CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2457041

Available online at: http://www.iajps.com ***Research Article***

RAPID VIROLOGICAL RESPONSE (RVR) AND END TREATMENT RESPONSE (ETR) IN HEPATITIS C GENOTYPE 3 INFECTED PATIENTS BEING GIVEN SOFOSBUVIR AND RIBAVIRIN COMBINATION (DUAL) THERAPY

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Abstract

Objective: *To analyze Rapid virological response (RVR) and End treatment response (ETR) in Hepatitis C genotype 3 infected patients being given Sofosbuvir and Ribavirin combination (dual) therapy presenting to Liver clinic of Benazir Bhutto Hospital.*

Methods: *It was a retrospective study, conducted at Benazir Bhutto Hospital from January 2016 to July 2017. For this study, data of HCV subjects attending liver clinic (OPD) was obtained from computerized hospital management system (HMS). Variables that were obtained through administrative data included age, sex, pretreatment hemoglobin, TLC and platelet counts, pretreatment ALT, pretreatment PCR, and pretreatment ultrasound Liver findings. Only data of patients who fulfilled the inclusion criteria was included and data for patients who met the exclusion criteria was omitted. The inclusion criteria for patients was 18 years of age or older, having PCR for HCV RNA positive for genotype 3, treatment naïve, both cirrhotic and non-cirrhotic. The exclusion criteria included those that did not give informed consent, pregnant patients, history of active drug abuse, overt infection with other hepatitis viruses, autoimmune disease and HIV positive patients.*

Keeping the selection criteria in view total number of patients included in the study from liver clinic records was 135 and all had received Sofosbuvir with Ribavirin dual therapy in our OPDs for a duration of 24 weeks. 3 PCRs were performed during therapy for monitoring. One at the start of treatment, then at 4 weeks to assess RVR, then at the end of treatment at 24 weeks therapy to see ETR.

Results: *A total of 135 patients were included in the study having genotype 3 amongst which 33(24.4%) were males and 102(75.6%) were females. The mean age of participants was 46.23259 (± 11.86040) years. Of 135 patients, PCR of all 135 was available at four weeks of treatment and 112 (83%) had achieved RVR while PCR of 131 patients was available at completion of treatment i.e. at 24 weeks amongst whom 112(85.5%) had attained ETR. The association between attainment of RVR and attainment of ETR was also assessed using Pearson's Chi square test and results were statistically significant, showing that patients who achieved RVR were more likely to go on to achieve ETR. The comparison of patients who attained RVR with those who did not was also executed based on gender and Pearson's chi square test revealed no statistically significant difference in the two groups with p values greater than 0.05. Comparison of the mean age of patients who attained RVR with those who did not was made using independent t test and similarly comparison of mean pretreatment CBC indices, mean pretreatment ALT, mean pretreatment viral load was also done for the two groups i.e RVR achieved/not achieved using independent T test. The impact of advancing liver disease (as evidence by progressively worsening ultrasound liver findings) on 4 week viral clearance was assessed ising Mann Whitney test and none of these found any statistically significant association, with p values being greater than 0.05 in each case.*

Conclusion: *In our study population, which was reflective of disease epidemiology in Rawalpindi, Pakistan: females were more affected than males, average age was 40 years and majority of patients presented early in the disease course with normal liver findings on ultrasound, followed by the non specific findings of fatty liver. Sofosbuvir plus Ribavirin combination therapy has shown to be very effective and successful in achievement of viral clearance with little or no resistance in genotype 3 infected patients in our study population regardless of the age, gender and other variable differences. 83% of the patients achieved RVR at completion of four weeks of treatment while 85.5% had attained ETR at end of therapy. Patients who achieved RVR were more likely to go on to achieve ETR.*

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Please cite this article in press Sidra Nisar et al., ***Rapid Virological Response (Rvr) And End Treatment Response (Etr) In Hepatitis C Genotype 3 Infected Patients Being Given Sofosbuvir And Ribavirin Combination (Dual) Therapy.,*** *Indo Am. J. P. Sci, 2018; 05(12).*

INTRODUCTION:

The hepatitis C virus is a blood borne virus and the most common modes of infection are through exposure to small quantities of blood. This may happen due to unsafe health care, including unsafe injection practices, transfusion of unscreened blood and blood products, use of unhygienic dental instruments, poor infrastructure for infectious waste disposal and also prominently due to the reuse of razor blades by barbers. Globally, an estimated 71 million people have chronic hepatitis C infection [1]. A significant number of those who are chronically infected will develop cirrhosis or liver cancer and approximately 400 000 people die each year from hepatitis C, mostly from cirrhosis and hepatocellular carcinoma [1]. Pakistan has the world's second highest prevalence of hepatitis C, second only to Egypt. A survey done in 2007 found that close to 7% of people in the province of Punjab had hepatitis C, while around 5% of people were infected in the entire country [1]. There is currently no vaccine for hepatitis C. Antiviral medicines can cure more than 95% of persons with hepatitis C infection, thereby reducing the risk of death from liver cancer and cirrhosis, but access to diagnosis and treatment is low.

Previously, interferon was considered the primary therapeutic agent for Hepatitis C patients. Although, the addition of Ribavirin and improvement of conventional interferon with pegylation had enhanced the rate of sustained virological response (SVR), a lot of the cases remained non-responders or relapsed after the completion of treatment. Low SVR rates along with prolonged duration of treatment and significant side effects made interferon a less than ideal therapeutic agent for Hepatitis C patients. In that regard, Sofosbuvir has proved to be a game-changer in the treatment of Hepatitis C. Sofosbuvir, a nucleotide analog, HCV NS5B polymerase inhibitor, is the first approved direct acting agent with excellent tolerability and favorable pharmacokinetic profile, limited potential for drug interactions, potent antiviral activity and high genetic barrier against all HCV genotypes [4].

According to international guidelines of EASL the response to therapy with Sofosbuvir is judged initially by the rapid virological response (RVR) that is the undetectable viral load on PCR done at one month while the ultimate goal is to get a sustained virological response (SVR) done after 12 weeks of completion of therapy. A study conducted from September 2012 through January 2013 at 77 sites in Europe concluded that therapy with sofosbuvir–ribavirin for 12 weeks in patients with HCV genotype 2 infection and for 24 weeks in patients with HCV genotype 3 infection resulted in high rates of sustained virologic response. Among patients with HCV genotype 2 infection who received 12 weeks of sofosbuvir–ribavirin, 68 of 73 (93%; 95% confidence interval [CI], 85 to 98) had a sustained virologic response 12 weeks after the cessation of treatment[2]. All 68 patients also had a sustained virologic response 24 weeks after treatment. Among patients with HCV genotype 3 who received 24 weeks of sofosbuvir–ribavirin, 213 of 250 patients (85%; 95% CI, 80 to 89) had a sustained virologic response 12 weeks after the cessation of treatment. Similarly an observational study was conducted at Memon Medical Institute in Karachi Pakistan from January 2016 to July 2017 with a total of 201 subjects included in the study. Of 201 patients most commonly genotype 3 n= 180 (89.6%) was present followed by genotype 1 n=9(4.5%), genotype 2 n=1(0.5%), genotype 4 n=1(0.5%). Of patients with genotype 3, 123 received dual therapy and 57 were given triple therapy. After 4 weeks of therapy HCV RNA by PCR, 200(99.5%) achieved RVR, 199(99%) achieved ETR and SVR was achieved in 178(88.5%) [3]

The main objective of the present study is to assess the response of double therapy i.e. Sofosbuvir and Ribavirin in Hepatitis C patients infected with genotype 3. Additionally, we were also interested to see the influence of patient's age, gender,baseline viral load, pretreatment ALT, pretreatment blood indices and ultrasound liver findings on treatment response; by evaluating their association with rapid viral response (RVR) at week-4 and end treatment virological response (EVR) at completion of therapy.

MATERIALS AND METHODS:

It was a retrospective study, conducted at Benazir Bhutto Hospital from January 2016 to July 2017. For this study, data of HCV subjects attending liver clinic (OPD) was obtained from computerized hospital management system (HMS). Variables that were obtained through administrative data included age, sex, pretreatment hemoglobin, TLC and platelet counts, pretreatment ALT, pretreatment PCR, and pretreatment ultrasound Liver findings.

Total number of patients selected for the purpose of the study from liver clinic records was 135 and all had received Sofosbuvir with Ribavirin dual therapy in our OPDs for a duration of 24 weeks. Dual therapy comprises of Sofosbuvir 400 mg once daily and weight based Ribavirin (1000mg daily for <75 kg and 1200mg for >75 kg in two divided doses). Initially genotyping and Quantitative PCR test were done. Three quantitative PCRs were performed during therapy for monitoring. One at the start of treatment, then at 4 weeks to assess RVR, then at the end of treatment at 24 weeks therapy to see ETR.

Investigations had been repeated on follow up visits to check for occurrence of any complications or side effects like anemia.

Only data of patients who fulfilled the inclusion criteria was included and data of patients who met the exclusion criteria was omitted. The inclusion criteria for patients was 18 years of age or older, having PCR for HCV RNA positive for genotype 3, treatment naïve, both cirrhotic and non-cirrhotic patients. The exclusion criteria included those that did not give informed consent, pregnant patients, history of active drug abuse, overt infection with other hepatitis viruses, autoimmune disease and HIV positive patients.

ETHICAL CONSIDERATION:

Aim of the study was conveyed to all the participants and they reported a written acceptance regarding their participation in the study. Moreover, anonymity of each subject was maintained and confidentiality of data was ensured.

EXTENT OF RESEARCHER INTERFERENCE:

Data is being presented without any manipulation in natural environment of hospital and normal flow of work. Therefore, extent of researcher interference is minimal.

STATISTICAL ANALYSIS:

The data was entered and analyzed in SPSS v.22. Different methods were used to analyze our qualitative and quantitative variables. Continuous data like age, pretreatment ALT and pretreatment PCR was expressed as mean ± SD, whereas categorical data like gender, ultrasound findings, RVR and EVR status was expressed in the form of frequencies, proportions and percentages. Independent samples t-test was applied at 5% level of significance to compare the mean age of patients who attained RVR with those who did not and similarly pretreatment ALT and pretreatment PCR of patients who attained negative PCR at 4 weeks was compared with those who did not. Pearson's Chi Square test was applied at 5% level of significance to compare proportions of the patients who attained RVR or ETR with those who did not, based on gender. P values equal to or less than 0.05 were considered statistically significant. Mann Whitney test was used for ordinal data like ultrasound liver findings to assess impact on attainment of viral clearance.

RESULTS:

A total of 135 patients were included in the study having genotype 3 amongst which 33(24.4%) were males and 102(75.6%) were females. The mean age of participants was 46.23259 (± 11.86040) years while their baseline serum profile showed mean pretreatment ALT as 64.1956 (±43.79656)U/L ,mean pretreatment hemoglobin level as 13.0407(± 1.82230)g/dl, mean serum platelet count as 13262.3333 (± 55115.57877) per liter and mean pretreatment total leukocyte count as 7.5877 (±2.44001)cells per microliter. Amongst 135 patients, PCR of 135 was available at completion of four weeks and 112 (83%) had achieved RVR at completion of four weeks of treatment while PCR of 131 patients was available at completion of treatment i.e. at 24 weeks amongst whom 112(85.5%) had attained ETR. Baseline USG liver findings were also recorded for all 135 patients with 79 (58.5%) showing evidence of normal liver architecture on USG, 37 (27.4%) showing fatty liver changes, 17 (12.6%) showing features of CLD (coarse liver) and 2 (1.5%) showing evidence of DCLD (portal hypertension and ascites).

Independent samples t-test was applied at 5% level of significance to compare the mean age of patients who attained RVR with those who did not; similarly mean pretreatment ALT and mean pretreatment PCR of patients who attained negative PCR at 4 weeks was compared with those who did not, and none revealed any significant statistical association with p values greater than 0.05.

Pretreatment Hemoglobin, TLC and platelet counts also demonstrated no significant association with viral clearance as independent t test revealed no significant difference in the mean values for these indices of patients who achieved RVR compared to those who did not.

The comparison of patients who attained RVR with those who did not was also executed based on gender and Pearson's chi square test revealed no statistically significant difference in the two groups with p value greater than 0.05.

The association between attainment of RVR and EVR was also assessed using Pearson's Chi square test and results were statistically significant showing that patients who achieved RVR were more likely to go on to achieve ETR.

The impact of progressively worsening liver findings on USG (used as an indicator of advancing liver disease) on attainment of RVR and SVR was assessed with Mann Whitney test and results showed no significant impact of liver architectural status (on USG) on viral clearance (p value 0.06).

gender * rvr Crosstabulation

			Rvr		
			achieved	not achieved	Total
gender	female	Count	84	18	102
		Expected Count	84.6	17.4	102.0
	male	Count	28	5	33
		Expected Count	27.4	5.6	33.0
Total		Count	112	23	135
		Expected Count	112.0	23.0	135.0

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.110[a]	1	.740		
Continuity Correction[b]	.004	1	.948		
Likelihood Ratio	.112	1	.738		
Fisher's Exact Test				1.000	.486
Linear-by-Linear Association	.109	1	.741		
N of Valid Cases	135				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 5.62.

b. Computed only for a 2x2 table

Group Statistics

	Rvr	N	Mean	Std. Deviation	Std. Error Mean
age	achieved	112	46.2768	12.16568	1.14955
	not achieved	23	46.5652	10.48733	2.18676

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Equal variances assumed	.759	.385	-.106	133	.916	-.28843	2.72522	-5.67881	5.10195
Equal variances not assumed			-.117	35.305	.908	-.28843	2.47050	-5.30227	4.72541

Group Statistics

	rvr	N	Mean	Std. Deviation	Std. Error Mean
PCR	achieved	112	3.0824E6	1.29865E7	1.22711E6
	not achieved	23	5.2951E6	1.41280E7	2.94589E6

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
PCR	Equal variances assumed	1.679	.197	-.733	133	.465	-2.21268E6	3.01772E6	-8.18162E6	3.75626E6
	Equal variances not assumed			-.693	30.117	.493	-2.21268E6	3.19124E6	-8.72901E6	4.30365E6

Group Statistics

	rvr	N	Mean	Std. Deviation	Std. Error Mean
preALT	achieved	112	66.8875	45.86908	4.33422
	not achieved	23	51.0870	29.17488	6.08338

Independent Samples Test

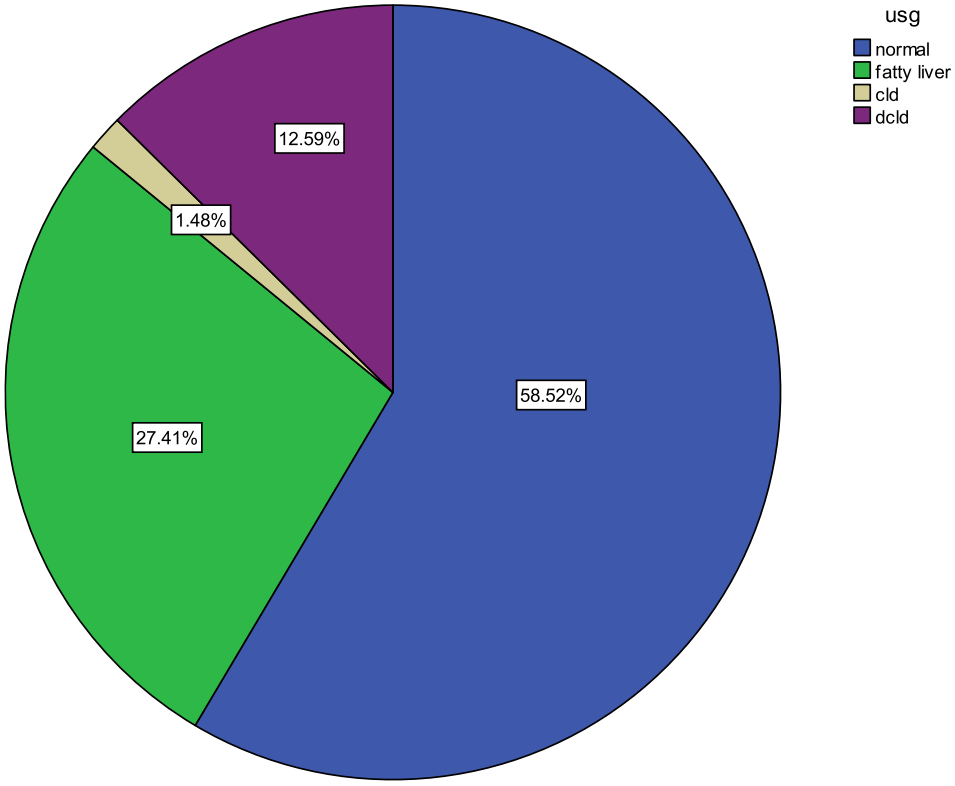
		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
preALT	Equal variances assumed	.890	.347	1.585	133	.115	15.80054	9.97007	-3.91987	35.52095
	Equal variances not assumed			2.115	47.574	.040	15.80054	7.46947	.77869	30.82240

	rvr	N	Mean Rank	Sum of Ranks
usg	achieved	112	65.55	7341.50
	not achieved	23	79.93	1838.50
	Total	135		

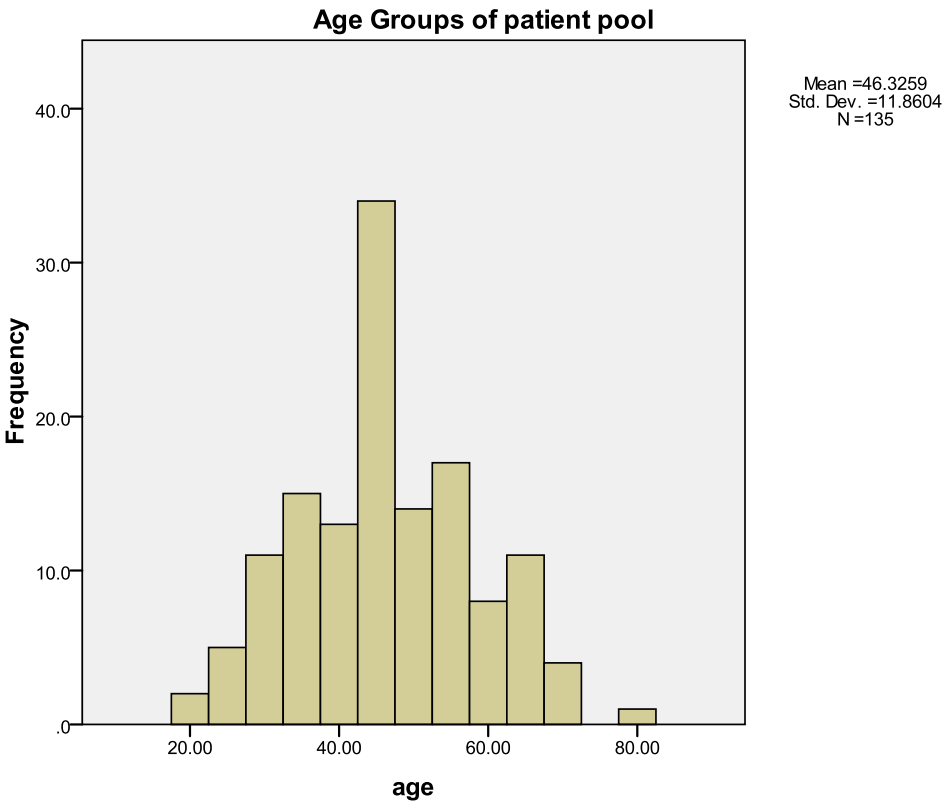
Test Statistics[a]

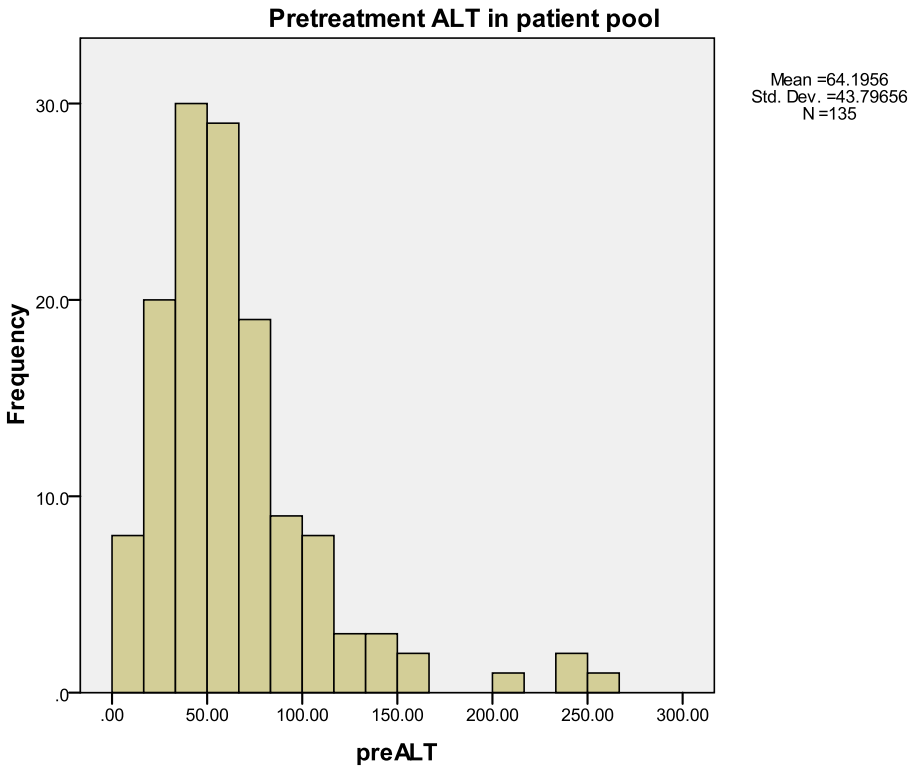
	usg
Mann-Whitney U	1013.500
Wilcoxon W	7341.500
Z	-1.822
Asymp. Sig. (2-tailed)	.068

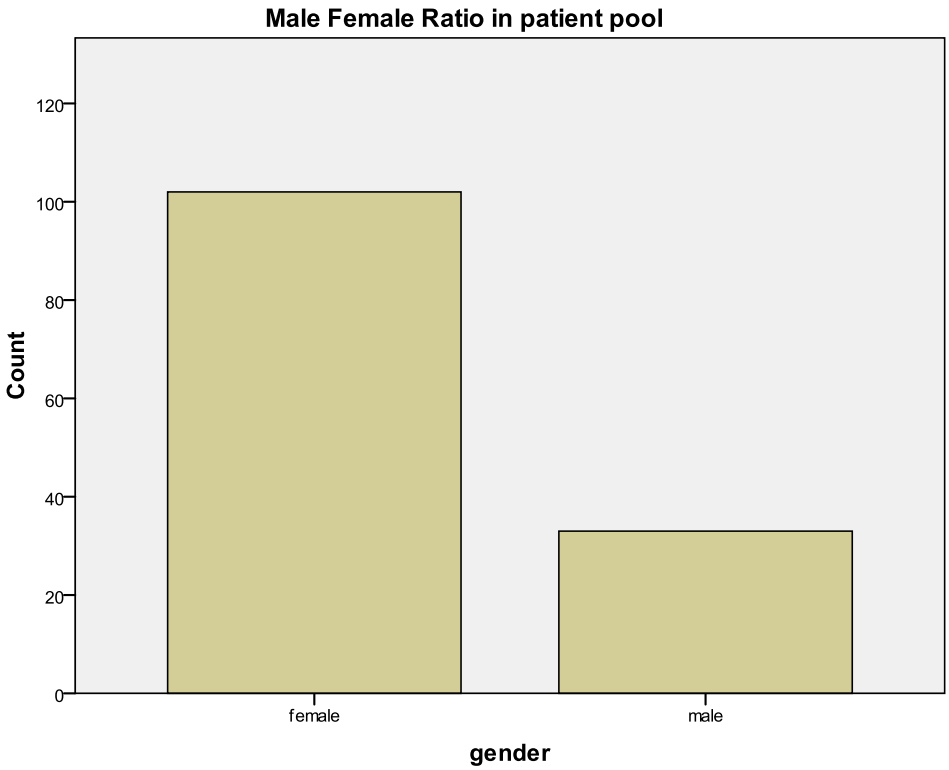
a. Grouping Variable: rvr

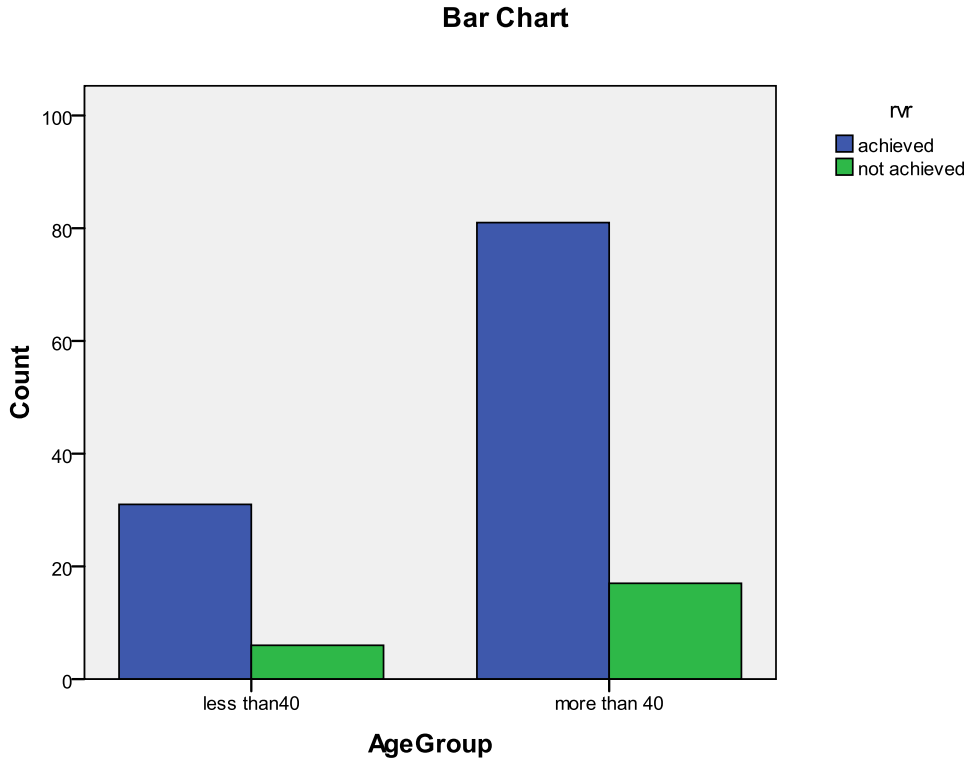


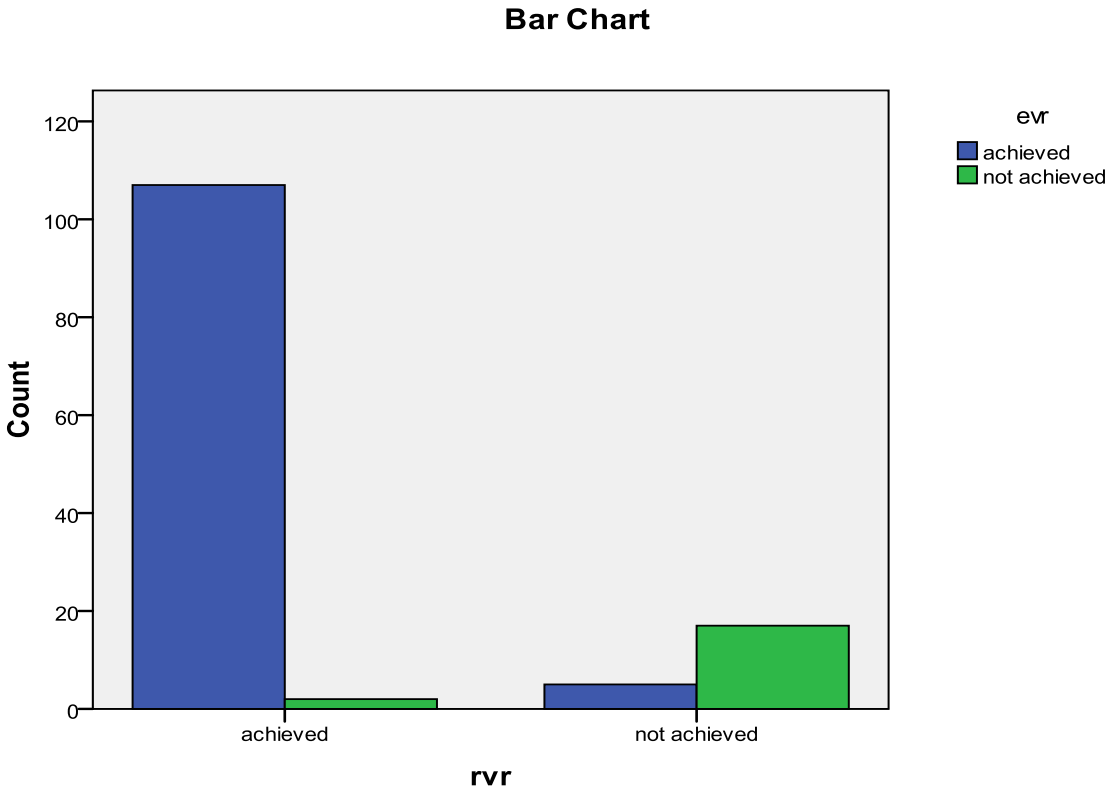
ultrasound liver findings in patient pool


Age Groups of patient pool
Mean =46.3259
Std. Dev. =11.8604
N =135
Frequency
40.0
30.0
20.0
10.0
.0
20.00
40.00
60.00
80.00
age


Pretreatment ALT in patient pool
Mean =64.1956
Std. Dev. =43.79656
N =135
Frequency
30.0
20.0
10.0
.0
.00
50.00
100.00
150.00
200.00
250.00
300.00
preALT


Male Female Ratio in patient pool
120
100
80
60
40
20
0
Count
female
male
gender


Bar Chart
100
80
60
40
20
0
Count
less than40
more than 40
AgeGroup
rvr
achieved
not achieved



DISCUSSION:

With the introduction of direct acting antivirals there has been a paradigm shift in the treatment of Hepatitis C from injectables to oral drugs; with fewer side effects, higher rates of sustained response and lower incidence of relapse. Sofosbuvir has been a key player in this pharmacologic revolution. Many significant studies have been carried out internationally assessing the effectiveness of Sofosbuvir for different genotypes but data is relatively scarce for genotype 3 as it is more prevalent in eastern countries. Hepatitis is rampant in the third world, prominently in Pakistan, where government is now making efforts to provide expensive oral anti viral drugs readily available at subsidized rates or free of cost to patients, which makes it all the more important to follow the response of these drugs and patient outcome.

In the study population, which was reflective of disease epidemiology in Rawalpindi, Pakistan: females were more affected than males, average age was 40 years and majority of patients presented early in the disease course with normal liver findings on ultrasound, followed by the non specific findings of fatty liver. This study showed excellent outcome for treatment naïve genotype 3 patients receiving dual therapy for 24 weeks in terms of achievement of RVR and ETR. However as this was a retrospective study, candidates were selected on the basis of fulfillment of inclusion criteria and data for all patients who met the exclusion criteria were also omitted. Hence this brought down the sample size to 135 and data on SVR was not available for this group due to loss of follow up or because 12 weeks had not been completed post treatment at the time of data collection or because of lack of affordability as PCR is a costly test and most patients presenting to liver clinic BBH belong to lower socioeconomic group, receiving medicine free of cost. It is recommended that further studies be carried out wherein attainment of SVR is also documented and relationship between RVR and SVR can be commented on; and recommendation be given about the possibility of shortening duration of treatment to less than 24 weeks in patients achieving RVR and ETR. RVR predicted SVR both in GT2 and GT3 in several studies conducted internationally[6,7] however a research conducted in India[8] in 2015 concluded that achievement of RVR has no relation with the achievement of SVR12; it does not make any difference in treatment duration or regimen and is

only relevant for checking patient compliance. It was recommended that RVR could even be omitted to improve cost effectiveness of treatment .

This study could not find an association between age, gender, pretreatment viral load and ALT or pretreatment CBC indices and viral clearance. But this could be because the study was limited by its small sample size and therefore further studies can be carried out to establish conclusively an association, or lack thereof, between these variables and RVR/ ETR/ SVR. A study conducted in Europe[2] in 2013 observed after a multivariate regression analysis of results, four possible predictors of a sustained virological response among patients with genotype 3 infection: female sex, absence of cirrhosis, younger age, and a low viral load at baseline. However another study conducted in Pakistan Holy family hospital Rawalpindi[5] from 2014 to 2016 with a sample size of 502 also found no statistically significant association between these variables and viral clearance except for gender; attainment of SVR was slightly more in females(p value=0.03). The lack of association with age as suggested by this study and the aforementioned offers a promising outlook for patients of all ages. This study found that advancing liver disease, as evidenced by progressively worsening ultrasound findings, had no association with RVR/ETR so it does not adversely impact response to dual therapy. This appears promising for hepatitis C patients with liver fibrosis, cirrhosis or decompensated liver disease. The HFH study[5] also had previously shown a good response in cirrhotics with a RVR of about 90% and SVR12 of 86.3% respectively.

LIMITATIONS:

This study was limited in that data on treatment experienced patients and on relapsers was not included in the study, hence it is not possible to comment on response of dual therapy in these patients.

CONCLUSION:

In our study population, which was reflective of disease epidemiology in Rawalpindi, Pakistan: females were more affected than males, average age was approximately 46 ±11 years and majority of patients presented early in the disease course with normal liver findings on ultrasound, followed by the non specific findings of fatty liver. Sofosbuvir plus Ribavirin combination therapy has shown to be very effective and successful in achievement of viral clearance with little or no resistance in genotype 3 infected patients in our study population regardless of the age, gender and other variable differences. 83% of the patients achieved RVR at completion of four weeks of treatment while 85.5% had attained ETR at end of therapy. Patients who achieved RVR were more likely to go on to achieve ETR.

CONFLICT OF INTEREST: none

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