ABENHA MEDICAL JOURNAL bmj
Print ISSN 1110-208X
Online ISSN 2357-0016

Original article

Comparative Study between Responders and Non Responders among Patients Treated for Hepatitis C virus Infection

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Received: 5 February 2022

Accepted: 6 June 2022

Abstract

Background: Infection with the hepatitis C virus is a public health problem due to its prevalence, morbidity and mortality. In spite of the high rate of SVR to treatment by DAAS, still failure to respond to treatment is a problem facing and delaying the achievement of HCV eradication. Identifying predictors of HCV treatment failure prior to the initiation of therapy is important in recognizing high-risk patients and alerting clinicians as to whether they should further intervene to address potential barriers. **Methods:** This retrospective cohort study was carried out from April 2016 to October 2018. The present study was conducted on 300 cases, 150 received SOF-DAC and 150 cases received SOF-DAC-RBV according to guidelines provided by Egyptian National HCV Control Program guidelines. **Results**: It was found that among all studied cases, non-response was significantly associated with older age, higher BMI and male gender ($p<0.001$, <0.001, $=0.002$ respectively). Non-response was significantly associated with presence of DM (25% versus 15.7%; $p=0.041$). As regard laboratory data, non-response was significantly associated with lower platelet count, albumin concentration ($p<0.001$, $=0.043$), high AST, ALT, FBG, HbA1c, FIB4, AST/platelet levels ($p<0.001$ for each) and higher baseline viral load ($p1<0.001$ for each).**Conclusion:** Multiple factors could predict non response to HCV treatment by using DAAs such as older age, male gender, higher BMI, Fib4, AST/platelets and basal viral load but only higher BMI, FIB4, AST/platelets and presence of DM could be considered as independent predictors of non-response.

Keywords; Responders; Hepatitis C virus; HCV; predictors

Abbreviations: SVR (sustained virological response), DAAs (direct acting antivirals), HCV (hepatitis c virus), SOF (sofosbuvir), DAC (daclatasiver), RBV (ribavirin), PCR (polymerase chain reaction), BMI (body mass index),

DM (diabetes mellitus), AST (aspartate transaminase), ALT (alanine transaminase), FBG (fasting blood glucose) and HbA1c (Hemoglobin A1c).

Introduction

Infection with the hepatitis C virus is a public health problem due to its prevalence, morbidity and mortality. It is a cosmopolitan affection with geographical disparities. It affects about 71 million people worldwide, making it one of the leading causes of chronic liver disease (1). There are approximately 399,000 deaths each year due to cirrhosis of viral hepatitis C origin and its complications (2).The prevalence of hepatitis C virus infection in the African region is estimated at about 1% of the population (11 million inhabitants) with a peak frequency in North Africa especially in Egypt (3). Egypt has the highest prevalence rate of HCV in the world (4) making it the most challenging public health problem facing the country.

Studies showed that 14.7% of the Egyptian population carries HCV-antibodies and 10% have an active infection with predominance of genotype 4 (about 93.1 % of cases) (5).In Egypt, the prevalence of HCV antibody was 13% and that of HCV RNA was 7.1% among adult aged from18 to 65 years old while In children, 1-17 years old, HCV antibody and HCV RNA prevalence was 0.48% and 0.26% respectively (6). More than 360000 patients die yearly from HCV. Chronic HCV is the most common cause of cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease (6). Sustained virologic response (SVR) is the most commonly used endpoint in clinical trials in hepatitis C virus treatment as it is more practical than the use of the incidence of HCC or liver-related mortality as an endpoint which is out of practice.

Patients with SVR 12 weeks or more after completing treatment can be considered totally cured. Patients who achieve SVR were approved to have low incidence of liver-related complications in comparison with those failed treatment (7). In-spite of the fact that the success rate of DAAs–based therapy is high, the response rate differs between cirrhotic and non-cirrhotic patients, therefore the presence of cirrhosis still has an impact on the likelihood of sustained virological response (SVR), so the degree of LS in prediction of treatment outcome is an important fact since the failure of treatment limits future treatment option. Thus, the role of liver stiffness (LS) in the prediction of

treatment response with the newly introduced direct-acting antiviral-based therapy isn't widely investigated (8,9). There is high association between chronic hepatitis due to HCV infection and prevalence of type 2 DM. That association is with HCV infection more than other causes of chronic hepatitis (10). Insulin resistance and type 2 DM may develop at any phase of HCV infection and various factors could contribute to that process such as the age, sex, family history, the African-American race, and HIV co-infection (11).

Improvement of blood glucose level following antiviral treatment was significant and the decrease in prevalence of glucose abnormalities was reported. Also, significant improvement of insulin resistance diabetes was only in patients who achieved a SVR and a significant relation between glucose abnormalities development and the absence of SVR (12). Identifying predictors of HCV treatment failure prior to the initiation of therapy is important in recognizing high-risk patients and alerting clinicians as to whether they should further intervene to address potential barriers. These efforts could ultimately provide a tool to guide additional treatment monitoring strategies, personalized interventions, and strategic allocation of resources or additional case management to more closely follow up with at-risk patients and work to avoid treatment failure. Ultimately, identification of predictors for treatment failure could help decrease health care costs for patients and the healthcare system by avoiding necessary retreatment and long-term patient and public health outcomes associated with unattained SVR.

The present study aimed to diagnose and predict possible factors and criteria that lead to failure of response to HCV treatment by using DAAs.

Patients and Methods:

Our study included HCV infected patients who received sofosbuvir & daclatasvir with or without ribavirin as a dual or triple therapy for 3 month according to the recommendations of The Egyptian National Committee for Control of Viral Hepatitis. This retrospective cohort study was conducted in in Banha University Hospital and HCV treatment unit and in Kafr Elshiekh Hepatology Research Centre. It was carried out from April 2016 to October 2018. Successful treatment is considered when PCR for HCV becomes negative at 12 weeks after the end of treatment.

The study protocol was approved by the ethical committee of Benha faculty of Medicine, Benha University. An informed written consent was obtained from all patients participating in this study after explaining the study measures in details.

The present study was conducted on 300 cases, 150 received SOF-DAC and 150 cases received SOF-DAC-RBV. Among those received SOF-DAC, 130 were non diabetics, 117 were responders and 13 were non responders. In addition, there were 20 diabetics, 17 were responders and 3 were non responders. Among those received SOF-DAC-RBV, 120 were non diabetics, 109 were responders and 11 were non responders. In addition there were 30 diabetics, 25 were responders and 5 were non responders. HCV patients known to have HIV infection, HBV infection, advanced liver cirrhosis (*child score above 6)*, renal impairment, severe cardiac disease, malignancy, post-transplant , those receiving any medications that may interfere with virological response and patients who develop complications during treatment were excluded from the study.

The exclusion criteria included the following: patients younger than 18 or older than 70 years old, females on oral contraception or during pregnancy, presence of Hepatocellular carcinoma or other malignancy. The presence of elevated total serum bilirubin more than 3mg/dl, decreased serum albumin to less than 2.8 g/dl, increased INR to more than 1.7 and Platelet count less than 50,000/mm. Finally, renal impairment and Non-compliance to treatment also rule out patients from our study.

All patients included in the study were subjected to: Full history taking, Full clinical examination, Measurement of BMI (body mass index), Base line ECG, basic Laboratory investigations (Routine investigations for treatment of HCV) including complete blood picture, complete liver function tests (s albumin, total bilirubin direct bilirubin, SGOT, SGPT, AFP and INR), serum creatinine, fasting blood glucose and HBsAg at the start of the study. PCR for HCV was assessed at the start of the study (before starting treatment) and at 12 weeks after treatment (24 weeks from the start of the study) to asses response to treatment (1), FIB-4 score (13) and APRI score (14) was done.

Pelvi - abdominal ultrasonography was used to assess;

i. Liver: size, texture, border, reflectivity, homogeneity, periportal thickening, hepatic veins and pattern.

ii. Portal vein: diameter, patency, direction of flow, respiratory variation and velocity by color Doppler assessment.

iii. Spleen: size, splenic vein diameter, collaterals.

iv. Presence of ascites and internal echoes.

v. Lymph nodes and extrahepatic spread.

vi. Portal hypertension and superior mesenteric vein patency.

Statistical analysis

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 20 to obtain: Descriptive data: Descriptive statistics were calculated for the data in the form of: Mean, standard deviation for quantitative data. Frequency and distribution for qualitative data. Analytical statistics: To compare two groups with categorical variables, Chi-Square test (or Fisher's exact test) were used. To compare two groups with normally distributed quantitative variables, independent samples (student's) t-test was used and Mann-Whitney U-test was used if the data were abnormally distributed. **Regression analysis**: Logistic regression analysis was used for prediction of risk factors, using generalized linear models. **An odds ratio (OR)** is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. OR=1 Exposure does not affect odds of outcome. OR >1 Exposure associated with higher odds (risk) of outcome. OR<1 Exposure associated with lower odds of outcome (protective). The 95 % confidence interval (CI) is used to estimate the precision of the OR. A large CI indicates a low level of precision of the OR, whereas a small CI indicates a higher precision of the OR.

Results:

No significant differences were found between those received SOF-DAC and SOF-DAC-RBV treatments regarding age, gender and BMI ($p>0.05$ for each). Table 1

No significant differences were found between those received SOF-DAC and SOF-DAC-RBV treatments regarding presence or absence of DM (p>0.05).Those received SOF-DAC-RBV had significantly lower platelets count, higher Fib4 and AST/platelet (p<0.001 for each). Otherwise, no significant differences were found regarding laboratory data between those received SOF-DAC and those received SOF-DAC-RBV (p>0.05 for each). Among those received SOF-DAC, non-response was significantly associated with older age, higher BMI and male gender (p<0.001, <0.001, =0.004 respectively).

Again non response was none significantly associated with higher frequency of DM, but did not reach significant level (p>0.05). Regarding laboratory data among the same group nonresponse was significantly associated with lower platelet count (p<0.001), high AST, ALT, FBG, HbA1c, FIB4, AST/platelet levels (p<0.00, p<0.001, =0.002, p<0.001, p<0.01, p<0.001 respectively) and finally with higher baseline viral load (p1<0.001). Among those received SOF-DAC-RBV, non-response was significantly associated with higher BMI (p<0.001). In addition, non-response was marginally significantly associated with older age (p=0.052). While , it was non significantly associated with higher frequency of DM, but did not reach significant level (p>0.05).Regarding laboratory data among the same group (those received SOF-DAC-RBV), non-response was significantly associated with lower platelet count, albumin concentration (p<0.001, =0.035), high AST, ALT, FBG, HbA1c, FIB4, AST/platelet levels (p=0.002, p=0.001, <0.001, p<0.001, p<0.01, p<0.001 respectively) and finally with higher baseline viral load (p1=0.004). table 2

Regression analysis was conducted for prediction of non-response using age, gender, BMI, DM, FIB4, AST/platelets, albumin, basal viral load, type of treatment as covariates. Older age, male gender, higher BMI, FIB4, AST/platelets, basal viral load were associated with non-response in Univariable analysis. However, multivariable analysis was conducted on significant covariates in Univariable analysis, which revealed that only higher BMI, FIB4, AST/platelets and presence of DM were considered as independent predictors of non-response. table 3&4

Table (1). Comparison of age, gender and BMI between responders and non-responders

		SOF-DAC					SOF-DAC-RBV				
		Responders		**Non responders**		***p***	**Responders**		**Non responders**		***p***
		n=134		**n=16**			**n=134**		**n=16**		
Age (years)	**Mean ±SD**	46.9	±8.6	58.5	±4.2	**<0.001**	51.6	±7.9	55.7	±6.5	0.052
Males	**N, %**	66	49.3%	14	87.5%	**0.004**	83	83	13	81.3%	0.128
Females	**N, %**	68	50.7%	2	12.5%		51	51	3	18.8%	
BMI (kg/m^2)	**Mean ±SD**	25.8	±0.7	29.8	±0.7	**<0.001**	25.1	±0.8	28.4	±0.6	**<0.001**
Non DM	**N, %**	117	87.3%	13	81.3%	0.450	109	81.3%	11	68.8%	0.317
DM	**N, %**	17	12.7%	3	18.8%		25	18.7%	5	31.3%	

DM (diabetes mellitus), BMI (body mass index), SOF(sofosbuvir), DAC(daclatasvir) and RBV(ribavirin).

Table (2). Comparison of laboratory parameters between responders and non-responders.

	SOF-DAC					SOF-DAC-RBV				
	Responders		**Non responders**			**Responders**		**Non responders**		
	n=134		**n=16**		***p '***	**n=134**		**n=16**		***p '***
	mean	**SD**	**mean**	**SD**		**mean**	**SD**	**mean**	**SD**	
platelet (X10^9/L)	184.4	21.0	157	5.6	**<0.001**	144.9	29.2	101.6	32.5	**<0.001**
ALT (U/L)	41.8	5.2	54.1	10.2	**<0.001**	41.8	4.6	47.9	5.6	**0.002**
AST (U/L)	45.6	6.7	57.6	6.2	**<0.001**	46.5	4.8	51.1	8.4	**0.001**
Albumin (g/dL)	4	0.2	3.8	0.1	0.138	3.7	0.3	3.2	0.3	**0.035**
bilirubin (mg/dL)	0.9	0.1	1	0.1	0.521	1.2	0.3	1.4	0.3	0.243
AFP (ng/mL)	8.6	1.3	8.2	1.2	0.179	8.5	1.6	8.3	1.1	0.600
creatinine (mg/dL)	0.9	0.1	1	0.1	0.359	1	0.1	1.1	0.1	0.251
FBG (mg/dL)	90.2	8.5	99.6	23.7	**0.002**	92	9.2	103	20.5	**<0.001**
HbA1c (%)	7	0.2	8	0.1	**<0.001**	7	0.2	7.7	0.2	**<0.001**
INR	0.9	0.1	1.1	0.1	0.241	1.1	0.1	1	0.1	**0.163**
FIB4	1.8	0.4	2.8	0.2	**<0.001**	2.6	0.6	4.4	1	**<0.001**
AST/platelet	0.6	0.1	0.9	0.1	**<0.001**	0.8	0.2	1.4	0.5	**<0.001**
	median	**Range**	**median**	**range**		**median**	**range**	**median**	**range**	
Baseline PCR (IU/ml)	9.05X10^5	1.46X10^5-8.75X10^6	2.50X10^6	1.76X10^6-8.85X10^6	**<0.001**	1.55X10^6	1.28 X10^5-9.78X 10^6	2.98X10^6	1.23X10^6-5.61X10^6	**0.004**

SOF (sofosbuvir), DAC (daclatasvir), RBV (ribavirin), AST (aspartate transaminases), ALT (alanine transaminases), PCR (polymerase chain reaction), INR (international normalized ratio), AFP (alpha fetoprotein), FBG (fasting blood glucose) and HbA1c (haemoglobin A1c).

Table (3-4). Regression analysis for prediction of non-response to treatment

	Univariable				Multivariable			
	P	**OR**	**95%**	CI	***P***	**OR**	**95%**	CI
Age	<0.001	1.075	1.038	1.114	0.077	1.124	0.988	1.279
Male gender	0.007	1.893	1.190	3.009	0.916	1.053	0.404	2.745
BMI	<0.001	4.896	3.087	7.764	0.026	1.395	1.072	2.176
DM	0.027	1.495	1.129	2.404	0.045	1.483	1.298	2.165
Fib4	<0.001	3.244	2.205	4.773	<0.001	5.851	2.948	11.614
AST/platelet	0.015	1.602	1.097	2.339	0.030	716.357	1.895	3.578
Albumin	0.893	1.044	0.562	1.938				
Baseline viral load	<0.001	1.015	1.003	1.043	0.343	1.018	0.994	1.037
SOF-DAC-RBV versus SOF-DAC	0.484	1.153	0.774	1.717				

SOF (sofosbuvir), DAC (daclatasvir), RBV (ribavirin),AST (aspartate transaminases), DM (diabetes mellitus) and BMI (body mass index).

Discussion

Among all studied cases of the present study, non-response was significantly associated with older age, higher BMI and male gender (p<0.001, <0.001, =0.002 respectively).Among two main subgroups included in this study, those received SOF-DAC, non-response was significantly associated with older age, higher BMI and male gender (p<0.001, <0.001, =0.004 respectively).On the other hand those received SOF-DAC-RBV, non-response was significantly associated with higher BMI (p<0.001) and marginally significantly associated with older age (p=0.052). Among non-diabetics receiving SOF-DAC, non-response was significantly associated with older age, higher BMI and male gender (p<0.001, <0.001, =0.012 respectively). While non- diabetics receiving SOF-DAC-RBV, non-response was significantly associated with higher BMI (p<0.001) only. Among diabetics receiving SOF-DAC, non-

response was significantly associated with higher BMI ($p<0.001$). Also, diabetics receiving SOF-DAC-RBV, non-response was significantly associated with higher BMI ($p<0.001$). Another study revealed that male gender, being a difficult-to-treat patient and previous interferon therapy were significant predictors of non-response in treatment groups (15).

The present study agrees with the above study in spite using DAAs. It was concluded that older age is one of independent risk factors of treatment non-response (16) and this agree with our results in spite that their study was conducted on patient with child B. While another study agree with the present results in that older age (above 50 years) are associated with non-response, they found that female sex is associated with non-response in difference from the present results in which non response was associated with male sex (17).

The present results support those who found that male sex, previous treatment and higher BMI were the independent predictors of non-response in HCV G4 patients (18). The present study agrees with these results especially as this study was conducted in Egypt in which HCV G4 is the predominant genotype. A recent study found that BMI ≥30 kg·m² affected negatively the response to antiviral treatment (19). This fact could be due to a lower bioavailability of RBV because there is more fatty tissue, as well as the chronic inflammatory state that the patients present associated with the release of cytokines and the development of more advanced steatosis and fibrosis. However, it is important to mention that the implication of this parameter in the achievement of SVR is controversial: in regimens based on PEG and RBV, A BMI ≥30 kg/m² is associated with worse SVR rates (20).

The present study agreed with the previous two studies in that higher BMI could affect treatment outcome and leads to non-response among HCV patients. On the other hand, a new study found that in DAA-based treatments it seems that BMI is not a factor that influences the outcome of the therapy (21) and this is not in agreement with the present study. As regards the effect of DM on response to treatment of HCV by DAAs, the present study found the following results. Among all studied cases, non-response was significantly associated with presence of DM (25% versus 15.7%; $p=0.041$). Among those received SOF-DAC, non-response was higher among diabetic patients (18.8%) versus (12.7%) in non-diabetic, but statistically non-response was

not significantly associated with higher frequency of DM (p>0.05). Again among those received SOF-DAC-RBV, non-response was higher among diabetic patients (31.3%) versus (18.7%) in non-diabetic, but statistically non-response was non-significantly associated with higher frequency of DM (p>0.05). This result agreed with the study which showed that type 2 diabetes mellitus and insulin resistance (IR) had no effect on virological response to telaprevir-based regimens or danoprevir monotherapy (22).

Diabetes mellitus has been another predictive factor of non-response found in our work. Before DAAs arrival, both diabetes and high blood glucose levels were positioned as predictive factors of non-response (18). As seen in our study worse response rates continued to be observed in diabetic patients (23) as well as those with high blood glucose levels. The above two results agree with results of the present study as regard the whole study population.

On the other hand, it has been shown that the presence of DM does not influence the outcome of antiviral treatments (24) and this disagree with results of the present study as regard the whole study population and agree with results regarding the two main groups of the study. According to the above mentioned results and studies, the effect of DM on response to treatment is not well established and need further studies.

As regards laboratory investigations of patients in the present study, it was found that among all studied cases, non-response was significantly associated with lower platelet count, albumin concentration (p<0.001, =0.043), high AST, ALT, FBG, HbA1c. Among the total cases who received SOF-DAC, non-response was significantly associated with lower platelet count (p<0.001), high AST, ALT, FBG, HbA1c. On further sub-grouping, the present study found that among non-diabetics receiving SOF-DAC, non-response was significantly associated with lower platelet count (p<0.001), high AST, ALT. while among diabetics receiving SOF-DAC, non-response was significantly associated with lower platelet count (p=0.016), high AST, ALT, FBG, HA1C. Among those received SOF-DAC-RBV, non-response was significantly associated with lower platelet count, albumin concentration (p<0.001, =0.035), high AST, ALT, FBG, HbA1c.

On further subgrouping, the present study found that among non-diabetics receiving SOF-DAC-RBV, non-response was

significantly associated with lower platelet count, albumin level ($p<0.001$, $=0.018$ respectively), high AST, ALT. While among diabetics receiving SOF-DAC-RBV, non-response was significantly associated with lower platelet count, albumin level ($p<0.001$, $=0.013$ respectively), high AST, ALT, FBG, HbA1c.

A more recent study aimed to identify simple factors associated with non-response to DAAs using routine pretreatment patient work- up showed that non-responders had significantly higher AST, AFP and INR and a significantly lower albumin level and platelet count (18)**.** Results of the present study agree with the above finding except that non-significant relation of AFP and INR to non-response. Higher platelet count has acted as a predictive factor for SVR: patients who obtain SVR present a higher level of platelets than those who do not respond to the treatment (19). This finding agreed with the present results which found that low platelet count is associated with non-response. It was found that the baseline AFP was significantly elevated in non-responders when compared to SVR12 achievers (25).

This is in accordance with another Egyptian study noting that the non-responder group had significantly higher frequency of cases with elevated AFP (26). The above two studies are not in agreement with this study in which AFP is non-significantly associated with non-response. This study found that among diabetic patients, poor diabetic control evidenced by high FBG and HbA1c was significantly associated with non-response to DAAs. This finding point to further study the effect of uncontrolled DM on HCV eradication and achievement of SVR as most of the studies before estimate the effect of HCV eradication on insulin resistance and control of DM. The present study found that non response was significantly associated with higher baseline viral load among all groups included in this work. This agree with Multivariate analyses from multiple studies regarding different populations have suggested that pretreatment viral load, irrespective of the HCV genotype, is an independent viral factor to predict the SVR (27).

It was provided that the baseline viral load 8×10^5 IU/ml was a significant factor of lower rate of SVR24 (83.1% vs. 93.9%) in patients receiving 24 weeks of daclatasvir and asunaprevir therapy (28) and this agree with the present study. A recent study concluded that high viral load (10^7 IU/ml) is associated with virologic failure in non-cirrhotic patients receiving 8-week GIE/PIB

therapy. Again the recent study agreed with this finding (29).

Conclusion

Multiple factors could predict nonresponse to HCV treatment by using DAAs such as older age, male gender, higher BMI, FIB4, AST/platelets and basal viral load but only higher BMI, FIB4, AST/platelets and presence of DM could be considered as independent predictors of non-response.

References

1. Pawlotsky J-M, Negro F, Aghemo A, Berenguer M, Dalgard O, Dusheiko G, et al. EASL recommendations on treatment of hepatitis C 2018. J Hepatol. 2018;69(2):461–511.

2. WHO. Global hepatitis report 2017. World Health Organization; 2017.

3. Hashim AEM, Kandeel HT, Hendy OM, El-Mola K, El-Raey FM, Attia MSM. Effect of new direct-acting antiviral drugs on insulin resistance and glycemic control after treatment of chronic hepatitis C virus infection in type 2 diabetic patients. Al-Azhar Assiut Med J. 2017;15(4):187.

4. Razavi H, Waked I, Sarrazin C, Myers RP, Idilman R, Calinas F, et al. The present and future disease burden of hepatitis C virus (HCV) infection with today's treatment paradigm. J Viral Hepat. 2014;21:34–59.

5. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014;61(1):S45–57.

6. Mohamed AA, Elbedewy TA, El-Serafy M, El-Toukhy N, Ahmed W, Ali El Din Z. Hepatitis C virus: a global view. World J Hepatol 7: 2676–2680. 2015.

7. Burgess S V, Hussaini T, Yoshida EM. Concordance of sustained virologic response at weeks 4, 12 and 24 post-treatment of hepatitis c in the era of new oral direct-acting antivirals: a concise review. Ann Hepatol. 2016;15(2):154–9.

8. Arias A, Aguilera A, Soriano V, Benítez-Gutiérrez L, Lledó G, Navarro D, et al. Rate and predictors of treatment failure to all-oral HCV regimens outside clinical trials. Antivir Ther. 2017;22(4):307–12.

9. Neukam K, Morano-Amado LE, Rivero-Juárez A, Macías J, Granados R, Romero-Palacios A, et al. Liver stiffness predicts the response to direct-acting antiviral-based therapy against chronic hepatitis C in cirrhotic patients. Eur J Clin Microbiol Infect Dis. 2017;36(5):853–61.

10. Naing C, Mak JW, Ahmed SI, Maung M. Relationship between hepatitis C virus infection and type 2 diabetes mellitus: meta-analysis. World J Gastroenterol WJG. 2012;18(14):1642.

11. Elhawary EI, Mahmoud GF, El-Daly MA, Mekky FA, Esmat GG, Abdel-Hamid M. Association of HCV with diabetes mellitus: an Egyptian case-control study. Virol J. 2011;8(1):1–9.

12. Thompson AJ, Patel K, Chuang W-L, Lawitz EJ, Rodriguez-Torres M, Rustgi VK, et al. Viral clearance is associated with improved insulin resistance in genotype 1 chronic hepatitis C but not genotype 2/3. Gut. 2012;61(1):128–34.

13. Kim BK, Kim DY, Park JY, Ahn SH, Chon CY, Kim JK, et al. Validation of FIB-4 and comparison with other simple noninvasive indices for predicting liver fibrosis and cirrhosis in hepatitis B virus-infected patients. Liver Int. 2010;30(4):546–53.

14. Yen Y-H, Kuo F-Y, Kee K-M, Chang K-C, Tsai M-C, Hu T-H, et al. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. PLoS One. 2018;13(6):e0199760.

15. Elsharkawy A, Eletreby R, Fouad R, Soliman Z, Abdallah M, Negm M, et al. Impact of different sofosbuvir based treatment regimens on the biochemical profile of chronic hepatitis C genotype 4 patients. Expert Rev Gastroenterol Hepatol. 2017;11(8):773–8.

16. Ahmed OA, Elsebaey MA, Fouad MHA, Elashry H, Elshafie AI, Elhadidy AA, et al. Outcomes and predictors of treatment response with sofosbuvir plus daclatasvir with or without ribavirin in Egyptian patients with genotype 4 hepatitis C virus infection. Infect Drug Resist. 2018;11:441.

17. Kouamé DH, Doffou SA, Anzouan-Kacou HK, Tchana YM, Bangoura AD, Alassan MK, et al. Predictors of Direct-Acting Antivirals Failure in Patients with Chronic Hepatitis C Virus in Ivory Coast: About 5 Cases. Open J Gastroenterol. 2019;9(10):193.

18. Shousha HI, Saad Y, Saleh DA, Dabes H, Alserafy M, ElShazly Y, et al. Simple predictors of nonresponse to direct-acting antivirals in chronic hepatitis C patients. Eur J Gastroenterol Hepatol. 2020;32(8):1017–22.

19. Cárdaba-García ME, Abad-Lecha E, Calleja-Hernández MÁ. Effectiveness of direct-acting antiviral drugs against hepatitis C virus: predictive factors of response to the treatment. Libyan J Med. 2021;16(1).

20. Jain A, Kalra BS, Srivastava S, Chawla S. Effect of sofosbuvir and daclatasvir on lipid profile, glycemic control and quality of life index in chronic hepatitis C, genotype 3 patients. Indian J Gastroenterol. 2019;38(1):39–43.

21. De Pace V, Morelli MC, Ravaioli M, Maggi F, Galli S, Vero V, et al. Efficacy, safety, and predictors of direct acting antivirals in hepatitis C virus patients with heterogeneous liver diseases. New Microbiol. 2019;42(4):189–96.

22. Serfaty L, Forns X, Goeser T, Ferenci P, Nevens F, Carosi G, et al. Insulin resistance and response to telaprevir plus peginterferon α and ribavirin in treatment-naive patients infected with HCV genotype 1. Gut. 2012;61(10):1473–80.

23. Aziz H, Aziz M, Gill ML. Analysis of host and viral-related factors associated to direct acting antiviral response in hepatitis C virus patients. Viral Immunol. 2018;31(3):256–63.

24. Colussi G, Donnini D, Brizzi RF, Maier S, Valenti L, Catena C, et al. Sustained virologic response to direct-acting antiviral agents predicts better outcomes in hepatitis C virus-infected patients: A retrospective study. World J Gastroenterol. 2019;25(40):6094.

25. Dina E, Nasser M, Sarah E, Mahmoud A, Islam M, Waleed E, et al. Pretreatment serum alpha fetoprotein and its relation to sustained virologic response in patients with chronic HCV infection treated with direct-acting antiviral therapy. Med J Viral Hepat. 2020;4(2):69–73.

26. Nagaty A, Abd El-Wahab EW. Real-life results of sofosbuvir based therapy in chronic hepatitis C-naïve and-experienced patients in Egypt. PLoS One. 2017;12(10):e0184654.

27. Jacobson IM, Brown Jr RS, Freilich B, Afdhal N, Kwo PY, Santoro J, et al. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. Hepatology. 2007;46(4):971–81.

28. Ueno T, Osawa M, Imai Y, Ishikawa H, Garimella T. Exposure-Response (Efficacy) Analysis of Daclatasvir and Asunaprevir in Japanese Patients With Hepatitis C Virus Infection. J Clin Pharmacol. 2018;58(11):1479–88.

29. Chen W-M, Wei K-L, Tung S-Y, Shen C-H, Chang T-S, Yen C-W, et al. High viral load predicts virologic failure in chronic genotype 2 hepatitis C virus-infected patients receiving glecaprevir/pibrentasvir therapy. J Formos Med Assoc. 2020;119(11):1593–600.

To cite this article: Amr M. Elhammadi, Dina H. Ziada , Wael M. Farrag. Comparative Study between Responders and Non Responders among Patients Treated for Hepatitis C virus Infection. BMFJ 2022;39(2):589-601. DOI: 10.21608/bmfj.2022.120253.1543