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## PREDICTORS OF ANTIVIRAL THERAPY INEFFECTIVENESS IN CHRONIC HEPATITIS C: A MATCHED CASE-CONTROL STUDY IN ALMATY, A MAJOR METROPOLIS OF KAZAKHSTAN

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### Abstract

This study aims to identify factors contributing to the ineffectiveness of antiviral therapy in patients with chronic hepatitis C (CHC) in Almaty. The rising prevalence and mortality associated with CHC, both in Kazakhstan and globally, underscore the need to improve treatment strategies. Despite the high efficacy of direct-acting antiviral agents (DAAs), some patients fail to achieve a sustained virological response (SVR). This retrospective case-control study included 136 CHC patients treated at healthcare facilities in Almaty, focusing on those who did not attain SVR. Variables such as demographic characteristics, virological status, liver disease stage, comorbidities, lifestyle factors, treatment regimens, and adherence to therapy were analyzed. Logistic regression identified risk factors for non-response to treatment, including comorbid conditions (arterial hypertension, hepatocellular carcinoma) and lifestyle factors. The findings highlight the complexity of CHC treatment in Almaty, emphasizing the importance of personalized approaches that address comorbidities and lifestyle influences. This study contributes to understanding the factors affecting CHC treatment outcomes and supports the optimization of therapeutic strategies in similar healthcare contexts.

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

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### Резюме

## ПРЕДИКТОРЫ НЕЭФФЕКТИВНОСТИ ПРОТИВОВИРУСНОЙ ТЕРАПИИ ПРИ ХРОНИЧЕСКОМ ГЕПАТИТЕ С: СОПОСТАВИМОЕ ИССЛЕДОВАНИЕ "СЛУЧАЙ-КОНТРОЛЬ", ПРОВЕДЕННОЕ В АЛМАТЫ, КРУПНОМ МЕГАПОЛИСЕ КАЗАХСТАНА

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Целью данного исследования является выявление факторов, способствующих неэффективности противовирусной терапии у пациентов с хроническим гепатитом С (ХГС) в Алматы. Рост распространенности и смертности, связанных с ХГС, как в Казахстане, так и во всем мире, подчеркивает необходимость совершенствования стратегий лечения. Несмотря на высокую эффективность противовирусных препаратов прямого действия (ППД), у некоторых пациентов не удается достичь устойчивого вирусологического ответа (УВО). Это ретроспективное исследование типа "случай-контроль" включало 136 пациентов с ХГС, проходивших лечение в медицинских учреждениях Алматы, уделяя особое внимание тем, у кого не было достигнуто УВО. Были проанализированы такие переменные, как демографические характеристики, вирусологический статус, стадия заболевания печени, сопутствующие заболевания, факторы образа жизни, схемы лечения и приверженность к терапии. Логистическая регрессия выявила факторы риска отсутствия ответа на лечение, включая сопутствующие заболевания (артериальная гипертензия, гепатоцеллюлярная карцинома) и факторы образа

жизни. Полученные данные подчеркивают сложность лечения ХГС в Алматы, подчеркивая важность персонализированных подходов, учитывающих сопутствующие заболевания и влияние образа жизни. Это исследование способствует пониманию факторов, влияющих на результаты лечения ХГС, и помогает оптимизировать терапевтические стратегии в аналогичных медицинских условиях.

**Ключевые слова.** Хронический гепатит С, противовирусные препараты прямого действия, устойчивый вирусологический ответ.

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#### Түйіндеме

## СОЗЫЛМАЛЫ С ГЕПАТИТІ ВИРУСЫНА ҚАРСЫ ТЕРАПИЯНЫҢ ТИІМСІЗДІГІНІҢ БОЛЖАУШЫ ФАКТОРЛАРЫ: ҚАЗАҚСТАННЫҢ ІРІ МЕГАПОЛИСІ - АЛМАТЫ ҚАЛАСЫНДА ЖҮРГІЗІЛГЕН ЖАҒДАЙ-БАҚЫЛАУ ЗЕРТТЕУІ

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Бұл зерттеудің мақсаты — Алматы қаласындағы созылмалы С гепатиті (СГС) науқастары арасында вирусқа қарсы терапияның тиімсіздігіне себеп болатын факторларды анықтау. Қазақстанда да, бұкіл әлемде де СГС-ға байланысты аурушаңдық пен өлім-жітімнің өсіу емдеу стратегияларын жетілдіру қажеттігін көрсетеді. Тікелей әсер ететін вирусқа қарсы препараттардың (ТӘВП) жоғары тиімділігіне қарамастан, кейбір науқастар тұрақты вирусологиялық жауапқа (ТВЖ) қол жеткізе алмайды. Бұл зерттеу "жағдай-бақылау" типіндегі ретроспективті талдау болып табылады және Алматыдағы медициналық мекемелерде емделген СГС бар 136 науқасты қамтыды, оның ішінде ТВЖ-қа қол жеткізбеген науқастарға ерекше көңіл бөлінді. Демографиялық көрсеткіштер, вирусологиялық статус, бауыр ауруының сатысы, қосалқы аурулар, өмір салты факторлары, емдеу схемалары және терапияға ұстанылыштық сияқты айнымалылар талданды. Логистикалық регрессия емдеуге жауап бермейтін қауіп факторларын, соның ішінде қатар жүретін ауруларды (arterиалық гипертензия, гепатоцеллюлярлық карцинома) және өмір салты факторларын анықтады. Алынған мәліметтер Алматыдағы СГС емдеудің курделілігін көрсетеді және қосалқы аурулар мен өмір салтының әсерін ескеретін жеке тәсілдердің маңыздылығын айқындаиды. Бұл зерттеу СГС емдеу нәтижелеріне әсер ететін факторларды түсінуге септігін тигізеді және үқсас медициналық жағдайларда терапевтік стратегияларды оңтайландыруға көмектеседі.

**Түйінді сездер:** Созылмалы С гепатиті, тікелей әрекет ететін вирусқа қарсы препараттар, тұрақты вирусологиялық жауап.

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#### Introduction

Chronic Hepatitis C (CHC) is recognized as a major contributor to the global burden of liver disease, playing a central role in the development of liver cirrhosis and hepatocellular carcinoma (HCC), and is associated with elevated rates of morbidity and mortality on a global scale, including in Kazakhstan [1][2]. Globally, approximately 58 million people live with CHC, with an estimated 1.5 million new infections reported annually [3]. The prevalence of CHC varies significantly across regions, underscoring the importance of localized research to address regional disparities in disease burden and treatment outcomes.

The advent of direct-acting antiviral (DAA) therapies has revolutionized the management of CHC, offering cure rates exceeding 90% in most cases [4]. Despite these advancements, certain factors continue to hinder optimal treatment outcomes, including patient-related variables, virological characteristics, disease severity, comorbidities, and adherence to therapy. Understanding the determinants that hinder the effectiveness of antiviral therapy is essential for optimizing treatment outcomes and enhancing patient management, particularly in settings such as Almaty, Kazakhstan, where chronic hepatitis C continues to pose a substantial public health burden [5].

The present study is designed to investigate and characterize the factors associated with suboptimal therapeutic response to direct-acting antiviral (DAA) treatment among CHC patients in Almaty. The analysis encompasses a broad range of variables, including demographic and constitutional features, previous treatment experience, virological profile, stage and activity of liver disease, comorbid conditions, behavioral and lifestyle-related factors, adherence to therapy, and pharmacological characteristics of the administered DAA regimens.

Through comprehensive evaluation of these parameters, this research aims to generate evidence-based recommendations to refine clinical decision-making and improve treatment effectiveness within the framework of the state-guaranteed benefit package, under which DAA therapy has been accessible to CHC patients since 2018.

### Methods

**Study site.** This retrospective case-control study was carried out in Almaty within state-funded primary healthcare institutions.

**Patient recruitment and compliance criteria.** The study population comprised adults ( $\geq 18$  years) diagnosed with chronic viral hepatitis C (CHC) and registered at the Hepatology Center in Almaty. Eligible participants included those who were either treatment-naïve or had previously received antiviral therapy based on pegylated interferon and ribavirin. The study specifically focused on patients who failed to achieve a virological response (VR), defined as a detectable HCV RNA by PCR either at the end of treatment and/or at least 12 weeks post-therapy with a regimen consisting of direct-acting antivirals (DAAs), namely Sofosbuvir + Daclatasvir with or without ribavirin. These therapeutic interventions have been available through the state-guaranteed volume of free medical care since 2018.

Cases were defined as patients with confirmed virological failure following standard DAA therapy, while controls were those who achieved a sustained virological response (SVR). All participants - residents of Almaty - were identified from various healthcare institutions based on medical records dating back to 2018. The selection period for cases and controls was from June to December 2022. Each case was matched with three controls (1:3 ratio) according to age, sex, and ethnicity. The matching process involved systematic screening of medical admission logs at participating centers to ensure comparability based on predefined criteria.

**Sample size.** To determine the appropriate sample size for this matched case-control study with a 3:1 control-to-case ratio, several methodological parameters were taken into account. These included the anticipated strength of association between exposure and outcome (expressed as the odds ratio), statistical power (set at 80%), significance level ( $\alpha = 0.05$ ), and the estimated proportion of exposure among the control group. The sample size was calculated using Fleiss' method, which is suitable for studies with unequal group sizes.

The following assumptions were applied in the calculation:

- Anticipated odds ratio (OR): 2.0, based on prior literature;
- Estimated proportion of exposed controls: 45%;
- Desired power: 80% ( $Z_{1-\beta} = 0.84$ );
- Significance level: 5% ( $Z_{1-\alpha/2} = 1.96$ );
- Control-to-case ratio: 3:1 ( $r = 3$ ).

Based on these parameters, the minimum required number of cases ( $n_1$ ) was calculated to be 34, with a corresponding number of 102 controls ( $n_0$ ), yielding a total sample size of 136 participants. This calculation ensured sufficient power to detect statistically meaningful differences in exposure between cases and controls.

### Study instruments and variables

Data for this study were extracted from archived medical records by trained clinicians at the Hepatology Center in Almaty. A comprehensive set of potential risk factors was evaluated, encompassing demographic variables (including age, sex, ethnicity, region of residence, height, and weight), virological characteristics (such as HCV genotype, history of prior antiviral treatment, and virological response following therapy with direct-acting antivirals), and clinical indicators of disease severity (fibrosis stage and duration of infection prior to therapy). Additionally, information was collected on coexisting medical conditions, behavioral risk factors (including tobacco use, alcohol intake, and consumption of psychoactive substances), as well as details of the prescribed antiviral regimen, treatment duration, and patient adherence to therapy.

### Statistical analysis

Descriptive statistics for the matched case and control groups were summarized as frequencies and proportions. Pearson's chi-square test was applied to assess differences in categorical matching variables. To explore associations between individual predictors and virological response status, univariable logistic regression was performed, yielding unadjusted odds ratios (ORs) with corresponding 95% confidence intervals (CIs). A significance threshold of  $p < 0.05$  was adopted.

Variables demonstrating a  $p$ -value  $< 0.25$  in the univariable analysis were considered for inclusion in the multivariable logistic regression model. This approach allowed for the simultaneous adjustment of potential confounders, with final model selection conducted through stepwise procedures. Unconditional logistic regression was employed due to the frequency-matched design (based on age, sex, and ethnicity) rather than individual matching. Interaction terms and multicollinearity were examined prior to finalizing the model. Model performance was evaluated using the Hosmer-Lemeshow test for calibration, as well as overall discrimination metrics including the classification table and the area under the receiver operating characteristic (ROC) curve.

All statistical analyses were conducted using SAS OnDemand for Academics (Version 3.81; Cary, NC, USA). The study design, conduct, and reporting were aligned with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

### Results

A total of 136 adult patients with confirmed chronic hepatitis C infection were included in the study cohort from Almaty. Participants were divided into two groups: the case group included patients who failed to achieve a virological response (VR) following treatment with direct-acting antivirals (DAAs), and the control group consisted of patients who achieved a sustained virological response (SVR). For each case, three controls matched by age, sex, and ethnicity were selected, yielding a 1:3 ratio. The demographic characteristics of both groups were comparable, with no statistically significant differences in age, gender, or ethnicity distribution (Table 1).

Table 1.

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

Characteristics	Case - 34, n (%)	Control - 102, n (%)	p-value*
Age groups			0.9834
≤ 29	1 (2.94)	3 (2.94)	
30–39	7 (20.59)	17 (16.67)	
40–49	12 (35.29)	36 (35.29)	
50–59	7 (20.59)	21 (20.59)	
≥ 60	7 (20.59)	25 (24.51)	
Sex			0.9038
Male	27 (79.41)	80 (78.43)	
Female	7 (20.59)	22 (21.54)	
Ethnicity			0.7662
Asian	17 (50.00)	54 (52.94)	
European	17 (50.00)	48 (47.06)	

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

The majority of participants were male (78.68%) and of Asian ethnicity (52.21%). The mean age of the study population was 46 years (range: 28–73), and most individuals were over 40 years of age. The average body mass index (BMI) was 26.3 kg/m<sup>2</sup> (range: 16.6–39.4). A small proportion of patients (3.73%) had previously received treatment with pegylated interferon and ribavirin. The mean duration of chronic hepatitis C prior to initiating DAA therapy was 19.5 months (Table 2).

Univariable logistic regression analysis was conducted to assess potential predictors of treatment failure. Several factors were found to be associated with an increased likelihood of non-response to DAA therapy, including: the presence of peptic ulcer disease ( $p = 0.0146$ ), HIV co-infection ( $p = 0.2184$ ), overweight or obesity ( $p < 0.0001$ ), arterial hypertension ( $p = 0.4381$ ), chronic kidney disease ( $p = 0.2481$ ), hepatocellular carcinoma ( $p = 0.7537$ ), alcohol use ( $p = 0.2272$ ), prior use of pegylated interferon-based regimens ( $p = 0.0147$ ), HCV genotype 3 ( $p = 0.7250$ ), advanced fibrosis (stage F4) ( $p < ?$ ), baseline ALT levels, treatment duration, and adherence to therapy (Table 3).

Table 2.

**Demographic characteristics of the main indicators.**

The main indicators		n	%
Sex	Male	107	78.68
	Female	29	21.32
Ethnicity	Asian	71	52.21
	European	65	47.79
Age	<29	4	2.94
	30-39	24	17.65
	40-49	48	35.29
	50-59	28	20.59
	>60	32	23.53
BMI		26.3 <sup>c</sup>	16.6-39.4 <sup>d</sup>
The presence of previously performed antiviral therapy with Peg interferon / Ribavirin	Yes	5	3.73
	No	129	96.27
Duration of chronic hepatitis C before initiation of antiviral therapy		19.5 <sup>c</sup>	1-372 <sup>d</sup>

Table 3.

**Demographic characteristics of the main indicators by case and control groups.**

The main indicators	Case - 203, n (%)	Control - 609, n (%)	p-value*
Age groups			0.9983
≤ 29	1 (2.94)	3 (2.94)	
30-39	7 (20.59)	17 (16.67)	
40-49	12 (35.29)	36 (35.29)	
50-59	7 (20.59)	21 (20.59)	
≥ 60	7 (20.59)	25 (24.51)	
Sex			0.9038
Male	27 (79.41)	80 (78.43)	
Female	7 (20.59)	22 (21.57)	
Ethnicity			0.7662
Asian	17 (50.00)	54 (52.94)	
European	17 (50.00)	48 (47.06)	
BMI <sup>b</sup>	26 (18.4-37.8)	28 (16.6-39.4)	0.1133 <sup>a</sup>
Age <sup>b</sup>	46 (28-73)	46 (28-73)	0.5730 <sup>a</sup>
Duration of chronic hepatitis C before initiation of antiviral therapy <sup>b</sup>	20 (1-372)	12 (1-192)	0.5554 <sup>a</sup>
The presence of previously performed antiviral therapy with Peg interferon / Ribavirin			0.0147**
Yes	4 (11.76)	1 (1.00)	
No	30 (88.24)	99 (99.00)	

Variables with p-values < 0.25 in univariable analysis were included in the multivariable logistic regression model. This analysis identified seven independent predictors associated with failure to achieve virological response (Table 4):

- Arterial hypertension was independently associated with reduced treatment efficacy (AOR: 1.94; 95% CI: 1.03–3.36).
- HCV genotype 3 significantly increased the likelihood of treatment failure compared to genotype 1 (AOR: 2.33; 95% CI: 1.26–3.35).
- Advanced fibrosis (F4) was associated with a two-fold increase in the odds of treatment failure relative to no fibrosis (F0) (AOR: 1.99; 95% CI: 1.21–4.07).

- Longer disease duration prior to treatment initiation was a significant but modest risk factor (AOR per unit increase: 1.006; 95% CI: 1.000–1.009).
- Elevated ALT levels before treatment were similarly associated with increased odds of non-response (AOR per unit: 1.006; 95% CI: 1.001–1.009).
- Extended treatment duration (24 weeks) was protective, reducing the odds of treatment failure by approximately 67% compared to 12-week regimens (AOR: 0.33; 95% CI: 0.10–0.75).
- Poor adherence to therapy was the strongest predictor of virological failure, with a markedly elevated risk (AOR: 87.12; 95% CI: 23.68–313.07).

Table 4.

#### Factors independently related to the absence of VR to AVT in patients with CHC.

Characteristics		Case, n (%)	Control, n (%)	P-value
Arterial hypertension	Yes	9 (27.27)	21 (20.79)	80 (79.21)
	No	24 (72.73)	80 (79.21)	
Genotype of hepatitis C virus	Genotype 1	14 (45.16)	45 (47.37)	0.7250
	Genotype 2	2 (6.45)	10 (10.53)	
	Genotype 3	15 (48.39)	40 (42.11)	
Indirect liver elastography before antiviral therapy, fibrosis stage	0 stage	2 (16.67)	21 (20.59)	0.0047
	1 stage	1 (8.33)	23 (22.55)	
	2 stage	3 (25)	22 (21.57)	
	3 stage	2 (16.67)	13 (12.75)	
	4 stage / cirrhosis of the liver	4 (33.33)	23 (22.55)	
Duration of CHC before AVT		20 (1-372)	12 (1-192)	0.5554 <sup>a</sup>
ALT before AVT		269.68 (825.57)	74.10 (64.26)	0.0158
Known duration of AVT	12 weeks	27 (79.41)	85 (83.33)	0.6034
	24 weeks	7 (20.59)	17 (16.67)	
Patient's adherence to therapy	Adhered	31 (91.18)	98 (97.03)	0.1328
	Did not adhere	3 (8.82)	3 (2.97)	

#### Discussion

To our knowledge, this is the first study in Almaty to utilize a matched case-control design to investigate predictors of non-response to standard direct-acting antiviral (DAA) therapy among patients with chronic hepatitis C (CHC). The analysis encompassed a broad spectrum of variables, including demographic profiles, virological characteristics, biochemical parameters, fibrosis staging, comorbidities, antiviral treatment regimens, adherence patterns, and the occurrence of adverse effects.

The results revealed that the majority of participants were males aged 40 years and above, consistent with existing literature [5] reporting a higher burden of CHC infection among older male populations.

Patients previously treated with peginterferon/ribavirin showed a significant association between lack of virological response (VR) to antiviral therapy (AVT) and prior treatment, suggesting that these agents may have reduced efficacy or induced resistance.

Several independent factors predicting the absence of virological response (VR) to antiviral therapy (AVT) in Hepatitis C were identified using multiparametric logistic regression. HCV genotype 3 was independently associated with a higher likelihood of virological non-response to antiviral therapy compared to genotype 1, in line with previously reported resistance patterns and reduced treatment efficacy observed in this subgroup [5]. Advanced liver fibrosis (cirrhosis) also independently predicted

absence of VR to AVT. Importantly, a 24-week treatment course demonstrated a significantly lower risk of absence of VR to AVT than a 12-week course, suggesting the potential benefit of extended therapy in specific patient subsets.

This investigation into chronic hepatitis C (CHC) in Almaty provides valuable insights through the integration of detailed demographic and clinical data, allowing for a comprehensive assessment of disease-related factors.

Nonetheless, as with all observational designs, the study is subject to certain methodological limitations, including potential confounding and selection biases. To corroborate these findings and further explore causal relationships, well-designed prospective cohorts and randomized controlled trials are necessary. The results underscore the multifactorial nature of treatment response, shaped by demographic, clinical, virological, host-related, and pharmacotherapeutic determinants. Future research incorporating prospective follow-up and molecular analyses of antiviral resistance may enhance our understanding and guide more effective therapeutic strategies.

This matched case-control study, the first of its kind in Almaty, investigated factors influencing direct-acting antiviral (DAA) treatment response in chronic hepatitis C (CHC). Analysis of 136 patients revealed that older men of Asian ethnicity had lower response rates, and prior pegylated interferon/ribavirin treatment was strongly associated with non-response. Multivariate analysis identified independent predictors including genotype 3,

advanced fibrosis/cirrhosis, and treatment duration (24 weeks showing improved response). Further prospective research, including molecular studies of viral resistance, is needed to fully elucidate these findings.

**Conflict of Interest.** The authors declare that they have no conflict of interest.

**Contribution of authors.** All authors were equally involved in the writing of this article.

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