### Best Practice/Intervention:

### Date of Review:
March 1, 2016

### Reviewer(s):
Christine Hu

#### Part A

**Category:**
- Basic Science
- Clinical Science
- Public Health/Epidemiology
- Social Science
- Programmatic Review

**Best Practice/Intervention:**
- Focus: Hepatitis C
- Level: Group
- Target Population: people with HCV infection
- Setting: Health care setting/Clinic
- Country of Origin: Pakistan
- Language: English

#### Part B

<table>
<thead>
<tr>
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<td><strong>Is the best practice/intervention a meta-analysis or primary research?</strong></td>
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<td><strong>Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?</strong></td>
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<td><strong>Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?</strong></td>
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Primary research: to analyze the factors that contributes to the antiviral treatment (interferon-alpha and ribavirin) response in patients with different genotypes of hepatitis C infection.
Are the best practices/methodology/results described applicable in developed countries? | ✗ | ☐ | ☐ | Results are applicable to other countries as interferon alpha and ribavirin are still widely used for HCV treatment around the world.

<table>
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</tr>
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Are the best practices/methodology/results described applicable in developing countries? | ✗ | ☐ | ☐ |


Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? Please go to Comments section | ☐ | ✗ | ☐ | No cost effective analysis was conducted.

Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary? | ☐ | ✗ | ☐ |

How is the research study/tool funded? Please go to Comments section | ☐ | ✗ | ☐ | No funding stated

Is the best practice/intervention dependent on external funds? | ☐ | ☐ | ☐ |

Other relevant criteria:
- Study showed 60.2% SVR to antiviral therapy
- Older female patients >60 years have not shown any response
- Female younger patients <40 years have SVR 77.2% compared to male patients with 67.5% SVR
- SVR rates for genotype 3 patients are significantly higher than those other genotype patient groups
- Younger age, low viral load, achieving early inhibition of viral replication and non fatty liver are positively independently associated with SVR.

WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW

Are these data regularly collected? | ✗ | ☐ | ☐ | Study included patients who attended the Nuclear Medicine Oncology and Radiotherapy institute from 2008-2013.
<table>
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**RESEARCH REPORTS**

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<tr>
<td>Has this research been published in a juried journal?</td>
<td>☒</td>
<td></td>
<td></td>
<td>Journal of Medical Virology</td>
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<td>Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?</td>
<td>☐</td>
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<td>New data/information</td>
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Optimum Predictors of Therapeutic Outcome in HCV Patients in Pakistan

Hafsa Aziz,* Abida Raza, and Javaid Irfan
Nuclear Medicine Oncology and Radiotherapy Institute, Islamabad, Pakistan

Hepatitis C virus (HCV) constitutes a major public health issue in Pakistan. Interferon α and ribavirin is used widely in routine practice in HCV infected patients in Pakistan. Treatment prediction is an important tool in therapy management. The present study aims to evaluate trends of predictive variables of treatment outcome in patients with different genotypes. The analysis comprised of 921 patients infected with different HCV genotypes. All the patients received IFN α-2b combined with ribavirin for 24 weeks. Overall, 60.2% patients achieved Sustained virologic response (SVR). In females sustained virologic response (SVR) was higher in age group <40 years (77.2%) than ≥40–50 years (60%) but in male SVR was almost equal in both age groups. We also found higher SVR with low pretreatment viral load (72.4%, P < 0.0001). Sustained Virologic Response in genotype 3a was 63.1%, 3b was 55%, 1a was 36.3% and 1b was 35% 3a + 3b was 55.0% and 1a + 3a was 42.9%. According to multivariable logistic regression analysis age <40 years (2.0; 95%CI, 1.49–2.84; P = 0.0001), low pretreatment RNA level <800,000 IU/ml (4.0; 95%CI, 2.64–6.17; P = 0.0001), early virologic response at week 12 (12.3; 95%CI, 8.18–18.58; P < 0.0001) and non-fatty liver (2.5; 95%CI, 3.6–6.2; P = 0.005) showed significance for SVR. Nucleotide substitution in 5′UTR before treatment failed to show any characteristic pattern that has correlation with sustained response. Subtype 3a showed 95% presence among patients with age <40 years while older patients showed 79.9%. J. Med. Virol. 88: 100–108, 2016. © 2015 Wiley Periodicals, Inc.

KEY WORDS: HCV genotypes; treatment response

INTRODUCTION

Hepatitis C virus constitutes a major public health issue and major cause of liver-related morbidity and mortality. About 130–170 million people are infected with HCV worldwide, which covers about 2.2–3% of the world’s population [Alter, 2007]. In Asian-Pacific regions, the prevalence of HCV infection ranges from 0.3% to 12% [Mc Caughan et al., 2007] and in Pakistan 5.9% (>10 million) individuals are living with HCV with high morbidity and mortality [Aziz et al., 2011].

The combination treatment with interferon α and ribavirin continues to be used widely in routine practice in HCV infected patients in Pakistan because PEG interferon therapy is very expensive, secondly in Pakistan infection is caused by HCV type three which is more sensitive to interferon therapy than type one. The main treatment goal in chronic hepatitis C is to suppress viral replication at maximal level to attain sustained virologic response (SVR, defined as an undetectable serum hepatitis C virus RNA level 6 months after the end of treatment) [Strader et al., 2004]. In addition HCV infected patients serve as the reservoir for transmission to others [Pyrsopoulos et al., 2011]. However response to antiviral treatment is not uniform in all the populations, reasons for failure of treatment are correlated with host, virus, and immune response variables [Conjeevaram et al., 2006). Additionally it has also been found that there is correlation between HCV genotyping and response to therapy [Simmonds, 1995]. Some studies reported genetic polymorphism influence antiviral response [Soler et al., 2002]. As HCV is an RNA virus, it have conserved and hyper variable region. Most conserved region is 5′UTR, it contains replication signal as IRES (Internal ribosomal entry site). 40S ribosomal unit bind with IRES for initiation of translation. These changes in nucleotide may have dramatic effect on translation [Van et al., 2004]. Some studies reported that nucleotide changes in IRES region have influence on response to therapy [Thelu et al., 2007].

Conflict of interest: None.

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It is valuable to analyze factors that enable us to predict the response to antiviral treatment. Several pretreatment and on treatment factors (gender, starting treatment at younger age, low level of HCV RNA, HCV genotype 2, and 3 and early inhibition of viral replication (EVR), steatosis) have an impact on antiviral treatment outcome [Yoshioka et al., 1992; Tsubota et al., 1993; Suzuki et al., 1995; Backus and Boothroyd, 2007; Kau et al., 2008]. However, it is not clear to what extent these factors contribute to the response, or how they relate to each other. Moreover we analyzed substitution in sub genomic 5'UTR (IIb domain contain IRES) region that may be associated with response to therapy.

MATERIALS AND METHODS

Patient Selection

A study was carried out on 921 patients with chronic HCV infection who attended the Nuclear Medicine Oncology and Radiotherapy institute (NORI) from multiple centers (Pakistan Institute of medical sciences, Islamabad specialist clinic, Federal Government Hospital) from 2008–2013. Patients included in this study have following characteristics, Positive for anti HCV antibody with normal and raised ALT level, HCV viremia confirmed by qualitative PCR, and negative for hepatitis B surface antigen, Moreover patients enrolled in this study had a hemoglobin level $>13$ g/dl in men or $>12$ g/dl in women a white blood cell count $>3000$ cells/mm$^3$, platelet count $>100,000$ cells/mm$^3$. The study was approved by local ethical committee of the center and consent form was received from all patients. Eligible patients received IFN 3MIU thrice a weeks for 24 weeks.

Assessments of Viremia, HCV Genotypes, and ALT

Viral load was measured by using instant virus RNA kit (AJ Roboscreen Berlin, Germany) according to manufacturer’s protocol on real-time PCR (RotorGene 3,000 Corbett Research, Sydney, Australia) at base line, 12 week, 24 weeks, and 24 weeks after treatment completion for sustained virologic response (SVR defined as absence of detectable HCV RNA 6 months after the completion of treatment). The lower limit of detection of the assay is 50IU/ml. Fatty liver was detected by ultra sonography [Yajima et al., 1983] at baseline. Genotyping was performed by core region genotype specific primer reported by Ohno et al. [1991] with some modification reported by Aziz et al. [2013]. The primary end point of the study was to find the factors that contribute to the sustained virologic response.

Sequencing

Amplified sample of selected responder and non-responder were subjected to sequencing by using ABI automated sequencer. Chromas version 2.0 were used to view nucleotide sequence and electro-pherograms. Ambiguities in the sequence are resolved by comparison of the results of both forward and reverse primers as well as by comparison with the HCV sequences in the NCBI database. Sequence was aligned by using CLC workbench software (www.clcbio.com). Nucleotide sequences were analyzed for substitutions by using software CLC Workbench.

Statistical Analysis

All the variable results were given in the form of rate (%). Chi square method was used to evaluate variable association with likelihood of achieving response to treatment. SPSS was used to carry out the logistic regression analysis, to find association between variables and SVR. $P$-value below 0.05 was considered significant. We made a sub-analysis by adding result of 5'UTR sequence analysis of patients achieved SVR versus non-SVR.

RESULT

Study Enrolments and Disposition of Patients

Nine hundred and twenty one patients included in final analysis that completed 24 weeks of treatment and follow up. Five hundred twenty three were females (n = 523) and three hundred ninety eight (n = 398) were males. The base line characteristics of the patients are summarized in Table I. Surgery and dental treatment was the main mode of acquiring HCV infection.

Virologic Response

Six hundred eighty nine patients (74.8%) showed end treatment response (ETR). Two hundred thirty two (25.2%) patients were virologically non responders, showing detectable HCV RNA at the end of treatment. Of the 921 patients, 554 (60.2%) achieved sustained virologic response (SVR). Among the patients (921) who completed the therapy 523 (56.8%) were females and 398 (43.2%) were males with end treatment response rate of 75.3% and 74.1%, respectively (Table II). The result is an indicative of the fact that no significant difference in response to IFN a-2b plus ribavirin treatment in males and females. Over all fatty liver was observed in 21.9% of patients. SVR rates in. patient with fatty liver was lower where as in patients without fatty liver was higher (66.7% vs. 36.6%, $P < 0.005$) (Table III).

The effect of different age groups on sustained virologic response in HCV patients is shown in Figure 1. Tendency to sustained virologic response is higher (77.2%) in females at the age of $<40$ years, 60% in $40–50$ years age group, and 27.3% in $>50–60$ years age group (Fig. 1). In males, sustained virologic response was almost equal for $<40$ and $40–50$ years age group 66.7%. SVR 16.7% was
observed in some cases of >60 year’s age group in male patients. SVR in female >60 years of age group was not observed. Moreover when study population was categorized into four groups same findings were observed. In females <40 years group, the sustained response rate was significantly higher (77.2%) as compared to females with age ≥40 years with response rate of 48.8% (77.2% vs. 48.8%, P = 0.001) (Table III).

Correlation between pretreatment viral load and SVR was also analyzed. A wide range of virus loads were observed among infected patients. For the purpose of analysis patients were categorized into two groups according to their baseline viral load (Table III). The percentage of SVR was found higher with low pretreatment viral load (72.4% vs. 55.95%, P < 0.0001). We examined SVR in HCV patients according to week 12 viral decline. For this purpose all patients were evaluated at week 12. Six hundred and sixty five patients (665) showed viral decline >2 log drop while two hundred and fifty six patients did not showed 2 log drop. The SVR was observed higher 73.8% (491/665) in patients who achieved early virologic response (EVR) than patients who did not achieve EVR 24.6% (63/256) (Table III).

### Treatment Outcome According to Genotypes

HCV genotype distribution pattern showed in all 921 patients (Table I). Overall, 816 patients (88.6%) were infected with genotype 3a, 20 (2.2%) with 3a + 3b, 44 (4.8%) with 1a, and 7 (0.8%) with both 1a + 3a. The relation for the age groups for different subtypes were also determined, we found subtype 3a strains showed higher presentation 95% among patients having age <40 years while older patients having age ≥40 years showed 79.9%. Sub type 1a showed presentation 10.4% among patients with age ≥40 years where as younger patients showed only 0.7% of subtype 1a while studying the SVR in relation to
HCV viral genotype (Table IV), response to IFN against patient infected with genotype 3a was 63.1% (515/816), 3b was 55% (9/20), 1a was 36.3% (16/44), and 1b was 35.0% (5/14). Rate of SVR in patients with mixed genotype were also analyzed. SVR rate in patients infected with 3a + 3b genotype was 55.0% and with 1a + 3a was 42.9%. Random distribution of viral load was noticed in HCV infected patients with different genotypes. A significant difference of SVR was found between the patients with an HCV RNA level ≥800,000 IU/ml with genotype 3 and genotype 1 (P < 0.0001) (Figure 2). Figure 2 also demonstrate that there is difference in response in genotype 3 patient with HCV RNA ≥800,000 IU/ml (73.0%) than HCV RNA <800,000 IU/ml (41.0%). High viral load had lower rate of SVR than with low viral load. In addition prevalence of fatty liver was 8.1% (70/856) among HCV genotype 3 and 6.1% was observed in other group of genotype.

### Biochemical Response

At the time of treatment subjects were classified as raised ALT group (Male ≥41 U/L, Female ≥31 U/L) and normal ALT group (Male <41 U/L, Female <31 U/L). Most of the patients 714 (77.4%) lie in the raised ALT group with end treatment response rate of 72.7%. The proportion of the patients with SVR was slightly higher in raised ALT group than normal ALT group that is 69.1% versus 57.6% (P < 0.005) (Table III). Serum ALT decreased to normal level after treatment completion in 73.5% (525/713) patients. All patients were assessed after 6 month of cessation of treatment for SVR and biochemical response. During follow up it was observed that undetectable HCV RNA had high predictive value for normalization of ALT level as 468 of 554 (84.5%) patients with undetectable HCV RNA had normal ALT at follow up. Patients with sustained biochemical response did not show sustained virological response. Thus ALT normalization has low predictive value for undetectable HCV RNA.

### Table IV. Rate of Sustained Response in Patients With Different HCV Genotypes

<table>
<thead>
<tr>
<th>S. No</th>
<th>HCV genotypes</th>
<th>Total treated patients (%)</th>
<th>SVR (%)</th>
<th>NSVR (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>44 (4.8)</td>
<td>16 (36.3)</td>
<td>28 (63.6)</td>
</tr>
<tr>
<td>2</td>
<td>1a + 3a</td>
<td>7 (0.7)</td>
<td>3 (42.9)</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>14 (1.5)</td>
<td>5 (35.0)</td>
<td>9 (64.2)</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>816 (88.6)</td>
<td>515 (63.1)</td>
<td>301 (36.9)</td>
</tr>
<tr>
<td>5</td>
<td>3a + 3b</td>
<td>20 (2.2)</td>
<td>11 (55)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>6</td>
<td>3b</td>
<td>20 (2.2)</td>
<td>11 (55)</td>
<td>9 (45)</td>
</tr>
</tbody>
</table>
Detection of Nucleotide Substitution in 5'UTR Region

Sequence region from nucleotide 88–403 of 5'UTR region was amplified and sequences were aligned using CLC sequence viewer to find nucleotide substitution. The sequences were graphically according to NZL1 (ac D17763). The alignment of sequence (region that confers sub domain IIIb of 5'UTR region) showed some specific pattern from patients who have SVR and in patients who did not have SVR (non-SVR) to antiviral treatment (Figure 3). It was observed that non-SVR patients have substitution at position 202 (nucleotide change from C to T) but substitution difference between patients who achieved SVR and Non-SVR is not significant.

Predictor of Sustained Virological Response to PEG IFN α-2a Univariable Logistic Regression Analysis

By univariable logistic regression analysis we found baseline HCV RNA level (<800,000 IU/ml OR, 2.0; 95%CI, 1.50–2.85; P < 0.0001); age (<40 years; OR, 2.8; 95%CI, 2.20–3.80; P < 0.0001); HCV genotype (Genotype 3 OR, 4.0 ; 95%CI, 2.3–7.00; P < 0.0001); achieving EVR (EVR OR, 8.6; 95%CI, 6.19–12.05; P < 0.0001) ; Viral load (<800,000 IU/ml OR, 1.8; 95%CI, 2.1–3.2; P < 0.0001); ALT level at the time of treatment (normal ALT OR, 1.6 ; 95%CI, 1.19–2.31; P > 0.003), Steatosis (Non-Fatty liver OR, 1.3;95% CI, 1.13–3.80; P <0.005) were significantly associated with treatment success. Sub-group analysis carried to find effect of substitution at IRES binding site on treatment response, including patient whose 5'UTR sequence carried we found difference in response, though it is not significant.

Multivariable Logistic Regression Analysis

When multivariable model was built with the factors exhibiting significance on univariable logistic regression analysis to clarify independent factor that contributing to SVR. It showed patient age [OR (for <40 vs. ≥40) 2.0; 95%CI, 1.49–2.87; P = 0.0001], HCV RNA level [OR for (<800,000 IU/ml vs. ≥800,000 IU/ml) 4.0; 95% CI, 2.64–6.17; P = 0.0001], EVR at week 12 [OR (for EVR vs. non-EVR) 12.3; 95% CI, 8.18–18.58; P < 0.0001] and steatosis [OR (for <Fatty Liver vs. Non-Fatty Liver) 2.5; 95% CI, 3.6–6.2; P < 0.005] remained significance for SVR.

Tolerance and Safety Assessment

Adverse events experienced by the patients during treatment were recorded in Table V. Most of the HCV treated patients experience headache 53%, myalgia 45%, and fatigue 45.5%. The commonly observed psychiatric side effect of therapy, insomnia is present in 20% of patients. Additionally it was noted that depression develops in 5% of patients. Diarrhoea was observed in 13% cases. Ten percent patients developed skin rash.

DISCUSSION

The current study showed SVR of 60.2% to antiviral therapy. This SVR is higher as compare to 57% and 53% reported by others [Poynard et al., 1998; McHutchison et al., 1998]. High overall rate of HCV RNA clearance may be due to the fact that majority of the population infected by HCV genotype 3. This implies that HCV genotype 3 have better response to antiviral treatment as compared to genotype 1[Sarrazin et al., 2001]. In a study Jacobson et al. reported higher rate of SVR as 78% among HCV genotype 2 and 3 patients treated with Sofosbuvir with RBV [Jacobson et al., 2013]. Another study showed that naïve HCV genotype 3 patients achieved SVR 95% [Zeuzem et al., 2014] after treatment with Sofosbuvir with RBV, so the new direct antiviral agents increase the sustained response against HCV infection.

In some previous studies response to interferon in female have not documented better than male but unable to observe such a relationship, we found almost equal SVR rate in male and female 59.8% versus 60.4% but the response rate was not statistically significant. Furthermore multivariable logistic regression analysis shows that gender has no significant correlated to SVR. In addition results revealed that female younger patients (<40) have SVR 77.2% as compared to male have 67.5%. In addition female response difference in younger and older female's patients is more (28.4%) than male who have shown 16.9%. Difference in younger and older age. More over in our study we also observed no difference in response in male patients with age <40years and 40–49 years. An important finding of the study is older female patients >60 years have not shown any response. This observation supported by Antonucci et al. [2007] who reported low chance of achieving SVR in patients older than 40 years of age. It shows that aging impart a negative effects on the treatment efficacy. Changing in immune system occurs as age
Fig. 3. Nucleotides alignment of 5'UTR region of hepatitis C virus isolated from SVR and non-SVR patients.
TABLE V. Incidences of Adverse Events During IFN α-2b Plus Ribavirin Treatment

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>No.</th>
<th>Percentage (%)</th>
</tr>
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<tbody>
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<tr>
<td>Headache</td>
<td>487</td>
<td>53</td>
</tr>
<tr>
<td>Fatigue</td>
<td>419</td>
<td>45.5</td>
</tr>
<tr>
<td>Fever</td>
<td>276</td>
<td>30</td>
</tr>
<tr>
<td>Myalgia</td>
<td>414</td>
<td>45</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>303</td>
<td>33</td>
</tr>
<tr>
<td>Decrease in appetite</td>
<td>200</td>
<td>21.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>120</td>
<td>13</td>
</tr>
<tr>
<td>Psychiatric symptoms</td>
<td></td>
<td></td>
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<tr>
<td>Depression</td>
<td>46</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>184</td>
<td>20</td>
</tr>
<tr>
<td>Dermatological symptoms</td>
<td></td>
<td></td>
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<tr>
<td>Alopecia</td>
<td>185</td>
<td>20</td>
</tr>
<tr>
<td>Rash</td>
<td>92</td>
<td>10</td>
</tr>
<tr>
<td>Inflammation at injection site</td>
<td>90</td>
<td>9</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>105</td>
<td>11.4</td>
</tr>
</tbody>
</table>

In this study prevalence of fatty liver was found 21.9%, this finding is in agreement with the observation that HCV hijacks the lipid-producing machinery of hepatocytes for its benefit and results in steatosis [Barba et al., 1997; Shi et al., 2002]. Patients with fatty liver have markedly lower SVR (36.6%) than those of non-fatty liver; this observation is in consensus with Jian et al. who suggest that fatty liver have adverse effect on the outcome of the treatment [Jian et al., 2006].

Genotype of HCV aid physicians in tailoring antiviral therapy. In agreement with previous report [Moatter et al., 2002] patients with HCV genotype 3α have higher response (63.1%) than other genotypes. In the population with genotype other than 3, most genotypes observed are 1a, 1b, and 1a-3a. Although number of these genotypes was too small in the current study but other studies also reported these genotypes associated with poor response. From the result it is clear that patient with genotype 3 and have higher baseline viral load >800,000IU/ml have response rate 41.0% where as patients infected genotype 1 have response rate 25.0% (Figure 2). The response rate may be increased by using direct antiviral agents. As number of studies reported that first generation HCV NS3/4A protease inhibitors (boceprevir and telaprevir) increase the likelihood of SVR to 67–75% in HCV genotype 1 patients [McHutchison et al., 2009; Kwo et al., 2010; Jacobson et al., 2011; Poordad et al., 2011; Kanda et al., 2014]. Simeprevir, second-generation hepatitis C virus protease inhibitor led to SVR 77–92% [Hayashi et al., 2014]. The Food and Drug Administration in 2013 approved the use of simeprevir and sofosbuvir (HCV polymerase inhibitor) for the treatment of patients infected with HCV, which will improve SVR of 89% in patients infected with HCV genotype 1 [Andrenesu et al., 2014].

Random distribution of HCV RNA among infected patients with different HCV genotypes was observed. This observation was in contrast to the study of Moatter et al, who have reported low level of viremia in HCV genotype 3 patients [Moatter et al., 2002]. But another study [Xie et al., 2005] reported viral load have no correlation with HCV genotypes. This discrepancy, in result may be caused by different quantification method in different laboratories. From data analysis we found significant association of EVR to SVR. Study showed higher SVR rate in patients who achieved EVR as compare to patients who did not achieve EVR (73.8% vs. 24.6% P < 0.0001) (Table III). Results also suggested that patients with early virological response had significant higher SVR. This finding is in agreement with Sarwar et al. [2012] and Yu et al. [2007]. Patient who attains SVR but did not attain EVR has slow response during the treatment. 174 (26.1%) patients not showing SVR though they showed EVR (72.2%) suggesting that HCV RNA can persist in PBMC of infected patients who have undetectable HCV RNA during interferon treatment [Zayed et al., 2010].

The ALT value rises with development of inflammation of liver. IFN α-2b plus ribavirin therapy response rate in patients with normal ALT was found higher (69.1%) to that achieved in patients with elevated ALT levels. This outcome was in consensus with Hui et al. who revealed that the end treatment response to IFN therapy in patients with normal ALT levels was 59.6% and in patients with elevated level was 56.6% [Hui et al., 2003]. In a study by Persico et al. [2000] 23% of their patients developed elevated ALT level, while 21% patients with normal
ALT developed elevated ALT level on follow up. Both have suggested that this raised ALT in these patients may be part of the natural history of patients with normal ALT levels [Persico et al., 2000]. But in this study we found only three (1.8%) patients, who had normal ALT during treatment but developed raised ALT levels at the end of treatment. Multivariable logistic regression did not showed ALT as predictive factor

Sequence region from nucleotide 88–403 of 5’UTR region was amplified and sequences were aligned using CLC sequence viewer to find nucleotide substitution. The sequences were graphically according to NZL1 (ac D17763). Alignment of sequence (region that confers sub domain IIb of 5’UTR region) showed that contact point between IRES and 40S ribosomal unit (Nucleotide 128–138,145–156 and 237–250) are highly conserved among all strains isolated from patient showed SVR and did not showed SVR to antiviral treatment [Hazari et al., 2005]. In agreement with Moratorio et al. [Moratorio et al., 2007] a rare nucleotide substitution is observed at G 243A, though did not disrupt stem loop III folding and suggesting that maintaining of the structure of the internal ribosomal entry site is prerequisite for survival of quasispecies in host cell (Thelu et al., 2004). In addition C–T and C–A substitution at position 202 among patients achieved SVR and non-SVR needs further study. These findings suggest that sequence variability found in IRES of Non-SVR does not affect the confirmation for binding of cellular factors. More over consensus alignment of sequence before treatment did not revealed any significant correlation with sustained response.

CONCLUSION
SVR in patients with genotype 3 were significantly higher than those of patients with other genotype group. Subtype 3a strains showed higher presentation 95% among patients having age <40years while older patients having age >40 years showed 79.9%. Over all, younger age, low viral load, achieving EVR and non fatty liver were independently but positively associated with SVR.

REFERENCES


