DOI: https://doi.org/10.54393/pjhs.v6i1.2603

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparative Analysis of Host and Virus-Driven Variables Affecting Response to Ribavirin and Interferon Therapy in Hepatitis C Patients

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ARTICLE INFO

Keywords:
Interferon Therapy, Ribavirin, Hepatitis C Host Factors, Hepatitis C Virus Factors.

How to Cite:
Jamal, I., Aslam Rind, M., Nazir, M., Saleem, M., Shah, M., & Rajput, A. (2025). Comparative Analysis of Host and Virus-Driven Variables Affecting Response to Ribavirin and Interferon Therapy in Hepatitis C Patients : Host and Virus-Driven Variables Affecting Ribavirin and Interferon Therapy in HCV. Pakistan Journal of Health Sciences, 6(1), 92-96. https://doi.org/10.54393/pjhs.v6i1.2603

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Received Date: 25th November, 2024
Acceptance Date: 17th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Current guidelines advocate for individualized treatment approaches for the management of Hepatitis C, that incorporate baseline assessments of viral genotype, host comorbidities, and socioeconomic factors to maximize therapeutic success. **Objectives:** To analyze the impact of host and virus-driven variables on treatment response in patients receiving ribavirin and interferon therapy. **Methods:** This prospective cohort study was conducted on 138 patients aged 18–65 with confirmed chronic HCV infection who were eligible for interferon and ribavirin therapy. The patients were followed up to a 24-week post-treatment to assess recovery measured in terms of sustained virological response (SVR). The host-driven factors included age, gender, BMI, and the presence of IL28B polymorphism while virus-driven factors included HCV genotype and baseline viral load. **Results:** The study sample predominantly consisted of male (55.1%), and genotype 3 virus accounted for 68.1% of participants. A high proportion (76.1%) of participants achieved SVR. Factors associated with better treatment outcomes included younger age (90.7% in the 31–45 age group), gender (89.5% of male), normal BMI (91.2% of those with a BMI of 18.5–24.9), and the favorable IL28B polymorphism CC genotype (91.8%). Low baseline viral load was observed in 60.1% of patients, and those with genotype 3 had better SVR rates. **Conclusions:** It was concluded that younger age, male gender, normal BMI, favorable IL28B polymorphism along with low baseline viral load, and genotype 3 were positively associated with achieving SVR.

INTRODUCTION

Hepatitis C virus (HCV) remains a pressing global health concern, affecting an estimated 58 million individuals worldwide as of 2024, with approximately 1.5 million new infections occurring annually [1, 2]. The virus is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The burden of the epidemic is particularly felt by low- and middle-income countries with limited access to diagnostic and therapeutic resources. The prevalence of HCV in Pakistan is 4.9%, which is dangerously high, even compared with other countries, mainly attributed to low public knowledge, unsafe medical practices, and unscreened blood transfusion [2, 3]. Especially in rural areas, the lack of healthcare infrastructure makes them more susceptible. HCV risk factors are behavioral or systemic, creating a paradigm of risk. Transmission usually occurs through the sharing of needles among intravenous drug users, unsafe medical procedures that involve the reuse of syringes, and transfusions of unscreened blood products. Sociodemographic factors like poverty, less education, and less access to health services amplify the virus's spread. Patients demonstrating a high baseline activation of interferon-stimulated genes (ISGs), termed interferon refractoriness, are less likely to mount a strong antiviral

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response and achieve viral clearance when placed on treatment. In addition, comorbid conditions like diabetes and obesity have also been linked to less effective treatment responses [4, 5]. Host genetic variation is a critical determinant of treatment success [6]. For instance, the IL28B polymorphism (rs12979860) is an independent favorable predictor of the SVR rates, as demonstrated in specific variants of the gene IL28B polymorphism is a genetic variation in the IL28B gene, which encodes interferon lambda-3. These variations significantly influence the immune response to the Hepatitis C Virus (HCV) and predict treatment response, especially to interferon-based therapies, with certain variants (e.g., CC genotype) associated with higher cure rates [6]. There are six major genotypes because of a variation of the virus genome. This heterogeneity impacts treatment response and disease course. While genotype 1 is the most prevalent globally, genotype 3 is the predominant genotype in Pakistan. Genotypes 2 and 3 tend to be more responsive to interferon (IFN)-based therapies, whereas genotype 1 correlates with low SVR rates [7]. Treatment approaches have evolved considerably over time. Direct-acting antivirals (DAAs) were the first truly new class of drugs to be developed in over fifty years and have revolutionized HCV therapy with cure rates ≥ 95% in most patient populations within eight weeks and with few adverse effects [8]. However, in resource-limited settings like Pakistan, where access to DAAs is constrained, ribavirin and pegylated interferon remain integral components of treatment. These regimens achieve SVR rates of 50-80% depending on the patient's genotype, viral load, and baseline characteristics [9]. Predictors of SVR include both host and virus-driven factors. Host factors such as age, sex, BMI, insulin resistance, and fibrosis stage play crucial roles. Virus-driven factors include genotype, baseline viral load, and mutations within the viral genome [10]. Despite therapeutic advancements, challenges remain, particularly in low-income settings. Affordability and accessibility of DAAs remain significant barriers, underscoring the need for optimized use of traditional therapies based on predictive factors. Current guidelines advocate for individualized treatment approaches that incorporate baseline assessments of viral genotype, host comorbidities, and socioeconomic factors to maximize therapeutic success [8, 11].

Hepatitis C virus infection continues to impose a substantial health burden in Pakistan, where interferon and ribavirin therapies remain important due to limited access to costly direct-acting antivirals. Although multiple host and viral factors are recognized to influence treatment response, there is limited localized evidence comprehensively evaluating how demographic, genetic, and virological predictors collectively affect sustained virological response in Pakistani patients. This study addressed this gap by investigating the comparative impact of host-related factors (age, gender, BMI, IL28B polymorphism) and virus-driven variables (genotype and baseline viral load) to optimize individualized treatment planning and improve therapeutic outcomes in high-prevalence, resource-constrained settings. This study aimed to analyze the impact of host and virus-driven variables on treatment response in patients receiving ribavirin and interferon therapy in high-prevalence regions like Pakistan.

METHODS

This prospective cohort study was conducted on 138 HCV patients, at Liaquat University Hospital, Jamshoro, Pakistan from January 2021 to June 2022. Adults patients aged 18–65 years with confirmed chronic HCV infection (anti-HCV positive and detectable HCV RNA) who were eligible for interferon and ribavirin therapy were included. Patients with co-infections (e.g., HBV or HIV), severe comorbidities, or prior HCV treatment were not included. The sample size was calculated using the Open Epi sample size calculator, with the proportion of sustained virological response (SVR) among HCV patients treated with interferon estimated at 52%, a margin of error of 7%, and a 90% confidence interval [12]. The study was approved by the Research Ethics Committee of Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan. (Reference No. LUMHS/REC/-037). After taking informed written consent, eligible participants were enrolled in the study and were provided with standardized treatment. Pegylated interferon-alpha (Peg-IFN-α) was given subcutaneously at a dose of 180 µg weekly and ribavirin, administered orally based on body weight (<75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day) [13]. The treatment duration was 48 weeks for genotypes 1 and 4 and 24 weeks for genotypes 3. The patients were followed at weeks 4, 12, 24, and the end of treatment, and a post-treatment follow-up at week 72 to assess recovery measured in terms of sustained virological response (SVR) which was defined as undetectable HCV RNA 24 weeks after treatment. The host-driven factors included age, gender, BMI, and presence of IL28B polymorphism. The IL28B polymorphism (rs12979860) was detected by PCR amplification followed by restriction fragment length polymorphism (RFLP) analysis. Virus-driven factors were HCV genotype (1, 3 & 4) and baseline viral load, categorized as low (<600,000 IU/mL) or high (≥600,000 IU/mL), quantified through real-time PCR [13]. Data were analyzed using SPSS version 22.0. Descriptive statistics were used to summarize patient characteristics and the chi-square test was used to assess the association of factors with SVR.

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RESULTS

The study population had a mean age of 42.5 ± 10.3 years, with most participants falling in the 31 to 45 years of age (39.1%). The male-to-female percentage was 55.1% to 44.9%. The mean BMI was 25.4 ± 3.1 kg/m^2, with nearly half of the participants (49.3%) having a normal BMI. Baseline viral load analysis showed that (60.1%) of participants had a low viral load (<600,000 IU/mL), and genotype distribution was dominated by genotype 3 (68.1%) (Table 1).

Table 1: Descriptive Statistics of Participants

Characteristic	Mean ± S.D / Frequency (%)
Age (Years)	42.5 ± 10.3
18 to 30	38 (27.5%)
31 to 45	54 (39.1%)
46 to 65	46 (33.3%)
Gender	
Male	76 (55.1%)
Female	62 (44.9%)
BMI (kg/m^2)	25.4 ± 3.1
<18.5 (Underweight)	4 (2.9%)
18.5–24.9 (Normal)	68 (49.3%)
25–29.9 (Overweight)	44 (31.9%)
≥30 (Obese)	22 (16.0%)
Baseline Viral Load	
Low (<600,000 IU/mL)	83 (60.1%)
High (≥600,000 IU/mL)	55 (39.9%)
Genotype	
Genotype 3	94 (68.1%)
Genotype 1 & 4	44 (31.9%)

76.1% of participants achieved sustained virological response (SVR), whereas 23.9% did not achieve SVR (Figure 1).

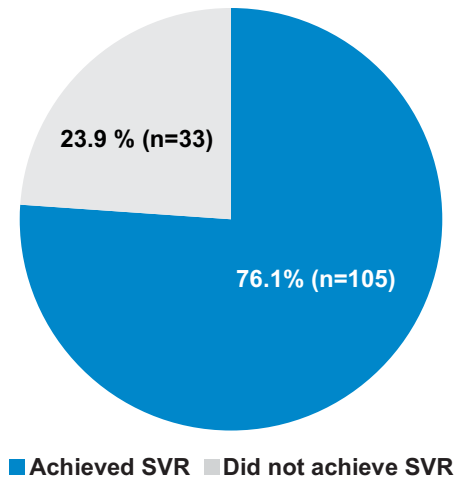

Figure 1: Treatment Outcomes of The Patients in Terms of Sustained Virological Response

Participants aged 18 to 45 years showed the highest SVR rates, while those aged 46 to 65 years had significantly lower SVR rates (47.8%, p=0.23). Male exhibited significantly higher SVR rates (89.5% vs. 59.7%, p=0.01). Regarding BMI, participants with normal BMI had the highest SVR rates (91.2%), while obese individuals had significantly lower success (36.4%, p=0.08). The presence of the CC genotype for the IL28B polymorphism was a strong predictor of SVR (91.8% vs. 49.2%, p<0.001) (Table 2).

Table 2: Association of Host Factors with SVR

Host Factor	SVR Achieved	SVR Not Achieved	p-value
Age (Years)			
18 to 30	34 (89.5%)	4 (10.5%)	0.230
31 to 45	49 (90.7%)	5 (9.3%)	
46 to 65	22 (47.8%)	24 (52.2%)	
Gender			
Male	68 (89.5%)	8 (10.5%)	0.010*
Female	37 (59.7%)	25 (40.3%)	
BMI (kg/m^2)			
<18.5 (Underweight)	3 (75.0%)	1 (25.0%)	0.080
18.5–24.9 (Normal)	62 (91.2%)	6 (8.8%)	
25–29.9 (Overweight)	32 (72.7%)	12 (27.3%)	
≥30 (Obese)	8 (36.4%)	14 (63.6%)	
Presence of IL28B Polymorphism (rs12979860)			
CC (Favorable)	67 (91.8%)	6 (8.2%)	<0.001**
CT/TT (Unfavorable)	18 (49.2%)	19 (50.8%)	

* Statistically significant
** Highly statistically significant

Participants with a low baseline viral load were significantly more likely to achieve SVR (95.2% vs. 47.3%, p<0.001). Regarding genotype, those with genotype 3 had higher SVR rates (86.2%) compared to genotypes 1 & 4 (25.0%, p<0.03) (Table 3).

Table 3: Association of Viral Factors with SVR

Viral Factor	SVR Achieved	SVR Not Achieved	p-value
Baseline Viral Load			
Low (<600,000 IU/mL)	79 (95.2%)	4 (4.8%)	<0.001**
High (≥600,000 IU/mL)	26 (47.3%)	29 (52.7%)	
Genotype			
Genotype 3	94 (86.2%)	15 (13.8%)	<0.030*
Genotype 1 & 4	11 (25.0%)	33 (75.0%)	

* Statistically significant
** Highly statistically significant

DISCUSSION

This study explored the host and virus-driven factors among patients of hepatitis C about the treatment success with ribavirin and interferon therapy. The overall sustained virological response (SVR) rate of 76.1% observed in this study aligns with global data on genotype-specific responses to interferon-based therapy. A meta-analysis reported an average SVR rate of approximately 70-80% for patients with genotype 3, similar to the 86.2% seen in our cohort [14]. However, the response rates for genotypes 1 and 4 in our study (25.0%) were lower than the global

DOI: https://doi.org/10.54393/pjhs.v6i1.2603

average of 40-50% for these genotypes, potentially reflecting regional differences in patient adherence, baseline health conditions, or genetic predispositions. The lower responsiveness to antiviral therapies is due to genetic resistance and slower viral clearance. Moreover, additional factors like regional differences in adherence, baseline health conditions, and genetic predispositions likely further reduced the sustained virologic response (SVR) compared to genotype 3, which generally responds more favorably to treatment [15]. Age was a major factor correlating with treatment response in this study, with younger participants (18 to 45 years) achieving significantly higher SVR rates than older participants. Such a univocal tendency has been reported by some studies among younger patients, who respond more durable to therapy [16]. Markedly, this could be due to the immune-senescence and co-morbidities found in the geriatric age group. Male gender was strongly associated with higher SVR rates (89.5%) than female (59.7%), which has been earlier reported. For example, a study from Croatia reported similar results, highlighting hormonal and metabolic differences that may influence therapy outcomes [17]. In this study, body mass index (BMI) was important in determining the treatment outcomes. It was found that patients with a normal BMI had the highest rates of SVR (91. 2%) whereas obese participants had relatively lower response rates (36. 4%). Obesity has been repeatedly found to be associated with a poor response to treatment, most likely because of added inflammation, insulin resistance, and changes in the pharmacokinetics of the drug [18]. A review supported these results, where lower rates of SVR were reported in obese patients receiving interferon therapy [19]. This cohort did show significantly higher figures (91.8%) when treated with interferon, especially those with the favorable IL28B polymorphism (CC genotype). This goes hand in hand with the findings of other studies which claim that the IL28B CC genotype provides superior immune responsiveness to interferon therapy [20]. A study in Myanmar also reported similar findings where SVR rates of this polymorphism were reported over 90%. This reinforces the predictive power of this polymorphism [21]. Baseline viral load and genotype significantly influenced outcomes in this study. Patients with a low baseline viral load (<600,000 IU/mL) had markedly higher SVR rates (95.2%) compared to those with high viral loads. This observation is consistent with global studies that have identified baseline viral load as a crucial determinant of treatment success [22]. Furthermore, the predominance of genotype 3 in this study reflects the regional epidemiology of hepatitis C, contrasting with genotype 1 dominance in the Middle East and North African countries [23]. The study adds value to the understanding of tailoring treatment strategies based on patient-specific and viral factors, which may result in better treatment outcomes.

The study was limited by its single-center design, moderate sample size, and reliance on interferon-based therapy, which may reduce broader applicability in the era of direct-acting antivirals. Important variables such as socioeconomic barriers, patient adherence, and long-term clinical outcomes were not extensively assessed. Future large-scale multicenter studies should include diverse populations, evaluate newer antiviral therapies alongside conventional regimens, and integrate socioeconomic determinants to develop more comprehensive and personalized hepatitis C treatment strategies.

CONCLUSIONS

The study revealed that both host and viral factors significantly influence treatment outcomes in patients receiving ribavirin and interferon therapy in high-prevalence regions like Pakistan. Younger age, male gender, normal BMI, favorable IL28B polymorphism along with low baseline viral load, and genotype 3 were positively associated with achieving SVR.

Authors' Contribution

Conceptualization: IJ
Methodology: MAR, MN, MS[1], AR
Formal analysis: IJ, MAR, MN, MS[1], MS[2], AR
Writing and Drafting: MAR, MN
Review and Editing: MAR, MN, IJ, MS[1], MS[2], AR

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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