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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.

Keywords: Hypertension, hepatobiliary diseases, comorbidity, gender, age, social status.

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...
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, cholangue, 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-amylos, bilirubin, glucose, glycyslated 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 3-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 I.

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
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 transnological 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 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                      |
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 РBP, 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 with isolated hypertension (by 4.5%).
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/m²)   | 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                         | p1.2<0.0001 p1.3<0.0001 |
| Alanine aminotransferase (ALT) (U/l) | 29.67±0.49             | 29.68±0.56                | 33±0.6                            | p1.2<0.0001 p1.3<0.0001 |
| Alkaline phosphatase (U/l) | 206.4±1.96               | 195.64±2.27               | 215.89±1.91                       | p1.2<0.0001 p1.3<0.0001 p1.2<0.01 |
| Total bilirubin (µmol/l)   | 16.9±0.19                 | 16.39±0.16                | 16.9±0.16                         | p1.2<0.0001 p1.3<0.0001 p2.3<0.0001 |
| Bilirubin straight (µmol/l) | 7.06±0.07                | 8.01±0.21                 | 7.99±0.14                         | p1.2<0.0001 p2.3<0.0001 |
| Thymol test (unit S-H)     | 1.78±0.03                 | 1.77±0.03                 | 1.9±0.04                          | p1.2<0.0001 p2.3<0.0001 |
| C-reactive protein (mg/l)  | 7.65±0.34                 | 6.42±0.35                 | 7.95±0.43                         | p1.2<0.0001 p2.3<0.0001 p1.3<0.05 |
| Alpha-amylase (u/l)        | 55.06±0.95                | 61.9±2.66                 | 56.39±0.71                        | p1.2<0.0001 p1.3<0.0001 p2.3<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                         | p1.2<0.0001 p2.3<0.0001 p1.2<0.0001 |
| HS-HDL (mmol/l)           | 1.3±0.01                  | 1.31±0.01                 | 1.28±0.01                         | p1.2<0.05 p2.3<0.05 |
| Atherogenic coefficient (U) | 3.75±0.03                 | 3.62±0.04                 | 3.94±0.03                         | p1.2<0.0001 p2.3<0.0001 p1.3<0.01 |
| Triglycerides (mmol/L)    | 1.79±0.02                 | 1.57±0.03                 | 1.80±0.02                         | p1.2<0.0001 p2.3<0.0001 |
| HS-LDL (mmol/l)           | 3.71±0.02                 | 3.63±0.03                 | 3.89±0.02                         | p1.2<0.0001 p2.3<0.0001 p1.3<0.05 |
| Uric acid (µmol/L)        | 323.45±1.98               | 307.83±2.78               | 349.21±2.27                       | p1.2<0.0001 p2.3<0.0001 p1.3<0.0001 |
| Glucose fasting capillary blood (mmol/l) | 5.13±0.02                 | 4.86±0.02                 | 5.03±0.03                         | p1.2<0.001 p2.3<0.05 p1.3<0.001 |
| Glycosylated hemoglobin (%) | 6.25±0.56                 | 6.15±0.14                 | 7.41±0.29                         | p1.2<0.001 p2.3<0.0001 |
| Fructosamine (µmol/l)     | 304.09±2.09               | 292.2±2.33                | 302.34±1.82                       | p1.2<0.0001 p1.3<0.001 |
| Urea (mmol/l)             | 6.51±0.12                 | 5.81±0.16                 | 6.3±0.04                          | p1.2<0.0001 p2.3<0.0001 |
| Creatinine (µmol/l)       | 85.55±0.32                | 82.55±0.32                | 88.78±0.59                        | p1.2<0.0001 p2.3<0.0001 p1.3<0.0001 |
| Total protein (g/l)       | 72.41±0.08                | 72.43±0.09                | 71.86±0.1                         | p1.2<0.0001 p2.3<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, 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 proatherogenic lipid profile, including an increased level of HLSLD, 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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