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NEURO-PSYCHOLOGICAL AND PHYSICAL SIDE EFFECTS OF HCV  
TREATMENT AND HEALTH RELATED QUALITY OF LIFE AMONG  
PATIENTS WITH HCV INFECTION

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**ABSTRACT**

There are multiple factors associated with the negative impact of hepatitis C treatment on the quality of life of patients. This cross-sectional study was conducted to investigate the difference in level of health-related quality of life (HRQoL) among four groups of patients receiving treatment for hepatitis C infection. Study was conducted on sample of 100 patients with age range 18-60, diagnosed with HCV and divided into four equal groups, each group containing 25 patients (n=25) with HCV receiving particular treatment. Group I was receiving conventional interferon injection (n=25), Group II was receiving pegylated interferon injections (n=25), while Group III was taking the oral antiviral plus interferon injections (n=25), and Group IV was under the treatment of oral antiviral alone (n=25). Urdu version of WHO health related quality of life-BREF questionnaire (WHOQOL-BREF) (Khan et al., 2003) and Scale for Neuro-Psychological and Physiological Side Effects of Interferon Therapy (NPPSI) (Hassan et al., 2019) were used for data collection. One-way ANOVA and correlation analysis were employed for the inferential analysis of data. Results revealed that patients receiving oral antiviral treatment without interferon injections showed statistically significant improvement in all four domains of WHOQOL-BREF when compared with the patients on interferon injections. HCV has a profound detrimental impact on both physical and mental

health of the individual. So, widespread actions are pivotal for the prevention, control and treatment of the problem.

### **INTRODUCTION**

After the discovery of the hepatitis C virus (HCV) in 1989, HCV was first thought to be a less important infection which was only found to be affecting selected groups of intravenous (IV) drug abuser, the recipients of multiple blood transfusions and their donors (Alter, 1989). Now almost years later, the global importance of HCV infection is very well known. HCV is among a leading global health issue affecting almost all countries and regions of the world.

According to an estimate three to four million individuals globally are reported to be infected with the hepatitis c virus annually, 170 million patients are at the chronic stage of the disease and also at risk of developing different liver diseases including the liver cancer and cirrhosis, and 35,000 people die annually due to the HCV related issues (Perz et al., 2006).

In 1999 more than 122 million people were infected by hepatitis C virus but six years later in 2005 number of people infected with hepatitis C virus was found to be more than 184 million (Shepard et al., 2005). This fact shows a steady rise in the number of cases with chronic hepatitis C, thereby making it one of the most prevalent infectious diseases in the world. Egypt has the maximum number of infected people with more than 14.7% of its population suffering from this disease (Mohamoud, 2013). With a country wide prevalence of 4.8%, Pakistan is carrying the world's second largest burden of Hepatitis C (Hussain et al., 2019; Ayoub, & Abu-Raddad, 2019). The prevalence of disease is showing homogeneity across the different areas and over time, with no prove of decline in past three decades (Mahmud et al., 2019). In past few years the incidence of hepatitis C virus infection in Pakistan has been raised approximately from 4.7 to 6.8 percent (Kamani et al., 2020; Khan et al., 2019). The enhanced efforts for the treatment of prevention of this widespread problem are needed.

### ***Treatment Regimens***

Hepatitis C is a serious public health problem that must be managed properly in order to prevent it from spreading, mainly the slow progression of the disease that make the early identification difficult. So, in recent years various treatment options came to light. In 1998-99, Alpha Interferon combined with ribavirin was introduced in Pakistan as the leading treatment approach for the Hepatitis C infection and even today, it is being used as the first line treatment for most of the cases of chronic hepatitis C infection. Different studies carried out in Pakistan report the cure rate of this treatment to be ranging from 50-80% (Abbas et al., 2017).

In 2000, discovery of a more advanced type of interferon i.e., pegylated interferon was assumed to be able to revolutionize the treatment of hepatitis C, nevertheless in Pakistan the cure rate of pegylated interferon was noted to be equal to or even less than that of the conventional interferon ranging from 60 to 85% (Umar & Bilal, 2012). Discovery of oral direct acting antiviral drugs for hepatitis C infection in 2014 has revolutionized the treatment outcomes. Sofosbuvir was the first drug approved and marketed for treatment of hepatitis

C infection (Butt & Shah, 2017; Sundberg 2018). Since then, a number of oral antiviral drugs has been introduced. With passage of time these drugs are becoming less costly and easy to access which is making interferon free regimes more common to select for the treatment purposes. With the introduction of a large number of oral antiviral regimes for eradication of HCV infection with very promising end of treatment results. Now the current guidelines for HCV treatment advocate the use of oral, injection free regimes for different genotypes of hepatitis C virus. However, soon after discovery of direct acting antiviral drugs the human kind has to face another dilemma, i.e., resistance to these drugs was noted in small portion of patients (Pawlotsky, 2015). Further studies are needed to elaborate the role of different treatment regimens and their psychological and physical outcomes.

### ***Side Effects of HCV Treatment***

Very few studies have focused on studying the impact of hepatitis C treatment choices on the health-related quality of life of patients and the complications related to their mental health. Both conventional and pegylated interferons are associated with numerous neuro-psychological and physical side effects, especially depression caused by interferon injections is a well-recognized side effect. A depression-specific syndrome characterized by mood, anxiety and cognitive complaints, and a neuro vegetative syndrome characterized by fatigue, anorexia, pain and psychomotor slowing are associated with use of interferon (Raison et al., 2005). Physiological side effects such as fever, pains, weight loss and anemia are also common with interferon (Davoodi et al, 2018). Neuropsychological side effects are the most problematic in these patients. These side effects contain asthenia, irritability, apathy, increased somnolence, confusion and indecisiveness. Severe depression and suicidal tendencies are well reported side effects of interferons among other cognitive and behavioral disorders associated with interferon treatment (Kraus, 2005). Preexisting conditions, including poor mental health and alcohol/substance use, can interfere with access to and successful completion of HCV treatment. Perceived stigma is highly prevalent and associated with psychological distress (Moore, 2009).

### ***Health Related Quality of Life (HRQOL)***

Quality of life (QOL) is an individual's insight of their status in life with in a frame of reference related to their ambitions, norms and cultures. It is a wide range approach which is influenced by multiple aspects such as the person's somatic fitness, psychological condition, autonomy, societal relationships, and alliance to significant facets of related environment. (Whoqol Group, 1998).

Chronic hepatitis C infection is associated with multiple extra hepatic complications such as depression, anxiety, overall reduced mental health and compromised HRQoL even in the absence of the hepatic impairment. Due to a long list of physical and psychological symptoms related to the problem, the burden of HCV infection multiplies by the psychological and emotional factors that influence the person's daily life functioning. This situation imposes a remarkable socio-economic burden on the patient and on health system. The

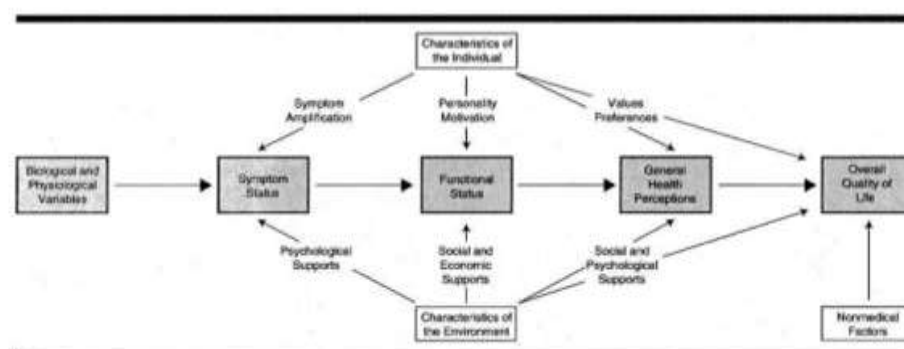
treatment of HCV may itself cause serious harm to the HRQoL at the beginning, due to some related adverse effects like depression, fatigue and consistent muscle ache (Marinho & Barreira, 2013). The fatigue and depression associated with this infection are the most common reasons of a decline in HRQOL. The diagnosis and stigma of the disease and financial constraints add in the stress of patients and hence result in the declines HRQoL. Moreover, interferon therapy is itself associated with the appearance or aggravation of neuro-psychological symptoms such as major depression, fever and fatigability, which in turn may lead to a further decrease in HRQOL of the patient. This is a major factor that leads to the discontinuity of the treatment by the patients (Bernstein et al, 2002).

### ***Wilson-Cleary Conceptual Model of HRQOL***

Wilson and Cleary (1995) presented a theoretical model of HRQoL that incorporate the biological and psychological features of health. There five dimensions in this model proposed by Wilson and Cleary (1995) are physiological features, symptom position, mobility status, general health approach and overall idea of quality of life.

According to Wilson and Cleary the clinical variables which are physiological condition status, symptom grade, functional health, general health concept and generalized quality of life are in synchronization with each other and these are mainly determined by the different traits of individual and environment. The model proposes causal linkages between five different types of patient outcome measurements. First dimension of this model is physiological and biological which further involves assessments of pathological lab reports, physical inspection, blood pressure and glucose levels. Next feature of proposed model is symptoms status which revolves around patient's experience of symptoms. Functional fitness is one's competency to execute chores which can be enunciate by patient and can be judged by others as well. The second last variable is one's ecumenical approach to his general health condition and perceptions and consideration of the importance that one gives to symptoms and his potentiality to perform. Final feature of this model quality of life is individuals on the whole contentment with life.

### **QOL Conceptual Model (Wilson & Cleary, 1995)**



**Figure 1: The Wilson-Cleary Conceptual Model of HRQOL**

Although the direct acting antiviral drugs are well tolerated and have fewer side effects yet some patients may complain of headache, insomnia, fatigue and nausea (Ghany et al., 2011; Kracht et al., 2018). Current study was aimed at quantification of HRQoL (physical, psychological, social relationships, environmental factors) in patients of hepatitis C who are receiving different regimes for eradication of the HCV infection. Different available treatment regimens and the effects of antiviral drug on quality of life of the consumers was also studied.

**OBJECTIVES OF THE STUDY**

Current study aims at the quantification of HRQoL in patients of hepatitis C who are receiving different regimes for eradication of the HCV infection. The purpose of this study is to critically analyze different available treatment regimens and find out the effects of antiviral drug on quality of life of the consumers. This study particularly looks into the four domains (physical, psychological, social relationships, environmental factors) of the HRQoL of the patients receiving treatment for HCV infection and compares quality of life in patients receiving different modes of treatment.

**METHODOLOGY**

This Correlational study was conducted in Pakpattan, from March to August, 2018. Using non-probability purposive sampling technique 100 patients diagnosed with HCV seeking treatment were selected. Selected participants were divided into four equal groups. Each group containing 25 patients (n=25) with HCV receiving particular treatment. Group I (n=25) was receiving conventional interferon treatment. Group II (n=25) was receiving pegylated interferon treatment for HCV infection. Group III (n=25) was seeking a combination treatment of oral antiviral with pegylated interferon. Group IV (n=25) was taking oral antiviral treatment for HCV infection. The age range of the participants was 18-60years (M= 41.2, SD= 10.1). This study was done using correlation research design.

***Instruments***

A brief demographic sheet along with the WHOQOL-BREF Scale, NPPSI scale and demographic sheet were used for data collection.

***WHOQOL-BREF***

WHO Health Related Quality of Life-BREF Questionnaire is a 26-item questionnaire which was developed by WHO in 1998. This questionnaire comprises of four domains containing total 26 questions. Four domains include physical strength, psychological wellness, social alliance and environmental elements affecting QoL (WHOQOL Group, 1998). This questionnaire has been translated in Urdu and validated by Khan et al. (2003). It is a 5-point Likert scale from extremely satisfied (5) to extremely dissatisfied (1). Cronbach alpha coefficient of the translated questionnaire was .88. Reliability of three domains was satisfactory with Cronbach alpha of physical psychological and

environmental factor as .81, .77 and .71 whereas social relationship domain had .42 Cronbach alpha (Khan et al., 2003).

### ***NPPSI-S***

Scale for the Neuro-Psychological and Physiological Side Effects of Interferon Therapy NPPSI (Hassan et al., 2019) NPPSI-S is an indigenously developed instrument in present research which assesses the neuro-psychological and physical side effects of antiviral therapy for HCV. It is a multidimensional 4-point rating scale. Alpha coefficient of NPPSI-S is .97. This scale has three factors physical factor, neurological factor and psychological factor. Each factor measures distinct side effects of antiviral treatment faced by the patients of HCV receiving antiviral treatment. Physical factor contains 19 items with good reliability of  $\alpha = .97$  and it measures physical complications of antiviral treatment. Neurological factor has 9 items and it covers the neurological side effects of antiviral treatment in HCV patients. Alpha coefficient of neurological factor is .93. Third factor of NPPSI-S is psychological factor with 12 items which measures the psychological side effects of antiviral treatment of HCV. Reliability coefficient of psychological factor is .98.

### ***Demographic Sheet***

The demographic sheet was designed to gather information related to patient's age, gender, marital status, type of treatment, education, occupations.

### ***Procedure***

For data collection WHOQOL-BREF, NPPSI and demographic sheet were used after obtaining permission for the use of this tool from relevant authorities. A translated version of the WHOQOL-BREF in Urdu language was used. After explaining the purpose of the study and obtaining consent from the patients, Urdu version of WHOQOL-BREF and NPPSI were presented to the patients and they were asked to answer the questions asked in the questionnaire. Where it was necessary the patients were helped by the researcher to understand and answer the questions. Demographic information was taken on a separate sheet regarding the gender, age, marital status, socio-economic status, choice of the treatment regime etc.

### ***Analysis of Data***

The analyses of the data were done using SPSS 21. Descriptive statistics was used for the analysis of basic variables. T test was used to find out mean difference in HRQoL among both genders receiving HCV treatment. One way ANOVA was employed to test if HRQoL is better in patients receiving oral antivirals and mixed treatment then patients receiving injectable interferons. Correlation analysis was used to explore the correlation among scores of HRQoL and physical, psychological and neurological side effects of different treatment approaches e.g., conventional interferon treatment, pegylated interferon treatment, pegylated interferon + oral antiviral treatment and oral antiviral treatment in HCV patients. Ethical clearance was taken from the

Ethical and Research Committee of Lahore College for Women University, Lahore.

## RESULTS

Among 100 participants 46 (46%) were men and 54 (54%) were women. Overall mean age was  $39.7 \pm 9.4$ . Most of the patients 28 (28%) were receiving conventional interferon, 25 (24%) pegylated interferon, 25 (25%) pegylated interferon + oral antiviral, and 25 (25%) were on oral antiviral treatment.

Difference in level of HRQoL among both genders receiving HCV treatment were explored. Findings revealed that there were no significant differences between both genders on all four domains of HRQoL ( $p > 0.05$ ) (Table I). One-way ANOVA was used to examine the effect of QoL on type of treatments in patients. Results revealed that there was a statistically significant difference between all four domains of QoL and type of treatments Conventional Interferon, Pegylated Interferon, Oral Antiviral + Interferon and Oral Antiviral treatment in patients ( $p < .01$ ) (Table II). Correlation analysis revealed a significant negative correlation among scores of HRQoL and physical, psychological and neurological side effects of different treatment approaches e.g., conventional interferon treatment ( $p < .05$ ) (Table III), pegylated interferon treatment ( $p < .05$ ) (Table IV), pegylated interferon + oral antiviral treatment ( $p < .05$ ) (Table V), and oral antiviral treatment in HCV patients ( $p < .05$ ) (Table VI).

**Table 1** Mean, SD and t-Value of Four Domains of HRQOL among Men and Women (N=100)

	Men (n=46)		Women (n=54)				95% CI		
Variables	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>T</i>	<i>P</i>	UL	LL	Cohen's d
D1	17.80	2.10	17.7	1.76	.260	.795	.868	-.667	1.6
D2	14.73	3.02	14.01	2.55	1.29	.199	1.82	-.385	1.5
D3	7.78	1.80	7.53	1.88	.664	.508	.979	-.488	2.1
D4	17.71	2.16	17.50	2.05	.514	.608	1.05	-.621	1.3

D1=Physical Health Domain, D2=Psychological Domain, D3=Social Relationships, D4=Environmental Domain of HRQOL. Note. CI= Confidence Interval; LL= Lower Limit; UL= Upper Limit.

**Table 2** One-Way Analysis of Variance of Quality of Life and Type of Treatments in Patients

Variables	Conventional Interferon (n= 25)	Pegylated Interferon (n=25)	Oral Antiviral + Interferon (n=25)	Oral Antiviral (n=25)		
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>F</i>	<i>p</i>
Physical Health	17.52 (1.33)	17.76 (1.74)	16.48 (1.83)	19.24 (1.74)	11.62	.000

Psychological Health	11.36 (0.91)	14.4 (2.38)	14.0 (1.74)	17.6 (1.44)	56.26	.000
Social relationship	6.68 (1.28)	7.68 (1.28)	7.92 (1.93)	8.32 (2.32)	3.93	.011
Environmental factors	15.6 (1.83)	15.1 (1.80)	18.36 (1.87)	18.32 (1.49)	14.22	.000

Between group  $df=3$ , within group  $df=96$ , total  $df=99$ ,  
\*\* $p<0.01$

**Table 3** Correlation between Physical, Psychological & Neurological Side Effects of Conventional Interferon Treatment for HCV Patients and Four Domains of HRQOL (n=25)

	Physical Side Effects	Psychological Side Effects	Neurological Side Effects
D1	-.30*	-.19*	-.08*
D2	-.22*	-.15*	-.03*
D3	.14*	-.04*	.08
D4	-.06	-.15*	-.13*

D1=Physical Health Domain, D2=Psychological Domain, D3=Social Relationships, D4= Environmental Domain of HRQOL

\* $p < .05$

**Table 4** Correlation between Physical, Psychological & Neurological Side Effects of Pegylated Interferon Treatment for HCV Patients and Four Domains of HRQOL (n=25)

	Physical Side Effects	Psychological Side Effects	Neurological Side Effects
D1	.07	-.07*	-.03*
D2	-.19*	-.13*	-.02*
D3	.14	-.06*	.08
D4	.10	-.06*	-.03*

D1=Physical Health Domain, D2=Psychological Domain, D3=Social Relationships, D4= Environmental Domain of HRQOL

\* $p < .05$

**Table 5** Correlation between Physical, Psychological & Neurological Side Effects of Oral Antiviral + Pegylated Interferon Treatment for HCV Patients and Four Domains of HRQOL (n=25)

	Physical Side Effects	Psychological Side Effects	Neurological Side Effects
D1	-.11	-.08*	-.03*
D2	-.46*	-.21*	-.20*
D3	.062	-.16*	-.24
D4	-.52*	-.96*	-.28*



D1=Physical Health Domain, D2=Psychological Domain, D3=Social Relationships, D4= Environmental Domain of HRQOL

\* $p < .05$

**Table 6** Correlation between Physical, Psychological & Neurological Side Effects of Oral Antiviral Treatment for HCV Patients and Four Domains of HRQOL (n=25)

	Physical Side Effects	Psychological Side Effects	Neurological Side Effects
D1	.00	.05	.10
D2	-.55*	-.15*	-.30*
D3	.25	-.49*	.51*
D4	.25	-.47*	-.24*

D1=Physical Health Domain, D2=Psychological Domain, D3=Social Relationships, D4= Environmental Domain of HRQOL

\* $p < .05$ .

## DISCUSSION

The monitoring of HRQoL in hepatitis C patients recently became a crucial component in various clinical trials. Nonetheless, the studies on this issue are still limited, especially in Pakistani population there is a need to focus more on the psychological aspects of HCV and role of its treatment choices. The current study compares the health-related quality of life among the patients receiving different treatment regimens for the cure of hepatitis C infection. The results of this study concludes that there is a significant difference in quality of life of patients in different treatment groups. This study clearly shows that the patients who received oral antiviral treatment showed better scores of qualities of life when compared with those patients who were treated with interferon injections. Gender difference in level of HRQoL among both genders receiving HCV treatment were explored. Results reported that there were no significant differences between both genders for all four domains of HRQoL. On contrary various studies suggest that females suffering from hepatitis c reported significant decline in their quality of life (Zhang et al., 2020). Another study proposed that the low socio-economic status, old age and being female is associated with the reduced HRQoL in HCV patients (Malik & Muazzam, 2018). It was reported that males with HCV significantly score higher on physical functioning as compared to females, whereas, females score higher on the QoL in regard to the emotional and mental state (Bianco, 2013). This contradiction in the findings might be due to the sample being small and collected from the limited geographical area.

This study further looks into the impact of oral antivirals and mixed treatment and the injectable interferons on the health-related quality of life of patients. Findings of the study revealed that HRQoL was better in patients receiving oral antivirals and mix treatment as compared to those receiving the injectable interferons. There are various side effects related to the HCV treatment, which make it difficult for the patients to perform better in their daily life activities (Younossi & Henry 2015). Especially in patients having some preexisting

depressive symptoms the use of the conventional interferon treatment could lead to various psychological problems including the development of acute mania (Raison, 2005). Fever, fatigue and depression are the most common side effects linked with hepatitis c treatment options, mostly these side effects are far more common in patients being treated with interferon injections as compared to oral antiviral treatment (Kraus, 2005; Terrault, 2013). The oral antivirals + pegylated interferon treatment provides number of advantages including greater efficacy and short duration of the treatment, but it might cause some adverse side effects that can reduce the HRQoL, especially during the treatment process (Trembling et al., 2012; Ridruejo 2014). Moreover, the injections are a stressor themselves, the pain and stigma associated with multiple needle pricks are a reason the patients getting thrice or once weekly injections show a decline in QoL (Höner Zu Siederdisen et al., 2018). The patients on oral regimes do not have to bear the stress and fear associated with syringes and injections therefore they show better results when measuring QoL (McGowan & Fried, 2012). The direct acting oral antiviral drugs are proved to be well tolerated and they have fewer side effects, such as, in some patients complains of headache, insomnia, fatigue and nausea were observed, yet most of the patients experience these side effects to a significantly milder degree (Munir et al., 2010).

The four domains of HRQoL (physical, psychological, social relationships and environmental factors) were compared in patients with HCV on conventional interferon, pegylated interferon, oral antivirals + pegylated interferon or just oral antivirals for the treatment. The results indicated a significant decline in almost all the four domains of health-related quality of life due to the detrimental side effects associated with different treatment choices. These findings are further supported by different studies that concluded similar results showing a decline in health-related quality of life amongst the patients receiving interferon therapy (Hassanein et al., 2004). Pegylated interferon-based regimens were considered as a standard treatment choice for HCV patients in the past, but it is now proved to severely impair the patients' related outcomes (Brook, 2011). Several studies elaborated concerns related to the compromised HRQoL as a result of interferon-based regimens. Moreover, interferon therapy is itself associated with the appearance or aggravation of neuro-psychological symptoms such as fever and fatigability, which in turn may lead to a further decrease in HRQOL of the patient (Bernstein et al, 2002). Such unpleasant side effects related to interferon treatment are a leading cause of anxiety, depression and irritability and are the major predictors HRQoL impairment (Conversano et al., 2018). Patients can also experience psychological distress due to the perceived impairment in their daily life functioning caused by their illness (Evon et al., 2019; Niazi et al., 2020).

Interferon-free treatment regimens reported significant improvement in the quality of life of patients after the successful treatment (Rowan & Bhulani 2015; Zientarska, 2020). The direct acting antivirals are also observed to be associated with some kind of neuropsychiatric side effects (Volpato, 2017), but the intensity of physical and neuro-psychological side effects is observed to be much lower in patients using oral antiviral drugs for the treatment than interferon injections (Adinolfi et al., 2015; Terrault, 2016). Furthermore, the use of oral antivirals treatment without interferon or ribavirin exhibited the

improved quality of life coinciding with the suppression of virus within the initial few months of treatment (McHutchison, 2001; Fried et al., 2002).

Findings of the study indicated significant difference in all four domains of the HRQoL, especially the third domain that deals with social relationship revealed low reliability when compared with other three domains. It may be due to some differences in the methodology of our study with the previous ones. Certain barriers are also thought to contribute in the lower degree of reliability in this domain. For example, the questionnaire asks about sexual relationships and level of sexual satisfaction in the life of patients. Keeping in view of cultural norms the discussion about an individual's sexual satisfaction is considered a taboo. This reason may cause a decline in the reliability of the domain of social relationships.

### ***Limitations and Recommendations:***

Due to lack of resources and time sample of the study was selected from few hospitals of Pakpattan only. It significantly influences the generalizability of the research. There are many other contributing factors that should be explored in future studies to understand the relationship of HCV and its psychological impact on patients. Large sized multi-institutional studies are essential to further validate the results of the current study.

### **CONCLUSION**

This study concludes that patients receiving oral anti-viral therapy for the treatment of chronic HCV infection show better quality of life than patients receiving injection of pegylated interferon for the eradication of hepatitis C. The current study also demonstrates the gender difference and prevalence of different groups of side effects. This study can help the physicians and psychologists to have an insight of the QoL of these patients and determine the steps that must be taken by treating team to improve the HRQOL. Findings in this study can help researchers to design better treatment regime that may have minimal negative impact on the HRQOL of the patients. The eminent increase in the prevalence of HCV globally, makes the assessment of the quality of life of HCV patients more crucial. It also necessitates the enhanced efforts for primary prevention by development of vaccines, as well as advancements in secondary and tertiary prevention and treatment approaches, aimed to reduce the burden of this chronic health issue and improve the patient's quality of life.

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