Predictors of Nonresponse to Direct Acting Antiviral Therapy in Chronic Hepatitis C Patients

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***Received:** 13-09-2024, **reversed:**15-10-2024, **Accepted:** 23-10-2024, **Published:** 08-11-2024*

ABSTRACT

Background: Identifying predictors of the hepatitis C virus (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. **Objective:** to diagnose and predict possible factors and criteria that lead to failure of response to HCV treatment by using direct-acting antivirals (DAAs). **Methods:** This retrospective study was conducted on 245 Egyptian patients with chronic genotype 4 HCV included according to The Egyptian National Committee for Control of Viral Hepatitis (NCCVH) Guidelines. **Results:** A total of 83.7% of all patients achieved SVR12. Non-response was significantly associated with older age, higher body weight and DM. Non-response was significantly associated with presence of liver cirrhosis. As regard laboratory data, non-response was significantly associated with thrombocytopenia, elevated transaminases, higher AFP and higher FIB-4. **Conclusion:** Routine pre-treatment work up for HCV (genotype 4) patients receiving DAAs can help in prediction of non-response.

Keywords: Direct-Acting Antiviral Therapy; Chronic Hepatitis C; Treatment Failure

Introduction

Chronic hepatitis C virus (HCV) infection remains a significant global health burden, affecting an estimated 58 million people worldwide and resulting in nearly 300,000 deaths annually due to liver-related complications such as cirrhosis and hepatocellular carcinoma **(1)**. The advent of direct-acting antiviral (DAA) therapy has revolutionized the treatment of HCV, offering cure rates exceeding 95% across most genotypes with shorter treatment durations and fewer side effects compared to interferon-based regimens **(2,3)**.

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 **(3,4)**. 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 **(5)**.

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:

This retrospective study was carried out in Gastroenterology and Hepatology unit of Internal Medicine department, Faculty of Medicine, Zagazig University Hospitals. A total number of 245 patients with chronic HCV infection were included after fulfillment of the inclusion and exclusion

criteria according to The National Committee for Control of Viral Hepatitis (NCCVH) Guidelines for the Management of Adult Patients with HCV Infection August 2020.

Approval was taken from the research ethical commitee and the institutional review board Faculty of Medicine, Zagazig University. Consent from all patient on participating in the study. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria

Positive HCV RNA within the past 6 months. If the patient has received HCV therapy during that period, a new test should be performed.

Exclusion criteria

Patients manifested liver decompensation (Child's class C and late B cirrhosis) with uncontrolled ascites, history of hepatic encephalopathy, hepatorenal syndrome. Serum albumin less than 2.8 g/dl, total bilirubin more than 3 mg/dl and INR 1.7 or more. Platelets count less than 50,000/mm3. HCC, except six months after receiving a curative intervention, with no evidence of residual activity by dynamic CT or MRI. Extra-hepatic malignancy except after two years of disease-free interval. Also, pregnancy or inability to use effective contraception was excluded.

Precautions before starting treatment

Check HCV treatment history. Ladies in the childbearing period should have a recent negative pregnancy test and should be counseled for effective contraception with the use of ribavirin. Check medications received by the patient especially cardiovascular disease therapy (particularly amiodarone), antipsychotic therapy and statins. Family counselling for the risk of transmission and prevention of infection.

Management of HCV

Patients are categorized into "easy" or "not easy" to treat groups according to pre-treatment tests **(Table 1&2).** Ribavirin cannot be given if the patient's hemoglobin is less than 10 g/dl, in case of depression, or cardiac dysfunction. A hemoglobin of 2 g, or less than 10 g/dl necessitates intervention either by dose reduction, possible use of erythropoietin or possible discontinuation.

Table (1): Management of HCV treatment-naïve patients

Criteria	**Easy to treat**	**Not easy to treat group**
	● Total serum bilirubin ≤ 1.2 mg/dl. ● Serum albumin ≥ 3.5 g/dl. ● INR ≤ 1.2. ● Platelets count ≥ 150,000/mm3.	●Total serum bilirubin > 1.2 mg/dl. ● Serum albumin < 3.5 g/dl. ● INR > 1.2. ● Platelets count < 150,000/mm3.
Treatment regimen	• SOF + DCV for 12 weeks. • SOF + LDV for 12 weeks. • SOF + SIM for 12 weeks.	● SOF + DCV + RBV* for 12 weeks. ● SOF + DCV for 24 weeks if cases of RBV ineligibility or intolerance.

** Ribavirin dose starts by 600 mg/day and is raised gradually to 1,000 mg/day according to tolerance. DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SIM, simeprevir.*

In patients with chronic kidney disease, Sofosbuvir-containing regimens could be used without dose adjustment in patients with renal disease, including those with an eGFR ≤ 30 ml/min

and those on dialysis. RBV dose adjusted according to eGFR and hemoglobin level: eGFR> 50: 600-1,200 mg daily as tolerated. eGFR 30-50: 400 mg alternating with 200 mg. eGFR< 30, not on dialysis: 200 mg daily to be reduced if not tolerated to 200 mg, 3 times weekly. eGFR< 30, on dialysis: 200 mg, every other day given on dialysis day, 4 hours before dialysis. Should be discontinued if hemoglobin level declines by more than 2 g/dl despite the use of erythropoietin.

Table (2): Management of HCV treatment-experienced patients

Previous Regimen	Child-Pugh class A	Child-Pugh class B
●IFN + RBV. ● INF+ SOF + RBV. ● SOF + RBV. ● SOF + SIM ± RBV. ● OBV/ PTV/r + RBV. ● SOF + DCV for 12 weeks. ● OBV/ PTV/r + SOF ± RBV for 12/24 weeks. ● SOF + SIM +DCV ±RBV for 12 weeks.	SOF + DCV + RBV for 24 weeks. SOF/VEL/VOX for 12 weeks. SOF/VEL/VOX for 12 weeks.	SOF + DCV + RBV for 24 weeks. SOF/VEL + RBV (initial dose 600 mg daily) for 24 weeks. **(Treatment in special centers)**
● SOF/VEL/VOX for 12 weeks. ● SOF/VEL + RBV for 24 weeks.	SOF/VEL/VOX + RBV for 24 weeks.	

DCV, daclatasvir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; VEL, velpatasvir; VOX, voxilaprevir.

Precautions after the end of treatment

Confirmatory PCR test for the SVR should be performed 12 weeks after the end of treatment. Patients with advanced liver fibrosis (FIB4 ≥ 3.25) should be enrolled in the HCC surveillance program using AFP and abdominal ultrasonography every 4 months. HBV vaccination should be initiated if not already received.

Written consents were taken from all patients included in the study. Results and possible adverse effects of the antiviral regimen were explored to all patients who received the therapy.

Clinical assessment

All subjects were subjected to thorough history and full physical examination. According to the work sheet included with special emphasis on history of hepatic encephalopathy, ascites and previous HCV treatment, and previous upper GIT bleeding or endoscopy.

Laboratory parameters were done in the laboratories of Zagazig University hospitals and included: Complete blood picture by automated blood counter. Liver function tests: serum bilirubin (total and direct), serum albumin, serum ALT and AST measured by kinetic method. Renal function tests: serum creatinine. Coagulation profile: PT, PTT and INR. TSH and ANA. Fasting blood sugar, HbA1C. Alpha fetoprotein (AFP). Hbs Ag9-PC IU/mlby Real time test. Ophthalmoscopic Fundus examination and Electrocardiogram.

Radiological investigation including pelvi abdominal Ultrasound, and triphasic Computed Tomography (CT) if HCC is suspected by AFP >100 ng/ml.

Special Investigations:

1- Upper GIT endoscopy: for diagnosis of signs of portal hypertension: Oesphageal varices, gastric varices or portal hypertensive gastropathy.

- ***Oesphageal varices are divided into 4 grades:***

Grade I: Distended veins at the level of the mucosa.
Grade II: Isolated straight varices, into the lumen with no significant narrowing (< 5 mm).
Grade III: Large tortuous varices that cause significant luminal narrowing (> 5 mm).

Grade IV: Almost complete luminal obstruction with signs of high bleeding risk.

- ***Portal hypertensive gastropathy is divided into three grades:***

Grade I: Mild reddening and congested mucosa.
Grade II: Severe redness and a reticular pattern separating the areas of raised edematous mucosa.
Grade III: Point bleeding + grade II.

Diagnosis of liver cirrhosis was done by physical signs, laboratory and ultrasonographic findings and severity of the liver disease was scored according to Child–Pugh's classification **(6)**.

Staging of liver fibrosis by:

1-METAVIR Score: A semiquantitative classifications system consisting of an activity and a fibrosis score is assessed on a five point scale (0= no fibrosis, 1= portal fibrosis without septa, 2= few septa, 3= numerous septa without cirrhosis, 4= cirrhosis). Compared to the Knodell fibrosis score, the Metavir score permits recognition of subtler variation in the degree of fibrosis**.** The activity score was graded according to the intensity of necro-inflammatory lesions (A0= no activity, A1= mild activity, A2= moderate activity, A3= severe activity) **(7).**
2-FIB-4: Non-invasive test which combines standard biochemical values (platelets, ALT, AST) and age, validated in the context of CHC **(8)**. FIB-4 index is calculated according to the following formula**:**

$$\text{FIB-4} = \frac{\text{Age } (years) \times \text{AST Level } (U/L)}{\text{Platelet } Count(109/L) \times \text{ALT}(U/L)}$$

3-Transient elastography (Fibroscan): it uses ultrasound to evaluate hepatic elasticity, which matches with the degree of hepatic fibrosis **(9)**. Fibroscan score: < 2.5 Kb= No fibrosis; 2.5:7.4Kb= mild fibrosis; 7.5:9.4Kb=moderate fibrosis; 9.5:12.4Kb= severe fibrosis ; >12.5Kb= cirrhosis.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Categorical variables were described using their absolute frequencies and were compared using chi square test, and Fisher exact tests when appropriate. Quantitative variables were described using their means and standard deviations or median and interquartile range. independents sample t test (for normally distributed data) and Mann Whitney test (for not normally distributed data) were used. Binary logistic regression was used to identify independent risk factors associated with certain health problems. The level statistical significance was set at $p<0.05$. Highly significant difference was present if $p\leq 0.001$.

Results

This study included 245 patients with a mean age of 57.32 years (range: 13- 75 years). Males represented 59.6% of them. Mean weight, height and BMI were 81.47 kg, 168.97 cm and 28.43 kg/m2, respectively. About 45% of patients were smokers, 35.9% had comorbid diabetes mellitus and 33.9% had comorbid hypertension **(Table 1)**.

Mean albumin and total protein were 3.82 g/dl and 6.91 g/dl. Mean direct bilirubin was 1.57 mg/dl. Median ALT, AST, AFP was 25 U/L, 32 U/L and 3.8 ng/dl, respectively. Mean TLC was 6.14 (103/mm3). Median platelet count and plasma glucose were 145 (103/mm3) and 120 mg/dl, respectively **(Table 2)**.

Larger percentage of patients (20%) had Child class B, 44.5% were cirrhotic. FIB-4 ranged from 0.22 to 12.95 with median 2.75 **(Table 3)**.

Ultrasound examination revealed abnormal liver pattern, size and texture in 51% of patients, 51% had splenomegaly, 22.9% had dilated portal vein and two patients had dilated splenic vein and also two patients had ascites **(Figure 1)**.

About 92% of patients were drug-naïve. About 52% received Sof + DCV + RBV and 31% received SoF + DCV. Only one patient was complicated with first hematemesis attack **(Table 4)**.

Eight patients stopped therapy (3.3%) while 13.1% were non-responders and 83.7% showed clinical response. Five out of eight patients who stopped therapy received only one dose and decline course as they developed first hematemesis attack in three of them and stopped without saying cause (one patient). One stopped after first dose owing to developing HCC. One patient stopped therapy after 8 weeks as he developed encephalopathy. One patient stopped therapy after 10 days as his bilirubin level increased. One patient stopped at 21 days as he developed ascites and hematemesis **(Table 5)**.

There is statistically significant relation between non-response and age of patient, weight, height, comorbid diabetes, and cirrhosis (cirrhosis, diabetes, older age, higher weight significantly associated with non-response). There is statistically non-significant relation between non-response and sex, smoking, hypertension, hypothyroidism or BMI **(Table 6)**.

There is statistically significant relation between non-response and child class and FIB-4 (Child B and higher FIB-4 significantly associated with non-response) **(Figure 2,3)**.

There is statistically significant relation between non-response and albumin, total protein, INR, TLC, HbA1c, total bilirubin, AST, ALT, alpha fetoprotein, platelet count and plasma glucose (non-response was associated with low albumin, protein, platelet count, and TLC, higher INR, AFP, AST, ALT, bilirubin, HbA1c, plasma glucose).There is statistically non-significant relation between non-response and hemoglobin, creatinine **(Table 7)**.

There is statistically significant relation between non-response and splenomegaly, and ascites (splenomegaly and ascites significantly associated with non-response).There is statistically non-significant relation between non-response and ultrasonographic findings of liver, dilated portal vein, or splenic vein **(Table 8)**.

There is statistically significant relation between non-response and regimen (Sof + DCV + RBV associated with non-response).There is statistically non-significant relation between non-response and being treatment-naïve, or complications **(Table 9)**.

Table (1) Clinical and demographic data of all participating patients

	N=245	***%***
Gender **Female** **Male**	 99 146	 40.4% 59.6%
Special habits :Smoker	109	44.5%
Mean ± SD		***Range***

Age (year)	57.32 ± 10.27	13 – 75
Weight (kg)	81.47 ± 12.77	47 – 135
Height (cm)	168.97 ± 2.42	162 – 178
BMI (kg/m^2)	28.43 ± 4.18	16.7 – 45.1
Comorbidities		
Diabetes	88	35.9%
Hypertension	83	33.9%
Hypothyroid	3	1.2%

Table (2) Baseline laboratory characteristics of all patients.

		Value	***Range***
Albumin (g/dl)	*Mean ± SD*	3.82 ± 0.62	2.7 – 5.8
Total protein (g/dl)	*Mean ± SD*	6.91 ± 0.66	5.1 – 6.8
Direct bilirubin (mg/dl)	*Mean ± SD*	1.1 ± 0.57	0.29 – 2.3
ALT	*Median (IQR)*	25(18 – 38)	6 – 164
AST	*Median (IQR)*	32(23 – 47)	8 – 192
AFP	*Median (IQR)*	3.8(2.8 – 6.6)	0.5 – 101
TLC (10^3/mm^3)	*Mean ± SD*	6.14 ± 2.15	1.7 – 12.3
Hemoglobin (g/dl)	*Mean ± SD*	12.32 ± 1.77	8.1 – 17
Platelet count (10^3/mm^3)	*Median (IQR)*	145(94 – 189.5)	52 – 361
Creatinine (mg/dl)	*Mean ± SD*	0.94 ± 0.33	0.3 – 3.5
Glucose (mg/dl)	*Median (IQR)*	120(102 – 168)	64 – 286
HbA1c (%)	*Mean ± SD*	5.92 ± 1.58	4.4 – 11.4%
HbsAg	*Negative* *Vaccinated*	244 1	99.6% 0.4%

Table (3) Distribution of patients according to Child's class and FIB-4:

	N=245	***%***
Child class :A **B**	196 49	80% 20%
Cirrhosis by ultrasound	109	44.5%
FIB-4	2.75(1.69 – 4.35)	0.22 – 12.95

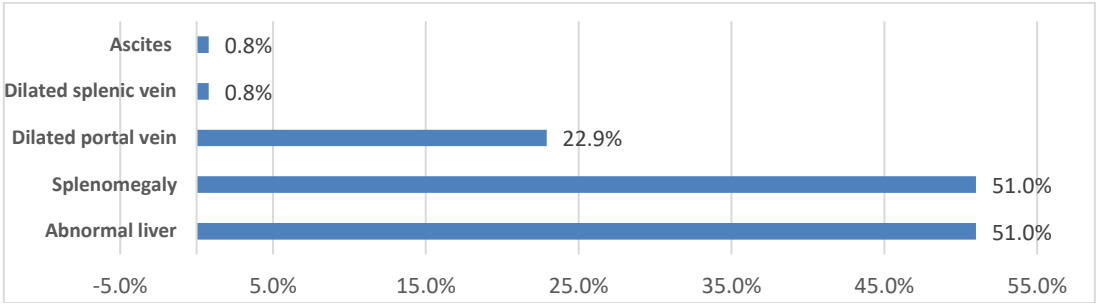

Figure (1) Simple bar chart showing distribution of patients according to ultrasound data

Table (4) Distribution of patients according to treatment-related data:

	N=245	**%**
Treatment: Naïve **Experienced**	226 19	92.2% 7.8%
Regimen		

SoF + DCV + RBV	128	52.2%
SOF + DCV	76	31%
SOF + Ledipasvir	22	9%
SOF + SIM	19	7.8%
Complications: First hematemesis attack	1	0.4%

Table (5) Distribution of patients according to response to therapy:

	N=245	*%*
Non-response	32	13.1%
Response	205	83.7%
Stopped therapy	8	3.3%

Table (6) Predictors of response among patients who adhere to therapy (n=237)

	Total N=237 (%)	***Responder N=205 (%)***	***Non-responder N=32(%)***	***χ2***	***p***
Gender **Female** **Male**	**96 (40.5%)** **141 (59.5%)**	**86 (42%)** **119 (58%)**	**10 (31.3%)** **22 (68.7%)**	**1.315**	**0.251**
Smoking	106 (44.7%)	93 (45.4%)	13 (40.6%)	0.252	0.616
Comorbidities					
Diabetes	85 (35.9%)	68 (33.2%)	17 (53.1%)	4.791	0.029*
Hypertension	81 (34.2%)	68 (33.2%)	13 (40.6%)	0.684	0.408
Hypothyroidism	3 (1.3%)	3 (100%)	0 (0%)	Fisher	>0.999
Cirrhosis	106 (44.7%)	86 (42%)	20 (62.5%)	4.728	0.03*
	N=85				
Oral hypoglycemic	75 (88.2%)	60 (80%)	15(20%)	Fisher	>0.999
Insulin	10 (11.8%)	8 (80%)	2 (20%)		
	Mean ± SD	***Mean ± SD***	***Mean ± SD***	*t*	*p*
Age (year)	57.2 ± 10.28	56.39 ± 10.56	62.38 ± 6.18	-4.541	<0.001**
Weight (kg)	81.28 ± 12.73	80.67 ± 13.41	85.19 ± 5.51	-3.344	<0.001**
Height (cm)	168.95 ± 2.44	168.79 ± 2.39	167.97 ± 4.36	-2.585	0.01*
BMI (kg/m^2)	28.38 ± 4.14	28.27 ± 4.36	29.04 ± 2.15	-1.571	0.12

χ^2Chi square test, t independent sample t test, *p<0.05 is statistically significant ,**p≤0.001 is statistically highly significant

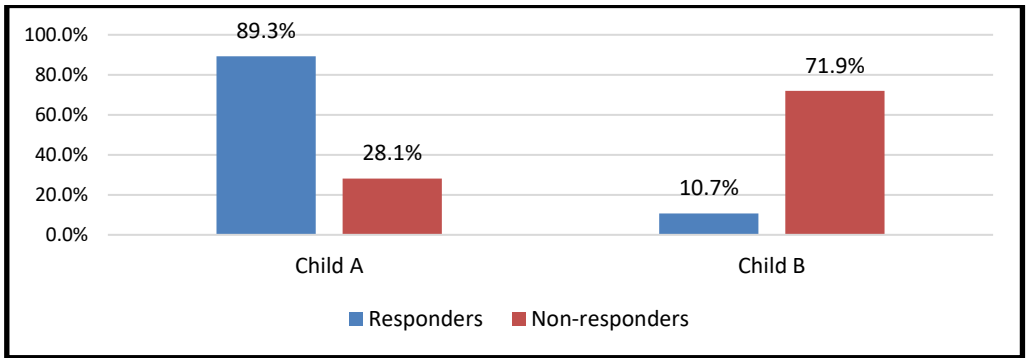

Figure (2) Compound bar chart showing relation between response and child class.

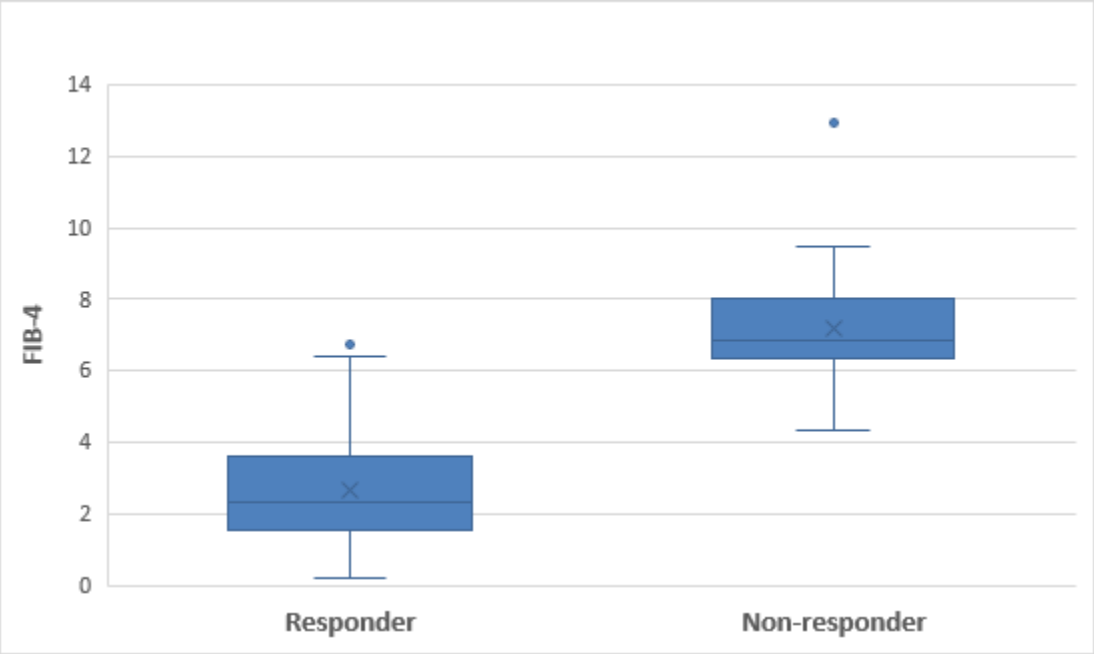

Figure (3) Boxplot showing relation between response and FIB-4.

Table (7) Relation between response of therapy and baseline laboratory data of the patients

	Total n=237	**Responder n=205**	**Non-responder n=32**	**t**	**p**
	Mean ± SD	***Mean ± SD***	***Mean ± SD***		
Albumin (g/dl)	3.84 ± 0.61	3.93 ± 0.59	3.27 ± 0.39	8.29	**<0.001****
Total protein (g/dl)	6.91 ± 0.66	7.01 ± 0.62	6.31 ± 0.57	5.989	**<0.001****
INR	1.17 ± 0.2	1.16 ± 0.2	1.29 ± 0.22	-3.515	**<0.001****
TLC (10^3/mm^3)	6.14 ± 2.16	6.29 ± 2.15	5.2 ± 1.95	2.689	**0.008***
Hemoglobin (g/dl)	12.31 ± 1.76	12.26 ± 1.79	12.67 ± 1.53	-1.234	0.219
Creatinine (mg/dl)	0.94 ± 0.33	0.94 ± 0.34	0.97 ± 0.23	-0.473	0.637
HbA1c (%)	5.9 ± 1.57	5.8 ± 1.54	6.56 ± 1.63	-2.576	**0.011***
	Median (IQR)	***Median (IQR)***	***Median (IQR)***	***Z***	***p***
Bilirubin (mg/dl)	0.9(0.67 – 1.5)	0.85(0.61 – 1.2)	2.1(1.2 – 2.1)	-5.259	**<0.001****
ALT	25(18 – 37)	24(17 – 34.45)	44.5(28.3 – 69.3)	-5.092	**<0.001****
AST	31(23 – 46)	30(22 – 39.5)	52(38.3 – 79.8)	-5.693	**<0.001****
AFP	3.7(2.75 – 6.3)	3.6(2.6 – 5.65)	6.25(3.93 – 27.3)	-4.154	**<0.001****
Platelet count (10^3/mm^3)	149(94.5–190.5)	152(112.5 –201)	74(65 – 80)	-7.554	**<0.001****
Glucose (mg/dl)	120(102 – 168)	120(102 – 166)	156.5(113.3–202.5)	-2.194	**0.028***

*χ^2Chi square test, t independent sample t test, Z Mann Whitney test, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant*

Table (8) Relation between response of therapy and ultrasound data of patients:

	Total N=237 (%)	**Responder N=205 (%)**	**Non-responder N=32(%)**	**χ^2**	**p**
Liver **Normal** **Abnormal**	 119 118	 112 (54.6%) 93 (45.4%)	 7 (21.9%) 25 (78.1%)	1.315	0.251
Splenomegaly					

Average **Present**	117 120	111 (54.1%) 94 (45.9%)	6 (18.7%) 26 (81.3%)	13.874	<0.001**
Dilated portal vein	55	47 (22.9%)	8 (25%)	0.067	0.796
Dilated splenic vein	2	1 (0.5%)	1 (3.1%)	Fisher	0.252
Ascites	2	0 (0%)	2(6.3%)	Fisher	0.018*

χ^2Chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (9) Relation between response of therapy and treatment related data of patients:

	Total N=237 (%)	**Responder N=205 (%)**	**Non-responder N=32(%)**	χ^2	**p**
Treatment **Naïve** **Experienced**	 218 (92%) 19 (8%)	 191 (93.2%) 14 (6.8%)	 27 (84.4%) 5 (15.6%)	 2.904	 0.088
Regimen **SoF-DCV-RBV** **SOF-DCV** **SOF-Ledipasvir** **SOF-SIM**	 128 (54%) 76 (32.1%) 22 (9.3%) 11 (4.6%)	 98 (47.8%) 74 (36.1%) 22 (10.7%) 11 (5.4%)	 30 (93.7%) 2 (6.3%) 0 (0%) 0 (0%)	 18.074	 <0.001**
Complications **First hematemesis attack**	1 (0.8%)	1 (0.4%)	0 (0%)	Fisher	>0.999

*χ^2Chi square test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant*

On doing multivariate regression analysis of predictors of non-response, it is found that increasing FIB-4, and ALT significantly increase risk of non-response by 137.932 and 1.138 folds respectively while increasing HbA1c non-significantly increases risk by 4.492 folds. Presence of cirrhosis in ultrasound non-significantly decreases risk of non-response **(Table 10)**.There is non-significant relation between non-response and hepatocellular carcinoma **(Table 11)**.

Table (10) Multivariate regression analysis of predictors of non-response among studied patients

	β	**p**	**AOR**	**95% C.I.**	
				Lower	**Upper**
Cirrhosis	-4.251	0.076	0.014	0.000	1.560
FIB-4	4.927	0.008*	137.932	3.615	5263.013
HA1C	1.502	0.079	4.492	0.840	24.007
ALT	0.130	0.013*	1.138	1.027	1.261

*AOR adjusted odds ratio CI Confidence interval *p<0.05 is statistically significant*

Table (11) Relation between response of therapy and incidence of HCC of patients:

	Total N=237 (%)	**Responder N=205 (%)**	**Non-responder N=32(%)**	χ^2	**p**
HCC **Absent** **Present**	 229 (96.6%) 8 (3.4%)	 200 (97.6%) 5 (2.4%)	 29 (90.6%) 3 (9.4%)	 Fisher	 >0.999

χ^2Chi square test

Discussion

Our study was conducted on 282 patients with chronic HCV infection but, 37 patients were excluded according to NCCVH guidelines and 245 patients who met inclusion criteria were included. Eight of the included patients stopped the course of treatment due to development of complications such as encephalopathy, new HCC, hyperbilirubinemia and hematemesis. 237 patients completed the course of treatment and were divided according to the virologic response to antiviral into two groups; responders (205) and non-responders (32). Among all studied cases of the present study, non-response was significantly associated with older age and cirrhosis ($p<0.001$, $=0.03$, respectively).

This came in accordance with previous studies. Older age, cirrhosis, especially Child–Pugh class B, and low platelet count were the predictors of non-response associated with sofosbuvir and daclatasvir therapy for genotype 4 HCV among Egyptian patients and explained this by the fact that most of elderly patients and those with thrombocytopenia had an associated liver cirrhosis at presentation likely due to a longer duration of HCV infection **(4,10)**.

Also, our results were in accordance with the study done by *Soliman et al.* **(11)** concluded that old age and liver cirrhosis was associated with non-response. The explanation of poor response to DAAs in liver cirrhosis may be due to impaired perfusion of the drug associated with liver stiffness , altered drug metabolism or impaired viral clearance as a result of immune defects caused by cirrhosis **(12)**.

In contrast, *Jain et al.* **(13)** observed no significant age difference between treatment responders and non-responders. Also, No any significant difference between responders and non-responders groups regarding age **(14)**. Cirrhosis was a main predictor of non-response. However, *Salmon et al.* **(15)** observed no significant difference in the treatment response between cirrhotic and non-cirrhotic patients.

Among the two main groups included in this study, non-response was significantly associated with presence of diabetes and higher body weight ($p=0.029$, <0.001, respectively) and this came in accordance with *Shousha et al.* **(4)** and *Jain et al.* **(13)** found that non-response was significantly associated with presence of DM (25% versus 15.7%; $p=0.041$).Also, Patients who achieved SVR had a lower blood glucose level. Also, *Cárdaba-García et al.* **(9)** noted that diabetic patients were significantly more in the treatment failure group (35.7%) as compared to the cured group (12.4%). The explanation of this may be due to the presence of more steatosis in diabetic patients.

In contrast, DM did not play a significant role in the treatment outcome of chronic hepatitis C patients. Also, DM (type 2) and insulin resistance (IR) had no effect on virological response to telaprevir-based regimens or danoprevir monotherapy and there was no significant difference between diabetic and no diabetic groups regarding SVR **(11,16)**.

The present results support the results documented by *Shousha et al.* **(17)** found that higher weight was an independent predictor of non-response in HCV (genotype 4) patients . The present study agrees with these results especially as this study was conducted in Egypt in which HCV (genotype 4) is the predominant genotype. A recent study done by *Cárdaba-García et al.* **(9)**found that BMI $\geq$30 kg/m² affected negatively the response to antiviral treatment . This fact could be due to a lower bioavailability of RBV because there is more fatty tissue, as well as the chronic inflammatory state related to obesity is 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 $\geq$30 kg/m² is associated with worse SVR rates.

The results of our study showed that non-response was higher in males than females(68.7% & 31.3%, respectively) but did not reach a significant level (p=0.251) and this came in agreement *Jain et al.* **(13)** reported that gender did not alter the treatment response and *Salmon et al., 2018* and Cárdaba-García *et al*. **(9)** reported the same result in their respective studies. In contrast, *Shousha et al.***(4)**reported in their retrospective study that male gender was independent factor associated with non-response to DAAs.

The results of our study showed that non-response was significantly higher in Child's class B than Child's class A (71.9% &28.1%, respectively, p<0.001) and this came in agreement with *Ahmed et al.* **(10)** who reported that cirrhosis, especially Child–Pugh class B was predictor of non-response associated with sofosbuvir and daclatasvir therapy for genotype 4 HCV among Egyptian patients.

The results of our study showed that non-response was significantly associated with higher FIB-4(p<0.001) and this came in agreement with many studies. A large study on 7256 subjects at Cairo University and found that higher FIB-4 was a predictor of DAA failure among patients with chronic HCV infection, and FIB-4 level of 2.4 was the best cut-off point to predict treatment failure. Also, the only independent predictor of treatment failure was the higher FIB-4 index, and the best FIB-4 cut-off point for prediction of treatment failure among CKD patients was 2.63. Higher FIB-4 scores were associated with lower SVR rates. This can be explained by the fact that the increased FIB-4 score (≥3.25) has a high specificity (>96%) for advanced liver fibrosis, while a low FIB-4 score (≤1.45) is related to low fibrosis stages **(18-21)**.

Our results showed that non-response was significantly associated with low albumin, higher INR, higher bilirubin, higher ALT, higher AST and low platelet count(p<0.001) and this came in agreement with *Gayam et al.* **(18)** observed a significant difference in the serum levels of albumin (P = 0.042) and bilirubin (P = 0.043) between the two groups, with bilirubin being higher and albumin lower in patients who did not achieve SVR. *Jain et al.* **(13)** found a statistically significant difference in the mean platelet count, ALT, and AST levels between the two groups.The mean platelet count was significantly lower in patients who did not achieve SVR (P < 0.001), while the mean ALT and AST levels were significantly higher in patients who did not achieve SVR. (P = 0.02 and P = 0.02, respectively). *Gayam et al.* **(18)** also reported significantly lower platelet count in patients who did not achieve SVR and concluded that thrombocytopenia is a predictor of treatment failure (P = 0.020). Also, Cárdaba-García *et al*. **(9)** observed a significant difference in AST, ALT, albumin, and platelet count between the two patient groups. *Ahmed et al.* **(10)** also observed that the platelet count was significantly lower in patients who did not achieve SVR.

Our results showed that non-response was significantly associated with higher AFP(p<0.001)and this came in the same line with *Shousha et al.* **(17)** showed that non-responders had significantly higher AFP. *Shousha et al.* **(4)** declared that high AFP more than 10ng, being a routine pretreatment laboratory assessment, is a predictor of non-response to DAAs in patients with chronic HCV genotype 4. We can explain this by that high pretreatment AFP may be a marker of more necrosis and fibrosis.

Our results showed that non-response was significantly associated with higher blood glucose level and higher HA1C(p=0.028& p=0.011, respectively)and this came in the same line with level. In contrast, *Gayam et al.* **(18)** and *Ahmed et al.* **(10)** observed that DM did not play a significant role in the treatment outcome of chronic hepatitis C patients.

The results of our study showed that non-response was higher in treatment-naïve than treatment-experienced patients (84.4%&15.6%, respectively) but did not reach a significant level (p=0.088) and this came in agreement with *Ahmed et al.* **(10)** (P = 0.06), *Nabulsi et al.***(8)** (P = 0.109), and *Cachay et al.* **(20)**(P = 0.71) who did not find any significant association between previous treatment experience and treatment failure. In contrast, *Jain et al.* **(13)** observed that 15.6% of patients in the treatment failure group had experienced the antiviral treatment previously while among patients who achieved SVR, only 6.8% of patients were treatment-experienced. This difference was statistically significant with more treatment failures among patients with previous treatment history (P = 0.03).

The results of our study showed that non-response was significantly associated with regimen (SOF+ DCV + RBV)(p<0.001) and this was inconsistent with *Jain, et al.* **(13)** who did not find any statistically significant differences in the treatment regimen (P = 0.151) and duration (P = 0.365) between the two patient groups. Therefore, the treatment regimen and duration did not alter the treatment outcome and this is coherent with results of the studies

Conclusion:

Several comorbidities were significant predictors of non- response to HCV treatment by using DAAs such as DM, older age, higher body weight, liver cirrhosis, thrombocytopenia, elevated transaminases, higher AFP and higher FIB-4.

So we concluded that routine pre-treatment work up for HCV (genotype 4) patients receiving DAAs can help in prediction of non-response.

Conflict of interest: *The authors declare no conflict of interest.*
Sources of funding: *This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.*
Author contribution: *Authors contributed equally in the study.*

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