



# Factors Affecting the Incidence of Recurrences and Complications of Peptic Ulcer Disease

Olga V. Shtygasheva<sup>1</sup>, Elizaveta S. Ageeva<sup>2\*</sup>, Elizaveta V. Matveeva<sup>1</sup>

<sup>1</sup> N.F. Katanov Khakass State University, Abakan, Russian Federation

<sup>2</sup> V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation

**Aim:** to analyze risk factors for relapses and complications of peptic ulcer disease in a cohort of patients.

**Materials and methods.** Retrospective analysis of hospital records of 253 patients (average age —  $52.1 \pm 8.2$  years) with peptic ulcer disease in the acute stage. Patients were stratified by gender, age and anamnestic risk factors, the phenotype of peptic ulcer disease being stratified by etiology, endoscopic characteristics of ulcerative defects of the gastric mucosa and duodenum.

**Results.** The proportion of complicated forms of peptic ulcer disease varies depending on gender, age and ulcer localization. The total number of complications in the cohort is 38.3 %, men developing complications in every second case (47.9 %). Among complications, bleeding is the most common one and accounts for 52.6 %, 42.9 % and 41.2 % of all complications in duodenal, simultaneous and gastric ulcers correspondingly. Cicatricial and ulcerative deformations are associated with localization in the duodenum and combined location of ulcerative defects, the complication being recorded in men 2 times more often than in women. Perforations of gastric ulcer are associated with the male gender (3 times more often). Stenosis is a rare complication, predominantly in women with duodenal ulcer. Significant predictors of complications of peptic ulcer disease are male gender and smoking. Factors associated with the manifestation of peptic ulcer disease include *H. pylori* and smoking in men, and *H. pylori*, nonsteroidal anti-inflammatory drugs or combination of these factors in women.

**Conclusions.** The factors influencing the incidence of complications and recurrences of peptic ulcer disease in the hospital cohort have been established: male gender, age of 36–59 years, *H. pylori* infection, tobacco smoking, NSAID use and simultaneous exposure to several factors in one individual.

**Keywords:** peptic ulcer, risk factors, gender, age, *H. pylori*, non-steroidal anti-inflammatory drug

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## Факторы, влияющие на возникновение рецидивов и осложнений язвенной болезни

О.В. Штыгашева<sup>1</sup>, Е.С. Агеева<sup>2\*</sup>, Е.В. Матвеева<sup>1</sup>

<sup>1</sup> ФГБОУ ВО «Хакасский государственный университет им. Н.Ф. Катанова», Абакан, Российская Федерация

<sup>2</sup> ФГАОУ ВО «Крымский федеральный университет им. В.И. Вернадского», Симферополь, Российская Федерация

**Цель исследования:** оценить потенциальные факторы, влияющие на возникновение рецидивов и осложнений язвенной болезни у госпитализированных пациентов.

**Материалы и методы.** Ретроспективный анализ карт стационарного наблюдения 253 пациентов с язвенной болезнью в стадии обострения (134 женщины и 119 мужчин, возраст — от 18 до 89 лет), отобранных сплошным методом. Пациенты стратифицированы по полу и возрасту, а язвенная болезнь — по факторам этиологии, риска и эндоскопическим характеристикам язвенных дефектов слизистой оболочки желудка и двенадцатиперстной кишки.

**Результаты.** Мужской пол и средний возраст ( $52,1 \pm 8,2$  года) являются факторами риска развития язвенной болезни. Удельный вес осложненных форм язвенной болезни меняется в зависимости от пола, возраста и локализации язвы. Частота осложнений в когорте пациентов составила 38,3 % случаев, среди мужчин — 47,9 %. В структуре осложнений лидируют кровотечения: при дуоденальных язвах — 52,6 %, язвах двойной локализации — 42,9 %, желудочных язвах — 41,2 %. Максимальная частота рубцово-язвенной деформации ассоциирована с локализацией язвы в двенадцатиперстной кишке двойной локализации, такое расположение язвенных дефектов и, как следствие, осложнение в 2 раза чаще фиксируется у мужчин. С мужским полом в 3 раза чаще связаны перфорации при язвенной болезни желудка. Стеноз — редкое осложнение, отмечается преимущественно у женщин с дуоденальной язвой. Наиболее значимые факторы риска язвенной

болезни у мужчин — курение и *H. pylori*, у женщин — *H. pylori*, нестероидные противовоспалительные препараты (НПВП) или их сочетание. Факторами риска осложненных форм язвенной болезни служат мужской пол и курение.

**Выводы.** Установлены факторы, влияющие на возникновение рецидивов и осложнений язвенной болезни в госпитальной когорте пациентов: мужской пол, увеличение возраста с пиком заболеваемости в 36–59 лет, инфекция *H. pylori*, курение табака, прием НПВП и одновременное воздействие нескольких факторов у одного пациента.

**Ключевые слова:** язвенная болезнь, факторы риска, пол, возраст, *H. pylori*, нестероидные противовоспалительные препараты

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## Introduction

Population-based screening of patients with dyspepsia shows a decrease in the occurrence of peptic ulcer disease associated with *Helicobacter pylori* (*H. pylori*) infection [1]. However, the high frequency of other etiological and risk factors should not be accompanied by a low prevalence of the pathology. It is in complications that peptic ulcer of the stomach and duodenum (DU) mostly manifests itself in modern patients: hemorrhage develops in 10–15 % of the patients, 10–14 % of which die in the clinic, in case of recurrent bleeding the mortality rate being up to 30–40 % [1, 2]. Thus, a promising direction to improve the outcomes is the prevention of recurrent bleeding [3]. Risk stratification has been proposed for patients with acute gastric and duodenal bleeding [4], but the problem has not been solved completely, since prognostic systems demonstrate low sensitivity, specificity, and popularity among surgeons [5].

**The aim of the study** is to analyze risk factors for recurrence and complications of peptic ulcer disease in a cohort of patients.

## Materials and methods

Retrospective analysis of inpatient hospital records (f-003u) of 253 patients with peptic ulcer in the acute stage (134 women and 119 men, aged 18 to 89), selected by a continuous method, has been applied. The patients of the cohort were stratified by gender and age. The following age groups were distinguished: 18–35 years (young), 36–59 years (middle-aged), 60–74 years (elderly), 75–89 years (senile).

The disease phenotype was determined based on endoscopic characteristics of ulcerative defects of the gastric and duodenal mucosa according to the examination protocols. The proximal (the cardiac section and fundus of the stomach), mesogastric (greater and lesser curvature of the body of the stomach) and distal (the antral and pyloric sections) types of localization were distinguished in the stomach, the bulb and the retrobulbar section — in the duodenum. Combined ulcerative

defects of the gastric and duodenal mucosa were referred to as combined ulcers. Depending on the number of ulcerative lesions, single and multiple (more than one defect at the same time) ulcers were distinguished. According to the size of the ulcerative defect (in diameter), ulcers were regarded as small (up to 0.5 cm) and medium (0.6–1.9 cm), large (2.0–3.0 cm) and giant (over 3.0 cm). The presence of complications was assessed as well: cicatricial ulcerative deformation of the stomach or duodenum, cicatricial ulcerative stenosis of the pylorus, bleeding, and perforation.

Statistical processing of the material was performed using Statistica 8.1 software package with nonparametric methods. Qualitative variables were described by absolute and relative frequencies —  $n$  (%). The Pearson criterion ( $\chi^2$ ) was used to assess the statistical significance of differences between patient groups. The critical significance level was  $p < 0.05$ . The odds ratio (OR) was used as a quantitative measure of effect when comparing relative values. Differences in the values were considered statistically significant at a level of significance of  $p < 0.05$ .

## Results

The peculiarities of the localization of the ulcer defect in the mucous membrane of the stomach and duodenum were established to depend on the age and gender of the patient. Every second case of ulcerative colitis in the hospital cohort of the patients was associated with localization in the stomach (47.8 %). The ratio between gastric ulcerative colitis, duodenal ulcerative colitis and combined ulcers was 3.7:3.0:1.0. The proportion of men and women was 1.0:1.4 in case of gastric ulcer and 1.2:1.0 if ulcer was located in the duodenum.

Gastric ulcer manifested itself most often at 36–59 (52.0 %) and 60–74 (42.0 %) years of age. Mesogastric ulcers were the most common in the middle-aged women (55.6 %), while the most widespread localization of ulcers in the middle-aged

men was distal (68.0 %). An opposite tendency for localization was observed in the elderly: women were more likely to have distal ulcers (48.0 %), while men developed mesogastric ulcers (56.3 %). The age for the manifestation of the duodenal ulcer was similar: at 36–59 (40.4 %) and 60–74 (35.4 %) years of age. Regardless of gender of the patients, the most common localization in the duodenum was its bulb. Combined ulcers were 1.56 times more common in men (61.1 %) than in women (38.9 %), and the middle age of the patients was also predominant (54.5 %) (Table 1).

Multiple ulcers were recorded in the hospital cohort of the patients more often than single ones (52.6 % vs. 47.4 %) and developed predominantly in the duodenal bulb (19.8 %) and distal stomach (13.1 %). Medium (49.8 %) and small (40.7 %) sizes of ulcer defects were the most widespread. Ulcers of atypical size, large (6.3 %) and giant (3.2 %), were found both in the stomach and in the duodenum, with a more pronounced distal orientation.

Complications of gastric ulcer were documented in 38.3 % of all the patients, men developing complications in every second case (47.9 %). Bleeding was the leading complication of gastric ulcers. The

incidence of bleeding depended on the localization of the ulcerative defects: 52.6 % of cases in the duodenum, 42.9 % with simultaneous combined ulcers, and 41.2 % in the stomach. Gastric ulcer was complicated with perforation in 11.8 % of all the cases, 3 times more often in men than in women. Cicatricial ulcerative deformation was recorded in 10.3 % of all the cases, mainly with duodenal (73.7 %) and simultaneous combined (100.0 %) ulcer location, the complication being twice as common in men than in women. The share of cicatricial ulcerative stenosis was 1.2 % of all the cases of complications with ulcer localization in the duodenum, mainly in women.

Sexual dimorphism was revealed in association with complications of peptic ulcer disease. Odds ratio (OR) analysis showed that male gender is a risk factor for complicated peptic ulcer disease (OR = 1.6; 95 % CI: 1.1–2.3) and ulcer perforation into the abdominal cavity (OR = 3.2; 95 % CI: 1.1–9.6) (Table 2).

The significance of the leading factors in the etiology of peptic ulcer disease and the risk of complications was confirmed in the cohort, namely, *H. pylori* infection (83.8 %), use of non-steroidal

**Table 1.** Distribution of patients by age, gender and localization of ulcerative defect in the mucous membrane of the stomach and duodenum, *n* (%)

**Таблица 1.** Распределение пациентов по возрасту, полу и локализации язвенного дефекта в слизистой оболочке желудка и двенадцатиперстной кишки, *n* (%)

Gender / Пол	Total 253 patients Всего 253 пациента							
	females / женщины ( <i>n</i> = 134)				males / мужчины ( <i>n</i> = 119)			
Age, years Возраст, лет	18–35	36–59	60–74	75–89	18–35	36–59	60–74	75–89
Localization of ulcer defect Локализация язвенного дефекта								
Stomach / Желудок ( <i>n</i> = 121)	10 (4.0 %)	27 (10.7 %)	25 (9.9 %)	13 (5.1 %)	2 (0.8 %)	25 (9.9 %)	16 (6.3 %)	3 (1.2 %)
proximal проксимальная ( <i>n</i> = 11)	0 (0 %)	2 (0.8 %)	0 (0 %)	2 (0.8 %)	1 (0.4 %)	1 (0.4 %)	3 (1.2 %)	2 (0.8 %)
mesogastric мезогастральная ( <i>n</i> = 48)	1 (0.4 %)	6 (2.4 %)	9 (3.6 %)	1 (0.4 %)	3 (1.2 %)	15 (5.9 %)	10 (4.0 %)	3 (1.2 %)
distal дистальная ( <i>n</i> = 62)	1 (0.4 %)	17 (6.7 %)	7 (2.8 %)	0 (0 %)	6 (2.4 %)	11 (4.4 %)	12 (4.8 %)	8 (3.2 %)
Duodenum / ДПК ( <i>n</i> = 99)	6 (2.4 %)	25 (9.9 %)	19 (7.5 %)	4 (1.6 %)	8 (3.2 %)	15 (5.9 %)	16 (6.3 %)	6 (2.4 %)
bulb луковица ( <i>n</i> = 90)	6 (2.4 %)	24 (9.5 %)	17 (6.7 %)	4 (1.6 %)	7 (2.8 %)	13 (5.1 %)	13 (5.1 %)	6 (2.4 %)
postbulbar постбульбарная ( <i>n</i> = 9)	0 (0 %)	1 (0.4 %)	2 (0.8 %)	0 (0 %)	1 (0.4 %)	2 (0.8 %)	3 (1.2 %)	0 (0 %)
dual localization (combined) двойной локализации (комбинированные) ( <i>n</i> = 33)	1 (0.4 %)	11 (4.4 %)	5 (2.0 %)	2 (0.8 %)	1 (0.4 %)	7 (2.8 %)	5 (2.0 %)	1 (0.4 %)

**Table 2.** Frequency of complications of peptic ulcer disease depending on the gender of patients  
**Таблица 2.** Частота осложнений язвенной болезни в зависимости от пола пациентов

Complications of ulcer disease Осложнения язвенной болезни	Number of patients / Количество пациентов n (%)			OR (95 % CI) ОШ (95 % ДИ)
	Total Все (n = 253)	Males Мужчины (n = 119)	Females Женщины (n = 134)	
Total burden of complications Суммарное бремя осложнений	97 (38.3 %)	57 (47.9 %)	40 (29.9 %)*	1.6 (1.1–2.3)
Cicatricial and ulcerative deformation of the pylorus and/or duodenum Рубцово-язвенная деформация выходного отдела желудка и/или ДПК	26 (10.3 %)	16 (13.4 %)	10 (7.5 %)	
Pyloric and/or duodenal stenosis Стеноз привратника и/или ДПК	3 (1.2 %)	0	3 (2.2 %)	
Gastrointestinal bleeding Желудочно-кишечное кровотечение	4 (18.2 %)	25 (21.0 %)	21 (15.7 %)	
Perforation of the ulcer into the abdominal cavity Перфорация язвы в брюшную полость	22 (8.7 %)	16 (13.4 %)	6 (4.5 %)*	3.2 (1.1–9.6)

**Note:** \* – statistical significance ( $p < 0.05$ ) when comparing men and women; OR – odds ratio; 95 % CI – 95 % confidence interval.

**Примечание:** \* – статистическая значимость ( $p < 0,05$ ) при сравнении мужчин и женщин; ОШ – отношение шансов; 95 % ДИ – 95%-ный доверительный интервал.

anti-inflammatory drugs (NSAIDs) (16.2 %), and a combination of NSAIDs with *H. pylori* infection (18.2 %). In women, the negative impact of NSAIDs was recorded 1.7 times more often than in men. A high smoking index ( $\geq 10$  cigarettes) was established in 15.4 % of cases, men having this risk factor 3.3 times more often than women. The role of the familial nature of the disease was confirmed in 5.5 % of patients with peptic ulcers, but this section of the anamnesis of life was absent in the medical histories of urgent patients (Table 3).

When assessing the factors influencing the risk of peptic ulcer disease development, the prevailing role of *H. pylori* was shown (Table 4). Taking NSAIDs increases the risk of gastric ulcers by almost three times compared to the risk of duodenal and combined ulcers. Concomitant *H. pylori* infection in combination with NSAIDs increases the risk of duodenal ulcer by 2 times and the risk of ulcers in combination by localization combined by 5 times.

We have shown that in men, duodenal ulcers were 3 times more common than any other localization. Female gender was a risk factor for the development of peptic ulcers localized in the stomach. Risk factors also include middle age (36–59 years), this period being particularly characteristic of the development of combined ulcers.

## Discussion

The manifestation of peptic ulcer disease is determined by endogenous and exogenous causes, and the development of life-threatening complications is often associated with the impact/expression of

risk factors. Understanding the causes of the increase in the incidence of peptic ulcer disease and life-threatening complications requires further study [6].

Ulcers localized in the duodenum are more common than those in the stomach. The prevalence of duodenal localization in the structure of ulcers corresponds to the global trend (60.1 % of ulcers in Pakistan [7, 8]), with the exception of Japan, Greenland and the highland Andes, where the structure of ulcers has an inverse ratio. The proportion of male patients with duodenal ulcer is significantly higher, especially in young and middle age [7]. A similar trend was observed in our study.

Recurrent bleeding is characterized by high postoperative mortality (26.8 %). Factors that increase the risk of recurrence have been identified and include ulcer localization on the lesser curvature of the stomach and the posterior wall of the duodenum, endoscopic type 2A according to the Forrest classification, low levels of red blood cells and total protein, and high levels of blood urea on the patient's admission [9].

According to a retrospective study in India, the mortality rate of patients operated on for peritonitis due to perforated peptic ulcer was 11.1 % of cases, and hypovolemic shock was the leading cause of death from complications of peptic ulcer [10].

Despite the lower incidence of *H. pylori* infection among the population in some regions of the world, its role in the development of peptic ulcer disease is significant. Active antral gastritis, developing in response to the persistence of *H. pylori* in the stomach, leads to the entry of excess hydrochloric acid into the duodenum, development of

**Table 3.** Frequency of potential factors influencing the occurrence of relapses and complications of peptic ulcer disease**Таблица 3.** Частота потенциальных факторов влияния на возникновение рецидивов и осложнений язвенной болезни

Potential influencing factors <i>Потенциальные факторы влияния</i>	Number of patients <i>Количество пациентов</i> <i>n (%)</i>			OR (95 % CI) <i>ОШ (95 % ДИ)</i>
	Total <i>Все</i> <i>(n = 253)</i>	Males <i>Мужчины</i> <i>(n = 119)</i>	Females <i>Женщины</i> <i>(n = 134)</i>	
Family history of peptic ulcer in 1st–2nd degree relatives <i>Семейный анамнез ЯБ у родственников 1–2-й степени родства</i>	14 (5.5 %)	6 (5.1 %)	8 (5.9 %)	
NSAIDs use preceding the manifestation of peptic ulcer <i>Прием НПВП, предшествующий манифестации ЯБ</i>	41 (16.2 %)	14 (11.8 %)	27 (20.1 %)	
Smoking index $\geq 10$ <i>Индекс курения <math>\geq 10</math></i>	39 (15.4 %)	29 (24.4 %)	10 (7.5 %)*	4.2 (1.7–10.2)
Positive status of <i>H. pylori</i> in stomach ulcer <i>Позитивный статус H. pylori при ЯБЖ</i>	113 (44.7 %)	54 (45.4 %)	59 (44.0 %)	
Positive status of <i>H. pylori</i> in duodenal ulcer <i>Позитивный статус H. pylori при ЯБ ДПК</i>	99 (39.1 %)	54 (45.4 %)	45 (33.6 %)	
Combination of <i>H. pylori</i> and NSAIDs use <i>Сочетание H. pylori и приема НПВП</i>	46 (18.2 %)	16 (13.4 %)	30 (22.4 %)	

**Note:** NSAIDs – non-steroidal anti-inflammatory drugs; \* – statistical significance ( $p < 0.05$ ) when comparing men and women; OR – odds ratio; 95 % CI – 95 % confidence interval.

**Примечание:** ЯБ – язвенная болезнь; ЯБЖ – язвенная болезнь желудка; ЯБ ДПК – язвенная болезнь двенадцатиперстной кишки; НПВП – нестероидные противовоспалительные препараты; \* – статистическая значимость ( $p < 0,05$ ) при сравнении мужчин и женщин; ОШ – отношение шансов; 95 % ДИ – 95%-ный доверительный интервал.

**Table 4.** Odds ratio for risk factors for recurrence and complications of peptic ulcer disease in patients of the cohort**Таблица 4.** Отношение шансов по факторам риска возникновения рецидивов и осложнений язвенной болезни у пациентов когорты

Risk factors <i>Факторы риска</i>	OR (95 % CI) <i>ОШ (95 % ДИ)</i>
Positive status for <i>H. pylori</i> infection <i>Позитивный статус по инфекции H. pylori</i>	1.1 (1.03–1.20)
Taking nonsteroidal anti-inflammatory drugs <i>Прием нестероидных противовоспалительных препаратов</i>	2.7 (1.2–5.8)
Combination of <i>H. pylori</i> infection and nonsteroidal anti-inflammatory drug use <i>Сочетание инфекции H. pylori и приема нестероидных противовоспалительных препаратов</i>	2.7 (1.67–4.38)
Complications of peptic ulcer disease <i>Осложнения язвенной болезни</i>	1.6 (1.1–2.3)
Male gender / <i>Мужской пол</i>	2.8 (1.7–4.6)
Female gender / <i>Женский пол</i>	3.4 (1.7–6.5)
Age 36–59 years / <i>Возраст 36–59 лет</i>	1.37 (1.02–1.85)



duodenitis with the appearance of areas of gastric metaplasia and manifestation of peptic ulcer disease. A study of epidemiological, social and demographic characteristics in the genesis of peptic ulcers involving 204 countries from 1990 to 2019 (the Global Burden of Disease (GBD) study) showed that *H. pylori* infection increased the risk of peptic ulcers by 4 times [6].

The age-standardized incidence rate of peptic ulcer disease demonstrated a trend of annual increase in incidence with age throughout the entire period. However, a comparison of the growth rate of peptic ulcer disease incidence in the population and the dynamics of changes in *H. pylori* contamination of the population revealed differences. A positive test for IgG antibodies to *H. pylori* in the blood serum is associated with a tendency to increase in the periods of 30–39 and 60–69 years of age, and then to decrease in patients over 70 years of age [11].

The use of NSAIDs in elderly people for the treatment of chronic diseases may be among the reasons explaining the increase in the incidence of ulcerative colitis. The main mechanism of development of ulcers when taking NSAIDs is a decrease in the synthesis of prostaglandins PGE2 and PGE1. Taking NSAIDs increases the risk of ulcer development by 3 times, and the risk of ulcers localized in the stomach and duodenum by 6 times compared to other parts of the gastrointestinal tract [12].

The 17-fold increase in the risk of peptic ulcers is due to the simultaneous effect of NSAIDs and *H. pylori* infection. The likelihood of bleeding increases with NSAIDs by 5 times, with *H. pylori* infection — by 2 times, and their simultaneous effect determines an increase in the risk of bleeding by 6–20 times. As aspirin, NSAIDs, and *H. pylori* infection are independent risk factors, testing for *H. pylori* infection is recommended when planning the use of aspirin and NSAIDs [13, 14].

Male gender is recognized as a conventional risk factor in the development of peptic ulcers and their complications. This phenomenon may be due to sex differences in basal acidity and selective secretion of bicarbonate by the duodenal mucosa stimulated by the estrogen receptor in women compared to men [15]. Estrogen, by inhibiting the synthesis and release of gastrin, reduces the secretion of

hydrochloric acid and exhibits a protective effect against acid-peptic damage to the duodenum in women. A decrease in the level of this hormone in females is associated with an increased risk of duodenal ulcerogenesis. It has been established that duodenal ulcer is more severe in postmenopausal women than in premenopausal women.

Estimated annual percentage changes showed an increasing trend in age-standardized prevalence and an increasing trend in the incidence of peptic ulcers from 1990 to 2019, mainly due to an increase in the incidence of the condition in women. The steady increase in the proportion of women with peptic ulcer may be associated with factors such as *H. pylori* infection and the use of medications for the treatment of other diseases.

The limitations of our study were the lack of dynamic follow-up of patients in the cohort, confirming recurrent complications and relapses.

## Conclusions

1. It has been established that male gender and the age of 36 to 59 years are risk factors for the development of ulcer. Depending on gender, age and ulcer localization, the proportion of complicated forms of ulcer changes. The prevalence of complications in the cohort of patients with ulcer was 38.3 % of cases, and among men they were observed in every second case (47.9 %).

2. Bleeding is the most widespread complication and accounts for 52.6 %, 42.9 % and 41.2 % of all the complications in duodenal, combined and gastric ulcers, respectively. The maximum incidence of cicatricial ulcerative deformations is associated with localization in the duodenum and simultaneous combined damage. Such location of ulcer defects and, as a consequence, such a complication is recorded 2 times more often in men than in women. Perforations in gastric ulcer disease are related to the male gender 3 times more often. Stenosis is a rare complication, occurring mainly in women with duodenal ulcers.

3. The most significant predictors of peptic ulcer disease were smoking and *H. pylori* in men and *H. pylori*, NSAIDs or combination of these factors in women, and the predictors of complicated forms of peptic ulcer disease were male gender and smoking.

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### Information about the authors

**Olga V. Shtygasheva** — Dr. Sci. (Med.), Professor of the Department of Internal Diseases, N.F. Katanov Khakass State University.

Contact information: olgashtygasheva@rambler.ru; 655000, Abakan, Lenina ave., 92.

ORCID: <https://orcid.org/0000-0002-5522-1148>

**Elizaveta S. Ageeva\*** — Dr. Sci. (Med.), Head of the Department of Medical Biology, V.I. Vernadsky Crimean Federal University.

Contact information: ageevaeliz@rambler.ru; 295051, Simferopol, Lenina blvd, 5/7.

ORCID: <https://orcid.org/0000-0003-4590-3580>

**Elizaveta V. Matveeva** — Resident of the Department of Internal Disease, N.F. Katanov Khakass State University.

Contact information: olgashtygasheva@rambler.ru; 655000, Abakan, Lenin ave., 92.

ORCID: <https://orcid.org/0000-0003-0767-0501>

### Authors' contributions

**Concept and design of the study:** Shtygasheva O.V.

**Collection and processing of the material:** Shtygasheva O.V., Matveeva E.V.

**Statistical processing:** Ageeva E.S.

**Writing of the text:** Shtygasheva O.V., Ageeva E.S.

**Editing:** Shtygasheva O.V., Ageeva E.S.

**Proof checking and approval with authors:** Ageeva E.S.

### Сведения об авторах

**Штыгашева Ольга Владимировна** — доктор медицинских наук, профессор кафедры внутренних болезней, ФГАОУ ВО «Хакасский государственный университет им. Н.Ф. Катанова». Контактная информация: olgashtygasheva@rambler.ru; 655000, г. Абакан, просп. Ленина, 92.

ORCID: <https://orcid.org/0000-0002-5522-1148>

**Агеева Елизавета Сергеевна\*** — доктор медицинских наук, заведующий кафедрой биологии медицинской, ФГАОУ ВО «Крымский федеральный университет им. В.И. Вернадского».

Контактная информация: ageevaeliz@rambler.ru; 295051, г. Симферополь, 6-й Ленин, 5/2.

ORCID: <https://orcid.org/0000-0003-4590-3580>

**Матвеева Елизавета Викторовна** — ординатор кафедры внутренних болезней, ФГАОУ ВО «Хакасский государственный университет им. Н.Ф. Катанова».

Контактная информация: olgashtygasheva@rambler.ru; 655000, г. Абакан, просп. Ленина, 92.

ORCID: <https://orcid.org/0000-0003-0767-0501>

### Вклад авторов

**Концепция и дизайн исследования:** Штыгашева О.В.

**Сбор и обработка материалов:** Штыгашева О.В., Матвеева Е.В.

**Статистическая обработка:** Агеева Е.С.

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\* Corresponding author / Автор, ответственный за переписку