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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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EVALUATION OF PREDICTORS OF INEFFECTIVENESS OF ANTIVIRAL THERAPY FOR CHRONIC HEPATITIS C IN THE REPUBLIC OF KAZAKHSTAN: A MATCHED CASE-CONTROL STUDY

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Abstract.

This study aims to identify the predictors of ineffectiveness in antiviral therapy for chronic hepatitis C (CHC) in Kazakhstan. The rising prevalence and mortality rates associated with CHC globally and within Kazakhstan underscore the need for effective antiviral treatment strategies. Despite the introduction of direct-acting antiviral agents (DAAs) with high cure rates, a subset of patients fails to achieve a sustained virological response (SVR). We conducted a multicenter retrospective matched case-control study across 13 regions of Kazakhstan, including 812 patients with CHC. The study involved patients registered in healthcare organizations who had received DAAs, focusing on those who did not reach SVR. Variables such as demographic characteristics, virological status, stage of liver disease, comorbidities, lifestyle factors, therapy regimen, and patient adherence were analyzed. Logistic regression analysis identified multiple factors associated with increased risk of non-response to therapy, including comorbid conditions like arterial hypertension, hepatocellular carcinoma, and lifestyle factors. The study highlights the complexity of CHC treatment in Kazakhstan, emphasizing the need for personalized treatment plans and addressing comorbid conditions and lifestyle factors. This research contributes to understanding the multifaceted nature of CHC treatment response and aids in optimizing therapeutic strategies in similar healthcare settings.

Key words. Chronic hepatitis C, direct-acting antiviral agents, virological response, Kazakhstan.

Introduction.

Chronic hepatitis C (CHC) is leading cause of cirrhosis and primary hepatocellular carcinoma globally [1] and in Kazakhstan [2]. The World Health Organization (WHO) estimates that approximately 58 million individuals worldwide live with chronic hepatitis C virus infection, with around 1.5 million new infections reported annually [3]. In 2019, WHO estimated that nearly 290,000 people died from hepatitis C (HC), primarily due to cirrhosis and primary liver cancer [3]. The prevalence of CHC varies significantly across different regions. The prevalence of CHC varies significantly across different regions.

In the Republic of Kazakhstan (KZ), the burden of CHC is palpable. Epidemiological data indicate a substantial prevalence of CHC infection, with some regions exhibiting higher rates due to varying transmission dynamics and risk populations [4]. As of September 25, 2020, the "Viral Hepatitis" Register listed 29,264 individuals with CHC in KZ. A 2017 epidemiological study by the Research Institute of Cardiology and Internal Diseases of the Ministry of Health of KZ reported a CHC incidence of 5.8% among the adult population in five KZ regions [5].

The advent of direct-acting antiviral agents (DAAs) has transformed CHC treatment, yielding cure rates over 90% in many cases [6]. Nevertheless, a subset of patients fails to achieve sustained virological response (SVR) despite standard DAA therapy.

Since 2011, KZ has provided antiviral therapy (AVT) against CHC as part of its guaranteed volume of free medical care (GBVM) [7]. Over this period, more than 7,000 patients have received pegylated interferon-based AVT, with effectiveness ranging from 65 to 85%, depending on the virus genotype [8]. In 2016-2017, 264 patients with HCV genotype 1 were treated with DAAs under GBVM, achieving an efficiency rate of 99%. However, as of 2017, the vast majority of patients were not receiving AVT [9].

Aligning with WHO's Global Strategy for Viral Hepatitis 2016–2021 and the Strategies for the Prevention and Management of Sexually Transmitted Infections (STIs), HIV, and Viral Hepatitis, WHO member states are focusing on identifying and eradicating viral hepatitis [10]. On September 26, 2017, KZ's Minister of Health approved a roadmap for implementing preventive measures, diagnosis, and elimination of parenteral viral hepatitis effects for 2017-2020.7 Since 2018, patients with all hepatitis C virus genotypes in KZ receive tablet-based AVT (sofosbuvir + daclatasvir ± ribavirin), centrally procured by the Ministry of Health through the United Nations Development Program. This integration of DAAs into national healthcare has spurred an initiative to treat and potentially eliminate HC infection. However, not all patients respond positively to the current treatment protocols.

Given the pressing need to optimize treatment outcomes for HC-infected individuals in KZ, this study aims to delve deeper into the factors that may hinder effective AVT. In light of this, it appears pertinent to investigate the factors contributing to the ineffectiveness of AVT for CHC in the KZ. This encompasses demographic factors, constitutional characteristics, previous therapy history, virological status, liver disease activity and stage, comorbidities, harmful habits, adherence to therapy, and the characteristics of administered AVT.

The aim of the study is to determine the risk factors associated with the absence of a virological response to standard therapy with direct–acting antiviral agents, provided within the guaranteed volume of free medical care since 2018, to patients with CHC registered in healthcare organizations of the Republic of Kazakhstan.

Methods.

Study site:

This was a multicenter retrospective matched case-control study conducted in 13 regions of Kazakhstan including Almaty and Nur-Sultan cities at hepatological centers, which are the government-funded tertiary care facilities for CHC patients in KZ.

Ethics statement:

The Local Ethics Committee of the Kazakh national medical university (# 14 (120) 28.10.2021) was approved the research. Informed consent was obtained from all participants and/or their legal guardians. Research had been performed in accordance with the Declaration of Helsinki.

Patient enrolment and matching criteria:

We included patients aged 18 years and older with chronic Hepatitis C Virus infection, registered in healthcare organizations of the Republic of Kazakhstan. Eligible participants were those who either had not previously received AVT or had received AVT based on Pegylated interferon and Ribavirin. Additionally, included patients were those who did not achieve VR, defined as having a positive HC RNA PCR result at the end of therapy and/or 12 weeks or more post-treatment, following AVT with direct-acting antiviral agents (Sofosbuvir + Daclatasvir ± Ribavirin). These treatments were provided as part of the guaranteed volume of free medical care since 2018.

Cases in this study were defined as CHC patients who did not achieve a VR to standard therapy with DAAs. Conversely, controls were those patients who attained an SVR. Both cases and controls were enrolled and identified from June to December 2022. These patients, all adult (≥18 years of age) citizens of Kazakhstan, were selected from various hepatological centers based on their records from 2018 onwards. Each eligible case was matched with three controls (1:3 ratio) based on age, sex, and ethnicity. The selection process involved identifying eligible control patients from the appointment lists at these centers, using the specified matching criteria.

Sample size:

To calculate the sample size for a 3:1 matched case-control study, we considered several factors:

- Expected odds ratio - the measure of association between exposure and outcome.
- Power (1 - β): we used 80%.
- Significance level (α): set at 0.05 (5%).
- Proportion of controls exposed.
- Case-to-control ratio (3:1).

We used the **Fleiss formula** for sample size calculation in our study with unequal groups. The formula for the number of cases (n_1) and controls (n_0) is as follows:

$$n_1 = \left(\frac{Z_{1-\alpha/2} + Z_{1-\beta}}{\log(OR)} \right)^2 \times \frac{(1+r)}{r \times P_0 \times (1-P_0)}$$

Where:

- $Z_{1-\alpha/2}$: for α = 0.05, Z = 1.96.
- $Z_{1-\beta}$: for power = 80%, Z = 0.84.
- The expected odds ratio from previous studies was 2.0.
- Proportion of controls exposed from previous studies is 0.45.
- Ratio of controls to cases (3:1), so r = 3.

The number of controls (n_0) is then $r \times n_1$

Using the above formula, we got:

$n_{1\ (cases)} = 203$

$n_{0\ (controls)} = 609$

Study instruments and variables:

The data was collected by local trained doctors in each hepatological center from medical history records. The risk factors assessed included the participants' demographic characteristics (e.g. age, sex, ethnicity, region, height, weight), virological status (virological response after AVT with direct antiviral agents, previous AVT, HC genotype), stage of the disease/fibrosis, comorbidities, smoking, alcohol consumption, use of other psychoactive substances, the regimen of prescribed antiviral therapy, duration of HCV before the start of AVT, known duration of antiviral therapy, patient's adherence to therapy.

Statistical analysis:

The matching characteristics of the case and control groups were presented as frequencies and percentages. Differences in the matching characteristics were assessed using Pearson's chi-square test. Crude odds ratios and 95% confidence intervals (CIs) were determined for each potential risk factor using univariable logistic regression analysis, and the significance level was fixed at $p < 0.05$. The associations between VR status and demographic characteristics, comorbidities and medical history were subsequently assessed using multivariable logistic regression analysis. Unconditional logistic regression was used in this study because the data were matched on basic variables (age, sex and ethnicity).

All variables with a p-value < 0.25 in the univariable analysis were included in the multivariable model. The variables in the final model were selected using stepwise procedures. The model was then checked for interactions between the included variables and for multicollinearity. Model fit was examined using the Hosmer– Lemeshow goodness-of-fit test, the classification table and the receiver operating characteristic curve. All analyses were performed using SAS OnDemand for Academics (release 3.81, Carry, NC, USA). The study methods and findings have been reported according to the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results.

In this study we analyzed 812 patients over 18 years of age with CHC in the KZ. Patients were divided into two groups: case (absence of VR to standard therapy with DAAs in patients with CHC) and control (patients who achieved an SVR). For each case recruited from the target population, controls of the appropriate age, gender and ethnicity were recruited in a ratio of 1:3. In both groups, the majority of patients were men aged 40 years and older. There were no significant differences between cases and control groups in terms of age, gender and ethnicity (Table 1).

Table 1. *Matching characteristics of the cases and controls.*

Characteristics	Case - 203, n (%)	Control - 609, n (%)	p-value*
Age groups			0.9934
≤ 29	8 (3.94)	24 (3.94)	
30–39	30 (14.87)	82 (13.46)	
40–49	51 (25.12)	157 (25.78)	
50–59	59 (29.06)	177 (29.06)	
≥ 60	55 (27.09)	169 (27.75)	
Sex			0.9334
Male	126 (62.07)	380 (62.40)	
Female	77 (37.93)	229 (37.60)	
Ethnicity			0.2144
Asian	127 (62.56)	410 (67.32)	
European	76 (37.44)	199 2.68)	

**- Pearson's chi-squared test; n-number; %-percent.*

Table 2. *Demographic characteristics of the key indicators.*

Key indicators	n	%
Sex		
Male	506	62.32
Female	306	37.68
Ethnicity		
Asian	537	66.13
European	275	33.87
Region		
Akmola region	36	4.43
Aktobe region	12	1.48
Almaty region	12	1.48
Almaty city	136	16.75
Atyrau region	48	5.91
East Kazakhstan region	48	5.91
Zhambyl region	60	7.39
West Kazakhstan region	28	3.45
Karaganda region	28	3.45
Kostanay region	48	5.91
Kyzylorda region	40	4.93
Mangystau region	24	2.96
Nur-Sultan city	100	12.32
North Kazakhstan region	24	2.96
Turkestan region	168	20.69
Age, years	52[c]	21-76[d]
Age		
<29	32	3.94
30-39	112	13.79
40-49	208	25.62
50-59	236	29.06
>60	224	27.59
BMI	25.4[c]	16.3-43.2[d]
The presence of previously performed antiviral therapy (12 weeks) with Peg interferon / Ribavirin		
Yes	27	3.35
No	778	96.65
Duration of chronic hepatitis C before the start of antiviral therapy	12[c]	1-372[d]

median; d – min-max; n-number; %-percent.

Table 2 shows the main demographic data. The majority of patients were men (62.32%) and Asians (66.13%). The average age of patients was 52 (21-76) and the majority of patients were 40 years and older. Many patients were from Turkestan region (27.59%), Almaty city (16.75) and Nur-sultan city (12.32%). The average body mass index was 25.39 (16.27-43.24). In 3.35% of patients, antiviral therapy with Peg interferon / Ribavirin was previously received. The duration of chronic hepatitis C before the start of antiviral therapy averaged 12 (1-372).

Table 3 shows univariable logistic regression analysis of the risk factors for the absence of a virological response to standard therapy with direct-acting antiviral agents in patients with CHC. The results of the analysis showed that those with stomach ulcer (p=0.0266), HIV (p=0.0279), overweight/obesity (p=0.0045), arterial hypertension (p=0.0057), chronic kidney disease (p=0.0169), hepatocellular carcinoma (p=0.0327), alcohol abuse (p=0.0003), presence of previously performed antiviral therapy with Peg interferon / Ribavirin (p=0.0005), genotype 3 of hepatitis C virus (p<.0001), stage 4 fibrosis (p<.0001), regimen of prescribed antiviral therapy (p<.0001), duration of CHC before the start of AVT (p=0.0057), the known duration of AVT (p<.0001) and the patient's adherence to therapy (p<.0001) were significantly associated with an increased risk of absence of VR to AVT. The chances of having HBV past infection were 0.09 (0.01-0.66) lower in cases than in the control groups.

All 16 variables with a p-value <0.05 in the univariate analysis were included in the multiparametric model. The relationship between the absence of VR on AVT and hypertension, hepatitis C virus genotypes, fibrosis stages, ALT before AVT, the duration of antiviral therapy and the patient's adherence to therapy was evaluated using a multivariate logistic regression analysis. In a multiparametric analysis, 7 factors were largely associated with the absence of VR to AVT in patients with CHC.

The results of the multivariate logistic regression analysis are shown in table 4. People with arterial hypertension (AH) had 1.94 times higher odds of VR absence to AVT than people without AH (AOR 1.94 (95% CI: 1.03–3.36). People with hepatitis C virus genotype-3 had a 2.33 times greater chance of VR absence to AVT compared to people with hepatitis C virus genotype-1 (AOR 2.33 (95% CI: 1.26–3.35). Compared with stage 0 liver fibrosis, people with stage 4 fibrosis had a 1.99 times greater chance of VR absence to AVT (AOR 1.99 (95% CI: 1.21–4.07). For a one unit increase in duration of CHC before AVT, we expect to see 0.1% increase in the odds of VR absence for AVT (AOR 1.006 (95% CI: 1–1.009). For a one unit increase in ALT before AVT, we expect to see 0.1% increase in the odds of VR absence for AVT (AOR 1.006 (95% CI: 1.001–1.009). The odds of VR absence for AVT were 0.33 times less in people with a duration of antiviral therapy of 24 weeks compared to people with a duration of antiviral therapy of 12 weeks (AOR 0.33 (95% CI: 0.1–0.75). Patients with an absence (the patient violated the AVT regimen) of adherence to therapy had a greater chance of VR absence to AVT than people who adhered to AVT (AOR 87.12 (95% CI: 23.68–313.07).

Discussion.

This is the first study employing the matched case–control design to explore the factors of the absence of a virological

Table 3. *Univariable logistic regression analysis of the risk factors of the absence of VR to AVT in patients with CHC.*

Characteristic	Case, n (%)	Control, n (%)	Crude OR (95% CI)	p-value
HBV pastinfection				
Yes	1 (0.50)	32 (5.25)	0.09 (0.01-0.66)	0.0179*
No	201 (99.50)	577 (94.75)	1	
Cholelithiasis				
Yes	8 (3.94)	16 (2.63)	1.52 (0.64-3.60)	0.3434
No	195 (96.06)	592 (97.37)	1	
Stomach ulcer				
Yes	5 (2.46)	3 (0.49)	5.10 (1.21-21.53)	0.0266*
No	198 (97.54)	606 (99.51)	1	
Liver cyst				
Yes	2 (0.99)	4 (0.66)	1.51 (0.27-8.28)	0.6382
No	201 (99.01)	605 (99.34)	1	
Malignant formation				
Yes	5 (2.46)	6 (0.99)	2.54 (0.77-8.41)	0.1273
No	198 (97.54)	603 (99.01)	1	
Gastritis				
Yes	11 (5.42)	25 (4.11)	1.34 (0.65-2.77)	0.4324
No	192 (94.58)	584 (95.89)	1	
Anemia				
Yes	2 (0.99)	7 (1.15)	0.86 (0.18-4.15)	0.8467
No	201 (99.01)	602 (98.85)	1	
GOITER				
Yes	3 (1.48)	2 (0.33)	4.55 (0.76-27.44)	0.0982
No	200 (98.52)	607 (99.67)	1	
Tuberculosis				
Yes	3 (1.48)	6 (0.99)	1.51 (0.37-6.08)	0.5639
No	200 (98.52)	603 (99.01)	1	
Gastroesophageal reflux disease				
Yes	4 (1.97)	8 (1.31)	1.51 (0.45-5.07)	0.5044
No	199 (98.03)	601 (98.69)	1	
Rheumatoid arthritis				
Yes	1 (0.49)	2 (0.33)	1.50 (0.14-16.66)	0.7400
No	202 (99.51)	607 (99.67)	1	
Stroke				
Yes	2 (0.99)	5 (0.82)	1.20 (0.23-6.24)	0.8267
No	201 (99.01)	604 (99.18)	1	
Atherosclerosis of cerebral vessels				
Yes	2 (0.99)	1 (0.16)	6.05 (0.55 – 67.04)	0.1426
No	201 (99.01)	608 (99.84)		
varicose veins of the lower extremities				
Yes	1 (0.49)	2 (0.33)	1.50 (0.14-16.66)	0.7400
No	202 (99.51)	607 (99.67)	1	
HIV				
Yes	15 (7.77)	23 (3.81)	2.13 (1.09-4.16)	0.0279*
No	178 (92.23)	580 (96.19)	1	
Diabetes mellitus /glycemia				
Yes	17 (8.76)	62 (10.28)	0.84 (0.48-1.47)	0.5384
No	177 (91.24)	541 (89.72)	1	
Overweight/obese				
Yes	71 (36.22)	156 (25.66)	1.65 (1.17-2.32)	0.0045*
No	125 (63.78)	452 (74.34)	1	
Coronary heart disease				

Yes	25 (13.02)	55 (9.08)	1.50 (0.91-2.48)	0.1144
No	167 (86.98)	551 (90.92)	1	
Arterial hypertension				
Yes	61 (31.44)	131 (21.65)	1.66 (1.16-2.38)	0.0057*
No	133 (68.56)	474 (78.35)	1	
Chronic kidney disease				
Yes	13 (6.70)	17 (2.83)	2.47 (1.18-5.18)	0.0169*
No	181 (93.30)	584 (97.17)	1	
Chronic obstructive pulmonary disease				
Yes	9 (4.62)	13 (2.14)	2.22 (0.93-5.26)	0.0718
No	186 (95.38)	595 (97.86)	1	
Hepatitis B				
Yes	12 (6.15)	23 (3.78)	1.67 (0.81-3.42)	0.1618
No	183 (93.85)	585 (96.22)	1	
Hepatitis D				
Yes	1 (0.51)	1 (0.17)	3.10 (0.19-49.8)	0.4246
No	194 (99.49)	603 (99.83)	1	
Hepatocellular carcinoma				
Yes	4 (2.07)	2 (0.33)	6.41 (1.17-35.3)	0.0327*
No	189 (97.93)	606 (99.67)	1	
Sex				
Male	126 (62.07)	380 (62.40)	0.99 (0.71-1.37)	0.9333
Female	77 (37.93)	229 (37.60)	1	
Age groups				
≤ 29	8 (3.94)	24 (3.94)	1	
30–39	30 (14.87)	82 (13.46)	1.10 (0.45-2.71)	0.8398
40–49	51 (25.12)	157 (25.78)	0.98 (0.41-2.30)	0.9531
50–59	59 (29.06)	177 (29.06)	1.00 (0.43-2.35)	1.0000
≥ 60	55 (27.09)	169 (27.75)	0.98 (0.42-2.30)	0.9563
Region				
Almaty city	34 (16.75)	102 (16.75)	1	
Akmola region	9 (4.43)	27 (4.43)	1 (0.43-2.34)	1.000
Aktobe region	2 (1.64)	10 (0.99)	0.6 (0.13-2.88)	0.524
Almaty region	3 (1.48)	9 (1.48)	1 (0.26-3.91)	1.000
Atyrau region	13 (5.75)	35 (6.4)	1.1 (0.53-2.35)	0.776
East Kazakhstan region	12 (5.91)	36 (5.91)	1 (0.47-2.14)	1.000
Zhambyl region	15 (7.39)	45 (7.39)	1 (0.50-2.02)	1.000
West Kazakhstan region	8 (3.28)	20 (3.94)	1.2 (0.48-2.97)	0.694
Karaganda region	6 (3.61)	22 (2.96)	0.82 (0.31-2.19)	0.689
Kostanay region	12 (5.91)	36 (5.91)	1 (0.47-2.14)	1.000
Kyzylorda region	10 (4.93)	30 (4.93)	1 (0.44-2.58)	1.000
Mangystau region	6 (2.96)	18 (2.96)	1 (0.37-2.74)	1.000
Nur-Sultan city	25 (12.32)	75 (12.32)	1 (0.55-1.82)	1.000
North Kazakhstan region	6 (2.96)	18 (2.96)	1 (0.37-2.72)	1.000
Turkestan region	42 (20.69)	126 (20.69)	1 (0.59-1.69)	1.000
BMI	25.2 (16.3-43.2)	25.4 (16.4-41)	1 (0.98-1.06)	0.3092
Ethnicity				
Asian	127 (62.56)	410 (67.32)	0.81 (0.58-1.13)	0.2148
European	76 (37.44)	199 (32.68)	1	
Smoking				
Yes	69 (37.91)	180 (32.37)	1.28 (0.90-1.81)	0.1707
No	113 (62.09)	376 (67.63)	1	
Alcohol consumption				
Yes	22 (12.64)	25 (4.58)	3.02 (1.65-5.50)	0.0003*
No	152 (87.36)	521 (95.42)	1	
Use of other psychoactive substances				

Yes	5 (2.79)	8 (1.43)	1.98 (0.64-6.12)	0.2370
No	174 (97.21)	550 (98.57)		
The presence of previously performed AVT with Peg interferon / Ribavirin				
Yes	15 (7.43)	12 (1.99)	3.95 (1.82-8.59)	0.0005*
No	187 (92.57)	591 (98.01)	1	
Genotype of HC virus				
Genotype 1	80 (40.20)	336 (56.38)	1	
Genotype 2	16 (8.04)	79 (13.26)	0.85 (0.47-1.54)	0.5910
Genotype 3	103 (51.76)	181 (30.37)	2.39 (1.70-3.37)	<.0001*
Indirect liver elastography before AVT, fibrosis stage				
0 stage	38 (21.23)	178 (29.52)	1	
1 stage	33 (18.44)	135 (22.39)	1.15 (0.68-1.92)	0.6078
2 stage	27 (15.08)	128 (21.23)	0.99 (0.57-1.70)	0.9655
3 stage	25 (13.97)	85 (14.10)	1.38 (0.78-2.43)	0.2681
4 stage / cirrhosis of the liver	56 (31.28)	77 (12.77)	3.41 (2.09-5.57)	<.0001*
The regimen of prescribed AVT				
Sofosbuvir+ Daclatasvir	167 (82.67)	583 (95.73)	1	
Sofosbuvir+ Daclatasvir+ Ribavirin	35 (17.33)	26 (4.27)	4.70 (2.75-8.03)	<.0001*
Duration of CHC before the start of AVT[a]	22 (1-252)	12 (1-375)	1.004 (1.001-1.008)	0.0057*
ALT before AVT[a]	57 (4.2-4878)	45.1 (0.45-358)	1.006 (1.003-1.008)	<.0001*
Known duration of AVT				
12 weeks	174 (85.71)	574 (94.41)	1	
24 weeks	29 (14.29)	34 (5.59)	2.81 (1.67-4.75)	<.0001*
Patient's adherence to therapy				
Presence (the patient did NOT violate the AVT regime)	156 (77.23)	603 (99.34)	1	
Absence (the patient violated the AVT regime)	46 (22.77)	4 (0.66)	44.43 (15.76-125.25)	<.0001*

*%-percent; OR-odds ratio; *-p<0.05; CI-confidence intervals; n-number; a-median (min-max).*

response to standard therapy with direct–acting antiviral agents in patients with CHC infection in Kazakhstan. Our study, involving 812 CHC patients, provides substantial insights into the epidemiology, demographic distribution, and potential risk factors influencing the lack of virological response to standard therapy with direct-acting antiviral agents.

Our findings indicate that the majority of patients were men aged 40 years and older, which aligns with literature that suggests a higher prevalence of CHCV among older men [11]. The ethnicity distribution, predominantly Asian, reflects Kazakhstan's demographic composition [12]. Furthermore, the data on regional distribution provides valuable insights into the geographical burden of CHC, with Turkestan region, Almaty city, and Nur-sultan city being the most represented. These variations could be attributed to differences in healthcare access, awareness initiatives, or population densities [13].

Univariable logistic regression analysis identified several risk factors associated with an increased likelihood of absent VR to AVT, including stomach ulcers, HIV, overweight/obesity, arterial hypertension, chronic kidney disease, hepatocellular carcinoma, and alcohol abuse. Many of these associations, such as the link between CHC and HIV or hepatocellular carcinoma, have been previously documented [14-17]. Notably, the strong correlation between alcohol abuse and decreased AVT response emphasizes the importance of addressing comorbidities and lifestyle factors in CHC management [18-20]. A significant finding was the association between the absence of VR to AVT and prior antiviral therapy with Peg interferon/Ribavirin, suggesting potential resistance or diminished efficacy in patients previously treated with these agents [21].

Multiparametric logistic regression analysis identified several independent factors associated with the absence of VR to AVT. Arterial hypertension was linked to nearly double the odds of VR absence (AOR 1.94, 95% CI: 1.03-3.36), possibly due to its impact on liver perfusion and antiviral drug efficacy [22]. Patients with hepatitis C virus genotype-3 had a significantly higher risk of VR absence compared to genotype-1 (AOR 2.33, 95% CI: 1.26-3.35), aligning with other studies [23,24]. Prior research has established that genotype-3 often presents more challenges in treatment due to its resistance profile [25]. Advanced liver fibrosis (stage 4/cirrhosis) was a significant predictor of VR absence, with almost two-fold increase in

Table 4. *Factors independently related to the absence of VR to AVT in patients with CHC.*

Characteristics	Case, n (%)	Control, n (%)	AOR¥ (95% CI)	p-value
Arterial hypertension				
Yes	61 (31.44)	131 (21.65)	1.94 (1.03-3.36)	0.0206*
No	133 (68.56)	474 (78.35)	1	
Genotype of hepatitis C virus				
Genotype 1	80 (40.20)	336 (56.38)	1	
Genotype 2	16 (8.04)	79 (13.26)	1.57 (0.68-3.07)	0.376
Genotype 3	103 (51.76)	181 (30.37)	2.33 (1.26-3.35)	0.0029*
Indirect liver elastography before antiviral therapy, fibrosis stage				
0 stage	38 (21.23)	178 (29.52)	1	
1 stage	33 (18.44)	135 (22.39)	0.80 (0.43-1.61)	0.5903
2 stage	27 (15.08)	128 (21.23)	0.62 (0.29-1.22)	0.1556
3 stage	25 (13.97)	85 (14.10)	0.87 (0.42-1.80)	0.7063
4 stage / cirrhosis of the liver	56 (31.28)	77 (12.77)	1.99 (1.21-4.07)	0.0231*
Duration of CHC before AVT	22 (1-252)	12 (1-375)	1.006 (1-1.009)	0.022*
ALT before AVT	57 (4.2-4878)	45.1 (0.45-358)	1.006 (1.001-1.009)	0.0105*
Known duration of AVT				
12 weeks	174 (85.71)	574 (94.41)	1	
24 weeks	29 (14.29)	34 (5.59)	0.33 (0.1-0.75)	0.0125*
Patient's adherence to therapy				
Adhered	156 (77.23)	603 (99.34)	1	
Did not adhere	46 (22.77)	4 (0.66)	87.12 (23.68-313.07)	<.0001*

*¥ - Multivariable logistic regression; AOR-adjusted odds ratio; %-percent; *-p<0.05; CI-confidence intervals; n-number.*

odds compared to stage 0 fibrosis (AOR 1.99, 95% CI: 1.21-4.07). As liver damage progresses, the organ's capacity to process medications might be compromised, leading to reduced therapeutic efficacy [26]. A longer therapy duration (24 weeks) was protective against VR absence compared to a 12-week regimen (AOR 0.33, 95% CI: 0.1-0.75), suggesting the benefit of extended treatment for certain patient groups [27]. Notably, non-adherence to AVT was a robust predictor of VR absence, with non-adherent patients having a staggering 87.12-fold increase in odds compared to adherent individuals (AOR 87.12, 95% CI: 23.68-313.07). Ensuring patient compliance is paramount to achieve desired therapeutic outcomes [28].

A major strength of our study is the comprehensive demographic and clinical data, providing a holistic view of CHC in Kazakhstan. However, as an observational study, it is subject to potential confounding and biases. Prospective studies and randomized trials are recommended for further validation and exploration of the underlying mechanisms.

In conclusion, our study sheds light on the complex interplay of demographic (gender, age, ethnicity, region), clinical (duration of CHC before AVT, genotype, ALT, stage of cirrhosis), virologic (viral load), host (comorbidities, adherence to therapy) and pharmacological (duration of AVT) factors influencing the response in CHC patients to antiviral therapy. Further research including molecular studies in virologic resistance is warranted for complete characterization of risk factors and improving treatment outcomes in CHC patients.

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Author contributions.

MK, AM, AN, EK, YY drafted the manuscript, MK conducted the analyses, AN, EK, MGC, ChP supervised the work, MK, AM, AN, EK, YY designed and conducted the data collection. All authors read, revised and approved the final manuscript.

Data availability.

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interest.

The authors have no conflicts of interest to declare.

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