 2(82): 84-91.

[68] Aryev A, Ovsyannikova NA, Aryeva GT, *et al.* Geriatric polymorbidity. Prac Oncol 2015; 16(3): 83-89.

[69] Efremov LI, Komisarenko IA. Metabolic continuum and polymorbidity in geriatrics. Exp Cllin Gastroenterol 2014; 106(6): 4-7.

[70] Tsanava IA, Sharonova LA, Verbovoy AF. Metabolic syndrome and cardiovascular diseases. RMJ. Med Rev 2017; 11: 785-9.

[71] Korneeva ON, Drapkina OM, Buyever AO, Ivashkin VT. Non-alcoholic fatty liver disease as a manifestation of the metabolic syndrome. Clin Perspec Gastroenterol Hepatol 2005; 4: 24.

[72] Nikolenko LA, Goloshchapova ZA, Golovneva ES, Nikolenko ES. Risk factors for cardiovascular diseases in postmenopausal women and prophylactic methods for reducing them (literature review). RMJ 2016; 5: 328-30.

[73] Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in nonalcoholic fatty liver disease (NAFLD). Medicine 2018; 97(13): e0214. http://dx.doi.org/10.1097/MD.0000000000010214 PMID: 29595666

[74] Zheng L, Lv GC, Sheng J, Yang YD. Effect of miRNA-10b in regulating cellular steatosis level by targeting PPAR-alpha expression, a novel mechanism for the pathogenesis of NAFLD. J Gastroenterol Hepatol 2010; 25(1): 156-63. http://dx.doi.org/10.1111/j.1440-1746.2009.05949.x PMID: 19780876

[75] Smirnova AV, Suhorukov VN, Karagodin VP, Orehov AN. Epigenetic factors in atherogenesis: miRNA. Biomeditsinskaya Chem 2016; 62(2): 134-140.