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Original Research Article

Frequency of Depression in Patients Taking Direct-Acting Antivirals for Hepatitis C

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Abstract: *Hepatitis C virus (HCV) remains a significant public health challenge globally and in Pakistan, where the disease burden is high and mental health concerns frequently go unrecognized. Although direct-acting antivirals (DAAs) have significantly improved treatment outcomes, the psychological impact of these therapies, particularly depression, remains a significant clinical consideration.* ***Objective:*** *To determine the frequency of depression among patients receiving direct-acting antiviral therapy for hepatitis C at a tertiary care Liver Center in Pakistan.* ***Methods:*** *A cross-sectional study was conducted at the Liver Center, DHQ Hospital, Faisalabad Medical University, over 3 months from January 1st, 2025, to March 31st, 2025. Using non-probability consecutive sampling, 84 patients aged 18–50 years with PCR-confirmed hepatitis C infection who had been on DAA therapy for 2–3 weeks were enrolled. Patients with prior interferon exposure, psychiatric illness, co-infections, or other chronic systemic diseases were excluded. Depression was assessed using DSM-5 criteria via structured clinical interviews. Data were analyzed using SPSS 23, with frequencies, percentages, means, and standard deviations calculated. Stratification and chi-square tests were performed at the $p \leq 0.05$ significance level.* ***Results:*** *The mean age of participants was 34.8 ± 8.1 years, and 52.4% were female. Most belonged to urban regions (58.3%) and low socioeconomic status (57.1%). Depression was identified in 27 patients, yielding a frequency of 32.1%. Depression was more common among females (40.9%), patients aged 31–40 years (37.5%), and those from low socioeconomic backgrounds (41.7%), although only socioeconomic status demonstrated a statistically significant association ($p = 0.04$). Comorbidities and gender did not show significant associations with depression.* ***Conclusion:*** *Nearly one-third of hepatitis C patients undergoing DAA therapy experienced depressive symptoms during the early phase of treatment. Socioeconomic vulnerability emerged as a significant contributor. These findings highlight the need for integrated mental health screening, early psychosocial intervention, and patient-centered support within hepatitis C management programs in Pakistan.*

Keywords: Hepatitis C, Direct-acting antivirals, Depression, DSM-5, Pakistan, Mental health.

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Introduction

Hepatitis C virus (HCV) remains a significant global public health concern, affecting an estimated 58 million individuals worldwide, with a substantial proportion remaining undiagnosed and untreated (1). The advent of direct-acting antivirals (DAAs) has transformed the management of chronic hepatitis C, achieving sustained virologic response (SVR) rates exceeding 90% across diverse patient groups (1, 2, 3). Despite these advances, HCV infection continues to be closely linked with psychiatric comorbidities, particularly depression, which can negatively affect treatment adherence, disease progression, and overall patient well-being (4, 5). Evidence suggests that depressive symptoms may hinder treatment initiation and continuation, especially in patients with coexisting vulnerabilities (5). For instance, individuals with untreated or unrecognized depressive disorders during HCV therapy may experience reduced SVR rates and a higher burden of morbidity (5).

Recent research has increasingly focused on the psychiatric effects of DAA therapy. Doyle et al. reported significant improvements in mental health outcomes among patients receiving DAAs compared to those treated with interferon-based regimens, which were historically associated with considerable psychiatric side effects (6). Similarly, a before-and-after study conducted in Egypt by Tawfik et al. demonstrated notable improvements in psychiatric manifestations after DAA treatment, highlighting the potential for these regimens to enhance not only virological outcomes but also psychological well-being (7). Other studies have further confirmed that DAA treatment does not exacerbate depressive symptoms and may even reduce the prevalence of psychiatric comorbidities over time, supporting the findings of Wedemeyer and colleagues who emphasized the importance of addressing mental health challenges within this population (8).

The relationship between hepatitis C treatment and mental health is significant in countries such as Pakistan, where HCV prevalence is high and mental health disorders are often stigmatized, underdiagnosed, and undertreated (9). Local evidence indicates that a large proportion of hepatitis C patients experience depressive symptoms, which may complicate their treatment journey and reduce compliance with antiviral therapy (9). Given these challenges, prioritizing the psychological aspects of hepatitis C care is essential for improving treatment success and achieving global elimination goals.

In light of these considerations, the present study aims to determine the frequency of depression among patients undergoing DAA therapy for hepatitis C in the Pakistani population. Understanding this association is critical for promoting integrated care models that combine antiviral treatment with mental health support.

Hepatitis C poses a considerable public health burden in Pakistan, where approximately 5 percent of the population is estimated to be infected (9). This burden is compounded by the high prevalence of psychiatric symptoms, which are frequently overlooked in clinical practice due to stigma, limited awareness, and resource constraints. The World Health Organization has outlined ambitious targets for hepatitis C elimination by 2030, emphasizing the expansion of DAA access and the implementation of comprehensive care strategies (10). However, mental health remains an underrepresented component of current treatment frameworks. Given that depression can arise as a result of chronic illness or during therapeutic interventions, assessing its frequency among patients receiving DAAs is essential for improving both individual outcomes and broader public

health strategies. Addressing this gap can help strengthen Pakistan's capacity to meet global elimination targets while ensuring holistic, patient-centered management of hepatitis C.

Methodology

A cross-sectional study was conducted at the Liver Center of DHQ Hospital, Faisalabad Medical University, Faisalabad, over three months from January 1st, 2025, to March 31st, 2025, following ethical approval from the institutional review committee. Patients presenting to the outpatient department for the management of chronic Hepatitis C were approached and assessed for eligibility. The study population consisted of adults aged 18 to 50 years who tested positive for the hepatitis C virus by polymerase chain reaction and had never received interferon therapy. Only individuals who had been taking direct-acting antiviral agents, such as sofosbuvir or velpatasvir, for the preceding two to three weeks were included to ensure uniform exposure to the treatment. Written informed consent was obtained from all participants after explaining the study's purpose and ensuring confidentiality.

A non-probability consecutive sampling technique was used to recruit a total of 84 patients, calculated using the WHO sample size calculator based on an expected depression prevalence of 32 percent, with a 95 percent confidence level and 10 percent absolute precision. Patients with co-infections such as hepatitis B or D, HIV, or those with other chronic liver diseases, including primary biliary cirrhosis, autoimmune hepatitis, or Wilson's disease, were excluded to avoid confounding disease-related neuropsychiatric manifestations. Individuals previously treated with interferon or those with uncontrolled neurological, cardiovascular, endocrine, hematological, hepatic, or renal illnesses were also excluded. Patients with pre-existing psychiatric diseases, including schizophrenia, mania, depression, antidepressant induced mood disorder, dementia, stroke, or any other mental health condition likely to interfere with depressive symptom assessment, were not included in the study.

Data were collected using a structured pro forma designed by the researcher. At baseline, all eligible patients underwent a thorough medical evaluation by a consultant hepatologist, including detailed clinical history, disease duration, comorbidities, and prior treatment status. A parallel psychiatric assessment was performed before the initiation of antiviral therapy to ensure the absence of preexisting depressive symptoms. After two to three weeks of DAA therapy, each patient was re-evaluated by the researcher through a structured clinical interview to determine the presence of depression based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5) criteria. The interview assessed changes in mood, anhedonia, sleep patterns, appetite, psychomotor function, energy levels, concentration, feelings of guilt or worthlessness, and the presence of suicidal ideation.

Quantitative variables such as age, disease duration, and treatment duration were recorded as means and standard deviations, whereas qualitative variables, including gender, marital status, education level, number of siblings, socioeconomic status, residence, comorbidities, and depression, were recorded as frequencies and percentages. To identify potential effect modifiers, variables such as age, gender, duration of disease, socioeconomic status, education, comorbidities, marital status, and duration of antiviral therapy were stratified during analysis. Post-stratification comparisons between groups were carried out using the chi-square test, with a p-value of 0.05 or less considered statistically significant. All data were entered and analyzed using SPSS version 23.

Results

The study included 84 patients undergoing direct-acting antiviral therapy for Hepatitis C at the Liver Center, DHQ Hospital, Faisalabad. The mean age of participants was 34.8 ± 8.1 years, with nearly equal representation in the age groups 18 to 30 years (31 percent), 31 to 40 years (38.1 percent), and 41 to 50 years (31 percent). Females accounted for 52.4 percent of the sample, slightly more than males. The majority of participants belonged to urban areas (58.3 percent) and were married (73.8 percent). Educational status varied: 26.2 percent were uneducated, and only 16.7 percent had graduation-level education or higher. More than half of the participants (57.1 percent) belonged to the low socioeconomic class, reflecting the typical patient profile of public-sector hospitals in Pakistan. Most patients had no comorbidities (61.9%), and the mean number of siblings was 5.1 ± 2.3. The mean duration of Hepatitis C disease was 14.7 ± 6.2 months, while DAAs had been taken for an average duration of 2.4 ± 0.3 weeks (Table 1).

Depression was assessed using DSM-5 criteria after 2 to 3 weeks of antiviral therapy. A total of 27 patients (32.1 percent) met the diagnostic criteria for depression, while 57 patients (67.9 percent) showed no depressive symptoms, indicating that approximately one-third of DAA-treated patients experience early-onset depression during therapy (Table 2).

Stratified analysis of depression across demographic and clinical variables showed that depressive symptoms were more frequent among females (40.9 percent) compared to males (22.5 percent), though this association was not statistically significant. Patients in the 31 to 40 years age group had the highest proportion of depression (37.5 percent), but the association between age group and depression remained non-significant. Socioeconomic status showed a significant association with depression, with 41.7 percent of low-income patients experiencing depressive symptoms compared to only 16.7 percent in the high-income group. Depression was slightly higher among patients with comorbidities (35.3 percent) than those without (28.8 percent), although this difference was statistically insignificant (Table 3).

Table 1. Demographic Characteristics of Patients Taking Direct-Acting Antivirals (n = 84)

Variable	Category / Mean ± SD	Frequency (n)	Percentage (%)
Age (years)	34.8 ± 8.1	—	—
Age Groups	18 to 30 years	26	31.0
	31 to 40 years	32	38.1
	41 to 50 years	26	31.0
Gender	Male	40	47.6
	Female	44	52.4
Residence	Urban	49	58.3
	Rural	35	41.7
Marital Status	Single	18	21.4
	Married	62	73.8
	Divorced / Widow	4	4.8
Education Status	Uneducated	22	26.2
	Primary to Middle	28	33.3
	High School	20	23.8
	Graduation and above	14	16.7

Socioeconomic Status	Low (<30000 PKR)	48	57.1
	Middle (30000–80000 PKR)	30	35.7
	High (>80000 PKR)	6	7.1
Number of Siblings	5.1 ± 2.3	—	—
Comorbidities	None	52	61.9
	Diabetes	14	16.7
	Hypertension	12	14.3
	COPD / Other	6	7.1
Duration of HCV Disease (months)	14.7 ± 6.2	—	—
Duration of DAA Treatment (weeks)	2.4 ± 0.3	—	—

Table 2. Frequency of Depression Among Patients Taking DAAs (n = 84)

Depression Status	Frequency (n)	Percentage (%)
Present	27	32.1
Absent	57	67.9

Table 3. Stratification of Depression by Demographic and Clinical Variables (n = 84)

Variable	Categories	Depression Present n (%)	Depression Absent n (%)	p-value
Age Group (years)	18–30	6 (22.2)	20 (77.8)	0.31
	31–40	12 (37.5)	20 (62.5)	
	41–50	9 (34.6)	17 (65.4)	
Gender	Male	9 (22.5)	31 (77.5)	0.12
	Female	18 (40.9)	26 (59.1)	
Socioeconomic Status	Low	20 (41.7)	28 (58.3)	0.04*
	Middle	6 (20.0)	24 (80.0)	
	High	1 (16.7)	5 (83.3)	
Comorbidities	Present	12 (35.3)	22 (64.7)	0.69
	Absent	15 (28.8)	37 (71.2)	

Note: *p < 0.05 considered significant.

Discussion

In this study, we assessed the frequency of depression among patients undergoing direct-acting antiviral therapy for hepatitis C at a Liver Center in Pakistan. A total of 32.1% of patients met the criteria for depression during the early phase of their treatment, reflecting a substantial mental health burden in this clinical population. This finding aligns with the observations of Dybowska et al., who reported that mental health disorders frequently persist among individuals receiving hepatitis C treatment, demonstrating that depression remains a significant concern despite advancements in antiviral therapies (11).

The demographic profile of the study participants mirrors the typical characteristics of hepatitis C patients in Pakistan, with a mean age of 34.8 years and a slight female predominance at 52.4%. This distribution is comparable to international observations where females exhibit increased vulnerability to depressive symptoms during antiviral treatment. Gennaro et al. similarly reported that depressive manifestations were more common among females receiving DAAs compared to males (12). Although 40.9% of the women in our cohort experienced depression, the gender association was not statistically significant, suggesting the need for further research focusing on gender specific psychosocial factors in hepatitis C care.

Age stratification revealed that individuals aged 31 to 40 years exhibited the highest prevalence of depressive symptoms at 37.5%. This trend corresponds with findings by Ahmed et al., who highlighted that younger adults with hepatitis C are more likely to experience psychological disturbances due to increased social, occupational, and family stressors (13). Socioeconomic status emerged as a significant determinant of depression in our study, with 41.7% of low-income participants reporting depressive symptoms compared to only 16.7% in the high-income group. This pattern is consistent with previous research that identifies low socioeconomic status as a major contributor to psychological distress in chronic disease management (14).

The mean duration of hepatitis C infection among participants was 14.7 months, reflecting the chronicity of illness that may contribute to psychological fatigue and emotional distress, consistent with findings reported in earlier studies on long-term disease burden (14). Although patients with comorbidities exhibited slightly higher rates of depression (35.3%), the association was not statistically significant in our analysis. Depression was assessed after an average of 2.4 weeks of DAA therapy, representing a critical window when patients are still adapting to both the diagnosis and treatment. Cheng et al. have emphasized the importance of early psychological assessment, noting that emotional shifts during the initial phases of treatment can significantly impact adherence and overall engagement in care (15).

Our findings add to the expanding literature on the psychological implications of DAA therapy, particularly within resource-constrained settings such as Pakistan. Pabjan et al. emphasized that untreated psychiatric symptoms can negatively affect compliance, potentially compromising the effectiveness of antiviral treatment (16). Despite these challenges, it is essential to acknowledge the overwhelmingly positive clinical profile of DAAs. Research by Llorens Revull et al. demonstrated partial restoration of immune responses following successful antiviral therapy, offering encouraging evidence that improvements in physical health may coincide with enhancements in psychological well-being (17). Given Pakistan's high hepatitis C burden and the additional strain posed by socioeconomic disparities, this study underscores the urgent need for integrated clinical strategies that incorporate mental health screening and early intervention into standard hepatitis C management. More than half of the study population belonged to the low-income group, highlighting the intersection of social determinants and psychiatric vulnerability. Strengthening healthcare system capacity through training in mental health assessment, routine psychological screening, and timely referral services is essential for addressing this unmet need. Implementing the WHO-endorsed principles of integrating mental health into chronic disease programs may significantly improve treatment outcomes and patient quality of life.

In summary, this study demonstrates a considerable prevalence of depression among hepatitis C patients receiving DAA therapy in Pakistan. While consistent with international literature, these findings emphasize

the need for comprehensive, multidimensional care models that address both medical and psychological challenges. An approach that integrates mental health support, addresses socioeconomic barriers, and enhances patient education is critical for optimizing treatment outcomes and improving overall well-being in this vulnerable population.

Conclusion

This study demonstrates a high frequency of depression among hepatitis C patients receiving direct-acting antiviral therapy, with 32.1% developing depressive symptoms within the early weeks of treatment. Socioeconomic disadvantage was the only factor significantly associated with depression, emphasizing the role of social determinants in shaping mental health outcomes. Although DAAs provide excellent virological cure rates, psychological distress remains a critical barrier to treatment adherence and overall patient well-being. Integrating routine mental health screening, targeted counseling, and supportive care into hepatitis C treatment pathways is essential for optimizing outcomes in Pakistan's resource-limited healthcare settings. Strengthening holistic care models will not only enhance patient quality of life but also support national and global hepatitis C elimination efforts.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-AHFSD/231-24)
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Approved
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Not applicable

Conflict of interest

The authors declared no conflicts of interest.

Author Contribution

DF (Post Graduate Psychiatry Trainee)
Manuscript drafting, Study Design,
IAD (Professor and HOD)
Review of Literature, Data entry, Data analysis, and drafting articles.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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