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Регистр пациентов с аутоиммунными заболеваниями печени в Санкт-Петербурге: клинико-эпидемиологические данные

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АННОТАЦИЯ

Обоснование. Проблема аутоиммунных заболеваний печени, включая аутоиммунный гепатит, первичный билиарный холангит, первичный склерозирующий холангит и их перекрестные синдромы актуальна для современной медицины. Это связано с ростом как заболеваемости, так и распространенности данных нозологий в разных регионах мира. Отсутствие установленного этиологического фактора, длительное бессимптомное или малосимптомное течение, отсутствие патогномоничной клинической картины, несовершенные критерии диагностики и недостаточная информированность врачей ведут к поздней диагностике аутоиммунных заболеваний печени и, соответственно, несвоевременному началу лечения, что нередко снижает его эффективность, влияя на дальнейший прогноз и выживаемость пациентов. Такие больные нуждаются в длительной, нередко пожизненной терапии и диспансерном наблюдении. Эпидемиологические регистры, в том числе и регистры аутоиммунных заболеваний печени, включающие различные нозологии, образуют важную базу данных о частоте, особенностях клинической картины, характере развития и течения заболевания, вариантах терапии и ответе на нее, наличии внепеченочных проявлений, а также позволяют анализировать все данные в динамике.

Цель исследования — проанализировать сведения о различных нозологиях аутоиммунных заболеваний печени, демографических показателях, клинической симптоматике, сроках между появлением первых симптомов и верификацией диагноза, характере внепеченочных проявлений.

Материалы и методы. В статье представлены данные регистра аутоиммунных заболеваний печени Северо-Западного центра гепатологии (Северо-Западного регистра аутоиммунных заболеваний печени) СЗГМУ им. И.И. Мечникова.

Результаты. Получены данные о нозологической структуре, демографических особенностях, сроках верификации диагноза, клинических симптомах и внепеченочных проявлениях аутоиммунных заболеваний печени.

Заключение. Создание регистров аутоиммунных заболеваний печени, включающих максимальный объем информации о пациентах с данными заболеваниями, поможет оценить эффективность используемых методов обследования и лечения, а также факторы, влияющие на течение и прогноз заболевания. Анализ полученных данных позволит разработать скрининговые программы, алгоритмы диагностики и дифференциальной диагностики аутоиммунных заболеваний печени, что, в свою очередь, облегчит и ускорит диагностический процесс, даст возможность начать терапию на более ранних сроках и соответственно улучшить дальнейший прогноз и выживаемость пациентов.

Ключевые слова: аутоиммунные заболевания печени; аутоиммунный гепатит; первичный билиарный холангит; первичный склерозирующий холангит; перекрестные синдромы; регистр; эпидемиология.

Как цитировать

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Registry of patients with autoimmune liver diseases in St. Petersburg: clinical and epidemiological data

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ABSTRACT

BACKGROUND: The problem of autoimmune liver diseases, which include autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis and their overlap syndromes is an urgent problem of modern medicine. This is associated with an increase in the incidence and prevalence of these nosologies in different regions of the world. Absence of an established etiological factor, prolonged asymptomatic or low-symptomatic course, lack of pathognomonic clinical picture, imperfect diagnostic criteria, insufficient awareness of physicians lead to late diagnosis of autoimmune liver diseases and, accordingly, untimely initiation of treatment, which often reduces its effectiveness, affecting the further prognosis and survival rate for this group of patients. Patients with autoimmune liver diseases require long-term, often lifelong therapy and dispensary observation. Epidemiological registries along with autoimmune liver diseases registries, including various nosologies of autoimmune liver diseases, form an important database on the incidence, clinical features, development and course of the disease, variants of therapy and response to therapy, presence of extrahepatic manifestations as well as allow analysis of all data in dynamics.

AIM: To analize data on various nosologies of autoimmune liver diseases, demographics, clinical symptoms, timing of the first symptoms, timing of diagnosis, and the nature of extrahepatic manifestations.

MATERIALS AND METHODS: This article presents data from the autoimmune liver diseases Register of the North-West Hepatology Centre (North-West Autoimmune Liver Diseases Register) of the North-Western State Medical University named after I.I. Mechnikov.

RESULTS: The study obtained data on the nosological structure, demographic characteristics, timing of diagnosis verification, clinical symptoms and extrahepatic manifestations of autoimmune liver diseases.

CONCLUSIONS: Establishing registers of autoimmune liver diseases, providing information about patients with these diseases, will help to assess the effectiveness of examination and treatment methods, factors affecting the course and prognosis of the disease. Analysis of the data obtained will help to develop screening programs, diagnostic algorithms and differential diagnostics of autoimmune liver diseases, which, in turn, will facilitate the diagnostic process, shorten the time of diagnosis, make it possible to start therapy earlier and, consequently, improve the prognosis and survival rate for this group of patients.

Keywords: autoimmune liver diseases; autoimmune hepatitis; primary biliary cholangitis; primary sclerosing cholangitis; overlap syndromes; register; epidemiology.

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BACKGROUND

Autoimmune liver diseases (AILDs), such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and their cross-syndromes, present a significant issue in modern gastroenterology and medicine. Data on the global incidence and prevalence of nosologic forms of AILDs are limited due to the need for large-scale, long-term, population-based studies using clear diagnostic criteria. The current epidemiological data indicate that the annual incidence of PBC in European, North American, Asian, and Australian populations ranges from 0.9 to 5.8 cases per 100,000 individuals. In comparison, the prevalence ranges from 1.9 to 40.2 cases per 100,000 population, depending on the country [1–3]. The annual incidence of AIH ranges from 0.67 to 2.0 cases per 100,000 population, with a prevalence of 4.0 to 42.9 cases per 100,000 population, depending on the geographic region [4, 5]. The incidence of PSC in different populations ranges from 0.07 to 1.31 cases per 100,000 population per year, while the prevalence ranges from 8.5 to 13.6 cases per 100,000 population [2, 6, 7]. Over the past decade, an increase in both the incidence and prevalence of AILDs has been noted in most regions of the world, as reported by the results of most epidemiologic studies [8–12]. However, in the Russian Federation, there are no generalized data on the incidence and prevalence of AILDs in general and by individual nosologies.

The late diagnosis of AILDs is influenced by several factors, including the absence of an established etiologic factor, a prolonged asymptomatic or asymptomatic course, the lack of a pathognomonic clinical picture, imperfect diagnostic criteria, and insufficient physicians' awareness. Consequently, the untimely initiation of treatment, which often reduces its effectiveness, affects patients' further prognosis and survival. Individuals diagnosed with AILDs require long-term, usually lifelong therapy and dispensary monitoring. This involves gastroenterologists and other specialists, including rheumatologists, dermatologists, transplantologists, and pathomorphologists. Therapy for patients with AILDs should be individualized, considering each patient's response and tolerability to the therapy. Furthermore, the efficacy of a specific group of drugs is not always optimal, necessitating personalized treatment regimens, the monitoring of therapeutic goals, and assessing the likelihood of potential adverse effects. Although AILDs are relatively rare, their clinical and economic burden is disproportionately high about their incidence and prevalence.

Epidemiologic registries, including those for AILDs that encompass various nosologies, provide a valuable database on the incidence, clinical features, development, and course of the disease, treatment options and response, and extrahepatic manifestations. They also have the capacity to analyze all data over time. Establishing AILD registries that include the most comprehensive data on patients with these diseases can facilitate the evaluation of the efficacy of diagnostic and therapeutic modalities and the factors influencing the course and prognosis of the disease.

Registry data can serve as a basis for clinical trials, hypothesis generation, and case planning (sampling frame) [13]. In addition, registries allow for dynamic monitoring of therapy safety and efficacy in patient groups usually excluded from clinical trials, such as pregnant women, children, elderly and senile patients, comorbid patients, etc. An important difference between registries and clinical trials, which are limited by clear timeframes, is the unlimited follow-up duration.

The analysis of registry data will facilitate the development of screening programs and algorithms for the diagnosis and differential diagnosis of AILDs. This, in turn, will streamline and accelerate the diagnostic process, enable the commencement of therapy at earlier stages of disease development, and consequently improve patients' further prognosis and survival.

National registers

In many foreign countries, registries of patients with AILDs are maintained, either with or without a division into nosologies. In some instances, these registries are incorporated into general registries of liver diseases [14–16].

In Portugal, a nationwide online registry of liver diseases has been established, accessible via the website Liver.pt. The registry includes data from patients with at least one liver disease as a principal diagnosis. The data collected encompasses the principal diagnosis, medical history, stage of liver disease, concomitant liver disease, other comorbidities, laboratory values, and treatment. All Portuguese hospitals can participate in this collaborative database, with patients being included voluntarily and consistently. This registry also includes data from patients with AILDs, allowing for analyzing various aspects of these diseases. For instance, in 2021, a study identifying predictors of incomplete response to ursodeoxycholic acid therapy in patients with PBC was published, and their data were included in a nationwide registry [17].

The results of a nationwide study on AILDs in the Faroe Islands, based on data from selected AILD registries, were published in 2023 [18]. This study included all cases of AIH, PBC, and PSC diagnosed in the Faroe Islands between January 1, 2004, and December 31, 2021. The results indicated that the incidence of AIH, PBC, and PSC in the Faroe Islands was 5.2, 2.5, and 0.7 per 100,000 population per year, respectively. The point prevalence per 100,000 population on December 31, 2021, was 71.8 for AIH, 38.5 for PBC, and 11.0 for PSC. These findings indicate that the incidence and prevalence of AILDs, especially AIH and PBC, are quite high in the Faroe Islands. This necessitates further local research on this disease group to better understand their course,

therapy response, and prognosis. The availability of a national registry helps address this need.

The Swiss AIH cohort study is a nationwide registry established in 2017. It collects retrospective and prospective clinical data and biological samples from patients of all ages with AIH treated in Swiss hepatology centers [16]. An analysis of the registry data for the first 5 years was published in 2023. A total of 291 patients with AIH, including 30 children, were registered. The mean age at diagnosis was 54 years (range: 42–64 years; interquartile range: 18–81 years) and 12.5 years for children (range: 1–17 years; interquartile range: 8–15 years). Among adults, 71% were female, and 29% were male. Twenty percent of patients had cross-syndrome of AIH with PBC, 8% had cross-syndrome of AIH with PBC, and 4% had inflammatory bowel disease. Additionally, 32% of adults were diagnosed with significant hepatic fibrosis at the time of diagnosis. In the pediatric cohort, 53% were girls, and 47% were boys. Type II AIH was diagnosed in 32% of children; 27% had cross-syndrome with autoimmune sclerosing cholangitis, one patient had cross-syndrome with PBC, and 15% had inflammatory bowel disease. The study found that 41% of children had severe fibrosis at diagnosis. The analysis also covered other comorbidities, therapy options, and efficacy [16].

In the United Kingdom, establishing a local registry at one of the London hospitals represents an important step toward improving the quality of care for patients with PBC. This initiative is part of a more comprehensive implementation program in other medical institutions across the country [19]. The decision to create this registry was driven by identified deficiencies in the quality of medical care provided to patients with PBC [20]. The data collected will be used to investigate the course and progression of PBC, its impact on quality of life, differences in the use of modern therapies and care delivery, therapy costs, disease outcomes, and mortality. These data will also assist in informing clinical decisions, examining healthcare resource utilization, and determining the costs of treating patients with PBC. Anonymized aggregated data will permit comparative analysis of patient outcomes across different UK healthcare settings [20].

There are sporadic data in the Russian Federation on the epidemiological, clinical, biochemical, and morphologic features of AILDs, both in general and for individual nosologies.

As published data indicates, only the Republic of Tatarstan maintains a register of AILDs. From 2008 to 2015, 138 patients with different variants of AILDs were included, and their sociodemographic and clinical features were analyzed [21]. Of the 138 patients, 52 (39%) were diagnosed with AIH, 27 (20%) with PBC, 51 (39%) with cross-syndrome, and 2 (2%) with PSC. The most common clinical manifestations in AIH were weakness (71.7%), skin itching (50%), jaundice (37%), and a sensation of heaviness in the right subcostal region (35.5%). Upon examination of the clinical symptomatology according to the nosology, it was found that the frequency of complaints was approximately the same for all diseases. Consequently, complaints manifested within 1 year before diagnosis in AIH (55.7%), PBC (59.3%), and cross-syndrome (53%). However, the clinical picture was most pronounced in AIH, with symptoms developing one month before diagnosis in 29% of cases of AIH, 7.4% of cases of PBC, and 5.8% of cases of cross-syndrome.

The aim of this study was to examine the North-West register of AILDs and provide a comparative epidemiological and clinical characterization of patients diagnosed with AILDs. This entailed identifying gender and age-specific characteristics, determining the patient's age at the onset of symptoms and the time to verify the diagnosis, and evaluating clinical symptoms and extrahepatic manifestations.

MATERIALS AND METHODS

In December 2019, the Department of Propedéutrics of Internal Medicine, Gastroenterology, and Dietetics of the North-Western State Medical University named after I.I. Mechnikov initiated the development of the AILD register of the North-Western Hepatology Center, also known as the *North-Western AILD Register*. The register includes data from patients who have attended primary and repeated outpatient appointments at the Consultative and Diagnostic Center and those who have been hospitalized at the clinic of the North-Western State Medical University named after I.I. Mechnikov.

Information is included with the voluntary written consent of patients, who have been informed that their data will be included in the general electronic registration system. Patients have the right to refuse. A questionnaire is prepared for each patient, serving as the primary documentation. Entering a patient's data into the registry does not affect the treatment and diagnostic tactics performed at the outpatient or inpatient level.

RESULTS AND DISCUSSION

Distribution by nosological forms

All patients with AILDs were categorized into groups according to diagnosed diseases, including AIH, PBC, PSC, drug-induced AIH (DIAIH), and cross-syndromes (AIH/PBC, AIH/PSC, AIH/PBC/PSC).

As of February 2, 2024, the North-Western AILD Registry prospectively included 215 patients with diagnosed AILD. Of these, 45 (21%) had AIH, 84 (39%) had PBC, 13 (6%) had PSC, 46 (21%) had AIH/PBC, 10 (5%) had AIH/PSC, 3 (1%) had PBC/PSC, 2 (1%) had PBC/PSC/AIH, and 12 (6%) had DIAIH. Consequently, the most prevalent nosologies are represented

by PBC, AIH, and autoimmune cross-syndrome AIH/PBC, collectively accounting for 81% of cases (Fig. 1).

Most (86% or 185 patients) in the North-Western AILD Registry reside in the North-Western Federal District, indicating that the registry data are locally specific.

Demographic characteristics

The age range of patients in the registry was 19 to 84 years, with a mean age of 54.7 ± 15.8 years. The mean age by nosology was as follows: 46.67 ± 18.19 years for AIH, 61.63 ± 12.15 years for PBC, 46.85 ± 15.9 years for PSC, 46.1 ± 11.1 years for DIAIH, 57.02 ± 12.98 years for AIH/PBC, 42.6 ± 21.26 years for AIH/PSC, 55 ± 15.71 years for PBC/ PSC, and for AIH/PBC/PSC it was 32.5 ± 13.43 years.

Excluding nosologies, 83 patients (39%) were classified as elderly (60–74 years), 66 (30%) were middle-aged (45–59 years), 54 (25%) were young (18–44 years), and 12 (6%) were senile (75–90 years) (Fig. 2).

A comparison of age distributions according to nosology reveals that young people are more prevalent among patients with AIH (19 individuals, 42%). In contrast, elderly individuals are more common among patients with PBC (43 individuals, 51%). Young and middle-aged patients are more common among patients with PSC (10 individuals, 77%). The majority of patients with AIH/PBC were elderly (19 individuals, 41%), while the majority of patients with AIH/PSC were young (6 individuals, 60%). Finally, the majority of patients with DIAIH were young and middle-aged (12 individuals, 100%).

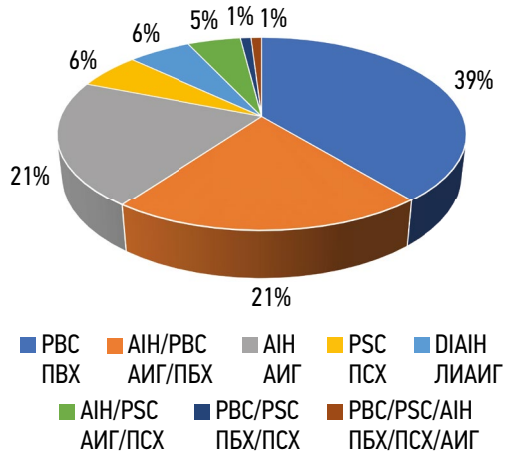

Fig. 1. Nosological structure of the register. AIH — autoimmune hepatitis; PBC — primary biliary cholangitis; PSC — primary sclerosing cholangitis; DIAIH — drug-induced autoimmune hepatitis

Рис. 1. Нозологическая структура регистра. АИГ — аутоиммунный гепатит; ПБХ — первичный билиарный холангит; ПСХ — первичный склерозирующий холангит; ЛИАИГ — лекарственно-индуцированный аутоиммунный гепатит

However, data on patients with PBC/PSC and AIH/PBC/PSC were insignificant due to a small sample size (Table 1).

Among the patients with AILD included in the registry, women predominate, accounting for 166 (77%) patients (Fig. 3).

In the distribution of patients by nosology, women predominated in the groups of patients with AIH, PBC, AIH/PBC,

Table 1. Distribution of patients by age according to nosology

Таблица 1. Распределение пациентов по возрасту в зависимости от нозологии

Age	AIH	PBC	PSC	DIAIH	AIH/PBC	AIH/PSC	PBC/PSC	AIH/PBC/PSC
Young, %	42	6	38.5	50	20	60	33.3	50
Middle-aged, %	22.	35	38.5	50	33	10	33.3	50
Elderly, %	33	51	23	–	41	20	33.3	–
Senile, %	3	8	–	–	6	10	–	–

Note. AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DIAIH, drug-induced autoimmune hepatitis. The most frequently occurring indicators are highlighted in gray.

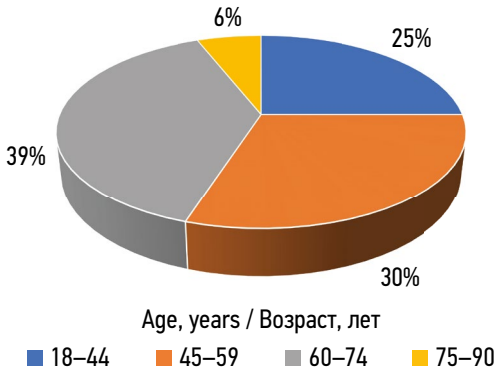

Fig. 2. Distribution of patients by age

Рис. 2. Распределение пациентов по возрасту

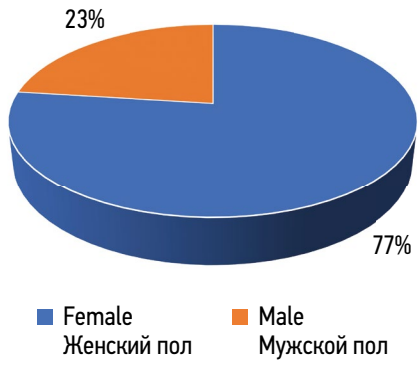

Fig. 3. Distribution of patients by gender

Рис. 3. Распределение пациентов по полу

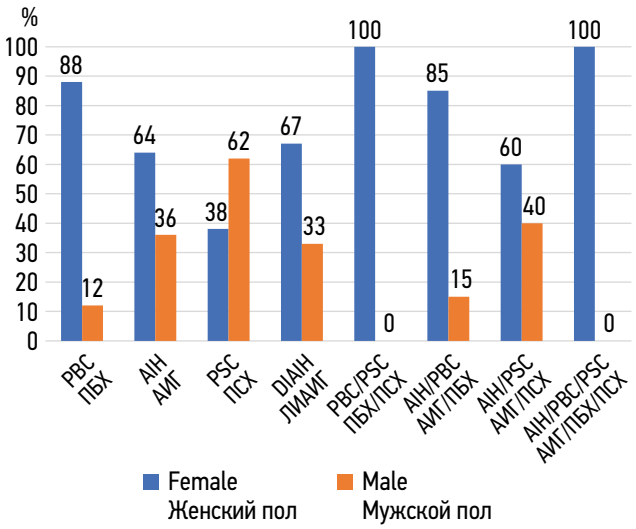

Fig. 4. Distribution patients by gender depending on nosology. AIH — autoimmune hepatitis; PBC — primary biliary cholangitis; PSC — primary sclerosing cholangitis; DIAIH — drug-induced autoimmune hepatitis

Рис. 4. Распределение пациентов по полу в зависимости от нозологии. АИГ — аутоиммунный гепатит; ПБХ — первичный билиарный холангит; ПСХ — первичный склерозирующий холангит; ЛИАИГ — лекарственно-индуцированный аутоиммунный гепатит

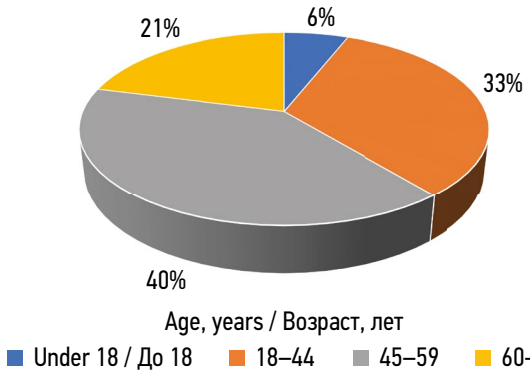

Fig. 5. Age of patients at the onset of symptoms of autoimmune liver diseases

Рис. 5. Возраст пациентов при дебюте симптомов аутоиммунных заболеваний печени

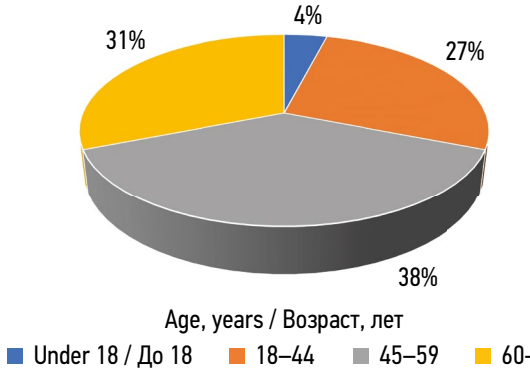

Fig. 6. Age of patients at diagnosis of autoimmune liver diseases

Рис. 6. Возраст пациентов при диагностировании аутоиммунных заболеваний печени

AIH/PSC, AIH/PBC/PSC, and DIAIH. In contrast, men account for a larger proportion of patients with PSC (Fig. 4).

Thus, among the patients of the North-Western AILD Registry, the predominant groups are those patients with PBC (84 [39%]); women (166 [77%]); and elderly and middle-aged people (83 [39%] and 66 [30%] patients, respectively).

Verification of diagnosis and clinical manifestations

Analysis of the registry data showed that the onset of clinical symptoms of AILD occurred at a median age that was consistent with the age at diagnosis (Figs. 5 and 6).

According to the registry data, the duration of symptoms before diagnosis was less than 1 year in 79 (37%) patients. However, this interval was 1–5 years in 73 (34%) patients, 6–10 years in 33 (15%) patients, and more than 10 years in 30 (14%) patients (Fig. 7).

On average, the time from symptom onset to AILD diagnosis is nearly 5 years (59.4 months), based on the registry.

When analyzing the individual nosologies of AILD, the onset of first symptoms in patients with PBC, DIAIH, and PBC/PCS occurred at middle age in 40 (48%), 6 (50%), and 2 (66.7%), respectively, whereas in AIH, PSC, AIH/PCS, and AIH/PBC/PCS, it occurred at young age in 17 (38%), 8 (62%), 4 (40%), and 2 (100%), respectively. For AIH/PBC, the onset of clinical symptoms was equal in young and middle-aged patients at 16 (35%) individuals in each group (Table 2).

According to the registry data, the age of diagnosis according to nosology was as follows: PBC, PSC, and PBC/PSC were diagnosed at middle age in 34 (41%), 7 (54%), and 2 (66.7%), respectively, whereas AIH and AIH/PSC were diagnosed at young age in 16 (36%) and 6 (60%), respectively. In AIH/PSC, the diagnosis was made at age 18 (39%), and in DIAIH and AIH/PBC/PSC in young and middle age in equal proportions (Table 3).

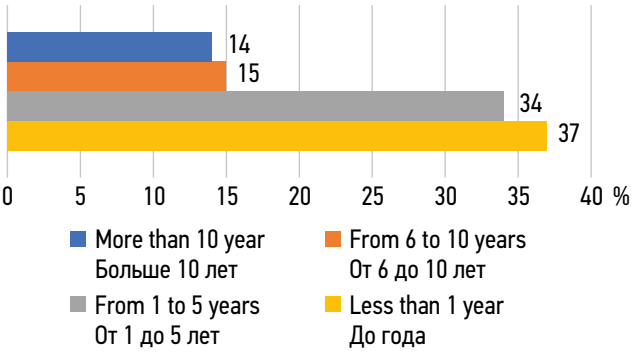

Fig. 7. Time from onset of symptoms to diagnosis of autoimmune liver disease

Рис. 7. Время от появления симптомов до диагностирования аутоиммунных заболеваний печени

Table 2. Age of the patients at the onset of symptoms of autoimmune liver diseases depending on nosology

Таблица 2. Возраст пациентов при дебюте симптомов аутоиммунных заболеваний печени в зависимости от нозологии

Age	PBC	AIH	PSC	DIAIH	AIH/PBH	AIH/PSC	PBC/PSC	AIH/PBH/PSC
Under 18 years of age, %	2	11	15	8	2	20	–	–
Young, %	18	38	62	42	35	40	33.3	100
Middle-aged, %	48	27	23	50	35	30	66.7	–
Elderly, %	25	24	–	–	26	–	–	–
Senile, %	7	–	–	–	2	10	–	–

Note. AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DIAIH, drug-induced autoimmune hepatitis. The most frequently occurring indicators are highlighted in gray.

Table 3. Age of the patients at diagnosis of autoimmune liver diseases depending on nosology

Таблица 3. Возраст пациентов при диагностировании аутоиммунных заболеваний печени в зависимости от нозологии

Age	PBC	AIH	PSC	DIAIH	AIH / PBC	AIH/PSC	PBC/PSC	AIH/PBC/PSC
Up to 18 years	–	11	15	–	2	–	–	–
18–44 years	13	36	31	50	24	60	33.3	50
45–59 years	41	24	54	50	33	20	66.7	50
60–74 years	39	29	–	–	39	10	–	–
75–90 years	7	–	–	–	2	10	–	–

Note. AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DIAIH, drug-induced autoimmune hepatitis. The most frequently occurring indicators are highlighted in gray.

The timing of diagnosis according to nosology was as follows: AIH and DIAIH were more frequently diagnosed within the first year in 24 (53%) and 6 (50%) patients, respectively; PBC and PSC were diagnosed within 1 year and between 1 and 5 years in equal proportions in 24 (29%) and 4 (31%) patients, respectively; AIH/PBC and AIH/PSC

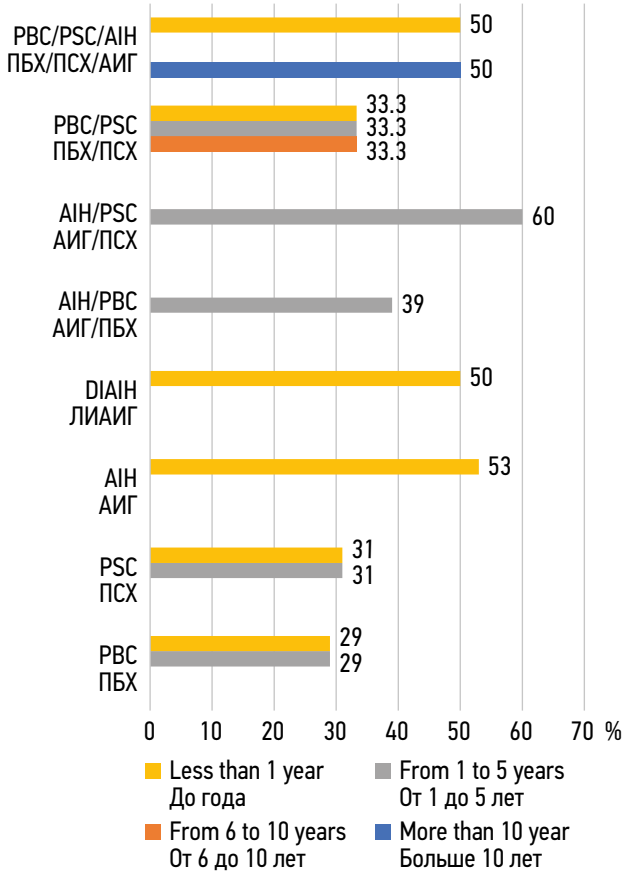

Fig. 8. Time from onset of symptoms to diagnosis of autoimmune liver disease depending on nosology. AIH — autoimmune hepatitis; PBC — primary biliary cholangitis; PSC — primary sclerosing cholangitis; DIAIH — drug-induced autoimmune hepatitis

Рис. 8. Время от появления симптомов до диагностирования аутоиммунных заболеваний печени в зависимости от нозологии. АИГ — аутоиммунный гепатит; ПБХ — первичный билиарный холангит; ПСХ — первичный склерозирующий холангит; ЛИАИГ — лекарственно-индуцированный аутоиммунный гепатит

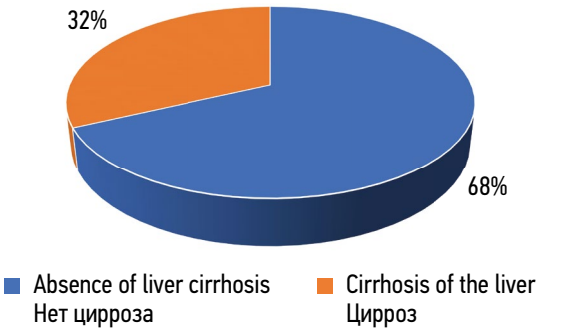

Fig. 9. Proportion of the patients with liver cirrhosis at the time of diagnosis of autoimmune liver diseases

Рис. 9. Доля пациентов с циррозом печени на момент диагностирования аутоиммунных заболеваний печени

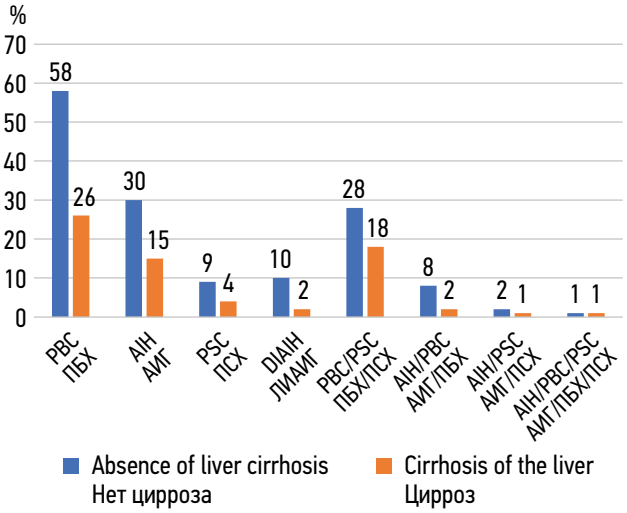

Fig. 10. Proportion of the patients with liver cirrhosis at the time of diagnosis of autoimmune liver diseases depending on nosology

Рис. 10. Доля пациентов с циррозом печени на момент диагностирования аутоиммунных заболеваний печени в зависимости от нозологии

between 1 and 5 years in 18 (39%) and 6 (60%) patients, respectively. Analysis of time to triple-crossing diagnosis did not show significance due to the small sample size (Fig. 8).

Among the 215 registry patients, 32% (69 patients) had cirrhosis at the time of diagnosis (Fig. 9). A total of 15 (33.3%) patients were diagnosed with liver cirrhosis and AIH, 26 (31%) with PBC, 4 (31%) with PSC, 2 (17%) with DIAIH, and 1 (33.3%) with AIH/PBC/PSC. In the case of AIH/PBC, it was observed in 18 (39%) patients; in the case of AIH/PSC, it was revealed in 2 (20%) patients; in the case of PBC/PSC and AIH/PBC/PSC, it was observed in 1 (33.3%) and 1 (50%) patient, respectively (Fig. 10). The detection of liver cirrhosis at the time of diagnosis likely reflects difficulties in diagnosis and late referral to specialized centers.

Thus, the onset of clinical symptoms and diagnosis were more frequently registered in middle-aged individuals, regardless of the specific nosology. The average duration from the onset of symptoms to the diagnosis of the disease was approximately 5 years, and 69 (32%) patients were diagnosed with liver cirrhosis at the time of diagnosis.

Clinical manifestations

A prolonged asymptomatic course, heterogeneity of clinical manifestations, and the absence of a pathognomonic clinical picture define AILD.

The registry data revealed that the most frequently occurring specific symptoms at disease onset included fatigue, right subcostal pain/discomfort, skin itching, dry skin and mucous membranes, jaundice, and joint pain. The rest of the rarely occurring symptoms were categorized under the “Other symptoms” group.

A total of 215 patients were included in the study. Of these, 31 (14.4%) were asymptomatic. Symptoms were present in 40 (89%) patients with AIH, 69 (82%) with PBC, 10 (77%) with PSC, 11 (92%) with DIAIH, 41 (89%) with PBC/AIH, and 9 (90%) with AIH/PSC. The observed rates in the groups of patients with PBC/PSC and AIH/PBC/PSC were not statistically significant due to the limited sample size (Table 4).

It is not uncommon for AILDs to be combined with other autoimmune or immune-mediated diseases. Patients with these pathologies are at a higher risk of developing additional

Table 4. Clinical symptoms at the onset of autoimmune liver diseases

Таблица 4. Клинические симптомы в дебюте аутоиммунных заболеваний печени

Symptoms	AIH	PBC	PSC	DIAIH	AIH/PBC	AIH/PSC	PBC/PSC	AIH/PBC/PSC
None, %	11	18	23	8	11	10	0	50
Fatigue, %	76	56	46	75	63	50	66.7	50
Pain/discomfort in the right subcostal region, %	16	25	31	33.3	17	10	66.7	0
Skin itching, %	18	42	38	17	48	40	33.3	50
Dryness of skin and mucous membranes, %	2,2	5	8	15	6.5	0	0	0
Jaundice, %	67	34	15	42	33	30	0	0
Joint pain, %	9	8	15	8	11	0	0	0
Other, %	60	37	77	50	54	30	0	50

Note. AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DIAIH, drug-induced autoimmune hepatitis.

Table 5. Extrahepatic manifestations in the patients of the registry
Таблица 5. Внепеченочные проявления у пациентов регистра

Nosology		AIH	PBC	PSC	DIAIH	AIH/PBC	AIH/PSC	PBC/PSC	AIH/PBC/PSC
Without extrahepatic manifestations, %		62	69	15.4	75	63	40	0	50
Inflammatory bowel disease	Crohn's disease, %	4.4	6	38.5	0	0	20	33.3	0
	Ulcerative colitis, %	4.4	1.2	23	0	2	30	0	0
Autoimmune thyroiditis, %		13	13	7.7	8	13	0	66.7	0
Autoimmune gastritis, %		0	3.6	0	0	2	0	0	0
Rheumatologic diseases, %		16	14	0	17	17	0	33.3	0
Dermatologic diseases, %		13	7	15.4	0	0	10	33.3	50

Note. AIH, autoimmune hepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; DIAIH, drug-induced autoimmune hepatitis.

immunoinflammatory diseases. According to the literature, various autoimmune or rheumatologic diseases are present in 32% to 63% of patients with PBC [2, 3, 22]. It is well documented that between 3.5% and 73% of patients with PBC also have Sjögren's syndrome and thyroid pathology in the form of hypothyroidism (more often Hashimoto's thyroiditis [5.6%–23.6% of patients]) and scleroderma (in most cases in the localized form [1.4%–12.3% of patients]). Less frequently observed in patients with PBC are diseases such as rheumatoid arthritis, systemic lupus erythematosus, and fibrosing alveolitis [23].

AIH is associated with a wide range of other autoimmune or immune-mediated diseases in 14% to 44% of patients [24, 25]. These include autoimmune thyroiditis (8%–23%), type 1 diabetes mellitus (1%–10%), Sjögren's syndrome (1%–7%), rheumatoid arthritis (2%–4%), inflammatory bowel disease (2%–8%), systemic lupus erythematosus (1%–3%), and celiac disease (1%–6%). The occurrence of fibrosing alveolitis, glomerulonephritis, hemolytic anemia, polymyositis, multiple sclerosis, and other conditions is less frequent in patients with AIH [5, 25].

A distinctive feature of PSC is its frequent association with inflammatory bowel disease. In Western European and North American populations, 60% to 80% of patients with PSC also have inflammatory bowel disease, with ulcerative colitis representing more than 75% to 80% of cases. The remaining 20% to 25% are either Crohn's disease or unclassified colitis (approximately 5%) [7, 26]. The North-Western Center for Inflammatory Bowel Diseases reports that the incidence of PSC in ulcerative colitis is 5%, and in patients with Crohn's disease, it is 1% [27, 28].

Autoimmune diseases associated with AILD can be considered as extrahepatic manifestations that precede the onset of liver damage or develop owing to the superimposition of symptoms on the clinical picture of AILD. Patients with AILD, both at the time of diagnosis and during dynamic follow-up, should be examined more thoroughly for the presence of autoimmune pathology associated with AILD. Conversely, the presence of autoimmune diseases, which are the most common in AILD, necessitates both a primary examination and dynamic monitoring of patients for the timely detection of AILDs.

Among the 215 patients in the registry, extrahepatic manifestations were observed in 84 (39%) patients. These included 26 (31%) were patients with PBC, 11 (85%) were patients with PSC, 17 (38%) were patients with AIH, 3 (25%) were patients with DIAIH, 17 (37%) were patients with PSC and AIH, and 6 (60%) were patients with AIH and PSC. No extrahepatic manifestations were observed in the patients with PBC/PSC and AIH/PBC/PSC, likely due to the limited sample size (Table 5).

According to the registry data, 31 (14.4%) individuals exhibited asymptomatic AILD, which is characterized by clinical heterogeneity. Extrahepatic manifestations were observed in 84 (39%) patients, including inflammatory bowel disease, autoimmune thyroiditis, gastritis, and various rheumatologic and dermatologic diseases.

CONCLUSIONS

Given the limited data on epidemiological, clinical, biochemical, and morphological features of AILDs (both in general and for individual nosologies) in the Russian Federation, the establishment of the AILD Registry of the North-Western Hepatology Center of the North-Western State Medical University named after I.I. Mechnikov is both justified and relevant. This registry, which includes comprehensive data on patients with various forms of AILD, will facilitate the assessments of disease progression, the efficacy of diagnostic and therapeutic modalities, and the identification of factors influencing disease progression and prognosis. Such a registry would ideally encompass epidemiological data, clinical symptomatology, laboratory and instrumental investigation results, therapeutic approaches, and patient responses. Analyzing registry data will facilitate the development of screening programs, diagnostic algorithms, and differential diagnosis of AILD. This, in turn, will lead to earlier diagnosis of AILD, enable the commencement of therapy at an earlier stage, and, ultimately, enhance the prognosis and survival of patients.

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Author contribution. All the authors have made an equally contribution to the development of the concept, research, and preparation of the article as well as read and approved the final version before its publication.

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Вклад авторов. Все авторы внесли равный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

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