Original Research Article

Predictors of Treatment Failure with Sofosbuvir/Daclatasvir Regimen for 12 Weeks in Chronic HCV Egyptian Patients

ABSTRACT

Background: Hepatitis C virus HCV infection is one of the main causes of chronic liver disease worldwide, Egypt has the highest national-level HCV prevalence in the world, Sofosbuvir/Daclatasvir (SOF/DAC) regimen widely used to treat HCV infection in Egypt.
Aims: to identify the predictors of treatment failure with Sofosbuvir/Daclatasvir regimen for 12 weeks in HCV Egyptian patients.
Methodology: We investigated the predictors of treatment failure in 2300 patients received the regimen from the baseline investigations.
Results: Patients who completed the treatment and follow up visits were 2079 patients,4 patients stopped treatment due to side effects, 35 due to incompliance and 182 patients missed their follow up visits after treatment, out of the 2079 patients 2043 (98.3%) patients responded to treatment with SVR12 and just 36 (1.7%) patients had treatment failure, presence of Hypertension (p=0.001), Diabetes Miletus (p=0.001), ALT level >51 (p=0.013) , AST level >60 (p=0.002), AFP > 6 (p=0.000) and abnormal liver echo-pattern all were found to have an impact on SVR12 rates, some other factors were found to be insignificant as age, sex, BMI, special habits, liver function tests, haemoglobin, total leucocytic count and serum creatinine, by multivariate analysis AFP was found to be the strongest predictor of treatment failure with cut off value >6 with sensitivity 66.67% and specificity 77.31%.
Conclusion: This study shows that ALT, AST, AFP, Abnormal Liver Echo-pattern and the Presence of Diabetes Miletus or Hypertension were found to affect SVR rates, but the strongest predictor was AFP level with a cutoff value of >6.

Keywords: Hepatitis C virus, HCV, Sofosbuvir, Daclatasvir, DAAs, Predictors, SVR12

1. INTRODUCTION

HCV infection is one of the main causes of chronic liver disease worldwide ***(1).*** The long-term impact of HCV infection, ranging from minimal histological changes to cirrhosis with or without hepatocellular carcinoma (HCC). The estimated number of chronically infected HCV patients worldwide is about 180 million ***(2).***

Egypt has the highest national-level HCV prevalence in the world, the percentage of adults aging from 15-59 testing positive on the HCV RNA test is 7% of the Egyptian population ***(3).***

HCVgenotype (GT) 4, is the most common variant in the HCV epidemic in Egypt with more than 90% of infections due to genotype 4***(2).***

The morbidity of HCV in untreated patients as regard liver cirrhosis, liver cell failure and hepatocellular carcinoma represent a major health problem and economic burden ***(4).***

In 2006, in recognition of the enormity of the HCV problem and burden of disease in Egypt, the Minister of Health established the National Committee for Control of Viral Hepatitis (NCCVH), the available regimen was Peginterferon alfa (PEG-a), 350000 patients had received therapy with SVR rates for patients treated with the PEG-IFN-α2a and alfa-2b were 54%-59% respectively***(5).***

The predictive factors of therapy response are also related to the virus and hosts, and they can be classified as clinical, biochemical, immunologic and genetic factors.

Male gender, advanced liver fibrosis, human immunodeficiency virus (HIV) and HBV coinfection, insulin resistance, poor treatment adherence, high viral load (≥ 600.000 UI/mL) and African ancestry have been related with the failure of interferon (IFN) based therapies, particularly with dual therapy (pegylated interferon and ribavirin) ***(6)***.

In early clinical trials of interferon and ribavirin, a baseline HCV RNA level over 800,000 IU/ml was found to be associated with a 9% lower chance of cure. Subsequent studies found that patients with high viral load had a 15 to 39% lower chance of achieving an SVR, but for IFN-free therapies, there is no clear data on predictive factors of SVR.

Recent advances in drug development have led to a number of direct anti-viral agents (DAAs) which deliver high rates of SVR with substantial improvements in the side effect profiles.One of these drugs, sofosbuvir (SOF), a potent inhibitor of the HCV NS5B polymerase, has been approved for the treatment of HCV in Egypt since2014 **(7).**

These regimens include either single DAA therapy SOF with RBV for 24 wks, or dual DAA combination therapy as, Sofosbuvir/Daclatasvir for 12 wks ***(8).***

Daclatasvir, another DAA which is one of the NS5A inhibitors which is associated with great results in HCV clearance, also it is pan-genotypic ***(9).***

In November 2015 the NCCVH issued a new protocol in which the Sofosbuvir/Daclatasvir for 12 weeks has been included to treat the Easy to treat Egyptian HCV patients according to the following criteria:

- INR<1.2.
- Serum Albumin > 3.5 gm/dl.
- Platelets Count > 150,000.
- Total bilirubin < 1.2 mg/dl.

In the current DAAs era, the baseline HCV RNA has little impact on the likelihood of achieving an SVR.

SOF/DAC regimen has achieved SVR in about 95% of all patients received it for 12 weeks however, predictors of relapse after treatment have not been studied before ***(10).***

2. MATERIAL AND METHODS

This study retrieved the following data of 2300 naieve patients who received SOF/DAC regimen for 12 weeks in New Cairo viral hepatitis treatment center from December 2015 to December 2016. The following data were collected from patients files, Gender, Age, Special habits, History of Diabetes or Hypertension, BMI, History of previous treatment, History of ascites, History of hepatic encephalopathy, Laboratory investigations including CBC, S.creatinine, LFTs, Liver enzymes, AFP, HCV RNA PCR, HbsAg and HbA1c, and imaging investigation like abdominal ultrasonography.

This study included all Patients aging between 18 and 65 years, Patients with chronic HCV confirmed by positive PCR for HCV and Patients with normal LFTs or Child A, and excluded all patients above 65 years old, also all patients with laboratory results not meeting the easy to treat patients criteria in NCCVH treatment protocol, Extra-hepatic malignancy except after two years of disease-free interval, Pregnancy or inability to use effective contraception.

All baseline data for patients who achieved SVR12 and for who did not, were compared to identify the predictors of treatment failure with SOF/DAC regimen.

3. RESULTS AND DISCUSSION

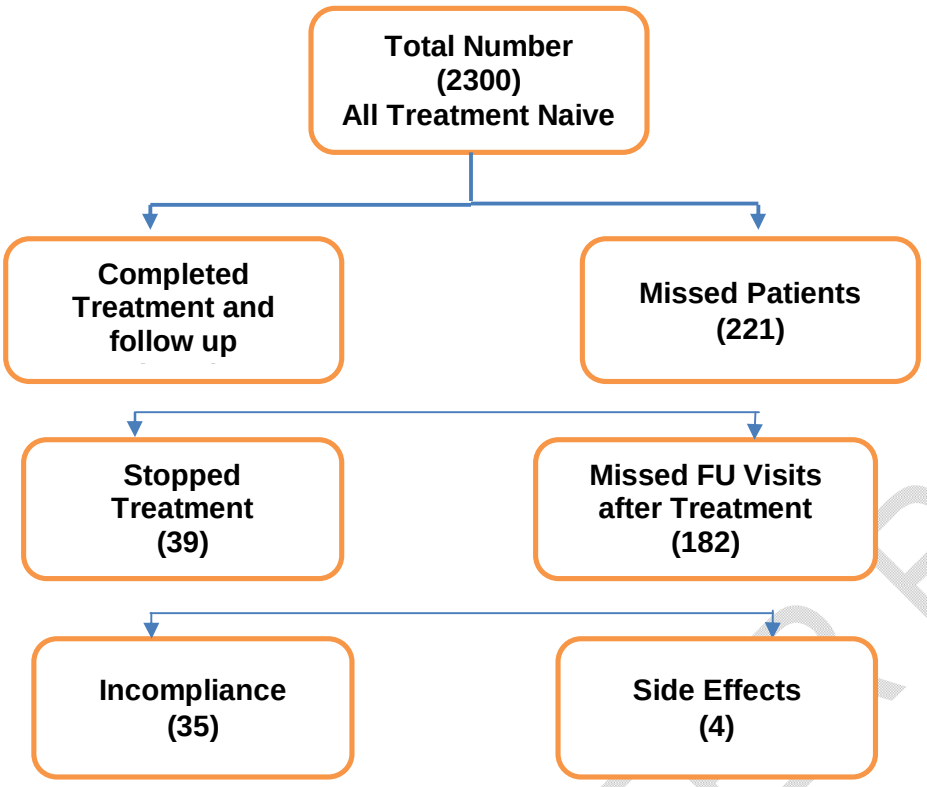

Figure (1): Number of patient who completed the treatment and those who missed their follow up or stopped treatment.

Table (1): Demographic data of the studied patients.

		Total no. = 2079
Age	Mean ± SD Range	47.73 ± 12.34 18 – 65
Gender	Females Males	1257 (60.5%) 822 (39.5%)
BMI	Mean ± SD Range	28.43 ± 5.54 17 – 51
Treatment Status	Treatment Naive	2079 (100.0%)

Table (1) showed that the mean age of the included patients was 47.73 ± 12.34 and 1257 (60.5%) were females, 822 (39.5%) were males, BMI ranged between 17 and 51 with a mean value 28.44 ± 5.58.

Table (2): Number of responders and non-responders at week 16 and week 24.

		Total no. = 2079
HCV RNA w16	Responder Non responder	2045 (98.4%) 34 (1.6%)
HCV RNA W24	Responder Non responder	2043 (98.3%) 36 (1.7%)

Four weeks after end of treatment 2045 patients had negative PCR while 34 had positive HCV viremia. HCV RNA Quantitative PCR was repeated in week 24 (12 weeks after the end of treatment) and showed that 2043 patients have achieved Sustained Virological Response (SVR12) (98.3%), with another two patients with treatment failure (1.7%) of total number of patients.

Table (3): Comparison between responders and non-responders regarding comorbidities.

		Responder		Non responder		Test value*	P-value	Sig.
		No.	%	No.	%			
Hypertension	**No** **Yes**	**1723** **320**	**84.3%** **15.7%**	**23** **13**	**63.9%** **36.1%**	**10.996**	**0.001**	**HS**
Diabetes	**No**	**1740**	**85.2%**	**24**	**66.7%**	**9.420**	**0.002**	**HS**
	Yes	**303**	**14.8%**	**12**	**33.3%**			
HBs Ag	**Negative** **Positive**	**2039** **4**	**99.8%** **0.2%)**	**36** **0**	**100.0%** **0.0%**	**0.071***	**0.790**	**NS**

While these table showed that there was highly statistically significant increase in the incidence of treatment failure among patients with hypertension and diabetes than patients without hypertension or diabetes with p-value = 0.001 and 0.002 respectively, while there was no statistically significant difference found between responders and non-responders regarding co-infection with HBV with p-value = 0.790.

Table (4): Comparison between responders and non-responders regarding HCV RNA Quantitative PCR, ALT, AST and AFP.

HCV RNA W24		**Responder**	**Non responder**	**Test value**	**P-value**	**Sig.**
		No. = 2043	**No. = 36**			
PCR Quantitative	Median (IQR) Range	668153 (186837 – 2300000) 200 – 97600000	181684 (53082 – 801251) 470 – 13100000	-3.206ǂ	0.001	HS
ALT (IU/L)	Median (IQR) Range	36 (25 – 55) 2 – 536	49.5 (28.5 – 67.5) 10 – 220	-2.097ǂ	0.036	S
AST (IU/L)	Median (IQR) Range	35 (25 – 50) 4 – 590	42.5 (33 – 84.5) 15 – 188	-3.037ǂ	0.002	HS
AFP (ng/mL)	Median (IQR) Range	4 (2 – 6) 1 – 93	10 (2 – 25.5) 1 – 116	-3.497	0.000	HS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant; NA: Non significant •: Independent t-test; ǂ: Mann-Whitney test

The previous table showed that there was statistically significant increase in the incidence of treatment failure found with high viral load, and increased levels of ALT, AST and AFP with p-value = 0.001, 0.036, 0.002 and 0.000 respectively.

Table (5): Multi-variate logistic regression analysis for predictors of treatment failure 12 weeks after treatment

	B	**S.E.**	**Wald**	**P-value**	**Odds ratio (OR)**	**95% C.I.for EXP(B)**	
						Lower	**Upper**
Hypertension	-3.021	2.751	1.206	0.272	0.049	0.000	10.705
Diabetes	1.236	1.779	0.483	0.487	3.444	0.105	112.603
ALT	-0.032	0.050	0.414	0.520	0.968	0.877	1.069
AST	0.012	0.052	0.051	0.821	1.012	0.914	1.120
AFP	0.085	0.031	7.346	**0.007**	1.089	1.024	1.158
Echo-pattern of Liver	17.287	2896.829	0.000	0.995	0.388	0.000	1.100
Constant	-25.965	2896.832	0.000	0.993	0.000		

The multivariate analysis showed that the strongest independent predictor for treatment failure 12 weeks after end of treatment was AFP level above > 6 (ng/mL) with sensitivity 66.67% and specificity 77.31%.

DISCUSSION

Although HCV genotype 4 was considered the “most difficult to treat” genotype, but after the introduction of new DAAs, SVR rates significantly improved, one of these regimens is the Sofosbuvir plus Daclatasvir (SOF/DAC) which is widely used nowadays in Egypt. **(11)**

Although genotyping was not performed at baseline not being a perquisite for antiviral therapy according to national treatment protocol, more than 90% of patients in Egypt are infected with HCV-GT4 in many published reports, and this report can thus be taken to represent results of HCV-GT4 treatment. **(12)**, also both sofosbuvir and daclatasvir are considered pan-genotypic antivirals. **(14)**

In our study an overall number of 2043 (98.2%) patients out of the 2079 studied patients, achieved SVR12, while just 36 (1.8%) patients did not, In the study by *Omar et al*.,**(13)** the investigators recruited 10,120 patients who received SOF/DAC regimen for 12 weeks, 9653 (95.4%) patients achieved SVR12 after treatment, in another study *El-Khayat and his colleagues***(14)** concluded that out of 368 patients completed treatment with SOF/DAC regimen and follow up visits, 346 (94%) patients achieved SVR12.

Six predictors were found to affect SVR rates in our patients, the presence of other comorbidities specifically diabetes mellitus or hypertension, baseline transaminases (ALT, AST), AFP and liver echo-pattern by abdominal ultrasound.

Our statistical analysis showed differences between both groups (SVR12 and non SVR), regarding the previous parameters.

First predictor was the presence of hypertension which in comparison with non-hypertensive patients was found to be associated with higher incidence of treatment failure rates, the study included 320 hypertensive patients who achieved SVR12 while 13 hypertensive patients did not with p value = 0.001.

Conti et al. (2017) **(15)** confirmed the previous results in which the study included 87 elderly patients who received SOF/DAC regimen. Among them 33 patients (38.5%) were hypertensive, and treatment failure rates were higher in those 33 patients.

Kutala et al. (2017) **(16)** recruited 141 patients received SOF/DAC regimen, the frequency of treatment failure at week 12 following end of treatment was not affected by the presence of hypertension which was in agreement with *Omar et al. (2018)* in which there were 55 hypertensive patients (4%) who did not achieve SVR out of 1323 hypertensive patients which was not statistically significant.

SVR rates were found to be highly associated with the presence of diabetes mellitus and insulin resistance in the IFN era, but there is limited studies that connecting the SVR in the new DAAs era with the presence of diabetes.

Despite of exclusion of all poorly controlled diabetic patients in our study as per our standard treatment protocol, diabetes were found to be associated with treatment failure 12 weeks after end of treatment, 12 patients did not achieve SVR12 out of 303 diabetic patients included in our study which was highly significant with a p-value = 0.002, so we can conclude that diabetes mellitus was the second predictor of treatment failure in our study, which was supported by *Omar et al. (2018)* study, in which 1913 diabetic patients were recruited with 119 patients (6%) did not achieve SVR12,

*Gastaldi et al. (2017)**(17)**; El-Khayat et al. (2018)* disagreed with that, also *Kutala et al. (2017)* included just 13 diabetic patients (10%) out of total 144 patients who received SOF/DAC regimen with p-value = 0.602 which was not statistically significant.

It is well known that the majority of patients (57–94%) demonstrate marked improvements in their necro-inflammation and aminotransferases' levels following SVR (18), but there is limited data on the aminotransferases' levels on the SVR rates.

The third and fourth predictors of treatment failure were aminotransferases' levels (AST and ALT levels), ALT was significant with a cut-off value >51, specificity of 71.9% and sensitivity of 50% while the AST was significant with a cut-off value of >60, specificity was 84.39% and sensitivity was 41.67%. *Omar et al. (2018)* reported that ALT and AST levels were not associated with SVR rates after treatment with SOF/DAC regimen without ribavirin (RBV), but only high AST level was found to be associated with higher incidence of treatment failure after treatment with SOF/DAC/RBV regimen without reporting a specific cut-off value.

One of the routine laboratory investigations before starting treatment with DAAs, and specifically in our study was AFP which is the fifth predictor of treatment failure.

Elevation in serum AFP may also occur with other malignancies, hepatic, pregnancy and chronic hepatitis which may raise AFP levels in about 20-40% of patients **(19).**

In our study AFP ranged from 1 to 116 in patients with treatment failure with p-value 0.000 which is highly statistically significant, however there is no recent studies about AFP as a predictor of response to SOF/DAC regimen or DAAs in general, but all the previous studies about AFP as a predictor of response were on patients who received pegylated-IFN/RBV, *Chen et al., (2007)* ***(20)*** confirmed that low AFP levels were associated with increased SVR levels to pegylated IFN.

Sixth predictor of treatment failure was the abnormal liver echo-pattern detected by U/S either bright or coarse liver.

In our study 911 patients (44%) had bright liver, 353 patients (16.9%) had coarse liver (so, collectively there were 60.5% of patients with SVR12) had abnormal liver echo-pattern, while 815 patients (39.2%) had normal liver echo-pattern 807 patients (39.5% of patients with SVR12), with p-value = 0.035 which was statistically significant.

Our results were concordant with *El-Khayat et al. (2018)* in which the cirrhotic or patients with abnormal echo-pattern found to have less SVR rate, Also *Doss et al. (2015)* confirmed that patients with abnormal echo pattern whom represented 17% of their study population who received SOF/RBV, and showed lower SVR compared with no cirrhotic and patients with normal echo-pattern (78% vs. 93%).12 Also in a previous phase III study of genotype 3 infection, SVR12 was achieved by 96% of patients without cirrhosis but by only 63% of patients with cirrhosis after 12 weeks of treatment with DAC/SOF

But it did not agree with *Omar et al. (2018)* which included 4.433 patients with abnormal liver echo-pattern, 4,196 patients with SVR12 while 237 patients with treatment failure with p-value= 0.25 which was not statistically significant.

Multiple other factors found to be insignificant, such as: LFTs**,** Demographic data**,** Special Habits**,** HBV co-infection with HCV**,** CBC parameters**,** Serum creatinine

Regarding LFTs, all our patients were non-cirrhotic or Child A but "easy to treat" according to NCCVH treatment protocol so Serum albumin, Total bilirubin, INR (LFTs) (except for patients on anticoagulation) were in normal range with p-value (0.650, 0.494, 0.552 and 0.139 respectively). So the data were statistically insignificant.

4. CONCLUSION

This study shows that ALT, AST, AFP, Abnormal Liver Echo-pattern and the Presence of Diabetes Miletus or Hypertension were found to affect SVR rates, but the strongest predictor was AFP level with a cutoff value of >6.

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