УДК 616.36-003.826-02:616.366-089.87

DOI: https://doi.org/10.17816/PAVLOVJ110948

Критерии формирования жировой дегенерации печени у лиц различных возрастных групп в отдаленном периоде после миниинвазивной холецистэктомии

А. Р. Амбарцумян[1], Б. А. Чумак[2], Л. Е. Дерягина[3]✉, С. С. Бацков[4], Е. Д. Пятибрат[2]

[1] Страховое общество газовой промышленности, Санкт-Петербург, Российская Федерация;
[2] Военно-медицинская академия имени С. М. Кирова, Санкт-Петербург, Российская Федерация;
[3] Московский университет Министерства внутренних дел Российской Федерации имени В. Я. Кикотя, Москва, Российская Федерация;
[4] Всероссийский центр экстренной и радиационной медицины имени А. М. Никифорова, Санкт-Петербург, Российская Федерация

АННОТАЦИЯ

Введение. Несмотря на технические достижения в медицине и применении миниинвазивных лапароскопических методик, осложнения холецистэктомии существенно снижают качество жизни прооперированных пациентов. Развитие наиболее распространенного и тяжелого осложнения жировой дегенерации печени (ЖДП) трудно прогнозируемо из-за множества факторов, виляющих на формирование этого заболевания.

Цель. Выявить прогностические критерии формирования ЖДП в отдаленном периоде после холецистэктомии и научно обосновать их значимость.

Материалы и методы. Для выявления прогностических критериев формирования ЖДП в отдаленном периоде после миниинвазивной холецистэктомии обследовано 330 пациентов (159 мужчин и 171 женщина), проходивших хирургическое лечение. Оценивали антропометрические данные, показатели гемодинамики, рассчитывали вегетативный индекс. Проводили ультразвуковую оценку холедоха и эластографию печени, магниторезонансную томографию печени и магниторезонансную холангиопанкреатографию. С помощью хромато-масс-спектрометрии определяли микробные маркеры пристеночного микробиома кишечника.

Результаты. Показатели индекса массы тела свидетельствуют о взаимосвязи формирования ЖДП с повышенной массой тела у пациентов в более старшем возрасте. В первой возрастной группе с ЖДП превалировал симпатический статус, а в контрольной группе того же возраста преобладала ваготония. В более старшем возрасте во второй и третьей подгруппах вегетативная регуляция не оказывала влияния на формирование ЖДП. Диаметр холедоха у мужчин и женщин, страдающих ЖДП, первой возрастной подгруппы был выше относительно лиц группы контроля и предоперационного периода, а также относительно более старших лиц этой же группы. В отдаленном периоде после холецистэктомии в группе с жировой дегенерацией печени условно патогенная микрофлора превалировала над эссенциальной, а аэробная — над анаэробной, наблюдалось повышение количества грибов и вирусов, изменялось распределение облигатной микрофлоры за счет снижения содержания эубактерий и превалирования лактобактерий над содержанием бифидобактерий в пристеночном слое кишечника. У лиц более старшего возраста определялось снижение облигатной микрофлоры и повышение условно патогенной, в т. ч. за счет аэробной.

Выводы. На формирование ЖДП в отдалённом периоде после холецистэктомии оказывают существенное влияние возраст, вегетативная регуляция и масса тела. В старшей группе вегетативная регуляция оказывает меньшее влияние, а повышение массы тела большее по сравнению с лицами более молодого возраста.

Ключевые слова: *жировая дегенерация печени; желчнокаменная болезнь; холецистэктомия; постхолецистэктомический синдром; вегетативная регуляция; ожирение*

Для цитирования:
Амбарцумян А.Р., Чумак Б.А., Дерягина Л.Е., Бацков С.С., Пятибрат Е.Д. Критерии формирования жировой дегенерации печени у лиц различных возрастных групп в отдаленном периоде после миниинвазивной холецистэктомии // Российский медико-биологический вестник имени академика И. П. Павлова. 2023. Т. 31, № 2. С. 231–242. DOI: https://doi.org/10.17816/PAVLOVJ110948

Рукопись получена: 16.09.2022 **Рукопись одобрена:** 13.01.2023 **Опубликована:** 30.06.2023

DOI: https://doi.org/10.17816/PAVLOVJ110948

Criteria of Formation of Fatty Liver Disease in Individuals of Different Age Groups in the Long-Term Period after Minimally Invasive Cholecystectomy

Aleksandr R. Ambartsumyan[1], Boris A. Chumak[2], Larisa E. Deryagina[3]✉, Sergey S. Batskov[4], Elena D. Pyatibrat[2]

[1] Gas Industry Insurance Company, Saint-Petersburg, Russian Federation;
[2] Kirov Military Medical Academy, Saint-Petersburg, Russian Federation;
[3] V. Ya. Kikot Moscow University of the Ministry of Internal Affairs of the Russian Federation, Moscow, Russian Federation;
[4] The Nikiforov Russian Center of Emergency and Radiation Medicine, Saint-Petersburg, Russian Federation

ABSTRACT

INTRODUCTION: Despite the technical advance in medicine and the use of minimally invasive laparoscopic techniques, complications of cholecystectomy considerably reduce the quality of life of the operated patients. Development of the most common and severe complication — fatty liver disease (FLD) — is difficult to predict due to numerous factors that influence its formation.

AIM: To identify prognostic criteria of formation of FLD in the long-term period after cholecystectomy and to scientifically substantiate their significance.

MATERIALS AND METHODS: To identify prognostic criteria of formation of FLD in the long-term period after minimally invasive cholecystectomy, 330 patients (159 men and 171 women) who underwent surgical treatment, were examined. Anthropometric data, hemodynamic parameters were evaluated, autonomic index was calculated. US evaluation of choledoch and Elastography of the liver, magnetic resonance tomography of the liver and magnetic resonance cholangiopancreatography were performed. Using chromatography-mass-spectrometry, microbial markers of parietal microbiome of the intestine were determined.

RESULTS: Parameters of body mass index indicate the interrelation between the formation of FLD and increased body mass in patients of older age. In the first group with FLD, sympathetic status prevailed, and in the control group of the same age, parasympathicotonia was predominating. At the older age, in the second and third subgroup, the autonomic regulation did not influence the formation of FLD. The choledoch diameter in men and women with FLD of the first age subgroup was greater relative to patients of the control group and of the preoperative period and also relative to older patients of the same group. In the long-term period after cholecystectomy in the group with fatty liver disease, the opportunistic microflora prevailed over essential one, and aerobic microflora — over anaerobic one. Besides, increased amount of fungi and viruses was noted, as well as a change in the distribution of obligate microflora due to decrease in the content of eubacteria and predomination of lactobacteria over bifidobacteria in the parietal layer of the intestine. In the individuals of older age, reduction of the obligate and increase in the opportunistic microflora including aerobic one, was noted.

CONCLUSIONS: Age, autonomic regulation and body mass have a significant influence on the formation of FLD in the long-term period after cholecystectomy. In the group of older patients, the influence of the autonomic regulation is lower, and increase in body mass is higher than in younger individuals.

Keywords: *fatty liver disease; cholelithiasis; cholecystectomy; postcholecystectomy syndrome; autonomic regulation; obesity*

For citation:
Ambartsumyan AR, Chumak BA, Deryagina LE, Batskov SS, Pyatibrat ED. Criteria of Formation of Fatty Liver Disease in Individuals of Different Age Groups in the Long-Term Period after Minimally Invasive Cholecystectomy. *I. P. Pavlov Russian Medical Biological Herald.* 2023;31(2):231–242. DOI: https://doi.org/10.17816/PAVLOVJ110948

Received: 16.09.2022 **Accepted:** 13.01.2023 **Published:** 30.06.2023

ECO•VECTOR

LIST OF ABBREVIATIONS

AD — arterial pressure
BMI — body mass index
CE — cholecystectomy
CL — cholelithiasis
DAP — diastolic arterial pressure
DOS — dysfunction of Oddi sphincter
FLD — fatty liver disease
MPI — magnetic resonance imaging
MRCPG — magnetic resonance cholangiopancreatography
PCCES — postcholecystectomy syndrome
PDFF — proton density fat fraction
PR — pulse rate
SAP — systolic arterial pressure
US — ultrasound
WHO — World Health Organization

INTRODUCTION

The incidence of cholelithiasis (CL) is currently taking catastrophic proportion — today the disease affects about 20% of the adult population. With this, women are affected 5 times more often than men, due to frustration of estrogenic background in the pathogenesis of gallstone formation [1]. In Russia alone, more than 100,000 cholecystectomies are performed annually. In the current stage of development of surgical treatment of CL, minimally invasive laparoscopic methods are widely used permitting to considerably reduce traumatic character of the surgery and shorten the rehabilitation period [2].

Even the use of the latest technologies does not always permit to obtain complete healing in the long-term period. More than 40% of operated patients complain of different disorders of the regulation of the gastrointestinal tract, often accompanied by pain and discomfort, which significantly reduces the quality of life of such patients [3]. The sympathocomplex of disorders of the digestive system directly related to surgical intervention was given the collective name 'postcholecystectomy syndrome' (PCCES) [4].

The consequences of cholecystectomy are not always associated with the biliary tract. In approximately 40% of cases of long-term postoperative disorders, fatty liver disease (FLD) develops due to both general etiological factors and pathogenetic peculiarities of passage of bile after the loss of the gall bladder [5–7].

The pathogenesis of FLD includes formation of insulin resistance and impaired excretion of cholesterol leading to increase in the infiltration of hepatocytes with lipids [8–10]. One of the key elements of pathogenesis is dysfunction of Oddi sphincter (DOS) which deranges the passage and recirculation of bile with the result of reduction of its bactericidal properties and excessive bacterial growth in the intestine [11, 12]. An important contribution to the formation of FLD after CE is made by the autonomic nervous system, therefore, in predicting postoperative outcomes, it is necessary to take into account the peculiarities of autonomic regulation and the age of patients.

The **aim** of this study to find prognostic criteria for the formation of fatty liver disease in the remote period after cholecystectomy and to scientifically substantiate their significance.

MATERIALS AND METHODS

To develop prognostic criteria for the formation of FLD in the long-term period after laparoscopic minimally invasive CE, clinical data of 330 patients (159 men and 171 women) who underwent planned surgical treatment, were analyzed.

Exclusion criteria: a coarse pathology of digestive, respiratory and circulatory system, hepatic steatosis, hepatic cirrhosis, active hepatitis, diabetes mellitus, alcoholism and oncologic diseases in the preoperative period.

On admission to hospital, patients signed a standard for a medical institution form of Informed content. The results of standard clinical procedures for this category of patients were analyzed on our clinical base, no other clinical intervention were conducted, so no approval of the Ethic Committee was required.

Patients included into the study, were divided to three ***age subgroups***: subgroup 1 — from 45 to 59 years; subgroup 2 — from 60 to 74; subgroup 3 — above 75 (Table 1).

A year after the operation, according to the results of the instrumental examination which included elastography and magnetic resonance imaging (MRI), the studied patients were divided to two groups — a g***roup of patients with signs of fatty hepatosis*** and patients with ***no fatty alterations of the liver***.

Patients were divided to groups depending on the severity of the echographic signs of the formation of the FLD according to the method of S. S. Batskov, that included assessment of liver enlargement, visualization of hepatic veins, measurement of distal attenuation of sound, verification of parenchymal hyperechogenicity, fixation of the diaphragmatic contour, determination of angioarchitectonics of hepatic veins, determination of the degree of expansion of the portal vein diameter and splenomegaly (Table 2).

DOI: https://doi.org/10.17816/PAVLOVJ110948

Table 1. Demographic Parameters of Analyzed Sample of Patients Who Underwent Cholecystectomy

Gender	Age Subgroups		
	First	Second	Third
	45–59 years	60–74 years	above 75 years
Men	50	68	41
Women	67	70	39

Table 2. Degree of Fatty Liver Disease by S. S. Batskov Method a Year after Cholecystectomy in Age Groups of Men and Women, n

Degree	First Group	Second Group	Third Group
	45–59 years	60–74 years	above 75 years
Men			
I degree	21	22	15
II degree	5	8	4
III degree	–	2	–
IV degree	–	–	–
Women			
I degree	27	25	18
II degree	4	9	2
III degree	–	–	1
IV degree	–	–	–

The results were more precisely defined using the quantitative evaluation of fatty hepatosis through measurement of fat concentration determined by proton density fat fraction (PDFF). PDFF was calculated by dividing the quantity of fat protons in the liver by the total quantity of protons in the liver (Table 3). To evaluate the degree of FLD by MRI-determined proton density, the scoring system of D. E. Kleiner, et al. was used [13–15] (Table 4).

By all parameters of the instrumental methods, statistically significant differences of the degree of liver infiltration with fat were determined that permitted to diagnose FLD and divide the groups by its presence (Table 5). FLD of different degree was determined after CE in 77 of 159 of study men and in 86 of 171 women.

After that, anthropometric data were evaluated, body mass index (BMI) was calculated in kg/m2. Hemodynamic parameters were determined:

- pulse rate (PR) by palpation in the projection of the radial artery;

- arterial pressure (AP including systolic (SAP) and diastolic (DAP)) was measured by Korotkoff method;

- autonomic index (Kérdö index) was calculated by the formula:

Kérdö index = (1 — DAP / Pulse) × 100,

where IKérdö — autonomic index, DAP — diastolic pressure.

Vagotonia — predomination of parasympathetic tone was determined by Kérdö index > (-1.6); amphotonia — the balance between sympathetic and parasympathetic tone was determined by the index value from (-1.5) to +1.5; sympathicotonia — by the index value > (+1.6).

For ultrasound evaluation of choledoch and liver elastography, Vivid S60 scanner (General Electric, USA), with curvilinear transducer 3–5 MHz was used. Examination to evaluate DOS was performed in the morning, the second examination was performed after cholecystectomy (during the second examination, no choleretic drugs were used) (7).

The data on the choledoch diameter obtained by ultrasound examination (US) were made more exact in magnetic resonance cholangiopancreatography (MRCPG). Determination of FLD degree and MRCPG [16, 17] were performed using Magnetom Aera 1.5T tomograph (Shimadzu, Japan). The quantitative and qualitative composition of the parietal intestinal microbiota was

Table 3. Criteria Used in Evaluation of Fatty Liver Disease Degree [13–15]

Degree	Condition	% of Fat Concentration
0	No fatty hepatosis	≤ 5
1	Mild fatty hepatosis	from 5 to 33
2	Moderate fatty hepatosis	from 33 to 66
3	Severe fatty hepatosis	> 66

Table 4. Results of Instrumental Examination in a Year after Cholecystectomy, M ± σ

Parameters	Control			Fatty Liver Disease		
	First Group	Second Group	Third Group	First Group	Second Group	Third Group
	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years
Men						
Elastography, kPa	5,8 ± 1,3	6,2 ± 0,9	6,1 ± 1,1	8,7 ± 1,4*	9,3 ± 0,7*	9,6 ± 0,5*
Liver MRI, % of fat	2,2 ± 1,8	4,1 ± 1,5	3,6 ± 2,1	17,6 ± 3,8	21,3 ± 7,3	25,4 ± 6,2
Women						
Elastography, kPa	5,4 ± 0,9	6,1 ± 1,2	6,3 ± 0,7	8,3 ± 1,5*	9,7 ± 0,8*	9,5 ± 1,1*
Liver MRI, % of fat	2,5 ± 1,6	3,2 ± 1,3	3,1 ± 1,8	12,5 ± 5,2*	24,6 ± 8,2*	26,3 ± 7,2*

Note: MRI — magnetic resonance imaging; * — to the control group, p < 0.001

Table 5. Distribution of Analyzed Sample of Patients Depending on Existence of Fatty Liver Disease in a Year after Cholecystectomy, n

Gender	Control, n = 167			Fatty Liver Disease, n = 163		
	First Group	Second Group	Third Group	First Group	Second Group	Third Group
	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years
Men	24	36	22	26	32	19
Women	31	36	18	31	34	21

determined on Shimadzu LCMS 8030 triple quadrupole mass spectrometer (Shimadzu, Japan).

Statistical analysis of the results was performed in the Office 2010 (Microsoft, USA), Statistica application software package for Windows 10.0 (Microsoft, USA). The character of the distribution of variables was determined using Kolmogorov–Smirnov test. The obtained results indicated normal distribution, which was the reason for using parametric statistical methods for subsequent data analysis. The results are presented in the form of M — arithmetic mean and σ — standard deviation. For comparison between the groups, Student's t-test for independent samples was used. The differences were considered statistically significant at $p < 0.05$.

RESULTS

No differences in the anthropometric parameters between the group of FLD and the control group were found (Table 6).

With that, higher parameters of BMI and weight were recorded in patients with FLD (both men and women) in the second and third age subgroups compared with the control group of the same age. Thus, the relationship between the formation of fatty liver disease and increased body weight was determined in patients of older age operated on for cholelithiasis.

The pulse rate in both men and women in most cases increased with age, and in the first age group in patients with developing FLD more significantly than in the control group (Table 7). A year after CE, no significant changes in pulse rate were detected. SAP at an older age, with rare exceptions, was higher than in the first age group and practically did not change within a year after CE. DAP changed without any visible pattern. In men, a year after CE, higher levels of DAP were observed in the first and third subgroups relative to the control group, and in the second age subgroup, on the contrary, lower than in the first group. In the second age subgroup of women, who subsequently developed FLD, DAP levels before surgery were lower. A year after CE, oppositely directed changes were noted relative to the control group: in the second subgroup they decreased, and in the third they increased.

Table 6. Anthropometric Data in Analyzed Sample of Patients, M ± σ

Parameters	Control			Fatty Liver Disease		
	First Group	**Second Group**	**Third Group**	**First Group**	**Second Group**	**Third Group**
	45–59 years	**60–74 years**	**above 75 years**	**45–59 years**	**60–74 years**	**above 75 years**
Men						
Age, years	53.2 ± 3.8	66.8 ± 3.7	76.7 ± 1.5	52.4 ± 4.6	66.7 ± 4.5	77.2 ± 1.5
Weight, kg	85.4 ± 11.2	95.7 ± 7.3	72.4 ± 6.4	92.8 ± 16.8	103.4 ± 11.1*	81.0 ± 11.6*
Height, cm	177.6 ± 5.8	176.6 ± 6.5	174.5 ± 4.9	177.7 ± 7.1	178.4 ± 6.7	175.5 ± 6.7
Body mass index, kg/m^2	27.4 ± 2.5	28.9 ± 1.6	23.4 ± 1.5	29.3 ± 4.6	33.1 ± 1.2*	27.3 ± 1.9*
Women						
Age, years	50.2 ± 3.7	66.5 ± 3.7	80.1 ± 2.6	50.0 ± 3.9	65.6 ± 4.0	79.0 ± 2.5
Weight, kg	78.6 ± 11.5	84.7 ± 10.3	64.2 ± 12.6	85.6 ± 13.2	90.9 ± 11.1*	69.8 ± 15.4*
Height, cm	167.2 ± 8.5	165.8 ± 8.1	161.5 ± 7.3	166.3 ± 9.3	166.1 ± 7.6	161.1 ± 8.2
Body mass index, kg/m^2	28.9 ± 1.7	29.3 ± 1.3	24.2 ± 1.2	30.2 ± 2.3	32.8 ± 1.8*	26.8 ± 1.3*

Note: * — to the control group, p < 0.001

Table 7. Parameters of Hemodynamics and Autonomic Status in Patients of Different Age Who Underwent Cholecystectomy, Depending on Formation of Fatty Liver Disease, M ± σ

Parameters	Before Cholecystectomy						In a Year after Cholecystectomy					
	Control			Fatty Liver Disease			Control			Fatty Liver Disease		
	First Group	**Second Group**	**Third Group**	**First Group**	**Second Group**	**Third Group**	**First Group**	**Second Group**	**Third Group**	**First Group**	**Second Group**	**Third Group**
	45–59 years	**60–74 years**	**above 75 years**	**45–59 years**	**60–74 years**	**above 75 years**	**45–59 years**	**60–74 years**	**above 75 years**	**45–59 years**	**60–74 years**	**above 75 years**
Men												
Pulse rate	72.1 ± 3.5	76.3 ± 3.6$^{\#}$	78.5 ± 2.7$^{\#}$	77.1 ± 2.2*	77.6 ± 5.2	79.6 ± 2.4$^{\#}$	73.2 ± 2.8	77.1 ± 3.2$^{\#}$	76.5 ± 1.3$^{\#}$	78.3 ± 3.7*	76.5 ± 4.1	78.3 ± 4.6*
Systolic arterial pressure	127.3 ± 2.4	135.2 ± 5.4$^{\#}$	141.4 ± 5.1$^{\#}$	127.1 ± 4.7	141.7 ± 11.3$^{\#*}$	147.4 ± 7.2$^{\#*}$	124.7 ± 2.7	135.6 ± 7.3$^{\#}$	139.2 ± 5.7$^{\#}$	142.6 ± 8.1$^{\&*}$	137.5 ± 7.9$^{\&}$	139.4 ± 8.1$^{\&}$
Diastolic arterial pressure	75.7 ± 4.3	77.4 ± 3.3	76.5 ± 2.2	74.3 ± 3.1	75.2 ± 4.8	78.2 ± 3.7$^{\#}$	73.3 ± 3.2	75.8 ± 2.8	73.4 ± 3.5	82.1 ± 3.1$^{*\&}$	74.4 ± 3.6$^{\#}$	77.2 ± 7.2$^{\#*}$
Autonomic index	-4.9 ± 1.2	-1.4 ± 0.5$^{\#}$	2.6 ± 1.3$^{\#}$	3.8 ± 0.7*	3.1 ± 0.7*	1.4 ± 0.7$^{*\#}$	-1.6 ± 0.5$^{\&}$	1.7 ± 1.4$^{\#}$	3.9 ± 1.5$^{\#\&}$	4.8 ± 1.3$^{*\&}$	2.8 ± 0.7$^{*\#}$	1.5 ± 0.4$^{*\#}$
Women												
Pulse rate	74.3 ± 3.2	75.4 ± 4.1	77.6 ± 3.1$^{\#}$	77.2 ± 3.2*	76.3 ± 2.3	77.4 ± 5.2	71.2 ± 2.4$^{\&}$	75.4 ± 3.2$^{\#}$	74.5 ± 2.9$^{\#}$	78.4 ± 4.2*	74.3 ± 3.9	76.4 ± 5.1
Systolic arterial pressure	125.2 ± 3.5	129.1 ± 2.6$^{\#}$	131.3 ± 5.4$^{\#}$	127.3 ± 4.2	141.5 ± 8.6$^{*\#}$	147.5 ± 6.4$^{*\#}$	122.3 ± 3.5	125.5 ± 8.7	129.6 ± 8.5$^{*\#}$	140.3 ± 7.5$^{\&}$	139.7 ± 12.1*	137.5 ± 7.8$^{\&*}$
Diastolic arterial pressure	76.7 ± 3.6	77.3 ± 3.1	76.7 ± 4.1	74.5 ± 3.7	73.6 ± 5.1*	76.1 ± 2.7	74.5 ± 2.1	77.2 ± 4.1	71.3 ± 2.8$^{\#\&}$	75.3 ± 2.9	72.5 ± 3.8*	77.6 ± 5.7*
Autonomic index	-3.2 ± 1.7	-2.5 ± 1.2$^{\#}$	1.2 ± 1.4$^{\#}$	3.5 ± 1.4*	2.4 ± 1.9$^{*\#}$	1.7 ± 1.4$^{\#}$	-4.6 ± 3.1$^{\&}$	-2.4 ± 1.5$^{\#}$	4.3 ± 1.7$^{\#}$	4.0 ± 1.5*	2.4 ± 1.2$^{*\#}$	-1.6 ± 0.8$^{*\#}$

Notes: * — to the control group, p < 0.001; # — to the analogous first age group, p < 0,001; & — to the period preceding cholecystectomy, p < 0.001

In evaluation of the autonomic status, of attention was the fact that in patients of the first age category of both genders with developed FLD, sympathetic tone predominated before and after CE, and in the control group of the same age, vagotonia predominated (Tables 7, 8). At an older age, in the second and third subgroups of patients with FLD, both amphotonia and poorly expressed sympathicotonia were determined.

Table 8. Number of Patients with Fatty Liver Disease Depending on Age, Gender and Autonomic Status, n (%)

Vegetative status	Control			Fatty Liver Disease		
	First Group 45–59 years	Second Group 60–74 years	Third Group above 75 years	First Group 45–59 years	Second Group 60–74 years	Third Group above 75 years
Men						
Patients with Sympathicotonia	5 (21)	8 (23)	11 (50)	19 (72)	20 (61)	4 (21)
Patients with vagotonia	15 (63)	5 (12)	3 (15)	3 (12)	8 (26)	5 (26)
Patients with amphotonia	3 (16)	23 (65)	8 (35)	4 (16)	4 (13)	10 (53)
Women						
Patients with Sympathicotonia	5 (15)	6 (16)	10 (54)	19 (62)	16 (47)	6 (28)
Patients with vagotonia	18 (58)	17 (48)	4 (23)	5 (15)	7 (21)	4 (19)
Patients with amphotonia	8 (27)	13 (36)	4 (23)	7 (23)	11 (32)	11 (53)

Distribution of patients depending on the autonomic status showed that among men with FLD formed in a year, there were 72% with sympathicotonia in the first group, 61% in the second and only 21% in the third group. Among women with FLD, there were 62% with sympathicotonia in the first group, 47% in the second, and 28% in the third. With this, in the groups of men and women without FLD, in patients of younger age and in the first age subgroup, vagotonia prevailed. Thus, there is *a relationship between formation of FLD and the autonomic status*; until 60, the formation of FLD after CE is associated with predomination of sympathetic tone, with age this relationship decreases and after 75 the autonomic status does not influence the formation of this disease.

Dysfunction of Oddi sphincter that was evaluated by increase in the width of the choledoch, signs of dysfunction were to a higher extent present in patients with FLD developed in a year after the surgery. The results of the width of choledoch obtained by US and MRCPG completely coincided by the degree of expansion and direction. In the groups of both men and women with FLD ,the parameters of width of choledoch were greater relative to the control group. Besides, parameters in these groups also changed relative to the preoperative period. In patients with FLD under 60, the choledoch diameter was greater than in older patients of the same group. In older groups without FLD, increase in the width of choledoch was determined relative to the first age subgroup and to the preoperative period (Table 9).

In patients with FLD in the first age subgroup both among men and women, 76% and 71% of patients respectively were determined with signs of DOS, while in the second subgroup signs of DOS were determined in 55% of men and 52% of women, and in the third subgroup in 47 and 42%, respectively.

Using high-performance liquid chromatography, microbial markers were determined in blood, characterizing the quantitative composition of the microbiome of the parietal layer of the intestine of patients with developed FLD and patients without fatty changes in the liver. Since there were no significant changes between the parameters for men and women depending on gender, we combined these groups. Changes in the amount of parietal microflora in individuals with FLD relative to the control group were registered only years after CE (Table 10), etc. *when obvious signs of FLD were present*. Before CE, on average, in all patients there was a significant predomination of essential microflora over opportunistic one, as well as of anaerobic over aerobic. In a year after the intervention, in the group with FLD, the opportunistic microflora predominated over the essential one, and the aerobic microflora predominated over the anaerobic one. Of attention is the change in the distribution of obligate microflora after CE — in a year, the amount of lactobacilli in the parietal layer of the intestine prevailed over that of bifidobacteria, and the concentration of eubacteria significantly decreased. Also, the concentrations of fungi and viruses significantly increased in these patients. It is worth noting a decrease in the obligate microflora and an increase in the opportunistic one, also due to aerobic microflora in older people relative to younger ones.

Table 9. Diameter (M ± σ, mm) of Choledoch after Cholecystectomy Depending on Formation of Fatty Liver Disease

Study method	Before Cholecystectomy						In a Year after Cholecystectomy					
	Control			Fatty Liver Disease			Control			Fatty Liver Disease		
	First Group	Second Group	Third Group	First Group	Second Group	Third Group	First Group	Second Group	Third Group	First Group	Second Group	Third Group
	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years
Men												
Ultrasound examination	5.2 ± 0.7	4.6 ± 0.5$^{\#}$	4.8 ± 0.6	5.5 ± 1.1	4.9 ± 1.2	5.3 ± 0.8	4.8 ± 0.6	5.6 ± 1.5$^{\#\&}$	5.4 ± 1.3$^{\#\&}$	9.4 ± 1.7$^{*\&}$	8.1 ± 1.1$^{*\#\&}$	7.3 ± 1.4$^{*\#\&}$
Magnetic resonance cholangiopancreatography	7.2 ± 0.7	6.7 ± 0.5$^{\#}$	7.1 ± 1.4	7.6 ± 0.6	7.1 ± 0.8	7.3 ± 0.9	6.7 ± 0.7	7.2 ± 1.2$^{\#\&}$	7.3 ± 0.9$^{\&}$	12.1 ± 1.4$^{*\&}$	10.2 ± 1.2$^{*\#\&}$	9.3 ± 1.2$^{*\#\&}$
Women												
Ultrasound examination	5.3 ± 0.6	4.5 ± 0.7$^{\#}$	4.7 ± 0.3	5.7 ± 0.9	5.1 ± 1.1	5.7 ± 1.2	4.9 ± 0.7	4.8 ± 1.2$^{\#}$	5.4 ± 1.3$^{\#\&}$	8.5 ± 1.3$^{*\&}$	7.6 ± 1.6$^{*\#\&}$	7.3 ± 1.2$^{*\#\&}$
Magnetic resonance cholangiopancreatography	7.5 ± 0.3	7.1 ± 0.4$^{\#}$	7.2 ± 1.1	7.8 ± 1.2	7.3 ± 0.7	7.5 ± 0.6	7.2 ± 1.2	7.3 ± 1.1#	7.5 ± 0.7$^{\#\&}$	11.3 ± 1.6$^{*\&}$	9.5 ± 1.8$^{*\#\&}$	9.1 ± 1.2$^{*\#\&}$

Notes: * — to the control group, p < 0.001; # — to the analogous first age subgroups, p < 0.001; & — to the period preceding cholecystectomy, p < 0.001

Table 10. Parameters of Microbial Markers of Parietal Microbiome of Intestine Depending on Development of Fatty Liver Disease, M ± σ

Microorganisms	Before Cholecystectomy						In a Year after Cholecystectomy					
	Control			Fatty Liver Disease			Control			Fatty Liver Disease		
	First Group	Second Group	Third Group	First Group	Second Group	Third Group	First Group	Second Group	Third Group	First Group	Second Group	Third Group
	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years	45–59 years	60–74 years	above 75 years
Obligate Anaerobes												
Bifidobacterium	3292 ± 576	3156 ± 876	2563 ± 753$^{\#}$	3524 ± 1152	2667 ± 782$^{\#}$	2745 ± 893$^{\#}$	2530 ± 682$^{\&}$	2672 ± 738$^{\&}$	2276 ± 497$^{\#}$	1247 ± 528$^{*\&}$	1352 ± 631$^{*\&}$	1545 ± 752$^{*\#\&}$
Eubacterium / Cl. Coocoides	9530 ± 1876	8231 ± 1572	7835 ± 1254	8635 ± 1618	8152 ± 1156	7529 ± 931$^{\#}$	8686 ± 952	7634 ± 857$^{\#}$	6670 ± 783$^{\&\#}$	1958 ± 892$^{*\&}$	2841 ± 934$^{*\#\&}$	2887 ± 1232$^{*\#\&}$
Propionibacterium / Cl. Subterm	21924 ± 852	2195 ± 743	2284 ± 816	3164 ± 925	2263 ± 749$^{\#}$	2428 ± 673$^{\#}$	2478 ± 426	1844 ± 382$^{\#\#}$	1941 ± 375$^{\#}$	1246 ± 562$^{*\&}$	1683 ± 421*	1537 ± 397$^{*\#}$
Lactobacillus	2429 ± 1142	2662 ± 1271	2161 ± 928	2776 ± 1558	2844 ± 925	2531 ± 847$^{\#}$	2721 ± 659$^{\&}$	2532 ± 752	2308 ± 689$^{\#}$	1476 ± 246$^{*\&}$	1754 ± 584$^{*\#\&}$	1868 ± 483$^{*\#\&}$
Opportunists												
Anaerobes												
Bacteroides fragilis	271 ± 21	325 ± 34$^{\#}$	292 ± 62	256 ± 31	273 ± 43	281 ± 35	323 ± 52	448 ± 49	554 ± 53$^{\#}$	1089 ± 217$^{*\&}$	562 ± 72$^{*\&\#}$	647 ± 84$^{*\&\#}$
Fusobacterium / Haemophylus	131 ± 29	157 ± 21	141 ± 32*	142 ± 18	156 ± 24$^{\#}$	153 ± 22	161 ± 18	216 ± 23$^{\#}$	267 ± 28$^{\#}$	244 ± 26$^{*\&}$	193 ± 21$^{*\&\#}$	221 ± 28$^{*\&}$
Eubacterium	24 ± 3	28 ± 12	25 ± 8	26 ± 9	28 ± 11	39 ± 13$^{\#}$	29 ± 11	38 ± 8$^{\#}$	47 ± 5$^{\#}$	28 ± 13*	30 ± 17*	34 ± 15$^{*\#}$
Peptostreptococcus anaerobius (Гр. 1)	257 ± 36	308 ± 29$^{\#}$	277 ± 64	268 ± 42	289 ± 32	328 ± 28$^{\#}$	316 ± 33	425 ± 41$^{\#}$	526 ± 71$^{\#}$	976 ± 92$^{*\&}$	646 ± 81$^{*\&\#}$	742 ± 78$^{\#*}$
Clostridium perfringens	956 ± 87	1147 ± 127	1032 ± 135$^{\#}$	882 ± 93	839 ± 94	952 ± 118$^{\#}$	1175 ± 174	1582 ± 231$^{\#}$	1648 ± 232$^{\#}$	936 ± 173$^{*\&}$	1251 ± 23$^{*\&\#}$	1138 ± 198$^{*\&}$
Enterobacteriacae (E. coli)	72 ± 9	86 ± 11	77 ± 14	69 ± 16	74 ± 12	77 ± 8	87 ± 13	118 ± 24$^{\#}$	146 ± 35$^{\#}$	73 ± 15	63 ± 14$^{*\&\#}$	72 ± 12*
Bacillus cereus	139 ± 12	166 ± 19	150 ± 23	154 ± 25	167 ± 17	172 ± 19	170 ± 23	229 ± 36$^{\#}$	285 ± 31$^{\#}$	314 ± 26$^{*\&}$	219 ± 23$^{*\&\#}$	251 ± 34$^{*\&\#\#}$
Ruminicoccus	134 ± 14	160 ± 17	144 ± 32	342 ± 38	276 ± 29	293 ± 34	164 ± 27	220 ± 28$^{\#}$	273 ± 28$^{\#}$	1503 ± 134$^{*\&}$	499 ± 46$^{*\&\#}$	574 ± 62$^{*\&\#}$

Aerobes												
Enterococcus	143 ± 16	153 ± 23	165 ± 27	171 ± 21	169 ± 24	158 ± 26	175 ± 21	$211 \pm 19^{\#}$	$313 \pm 37^{\#}$	$1661 \pm 518^{*\&}$	$5079 \pm 1256^{*\&\#}$	$5840 \pm 1438^{*\&\#}$
Staphylococcus intermedius	256 ± 31	273 ± 36	291 ± 31#	239 ± 37	254 ± 35	237 ± 48	314 ± 39	$376 \pm 54^{\#}$	$552 \pm 62^{\#}$	$1267 \pm 568^{*\&}$	$1269 \pm 382^{*\&\#}$	$1459 \pm 285^{*\&\#}$
Bacillus megaterium	2372 ± 242	2538 ± 251	$2762 \pm 416^{\#}$	2287 ± 324	$2612 \pm 653^{\#}$	2458 ± 821	2917 ± 962	$3502 \pm 749^{\#}$	$5247 \pm 675^{\#}$	$3521 \pm 482^{*\&}$	$4308 \pm 671^{*\&\#}$	$4954 \pm 538^{*\&\#}$
Nocardia	273 ± 54	292 ± 37	$314 \pm 32^{\#}$	258 ± 28	$341 \pm 35^{\#}$	317 ± 34#	335 ± 45	402 ± 38	$596 \pm 63^{\#}$	1326 ± 71*	$548 \pm 52^{*\&\#}$	$630 \pm 67^{*\&\#}$
Mycobacterium / Candida	152 ± 46	231 ± 28	$352 \pm 31^{\#}$	187 ± 21	$265 \pm 24^{\#}$	$479 \pm 56^{\#}$	639 ± 83	724 ± 93	756 ± 81	$1089 \pm 148^{*\&}$	$659 \pm 73^{*\&\#}$	$756 \pm 85^{*\&\#}$

Notes: * — to the control group, $p < 0.001$; # — to the analogous age subgroup, $p < 0.001$; & — to the period preceding cholecystectomy, $p < 0.001$

DISCUSSION

Evaluation of the anthropometric data permitted to determine the relationship between BMI and development of FLD in the long-term period after CE, which is more characteristic of older age groups, men and women over 60. We share the opinion of some authors that this is associated with impaired regulation of lipid and carbohydrate metabolism, which more quickly leads to formation of a persistent insulin resistance and hyperinsulinemia at an older age. With this, imbalance between consumption and utilization of lipids promotes their increased entry to the liver, where, due to decrease in oxidation processes in mitochondria and synthesis of very low density lipoproteins (characteristic of the older age) lipids accumulate in hepatocytes. A decreased number of patients over 75 with I and higher degree obesity has a simple explanation in the fact that most patients with this pathology seldom live to this age [18–20]. The results of the study showing age-related peculiarities of formation and course of FLD correlate with the data presented by some researchers about leveling out of the differences in the number of patients between men and women with cholelithiasis above 60; here, the difference is considerable until 45 when affected women 7 times outnumber men, but only twice at the age from 45 to 60 [1,21,22].

In the analysis of hemodynamic parameters and the autonomic status, of attention is a greater occurrence of sympathicotonia in patients with FLD of the first age group. It is known that in elderly and senile patients sympathetic regulation predominates with a general reduction of the autonomic tone. Here, due to age-related degeneration of the adrenergic synapses, the level of the autonomic regulation of the physiological system decreases [23]. At the same time, in individuals under 60, the autonomic regulation has a considerable effect on physiological systems and organs. Here, formation of insulin resistance leads to predomination of sympathetic regulation which facilitates spasm of Oddi sphincter [7, 24]. DOS (both insufficiency and spasm) impairs passage of bile, which, in turn, deranges the composition of the parietal microbiome of the intestine. Spasm of Oddi sphincter impairs regulation of the entry of bile acids which results in alterations of physiological circulation of bile and reduction of its bactericidal properties that provokes excessive microbial growth suppressing essential microorganisms [25, 26]. Since in the older age, sympathetic influence causing spasm of Oddi sphincter, diminishes, the regularity being more characteristic of individuals under 60 [12, 27–29].

Taking into account different mechanisms of formation of FLD in different age groups, it is possible to differentiate therapeutic tactics depending on predomination of the autonomic or metabolic disorders, which must increase the effectiveness of treatment.

CONCLUSIONS

1. In the pathogenesis of fatty liver disease developed in the long-term period (1 year) after cholecystectomy, the age-related differences are found: the lower autonomic regulation and the higher body mass in patients of the older group in comparison with patients of younger age.
2. Predomination of sympathetic regulation in patients under 60 is associated with dysfunction of Oddi sphincter that accelerates the formation of fatty liver disease.
3. In the long-term period after cholecystectomy in individuals with fatty liver disease developed within a year, significant changes in the microbial markers of the parietal microbiome of the intestine were determined that consisted in predomination of pathogenic microflora over essential one, and of aerobic microflora over anaerobic and in increase in the concentration of fungi and viruses.
4. In a year after cholecystectomy, in patients above 60 years reduction of obligate microflora and proliferation of opportunistic microflora, including due to aerobic microflora, were noted.

ADDITIONALLY

Funding. This study was not supported by any external sources of funding.
Conflict of interests. The authors declares no conflicts of interests.
Contribution of the authors: *A. R. Ambartsumyan* — concept and design of the study, writing the text; *B. A. Chumak* — processing of the material, writing the text; *L. E. Deryagina* — study concept and design, general guidance, text editing; *S. S. Batskov* — study design and text editing; *E. D. Pyatibrat* — concept and text editing. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.
Вклад авторов: *Амбарцумян А. Р.* — концепция и дизайн исследования, написание текста; *Чумак Б. А.* — обработка материала, написание текста; *Дерягина Л. Е.* — концепция и дизайн исследования, общее руководство, редактирование текста; *Бацков С. С.* — дизайн исследования и редактирование текста; *Пятибрат Е. Д.* — концепция и редактирование текста. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

СПИСОК ИСТОЧНИКОВ

1. Вахрушев Я.М., Хохлачева Н.А. Желчнокаменная болезнь: эпидемиология, факторы риска, особенности клинического течения, профилактика // Архивъ внутренней медицины. 2016. Т. 6, № 3. С. 30–35. doi: 10.20514/2226-6704-2016-6-3-30-35

2. Михин И.В., Кухтенко Ю.В., Доронин М.Б. Холецистэктомия: эволюция лапароскопического доступа // Эндоскопическая хирургия. 2015. Т. 21, № 1. С. 42–60. doi: 10.17116/endoskop201521142-60

3. Буеверов А.О. Дисфункция сфинктера Одди в постхолецистэктомическом периоде // Медицинский Совет. 2020. № 15. С. 90–95. doi: 10.21518/2079-701X-2020-15-90-95

4. Горбунова К.А., Кондакова Ю.В., Стяжкина С.Н. Постхолецистэктомический синдром // Modern Science. 2020. № 11-1. С. 151–157.

5. Жирков И.И., Гордиенко А.В., Павлович И.М., и др. Диагностика фиброза печени: акцент на эластографию // Экспериментальная и клиническая гастроэнтерология. 2021. № 10. С. 72–81. doi: 10.31146/1682-8658-ecg-194-10-72-81

6. Мехтиев С.Н., Мехтиева О.А. Желчнокаменная болезнь и неалкогольная жировая болезнь печени: сочетание и прогноз // Лечащий врач. 2017. № 3. С. 77.

7. Силина Е.В., Ступин В.А., Орлова А.С., и др. Дисфункция сфинктера Одди после холецистэктомии (обзор) // Справочник врача общей практики. 2015. № 10. С. 17–22.

8. Бацков С.С. Ультразвуковой метод исследования в гастроэнтерологии. СПб.; 1995.

9. Маньяков А.В., Радченко В.Г., Селиверстов П.В. Возможности профилактики неалкогольной жировой болезни печени после холецистэктомии // Гастроэнтерология Санкт-Петербурга. 2017. № 1. С. 92–92b.

10. Мехтиев С.Н., Мехтиева О.А., Ухова М.В., и др. Современный взгляд на значение холецистэктомии в прогнозе пациента с неалкогольной жировой болезнью печени: алгоритм наблюдения и терапевтические подходы // РМЖ. Медицинское обозрение. 2021. Т. 5, № 6. С. 438–445. doi: 10.32364/2587-6821-2021-5-6-438-445

11. Винник Ю.С., Серова Е.В., Миллер С.В., и др. Диагностические критерии дисфункции сфинктера Одди после холецистэктомии // Анналы хирургии. 2012. № 6. С. 5–9.

12. Панцырев Ю.М., Шаповальянц С.Г., Чернякевич С.А., и др. Функциональные расстройства сфинктера Одди после холецистэктомии // Российский журнал гастроэнтерологии, гепатологии, колопроктологии. 2011. Т. 21, № 3. С. 28–34.

13. Черкащенко Н.А., Ливзан М.А., Кролевец Т.С., и др. Система поддержки врачебных решений по прогнозу метаболических рисков у больных с коморбидным течением неалкогольной жировой болезни печени и желчнокаменной болезни после холецистэктомии // Медицинский алфавит. 2020. № 30. С. 11–17. doi: 10.33667/2078-5631-2020-30-11-17

14. Kleiner D.E., Brunt E.M., van Natta M., et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease // Hepatology. 2005. Vol. 41, No. 6. P. 1313–1321. doi: 10.1002/hep.20701

15. Permutt Z., Le T.–A., Peterson M.R., et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease — MRI accurately quantifies hepatic steatosis in NAFLD // Alimentary Pharmacology & Therapeutics. 2012. Vol. 36, No. 1. P. 22–29. doi: 10.1111/j.1365-2036.2012.05121.x

16. Аллахвердиева Я.С., Воробьев С.В., Минеев Н.И. Современные возможности магнитно-резонансных технологий в диагностике ожирения печени // Медицинский вестник Северного Кавказа. 2018. Т. 13, № 4. С. 695–700. doi: 10.14300/mnnc.2018.13140

17. Леушина Е.А. Магнитно-резонансная холангиопанкреатография при абдоминальной боли у пациентов с дисфункцией сфинктера Одди // Российский журнал боли. 2021. Т. 19, Suppl. С. 54.

18. Буеверов А.О., Рощина К.М., Богомолов П.О. Неалкогольная жировая болезнь печени: новый взгляд на аспекты коморбидности // Эффективная фармакотерапия. 2022. Т. 18, № 6. Р. 32–38. doi: 10.33978/2307-3586-2022-18-6-32-38

19. Винницкая Е.В., Сандлер Ю.Г., Бордин Д.С. Новая парадигма неалкогольной жировой болезни печени: фенотипическое многообразие метаболически ассоциированной жировой болезни печени // Эффективная фармакотерапия. 2020. Т. 16, № 24. С. 54–63. doi: 10.33978/2307-3586-2020-16-24-54-63

20. Никонов Е.Л., Аксенов В.А. Современные подходы к диагностике и лечению неалкогольной жировой болезни печени // Профилактическая медицина. 2018. Т. 21, № 3. С. 62–69. doi: 10.17116/profmed201831262

21. Савельев В.С., Петухов В.А. Желчнокаменная болезнь и синдром нарушенного пищеварения. М.: Боргес; 2011.

22. Хохлачева Н.А., Сергеева Н.Н., Вахрушев Я.М. Возрастные и гендерные особенности развития желчнокаменной болезни // Архивъ внутренней медицины. 2016. Т. 6, № 1. С. 34–39. doi: 10.20514/2226-6704-2016-6-1-34-39

23. Зефиров Т.Д. Новый взгляд на механизмы возрастных изменений сердечного ритма // Бюллетень экспериментальной биологии и медицины. 2001. Т. 131, № 6. С. 612–616.
24. Селиверстов П.В., Скворцова Т.Э., Ситкин С.И., и др. Неалкогольная жировая болезнь печени и желчнокаменная болезнь: новый взгляд на старые взаимоотношения // Фарматека. 2018. № S3. С. 68–75. doi: 10.18565/pharmateca.2018.s3.68-74
25. Лялюкова Е.А., Ливзан М.А. Дисфункция сфинктера Одди и синдром избыточного бактериального роста в кишечнике // Лечащий врач. 2013. № 1. С. 61–66.
26. Ляпина М.В., Вахрушев Я.М. Значение пристеночной микробиоты тонкой кишки в нарушении энтерального переваривания и всасывания при метаболическом синдроме // Терапевтический архив. 2019. Т. 91, № 11. С. 37–42. doi: 10.26442/00403660.2019.11.000300
27. Буеверов А.О. Холецистэктомия как фактор риска прогрессирования неалкогольной жировой болезни печени // Consilium Medicum. 2019. Т. 21, № 8. С. 93–97. doi: 10.26442/20751753.2019.8.190503
28. Tang A., Tan J., Sun M., et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis // Radiology. 2013. Vol. 267, No. 2. P. 422–431. doi: 10.1148/radiol.12120896
29. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation // World Health Organization Technical Report Series. 2000. Vol. 894. P. i–xii, 1–253.

REFERENCES

1. Vakhrushev JM, Khokhlacheva NA. Gallstone disease: epidemiology, risk factors, clinical features, prevention. *The Russian Archives of Internal Medicine*. 2016;6(3):30–5. (In Russ). doi: 10.20514/2226-6704-2016-6-3-30-35
2. Mikhin IV, Kukhtenko YuV, Doronin MB. Cholecystectomy: evolution of laparoscopic approach. *Endoscopic Surgery*. 2015;21(1):42–60. (In Russ). doi: 10.17116/endoskop201521142-60
3. Bueverov AO. Sphincter of Oddi dysfunction in the post-cholecystectomy period. *Meditsinskiy Sovet*. 2020;(15):90–5. (In Russ). doi: 10.21518/2079-701X-2020-15-90-95
4. Gorbunova KA, Kondakova YuV, Styazhkina SN. Postkholetsist·ektomicheskiy sindrom. *Modern Science*. 2020;(11–1):151–7. (In Russ).
5. Zhirkov II, Gordienko AV, Pavlovich IM, et al. Diagnosis of liver fibrosis: an emphasis on elastography. *Experimental and Clinical Gastroenterology*. 2021;(10):72–81. (In Russ). doi: 10.31146/1682-8658-ecg-194-10-72-81
6. Mekhtiev SN, Mekhtieva OA. Cholelithiasis and non-alcohol fat hepatic disease: combination and forecast. *Lechashchiy Vrach*. 2017;(3):77. (In Russ).
7. Silina EV, Stupin VA, Orlova AS, et al. Sphincter of Oddi dysfunction after cholecystectomy (review). *Spravochnik Vracha Obshchej Praktiki*. 2015;(10):17–22. (In Russ).
8. Batskov SS. *Ul'trazvukovoy metod issledovaniya v gastroenterologii*. Saint-Petersburg; 1995. (In Russ).
9. Man'yakov AV, Radchenko VG, Seliverstov PV. Vozmozhnosti profilaktiki nealkogol'noy zhirovoy bolezni pecheni posle kholetsist·ektomii. *Gastroenterologiya Sankt-Peterburga*. 2017;(1):92–92b. (In Russ).
10. Mekhtiev SN, Mekhtieva OA, Ukhova MV, et al. Modern view of the importance of cholecystectomy in the prognosis of a patient with non-alcoholic fatty liver disease: follow-up algorithm and therapeutic approaches. *Russian Medical Inquiry*. 2021;5(6):438–45. (In Russ). doi: 10.32364/2587-6821-2021-5-6-438-445
11. Vinnik YuS, Serova EV, Miller SV, et al. Diagnostic aids of sphincter of Oddi dysfunction after cholecystectomy. *Annaly Hirurgii*. 2012;(6):5–9. (In Russ).
12. Pantsyrev YuM, Shapoval'yants SG, Chernyakevich SA, et al. Postcholecystectomy functional disorders of the sphincter of Oddi after. *Russian Journal of Gastroenterology, Hepatology, Coloproctology*. 2011;21(3):28–34. (In Russ).
13. Cherkashchenko NA, Livzan MA, Krolevets TS, et al. Decision support system for predicting metabolic risks in patients with comorbid non-alcoholic fatty liver disease and gallstone disease after cholecystectomy. *Medical Alphabet*. 2020;(30):11–7. (In Russ). doi: 10.33667/2078-5631-2020-30-11-17
14. Kleiner DE, Brunt EM, van Natta M, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. *Hepatology*. 2005;41(6):1313–21. doi: 10.1002/hep.20701
15. Permutt Z, Le T–A, Peterson MR, et al. Correlation between liver histology and novel magnetic resonance imaging in adult patients with non-alcoholic fatty liver disease — MRI accurately quantifies hepatic steatosis in NAFLD. *Aliment Pharmacol Ther*. 2012;36(1):22–9. doi: 10.1111/j.1365-2036.2012.05121.x
16. Allahverdieva YaS, Vorob'ev SV, Mineev NI. Modern opportunities of magnetic-resonance technologies in diagnostics of the fatty live. *Medical News of the North Caucasus*. 2018;13(4):695–701. (In Russ). doi: 10.14300/mnnc.2018.13140
17. Leushina EA. Magnitno-rezonansnaya kholangiopankreatografiya pri abdominal'noy boli u patsiyentov s disfunktsiyey sfinktera Oddi. *Russian Journal of Pain*. 2021;19(Suppl):54. (In Russ).
18. Buyeverov AO, Roshchina KM, Bogomolov PO. Non-Alcoholic Fatty Liver Disease: a New Look at Aspects of Comorbidity. *Effective Pharmacotherapy*. 2022;18(6):32–8. (In Russ). doi: 10.33978/2307-3586-2022-18-6-32-38
19. Vinnitskaya YeV, Sandler YuG, Bordin DS. The New Paradigm of Non-Alcoholic Fatty Liver Disease: Phenotypic Diversity of Metabolically Associated Fatty Liver Disease. *Effective Pharmacotherapy*. 2020;16(24):54–63. (In Russ). doi: 10.33978/2307-3586-2020-16-24-54-63
20. Nikonov EL, Aksenov VA. Current approaches to diagnosing and treating nonalcoholic fatty liver disease. *The Russian Journal of Preventive Medicine*. 2018;21(3):62–9. (In Russ). doi: 10.17116/profmed201831262
21. Savel'yev VS, Petukhov VA. *Zhelchnokamennaya bolezn' i sindrom narushennogo pishchevareniya*. Moscow: Borges; 2011. (In Russ).
22. Hohlacheva NA, Sergeeva NN, Vahrushev YM. Age and gender peculiarities of development of gallstone disease. *The Russian Archives of Internal Medicine*. 2016;6(1):34–9. (In Russ). doi: 10.20514/2226-6704-2016-6-1-34-39

23. Zefirov TD. Novyy vzglyad na mekhanizmy vozrastnykh izmeneniy serdechnogo ritma. *Bulletin of Experimental Biology and Medicine*. 2001;131(6) 612–6. (In Russ).
24. Seliverstov PV, Skvortsova TE, Sitkin SI, et al. Non-alcoholic fatty liver disease and cholelithiasis: a new view on old relationships. *Farmateka.* 2018;(S3):68–75. (In Russ). doi: 10.18565/pharmateca.2018.s3.68-74
25. Lyalyukova EA, Livzan MA. Dysfunction of Oddi sphincter and the syndrome of excess increase in the intestine. *Lechashchiy Vrach.* 2013;(1):61–6. (In Russ).
26. Lyapina MV, Vakhrushev YaM. The value of mucosal small intestine microbiota in digestion and absorption disorders in metabolic syndrome. *Therapeutic Archive.* 2019;91(11):37–42. (In Russ). doi: 10.26442/00403660.2019.11.000300
27. Bueverov AO. Cholecystectomy as a risk factor of non-alcoholic fatty liver diseaseprogression. *Consilium Medicum.* 2019;21(8):93–7. (In Russ). doi: 10.26442/20751753.2019.8.190503
28. Tang A, Tan J, Sun M, et al. Nonalcoholic fatty liver disease: MR imaging of liver proton density fat fraction to assess hepatic steatosis. *Radiology.* 2013;267(2):422–31. doi: 10.1148/radiol.12120896
29. Obesity: Preventing and Managing the Global Epidemic. Report of a WHO Consultation. *World Health Organ Tech Rep Ser.* 2000;894:i–xii, 1–253.

ОБ АВТОРАХ

Амбарцумян Александр Рафаелович;
ORCID: https://orcid.org/0000-0001-9689-6929;
eLibrary SPIN: 5403-8181, e-mail: ambartsumyan_al@mail.ru

Чумак Борис Анатольевич, к.м.н.;
ORCID: https://orcid.org/0000–0001–5310–0812;
eLibrary SPIN: 1973-6961; e-mail: borchum07@yandex.ru

***Дерягина Лариса Евгеньевна**, д.м.н., профессор;
ORCID: https://orcid.org/0000-0001-5522-5950;
eLibrary SPIN: 6606-6628; e-mail: lderyagina@mail.ru

Бацков Сергей Сергеевич, д.м.н. профессор;
ORCID: https://orcid.org/0000-0002-8196-3831;
eLibrary SPIN: 8914-2094; e-mail: rokotyanskaya.ea@mail.ru

Пятибрат Елена Дмитриевна, д.м.н.;
ORCID: https://orcid.org/0000-0003-4070-5374;
eLibrary SPIN: 9463-7160; e-mail: e5brat@yandex.ru

AUTHOR'S INFO

Aleksandr R. Ambartsumyan, MD;
ORCID: https://orcid.org/0000-0001-9689-6929;
eLibrary SPIN: 5403-8181, e-mail: ambartsumyan_al@mail.ru

Boris A. Chumak, MD, Cand. Sci. (Med.);
ORCID: https://orcid.org/0000–0001–5310–0812;
eLibrary SPIN: 1973-6961; e-mail: borchum07@yandex.ru

***Larisa E. Deryagina**, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0001-5522-5950;
eLibrary SPIN: 6606-6628; e-mail: lderyagina@mail.ru

Sergey S. Batskov, MD, Dr. Sci. (Med.), Professor;
ORCID: https://orcid.org/0000-0002-8196-3831;
eLibrary SPIN: 8914-2094; e-mail: rokotyanskaya.ea@mail.ru

Elena D. Pyatibrat, MD, Dr. Sci. (Med.);
ORCID: https://orcid.org/0000-0003-4070-5374;
eLibrary SPIN: 9463-7160; e-mail: e5brat@yandex.ru

* Автор, ответственный за переписку / Corresponding author