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Factors Associated with Hepatitis C Treatment Failure: a Regional Case-Control Study in Kazakhstan

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ABSTRACT

Introduction: Direct-acting antiviral therapy achieves high cure rates in chronic hepatitis C; however, a minority of patients do not achieve a sustained virologic response. The aim of this study was to evaluate clinical, demographic, and virologic factors associated with failure to achieve a sustained virologic response among patients with chronic hepatitis C treated in the Turkestan Region of Kazakhstan.

Methods: We performed a retrospective case-control study of 168 adults treated with direct-acting antivirals between January 2018 and December 2022. The control group comprised 126 patients who achieved a sustained virologic response, and the case group comprised 42 patients without a sustained virologic response. Demographic characteristics, disease duration, treatment duration, adherence, hepatitis C virus genotype, pretreatment alanine aminotransferase level, liver elastography, and fibrosis stage were analyzed.

Results: Patients without a sustained virologic response had higher pretreatment alanine aminotransferase levels (p=0.03), higher liver stiffness values on elastography (p=0.007), and a longer duration of chronic hepatitis C before treatment (p<0.0001). Genotype 3 was more frequent among cases than controls (59.5% vs 24.6%; p<0.0001), and F4 fibrosis was also more common (40.5% vs 10.3%; p<0.0001). Treatment duration greater than 12 weeks (p=0.02) and lower treatment adherence (p<0.0001) were more frequent in the case group. Age, sex, ethnicity, and previous pegylated interferon/ribavirin therapy did not differ significantly between groups.

Conclusion: Failure to achieve a sustained virologic response was associated with greater biochemical activity, more advanced liver fibrosis, longer disease duration, genotype 3 infection, and lower treatment adherence. Adherence represents a potentially modifiable factor that may be addressed through structured follow-up and patient counseling.

Keywords: Hepatitis C; Antiviral Agents; Sustained Virologic Response; Liver Fibrosis; Treatment Adherence.

Introduction

Chronic hepatitis C remains an important public health problem despite major advances in diagnosis and treatment. According to the World Health Organization, approximately 47 million people worldwide were living with chronic hepatitis C virus infection in 2024. Preliminary estimates indicate that approximately 239,000 deaths in 2024 were attributable to consequences of hepatitis C virus infection, predominantly cirrhosis and hepatocellular carcinoma [1,2].

Chronic hepatitis C is frequently asymptomatic or minimally symptomatic; consequently, a substantial proportion of patients are diagnosed only after liver fibrosis has developed. Most infected individuals develop chronic infection, which may progress over time to fibrosis, cirrhosis, and hepatocellular carcinoma [3,4].

A meta-analysis identified duration of infection as one of the most consistent factors associated with progression of liver fibrosis [5].

Oral direct-acting antivirals are currently the main etiologic treatment for chronic hepatitis C. Their introduction represented a major advance over earlier regimens based predominantly on pegylated interferon and ribavirin [6]. The first direct-acting protease inhibitors, boceprevir and telaprevir, were approved in 2011 but were used together with pegylated interferon and ribavirin and were associated with substantial adverse effects. A new treatment era began in 2013-2014 with the introduction of fully interferon-free regimens, including sofosbuvir. Depending on genotype, cirrhosis status, previous treatment, and other clinical characteristics, treatment generally lasts 8-12 weeks and may be extended to 24 weeks in selected clinical situations. Sustained virologic response rates in contemporary trials and real-world practice generally exceed 90-95% [1,7,8].

Achievement of a sustained virologic response has important long-term clinical implications. Backus and colleagues demonstrated that sustained virologic response was independently associated with lower mortality among patients with chronic hepatitis C [9]. Regression of fibrosis may also occur after viral eradication [10]. Nevertheless, patients with advanced fibrosis or cirrhosis remain at risk of complications, including hepatocellular carcinoma [7,8,10].

Despite the high effectiveness of modern direct-acting antiviral regimens, treatment failure still occurs in a minority of patients. Potential contributors include viral characteristics, patient factors, severity of liver disease, previous antiviral therapy, treatment regimen, drug-drug interactions, resistance-associated substitutions, and inadequate adherence [11,12]. Therefore, evaluation of factors associated with failure to achieve a sustained virologic response remains relevant in real-world clinical practice.

In Kazakhstan, the transition to direct-acting antiviral therapy occurred around 2017s. In particular, sofosbuvir plus daclatasvir became an important regimen within the national system for treatment of chronic hepatitis C [13].

Data on factors associated with failure to achieve a sustained virologic response among patients receiving direct-acting antivirals in Kazakhstan remain limited. Regional evaluation is particularly relevant because the epidemiology of viral hepatitis varies across Kazakhstan. Jumabayeva and colleagues reported that in 2020 the Turkestan Region had one of the country's highest reported prevalences of chronic hepatitis C, at 265.1 cases per 100,000 population [14].

The aim of this study was to evaluate clinical, demographic, and virologic factors associated with failure to achieve a sustained virologic response among patients with chronic hepatitis C treated with direct-acting antivirals in the Turkestan Region of the Republic of Kazakhstan.

Methods

This retrospective case-control study included 168 adults. The control group consisted of 126 patients who achieved a sustained virologic response, whereas the case group consisted of 42 patients who did not achieve a sustained virologic response. Data were retrospectively collected from medical records of patients registered for chronic hepatitis C in the Turkestan Region between January 2018 and December 2022.

Participant Selection and Eligibility

Patients aged 18 years or older with confirmed chronic hepatitis C were eligible. Patients were either treatment-naive or had previously received pegylated interferon plus ribavirin. Virologic failure was defined as detectable hepatitis C virus RNA by polymerase chain reaction at the end of treatment and/or at least 12 weeks after completion of therapy. All patients received the standard direct-acting antiviral regimen available under the Guaranteed Volume of Free Medical Care (GVFMC): sofosbuvir plus daclatasvir, with or without ribavirin. Virologic response was assessed by polymerase chain reaction at the end of treatment and/or 12 weeks after treatment completion.

Study Variables and Outcomes

The retrospectively analyzed variables included age, sex, ethnicity, previous pegylated interferon/ribavirin therapy, duration of chronic hepatitis C before treatment, known duration of antiviral therapy, treatment adherence, hepatitis C virus genotype, pretreatment alanine aminotransferase level, liver elastography findings, and fibrosis stage. The primary outcome was failure to achieve a sustained virologic response. Secondary analyses compared clinical, virologic, and treatment-related characteristics between patients with and without a sustained virologic response.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0. Quantitative variables are presented as median and interquartile range, Me (Q1; Q3). Categorical variables are presented as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. Quantitative variables were compared between two independent groups using the Mann-Whitney U test. Dichotomous and categorical variables were analyzed using the chi-square test. A two-sided p value <0.05 was considered statistically significant.

Ethics

The study was conducted in accordance with generally accepted principles for biomedical research involving humans and the Declaration of Helsinki. Secondary analysis of de-identified medical data was approved by the Local Bioethics Committee (Protocol No. 26(162) dated March 28, 2025).

Results

The median age was 56.0 years in both groups and did not differ significantly. Men comprised 52.4% of both groups. Most participants were classified as Asian in the source dataset (89.7% of controls and 90.5% of cases). Previous pegylated interferon/ribavirin therapy was uncommon and did not differ significantly between groups (Table 1).

Table 1 Sociodemographic and Anamnestic Characteristics of Patients Treated With Direct-Acting Antivirals

Characteristics	Control (SVR, n=126)	Case (non-SVR, n=42)	p value
Age, years	56.0 (41.8 -63.0)	56.0 (42.0-62.8)	0.98
Gender			
Male	66 (52.4%)	22 (52.4%)	0.57
Female	60 (47.6%)	20 (47.6%)	
Ethnicity			
European	13 (10.3%)	4 (9.5%)	0.88
Asian	113 (89.7%)	38 (90.5%)	
Previous pegylated interferon/ribavirin therapy			
No	123 (97.6%)	42 (100%)	0.31
Yes	3 (2.4%)	0	

Abbreviations: SVR – sustained virologic response.

Table 2 Clinical, Virologic, and Treatment Characteristics of Patients Treated With Direct-Acting Antivirals

Characteristics	Control (SVR, n=126)	Case (non-SVR, n=42)	p value
ALT before AVT, median	45.0 (26.0-77.6)	56.7 (40.8-102.3)	0.03
Liver stiffness, kPa, median	6.3 (4.4-9.8)	10.2 (5.6-13.2)	0.007
Duration of CHC before AVT, years, median	8.0 (5.0-12.0)	12.0 (8.0-24.0)	<0.0001
Genotype			
Genotype 1, n (%)	78 (61.9%)	11(26.2%)	<0.0001
Genotype 2, n (%)	17 (13.5%)	6 (14.3%)	
Genotype 3, n (%)	31 (24.6%)	25 (59.5%)	
Fibrosis			
F0, n (%)	36 (28.6%)	10 (23.7%)	<0.0001
F1, n (%)	35 (27.7%)	7 (16.7%)	
F2, n (%)	23 (18.3%)	2 (4.8%)	
F3, n (%)	19 (15.1%)	6 (14.3%)	
F4, n (%)	13(10.3%)	17 (40.5%)	
AVR duration			
≤12 weeks, n (%)	125 (99.2%)	39 (92.9%)	0.02
>12 weeks, n (%)	1 (0.8%)	3 (7.1%)	
Patients adherence			
Non-adherent, n (%)	0	5 (11.9%)	<0.0001
Adherent, n (%)	126 (100%)	37 (88.1%)	

Abbreviations: ALT – alanine aminotransferase; AVT – antiviral therapy; CHC – chronic hepatitis C; SVR – sustained virologic response.

Pretreatment alanine aminotransferase levels were significantly higher among patients who did not achieve a sustained virologic response than among controls (56.7 [40.8-102.3] vs 45.0 [26.0-77.6]; p=0.03). Liver stiffness on elastography was also higher in the case group (10.2 [5.6-13.2] vs 6.3 [4.4-9.8]; p=0.007). The known duration of chronic hepatitis C before antiviral therapy was longer among cases (12.0 [8.0-24.0] vs 8.0 [5.0-12.0]; p<0.0001) (Table 2).

Hepatitis C virus genotype distribution differed significantly between groups (p<0.0001). Genotype 1 predominated among controls (61.9%), whereas genotype 3 predominated among cases (59.5%). Genotype 2 was less frequent in both groups.

Fibrosis stage also differed significantly between groups (p<0.0001). F4 fibrosis was present in 40.5% of cases compared with 10.3% of controls. In contrast, F0 fibrosis was the most common stage in the control group.

Known treatment duration differed significantly between groups. Although treatment duration was less than 12 weeks in most patients, a duration greater than 12 weeks was more frequent among cases than controls (7.1% vs 0.8%; p=0.02). Treatment adherence was 100% in the control group and 88.1% in the case group; 11.9% of cases were classified as non-adherent (p<0.0001) (Table 2).

Discussion

In this study, patients who did not achieve a sustained virologic response had greater biochemical activity, more advanced liver fibrosis, a longer history of chronic hepatitis C, a different genotype distribution, and lower treatment adherence.

Our findings regarding fibrosis are consistent with published data. Morio and colleagues reported that a FIB-4 index ≥3.25 was independently associated with a lower probability of sustained virologic response, particularly with sofosbuvir-based regimens [15]. Another real-world study identified genotype 3, advanced fibrosis, and decompensated liver disease as factors associated with lower sustained virologic response rates [16].

Fibrosis stage should not be interpreted solely as a direct determinant of antiviral efficacy. It also reflects cumulative duration and severity of chronic liver injury. In our study, patients without a sustained virologic response had a significantly longer duration of chronic hepatitis C before antiviral therapy. Longer disease duration may therefore be associated with structural liver changes that coexist with a lower probability of treatment success.

The association between genotype and virologic response is also consistent with previous evidence. Belperio and colleagues reported lower sustained virologic response rates in genotype 3 than in genotype 2 infection (90% vs 94%) [16].

Treatment adherence was associated with virologic outcome in our cohort. This finding is consistent with evidence that inadequate adherence is an important contributor to treatment failure. Benitez-Gutierrez and colleagues emphasized that, in addition to unfavorable baseline factors, poor adherence and adverse effects arising during therapy may contribute to failure [6].

Longer treatment duration may reflect greater baseline disease severity, advanced fibrosis, previous treatment experience, or an insufficient treatment response rather than acting as an independent cause of treatment failure. In the study by Belperio and colleagues, patients with genotype 3 and unfavorable disease characteristics more often received longer treatment courses [16].

Previous data from the Almaty Region similarly suggested that genotype 3, advanced liver fibrosis, and treatment duration were associated with lack of virologic response [17, 18].

This study has several limitations. First, its retrospective design does not allow causal inference. Second, the relatively small sample size limits statistical power. Comorbidities, drug-drug interactions, and resistance-associated viral substitutions were not included in the analysis. Because the study was conducted only in the Turkestan Region, the findings cannot be directly generalized to the entire population of Kazakhstan. The observed association between fibrosis and virologic outcome

should not be interpreted as evidence that fibrosis itself prevents viral elimination; advanced fibrosis may instead be a marker of longer disease duration and greater disease severity. Similarly, the association between baseline alanine aminotransferase level and virologic outcome should be interpreted as a marker of baseline disease activity rather than proof that alanine aminotransferase directly determines treatment effectiveness.

Despite these limitations, this study provides regional real-world data on factors associated with direct-acting antiviral treatment failure in chronic hepatitis C. The observed associations support further prospective research with larger samples and multivariable modeling.

Conclusion

Failure to achieve a sustained virologic response among patients with chronic hepatitis C in the Turkestan Region was associated with higher pretreatment alanine aminotransferase levels, greater liver stiffness, advanced fibrosis, longer disease duration, genotype 3 infection, longer recorded treatment duration, and lower treatment adherence. These findings describe associations and should not be interpreted as proof of causality. Treatment adherence is a potentially modifiable factor and may be improved through regular follow-up, patient counseling, monitoring of medication intake, and early identification of reasons for missed doses. Larger prospective studies are needed to determine the independent contribution of these factors and to improve prediction of treatment failure.

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