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

Iffat Jamal[1*], Muhammad Aslam Rind[2], Maria Nazir[2], Muhammad Saleem[3], Madiha Shah[2] and Asma Rajput[4]

[1]Department of Medicine, Liaquat University Hospital, Hyderabad, Pakistan
[2]Department of Medicine, Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan
[3]Department of Medicine, Peoples University of Medical & Health Sciences for Women, Nawabshah, Pakistan
[4]Department of Pathology, Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan

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

***Corresponding Author:**
Iffat Jamal
Department of Medicine, Liaquat University Hospital, Hyderabad, Pakistan
dr.iffatjamal@yahoo.com

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

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

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].

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.

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%)

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

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).

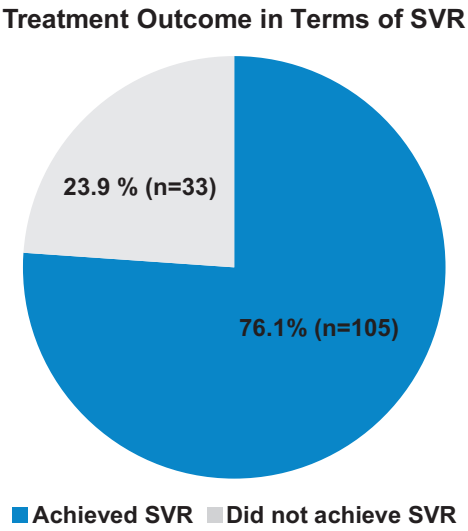

Figure 1: Treatment Outcomes of The Patients in Terms of Sustained Virological Response

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%)	0.23
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%)	0.01*
Female	37 (59.7%)	25 (40.3%)	
BMI (kg/m^2)			
<18.5 (Underweight)	3 (75.0%)	1 (25.0%)	0.08
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%)	<0.03*
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 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-

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

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.

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 review and editing: MAR, MN
All authors have read and agreed to the published version of the manuscript

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.

REFERENCES

[1] World Health Organization. Hepatitis C Fact Sheet. 2023. [Last Cited Oct 12, 2024]. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.

[2] Jamali Ya, Farzana R, Khan Ja, Mughal Aa, Khan Hs, Kazi S. Risk Factors and Prevalence of Hepatitis B and C in Badin City, Pakistan: Prevalence and Risk Factors of Hepatitis. Pakistan Journal of Health Sciences. 2024 May: 126-31. doi: 10.54393/pjhs.v5i05.1599.

[3] Waheed U, Khokhar Ok, Saba N, Shahid S, Ghaffari A, Hassan N *et al.* The National Burden of Hepatitis C Among Blood Donors in Pakistan: A Systematic Review and Meta-Analysis (1996-2024). Annals of Pims-Shaheed Zulfiqar Ali Bhutto Medical University. 2024 Nov;20(2): 848-63. doi:10.1016/j.jceh.2022.06.003.

[4] Read SA, Tay ES, Shahidi M, O'Connor KS, Booth DR, George J *et al.* Hepatitis C virus driven AXL expression suppresses the hepatic type I interferon response. PLOS One. 2015 Aug; 10(8): e0136227.

[5] Priya S, Gupta H, Bansal B, Elhence A, Kishore Rv, Goel A. A Systematic Review of Risk Factors for Hepatitis C Virus Infection Among Low-Risk Population in India. Journal of Clinical and Experimental Hepatology. 2022 Nov;12(6):1438-44.doi:10.1016/j.jceh.2022.06.003.

[6] Attallah Am, Omran D, Marie Ms, Abdelrazek M, Salama A, El Essawey R *et al.* Il-28b Rs12979860 Polymorphism Affect the Course of Chronic Hepatitis and the Development of Hcc in Egyptian Patients with Hepatitis C Type 4. British Journal of Biomedical Science. 2018 Oct; 75(4): 157-62. doi: 10.1080/ 09674845.2018.1489599.

[7] Mumtaz S, Ahmed J, Gul A, Tariq Sa, Siraj S, Sarwar T. Genetic Diversity of Hepatitis C Virus Genotype 3a Based on Complete Core Protein in Peshawar, Pakistan. Jundishapur Journal of Microbiology. 2020; 13(3). doi: 10.5812/jjm.98942.

[8] Brzdęk M, Zarębska-Michaluk D, Invernizzi F, Cilla M, Dobrowolska K *et al.* Decade of Optimizing Therapy with Direct-Acting Antiviral Drugs and the Changing Profile of Patients with Chronic Hepatitis C. World Journal of Gastroenterology.2023 Feb; 29(6): 949. doi:

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

10.3748/wjg.v29.i6.949.

[9] Khaliq S and Raza Sm. Current Status of Direct Acting Antiviral Agents Against Hepatitis C Virus Infection in Pakistan.Medicina.2018 Nov; 54(5): 80. doi: 10.3390/ medicina54050080.

[10] Pawlotsky JM, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G *et al.* European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series☆. Journal of hepatology.2020 Nov; 73(5): 1170-218. doi:10.1016/j.jhep.2020.08.018.

[11] Dai Cy, Chuang Wl, Yu Ml. Easl Recommendations on Treatment of Hepatitis C: Final Update of the Series-Some Issues. Journal of Hepatology.2021 Feb; 74(2): 473-4. doi: 10.1016/j.jhep.2020.10.013.

[12] Krassenburg La, Zanjir Wr, Georgie F, Stotland E, Janssen Hl, Hansen Be *et al.* Evaluation of Sustained Virologic Response as A Relevant Surrogate Endpoint for Long-Term Outcomes of Hepatitis C Virus Infection. Clinical Infectious Diseases. 2021 Mar; 72(5): 780-6. doi: 10.1093/cid/ciaa144.

[13] Bhattacharya D, Aronsohn A, Price J, Lo Re V, AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2023 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clinical Infectious Diseases.2023. doi:10. 1093/ cid/ ciad319.

[14] Yee Be, Nguyen Nh, Zhang B, Lin D, Vutien P, Wong Cr *et al.* Sustained Virological Response and Its Treatment Predictors in Hepatitis C Virus Genotype 4 Compared to Genotypes 1, 2, And 3: A Meta-Analysis. BMJ Open Gastroenterology.2015 Dec; 2(1): E000049. doi: 10.1 09 3/cid/ciaa144.

[15] Haciseyitoğlu D, Sarinoğlu Rc, Gözalan A, Batirel A, Söyletir G. Hastanemizde Hepatit C Tanisi Alan Hastalarda Hepatit C Virüs Genotiplerinin Dağilimi: 2015-2018. Mediterranean Journal of Infection, Microbes and Antimicrobials. 2021; 10: 7.

[16] Harris He, Costella A, Amirthalingam G, Alexander G, Ramsay Me, Andrews N. Improved Hepatitis C Treatment Response in Younger Patients: Findings from The UK HCV National Register Cohort Study. Epidemiology & Infection.2012 Oct;140(10):1830-7. doi:10.1017/S0950268811002317.

[17] Papić N, Budimir J, Kurelac I, Dušek D, Jugović D, Krajcar N *et al.* Treatment of Elderly Patients with Chronic Hepatitis C: A Retrospective Cohort Study. Acta Clinica Croatica.2018 Mar; 57(1): 61-70. doi: 10.204 71/acc.2018.57.01.07.

[18] El Kassas M, Alboraie M, Naguib M, Omar H, El Tahan A, Moaz I *et al.* A Significant Upsurge of Body Mass Index in Patients with Chronic Hepatitis C Successfully Treated with Direct-Acting Antiviral Regimens. The Turkish Journal of Gastroenterology.2018 Aug; 30(8): 708.

[19] Manns Mp and Maasoumy B. Breakthroughs in Hepatitis C Research: From Discovery to Cure. Nature Reviews Gastroenterology & Hepatology.2022 Aug;19 (8): 533-50. doi: 10.1038/s41575-022-00608-8.

[20] Zaki SM, Ahmed HS, Yousif MM, Awad EM. Interleukin 28b Polymorphism as A Predictor of Sustained Virological Response to Sofosbuvir-Based Therapy for Hepatitis C Virus Patients. Tropical Medicine and Infectious Disease.2022 Sep; 7(9): 230. doi: 10.339 0/ tropicalmed7090230.

[21] Hlaing Nk, Banerjee D, Mitrani R, Arker Sh, San Win K, Tun Nl *et al.* Hepatitis C Virus Therapy with Peg-Interferon and Ribavirin in Myanmar: A Resource-Constrained Country. World Journal of Gastroenterology. 2016 Nov; 22(43): 9613. doi: 10.3748/ wjg.v22.i43.9613.

[22] Dhawan Vk and Anand Bs. Hepatitis C Treatment and Management.In: Drugs & Diseases > Gastroenterology. 2024 June.

[23] Athamneh Ry, Abudalo R, Sallam M, Alqudah A, Alquran H, Amawi Kf et al. Sub-Genotypes of Hepatitis C Virus in the Middle East and North Africa: Patterns of Distribution and Temporal Changes. Infection, Genetics and Evolution.2023 Apr; 109: 105412. doi:10. 1016/j.meegid.2023.105412.