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Predictive value &changes in Child-Pugh score in chronic hepatitis C cirrhotic patients treated with Direct Acting Antiviral agents

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Abstract

Background: Hepatitis C is a worldwide problem with a prevalence estimated to be 3 % according to the World Health Organization (WHO) about 130-150 million people worldwide are chronically infected with hepatitis C virus (HCV). Egypt has the highest prevalence of HCV estimated to be 7.3% with predominance of genotype 4. Direct -acting antiviral agents (DAAs) are highly effective and well tolerated in patients with chronic hepatitis C virus infection, including those with compensated cirrhosis. The availability of antiviral agents, which can be administered in short, interferon (IFN)-free regimens, has improved the management of patients with HCV infection dramatically. Clinical studies have demonstrated rates of sustained virologic response (SVR) of over 90% with these regimens, even in patients with compensated cirrhosis. **Aim**: The aim was to assess the clinical impact of direct-acting antiviral treatment in patients with compensated hepatitis C virus-related cirrhosis after one year of follow-up. **Methods:** An observational prospective study was conducted on 100 patients with compensated cirrhosis treated in 2017, analyzing the evolution of liver function and the development of hepatocellular carcinoma and clinical decompensation. **Results:** Most patients were males (60%), the mean age was 57.3±6.1years. All participants were Child-Pugh A class at the start of the treatment. SVR 12 was achieved in all patients (100%). Eight patients suffered clinical decompensation, three(3.3%) of them changed to Child B and five (5.5%) patients changed to Child C. The incidence of de novo hepatocellular carcinoma during the follow-up was (4 %). There was a significant improvement in the mean platelets count, AST, ALT ($P < 0.001$) after treatment and the mean albumin level decreased but still in the normal range. **Conclusion:** Treatment with Direct-acting antiviral was assosciated with high rates of SVR, but not associated in the short term with a decrease in the development of hepatic decompensation or hepatocellular carcinoma compared to what it was reported for untreated compensated cirrhotic patients.

1. Introduction

Hepatitis C is a worldwide problem with a prevalence estimated to be 3 % according to the World Health Organization (WHO) about 130-150 million people worldwide are chronically infected with hepatitis C virus (HCV). Egypt has the highest prevalence of HCV estimated to be 7.3% with predominance of genotype 4 **(1).**

Acute HCV infection usually lead to no symptoms and about 75 % of cases infected with HCV reach a chronic stage leading to chronic HCV infection (**2).** Sequelae of chronic HCV may lead to liver cirrhosis in nearly 20-50 % of patients infected; this may be complicated by liver cell failure and hepatocellular carcinoma later on and can occur relatively rapidly. Several non invasive methods for assessment of fibrosis such as aspartate aminotransferase-to-platelet ratio index (APRI), and fibrosis index based on the four factors (FIB-4) have been used to assess disease severity **(3)**

Direct -acting antiviral agents (DAAs) are highly effective and well tolerated in patients with chronic hepatitis C virus infection, including those with compensated cirrhosis.

The availability of potent, well-tolerated direct-acting antiviral agents (DAAs), which can be administered in short, interferon (IFN)-free regimens, has improved the management of patients with HCV infection dramatically. Clinical studies have demonstrated rates of sustained virologic response (SVR) of over 90% with these regimens, even in patients with compensated cirrhosis (**4**). Lower virologic response rates have been reported in patients with advanced liver disease and decompensated cirrhosis.(**5**). Achievement of SVR with IFN-free regimens in patients with cirrhosis decreases hepatic decompensation, HCC, and liver-related mortality.

Hepatic decompensation: The criteria for hepatic decompensation were as follows : (1) new-onset variceal bleeding or ascites leading to hospital admission, or hepatic encephalopathy in patients who had never experienced hepatic decompensation; (2) if patients experienced worsening of existing hepatic decompensation (required increased dose of diuretics, addition of rifaximin for pre-existing hepatic encephalopathy, or hospital admission for a decompensation event); or (3) if patients experienced a new decompensation event other than that already present at the start of antiviral therapy (**6**).

2. Patients and Methods:

This is an observational prospective study that was conducted on 100 patients, who had received Direct Acting Antiviral agents in 2017. Patients were collected from the tropical medicine department, outpatient clinic and centre of control of viral hepatitis at Beni-Seuf University hospital between December 2018 and May 2019.

Inclusion Criteria:

1. HCV RNA PCR positivity.
2. Age ≥ 18years old.

Patients ≥ 65 years old should undergo cardiological assessment prior to therapy by ECG, Echocardiography &cardiac consultation

Exclusion Criteria:

1. T.Bilirubin > 3mg/dl.
2. S, albumin < 2.8 gm\dl.
3. INR > 1.7.
4. Platelet count < 50,000\mm3
5. HCC except 6 months after intervention aiming at cure with no evidence of activity by dynamic imaging (CT or MRI).
6. Extrahepatic malignancy except after 2 years of disease free interval .In case of lymphomas or CLL, treatment can be initiated immediately after remission based on the treating oncologist report.
7. Pregnancy or inability to use effective contraception.
8. Inadequately controlled DM (HbA1c>9).
9. Patients who refused to be included in the study.

Methods:

All patients subjected to:

- Full history taking from the patients including (personal history, manifestations of liver cell failure) .
- Thorough clinical examination including manifestation of liver decompensation as ascites, lower limb edema, jaundice, palmer erythema, spider nevi, hepatic encephalopathy).

Investigations:

- Complete blood picture, liver function tests (AST, ALT, serum albumin, total bilirubin, prothrombin time, concentration & INR), serum creatinine, AFP.
- Abdominal ultrasound: for evaluation of cirrhosis & detection of signs of decompensation as (coarse echopattern, irregular outline, attenuated hepatic veins, ascites, portal hypertension, collaterals indicate portosystemic shunts, splenomegaly) & also appearance of hepatic focal lesions confirmed by dynamic study CT or MRI as HCC).

Statistical analysis

Analysis of data was performed using SPSS v. 25 (Statistical Package for Social science) for Windows. Description of variables was presented as follows:

- Description of quantitative variables was presented in the form of mean, standard deviation (SD), median, minimum and maximum.
- Description of qualitative variables was presented in the form of numbers (No.) and percent's (%).
- Paired T-test was used to detect the effect of treatment on the laboratory scale variables.
- Mc Nemar test was used to detect the effect of treatment on the categorical variables.

- Chi-Square test was used to detect the relation between the categorical variables.
- The significance of the results was assessed in the form of P-value that was differentiated into:
- Non-significant when P-value > 0.05
- Significant when P-value ≤ 0.05
- Highly significant when P-value ≤ 0.001.

3. Results

This study was conducted on 100 chronic hepatitis C cirrhotic patients, presented to Beni Suef University at tropical medicine department, outpatient clinic & center of control of viral hepatitis who were treated in 2017 by direct acting antiviral agents in the form of sofosbuvir, dacaltasvir with or without ribavirin to detect the effect of these drugs on Child-Pugh score, APRI and FIB 4 scores, Ultrasound, Upper GI endoscope and the development of HCC.

Table (1) Baseline characteristics of the studied patients:

Characteristics	Values
Age: Mean ± SD Range(min-max) Median	57.39±6.1 (44-75) 57
Sex: Males Females	60(60%) 40(40%)

Scale data is presented as mean ± SD and categorical data is presented as number and percent.

Table (1) showed that the mean age of the studied patients was 57.39±6.1 years and ranged from 44 to 75 years.

Figure (1) Child Pugh score before treatment

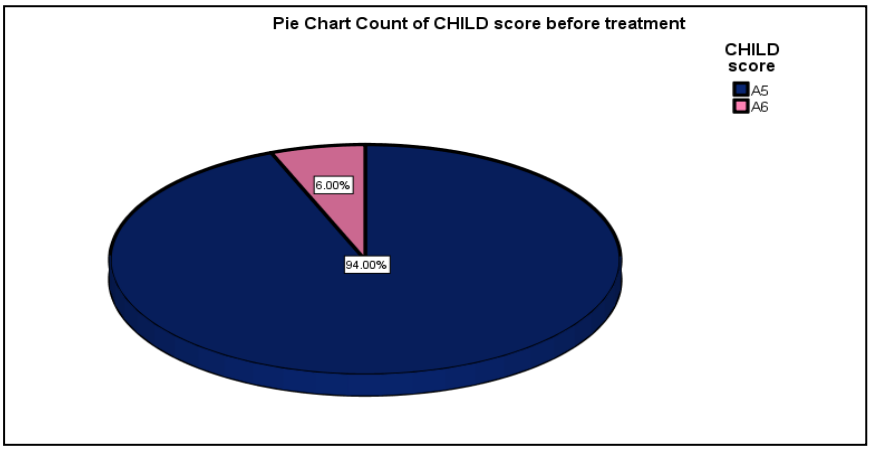


Figure (1) illustrates that all patients under the study had Child A and 94% of them had Child A5 and 6% had Child A6.

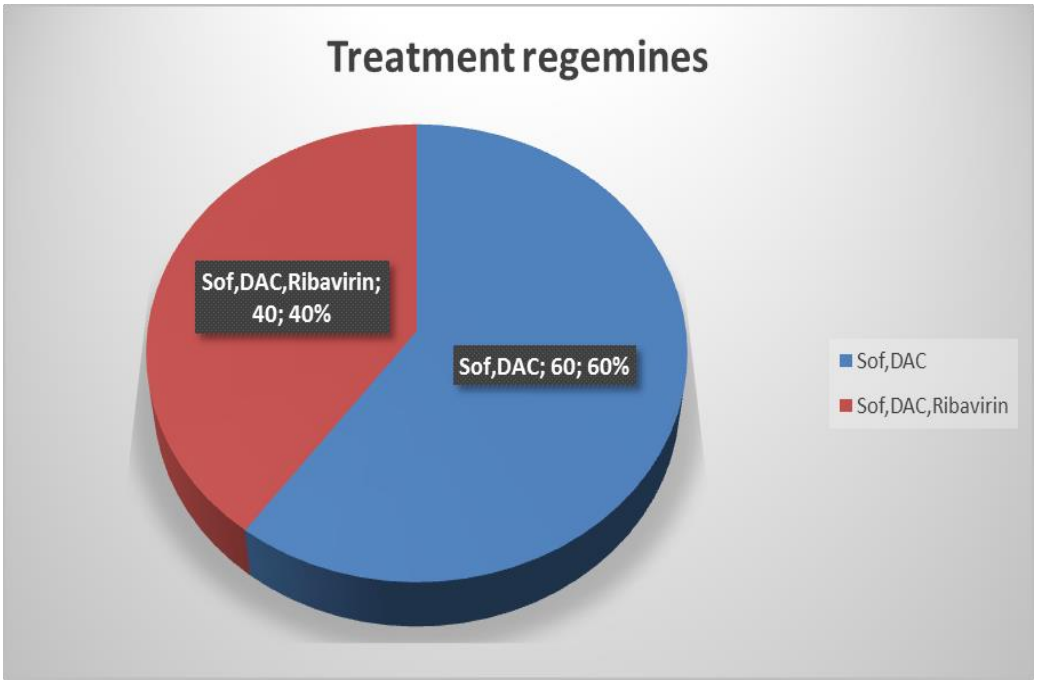


Figure (2) Treatment modalities of all patients under the study

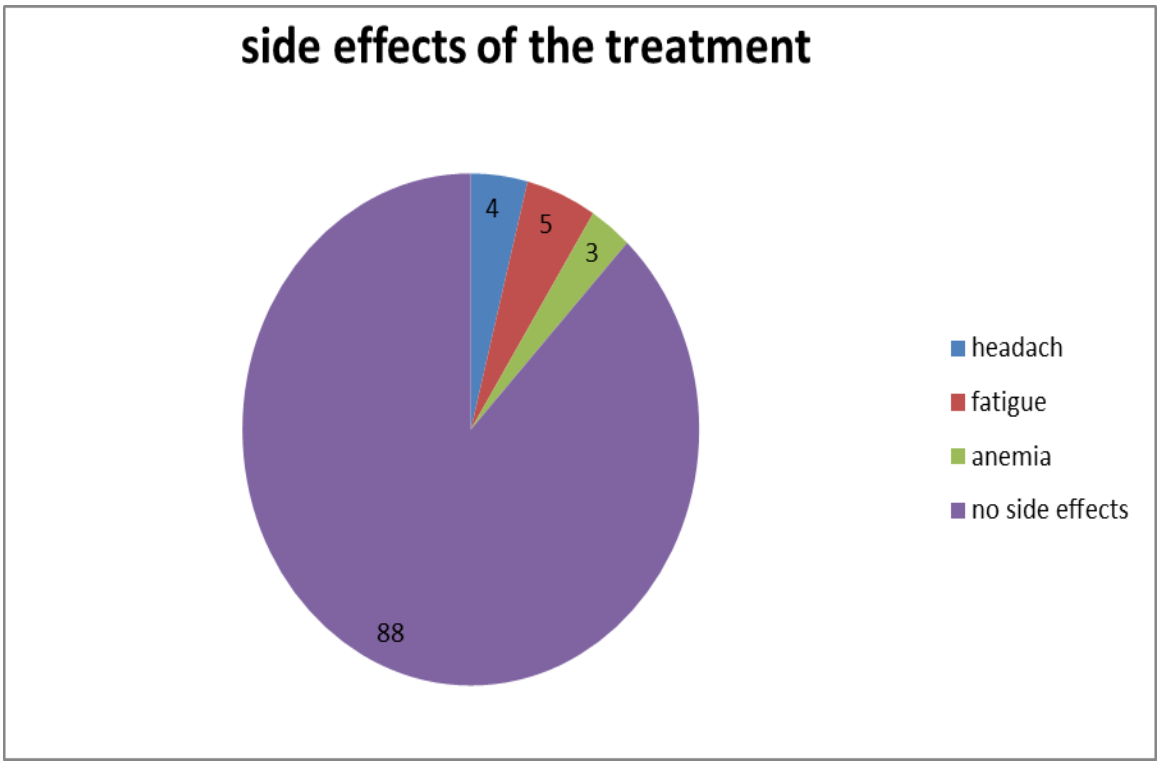


Figure (3) shows the side effects reported during the treatment course as follows: 5 patients reported fatigue, 4 patients reported headache, 3 patients reported anemia were more common in patients where RBV was added to the DAAs and improved with dose reduction.

Table (2) Effect of treatment on CBC, bleeding profile, kidney, liver function tests and HBA1c

Lab parameters		Mean	Std. Deviation	P-value
WBC $\times 10^3$	**Pre treatment**	5.58	2	0.999
	Post treatment	5.58	2.2	
Hb (gm%)	**Pre treatment**	12.4	2.4	0.135
	Post treatment	12.3	2.4	
Albumin (gm/dl)	**Pre treatment**	4.08	0.47	**0.001****
	Post treatment	3.8	0.73	
Bilirubin (mg/dl)	**Pre treatment**	0.83	0.38	**0.013***
	Post treatment	1.2	1.6	
INR	**Pre treatment**	1	0.15	**0.005***
	Post treatment	1.2	0.22	
Creatinine (mg/dl)	**Pre treatment**	0.93	0.25	0.195
	Post treatment	0.95	0.27	
AFP ng/l	**Pre treatment**	5.7	8.87	0.126
	Post treatment	33.6	18.5	
AST (U/L)	**Pre treatment**	60.6	16.7	**0.011***
	Post treatment	48.8	45.8	
ALT (U/L)	**Pre treatment**	41.8	16.2	**0.041***
	Post treatment	37.3	26.2	
PLT$\times 10^3$	**Pre treatment**	159	58.2	0.411
	Post treatment	161.6	73.4	
HBA1c	**Pre treatment**	6.77	1.4	**0.043***
	Post treatment	6.25	0.79	

Data presented as mean ±SD

Table (2) shows that the bilirubin and the INR, platelets increased significantly after treatment but still in the normal range. ALT, AST and HBA1c decreased significantly after treatment (P-value <0.05), albumin decreased after treatment but still in the normal range.

Table (3) Effect of treatment on APRI and FIB 4 scores:

Scores		Mean	Std. Deviation	P-value
APRI	**Pre treatment (median=1)**	**1.1**	0.45	**<0.001****
	Post treatment (median=0.9)	1	0.41	
FIB 4	**Pre treatment (median=3.6)**	**3.9**	1.7	**0.002***
	Post treatment (median=2.7)	3.7	3.5	

Data presented as mean ±SD

Table (3) shows that the treatment succeeded in decreasing the APRI and the FIB 4 significantly (P-value <0.05).

Table (4) Follow up of Child score after treatment:

Pre-treatment CHILD score		Post-treatment CHILD score				Total
		A5	A6	B	C	
A5	Number	80	6	3	5	94
	%within row	85.1%	6.6%	3.3%	5.5%	100%
	%within column	100%	50%	100%	100%	94%
A6	Number	0	6	0	0	6
	% within row	0%	100%	0.0%	0.0%	100%
	% within column	0%	50%	0.0%	0.0%	6%
Total	Number	80	12	3	5	100
	% within row	80%	12%	3%	5%	100%
	% within column	100%	100%	100%	100%	100%

Data is presented as number and percent.

Table (4) & figure (4) show that there 94 (94%) of cases had Child A5 before treatment but after treatment there were 14 cases (14%) changed to higher Child categories, six of them (6.6%) were Child A6, three of them (3.3%) were Child B, five of them (5.5 %) were Child C and only 80 cases still in the same A5. There were 6 cases (6%) with Child A6 and they didn't change after treatment.

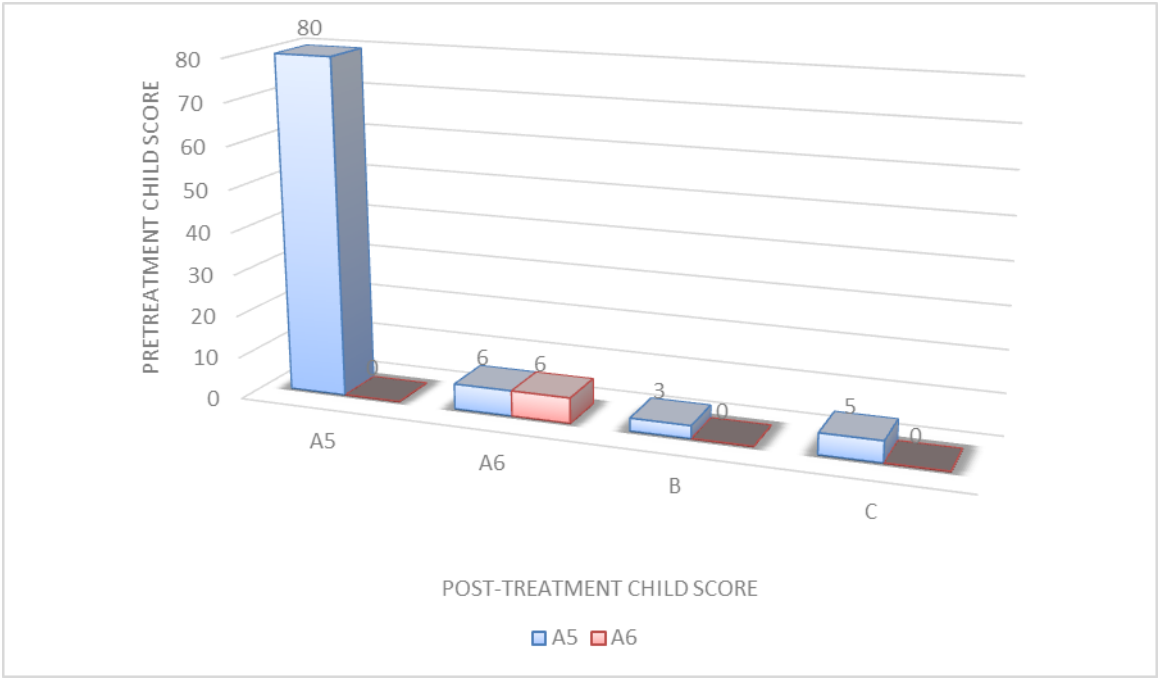


Figure (4) Follow up of child score after treatment

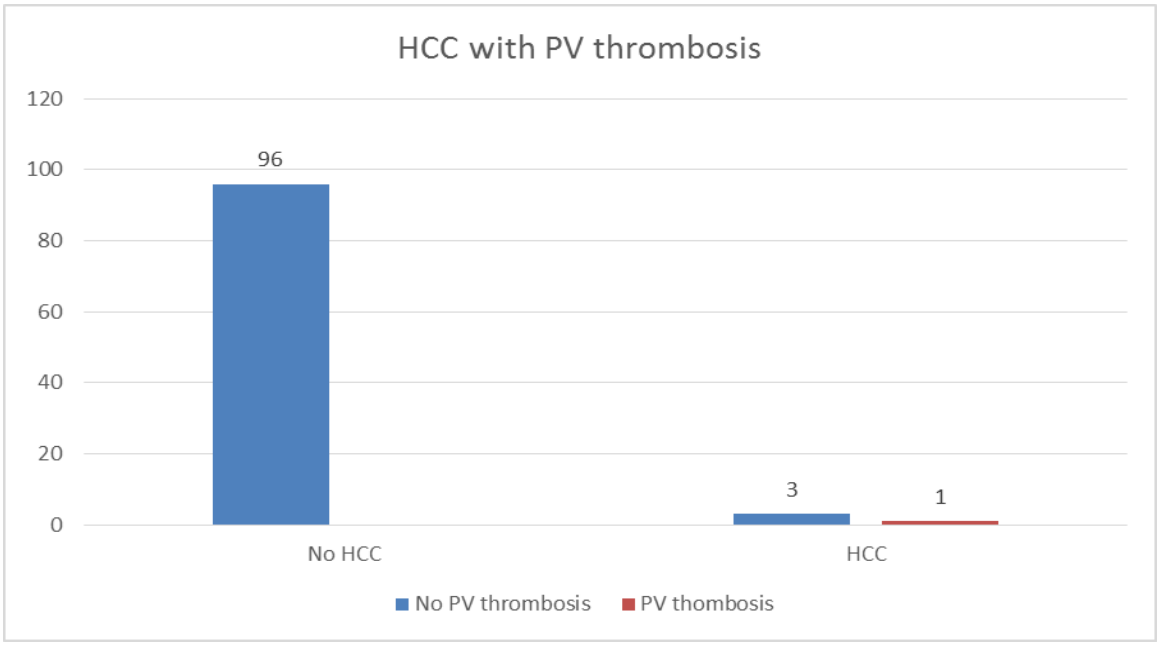
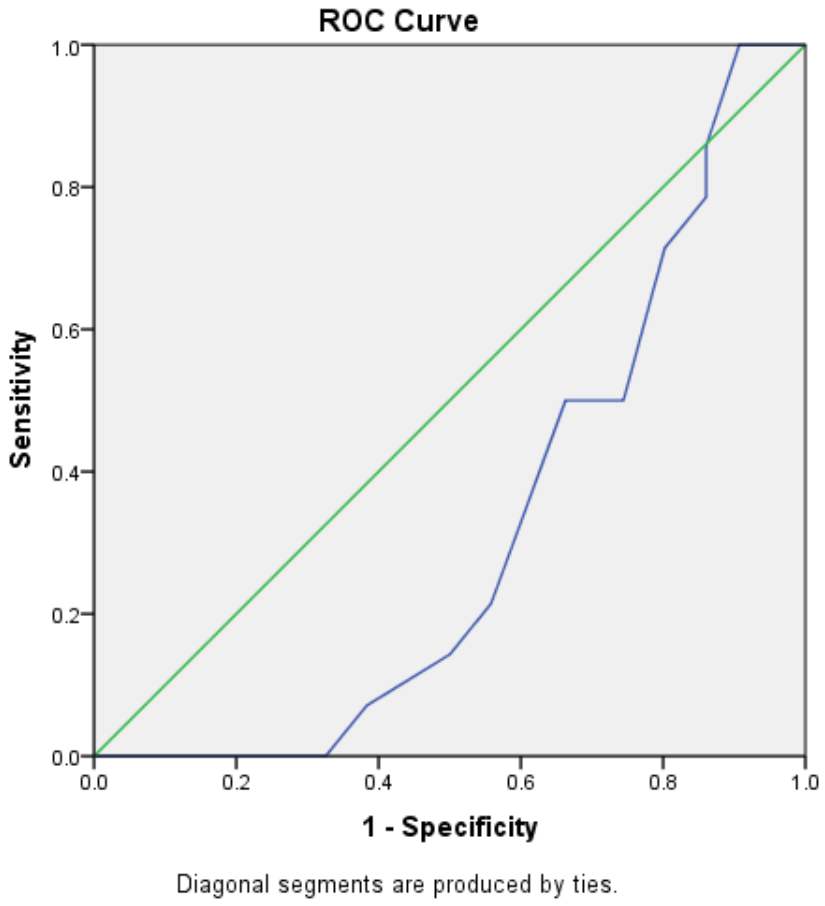


Figure (5) Incidence of HCC after treatment as follows: there were 4 cases of HCC after ttt and one case of them with PV thrombosis



Test Result Variable(s)	Area under the curve	Cut off value	Sensitivity	Specificity
Pre albumin	0.318	3.5	85.7%	15%

Table (5) and figure (6) shows that the albumin level before treatment may be used as predictor for deterioration of Child score after treatment at a cutoff point of 3.5 it can predict the deterioration of Child score by sensitivity 85.7% and specificity 15%.

4. Discussion

Chronic HCV is one of the main etiologies for the morbidity of viral hepatitis worldwide that can lead to long-term complications, including HCV-related cirrhosis and hepatocellular carcinoma (HCC) in a proportion of cases **(7).**

A remarkable revolution has recently occurred with the availability of direct-acting antivirals (DAAs) with different modes of action, leading to high chance of cure and a good tolerance profile. The primary goal of treatment is to achieve a sustained virological response (SVR) defined as undetectable serum HCV RNA 12 weeks after the end of treatment. SVR indicates that viral infection has been cured. In addition, viral eradication is associated with regression of fibrosis and significant improvement in clinical outcome and survival with a decreased incidence of complications, especially hepatocellular carcinoma.

Our study was conducted on chronic hepatitis C cirrhotic patients treated with Direct Acting Antiviral agents to detect the changes in Child Pugh score & ultrasound for detection of signs of decompensation or HFLs diagnosed as HCC with dynamic CT or MRI, also changes in APRI &FIB 4 scores after a median follow up 12 months from the end of treatment. Enrolled patients received sofosbuvir-based treatment regimens according to protocol approved by the National Committee for Control of Viral Hepatitis (NCCVH) in Egypt and the European Association for the Study of the Liver guidelines.

Concerning the demographics of the studied patients the mean age was 57.39±6.1 years and ranged from 44 to 75 years. More than half of the cases were males 60% and the other 40% were females.

This observation is in agreement with Egypt Demographic and health survey (**EDHS, 2015)** as males were more likely to be infected than females and, the levels of infection increased sharply with age among both females and males. Also as males are more likely to travel or joining jobs at which situations viral markers should be investigated.

Our study outcome was as follows: rate of SVR 12 was achieved in 100% on both treatment regimens Sofosbuvir plus Daclatasvir with or without ribavirin.

This result was similar to **Herzer K et al (8**), this Indian study that reported high SVR rates between 97-100% between the studied groups. A recent Swedish study also identified that SVR12 was achieved in (97.8%) of patients, with 100% rates for genotype 2, 3, and 4, and a 96% rate for genotype 1**(9)**.

Ninety two patients (92%) stayed in stage A of Child-Pugh score in a median of 12 months follow-up and 3 patients (3.3%) changed to Child-Pugh B class, 5 patients (5.5%) changed to Child-Pugh C class. This result is near to the study of **Estefania Berge et al (10)** that was conducted on 129 consecutive patients with compensated cirrhosis treated with DAAs, analyzing the evolution of liver function and the development of hepatocellular carcinoma and clinical decompensation after one year follow up. The development of HCC was in 4 patients (4%) and one patient of them associated with PV thrombosis, this result within the expected annual risk 2%-8% . This observation is in agreement with **Kozbial et al (11)** that reported an overall cumulative incidence of de novo HCC after DAA treatment of (6.6%) in patients achieving SVR, with a follow-up time of 48 wk.

Ultimately, the results of these studies did not show an increased risk of HCC in comparison to the expected annual risk for patients treated with DAAs. In any case, neither direct-acting antivirals nor interferon-based treatments eliminate the risk of hepatocellular carcinoma and patients should continue screening every 6 months after the achievement of sustained virological response.

In terms of the hepatic function, our study did not show a significant improvement in the Child-Pugh. This may be because pre-treatment scores were already low. We also had no control group, making it difficult to determine if the outcomes were better or worse than expected. We therefore performed a statistical analysis comparing the mean platelets count, bilirubin, albumin levels & INR pre and post treatment which reflects the hepatic function. We found that there was improvement in platelets count, but albumin show decrease after treatment (P-value <0.05), bilirubin and INR increased after treatment but they still in the normal range, On the other hand another prospective study showed that there was a statistically significant improvement in platelets count and in albumin level showing some benefit in direct-acting antiviral treatment in the short term, although in this study did not show a significant improvement in the Child-Pugh and MELD scores after one year follow up from initiation of DAAs (**12).**

In our study, there was a highly significant relation between the low level albumin and the occurrence of deterioration. Also the albumin level before treatment may be used as a predictor for deterioration of Child- Pugh score after treatment at a cutoff point of 3.5 it can predict the deterioration of Child Pugh score by sensitivity 85.7% and specificity 15%.

This result goes with **Foster et al (13)** that showed that baseline albumin level less than 3.5 gm/dl was a predictive of decompensation. Although serum albumin is a well-known parameter of liver synthetic function, it is not clear why it is specifically more useful in predicting adverse outcomes in patients treated with DAAs. Beyond reflecting hepatocyte protein synthesis, a low albumin level may worsen complications of portal hypertension such as ascites, and albumin may have a specific role in reducing the risk of infection, a major precipitant for hepatic decompensation **(14).**

In our study the effect of treatment on aminotransferases showed that there was a significant improvement in ALT, AST after treatment (P-value <0.05) ,also there was increase in platelets count and this was associated with improvement in FIB 4&APRI scores.

This observation is in agreement with **Martini et al (15)** study that showed that SVR was associated with the decline of aminotransferases and improvement of platelets count, denoting improvement of liver fibrosis and necroinflammation (AST and ALT) following sofosbuvir-based therapy. These parameters are the major components for calculating fibrosis scores, such as FIB-4 and APRI.

In our study there was a significant improvement in HBA1C in diabetic patients, this in agreement with an Italian study that found a drop in HbA1C of patients with chronic hepatitis C and T2DM **P Pavone et al (16).** Though a few patients experienced minor side effects, none of them had to stop therapy due to drug intolerance or adverse events.

Our study shows the side effects reported during the treatment course as the following : 5 patients reported fatigue , 4 patients reported headache and 3 patients reported anemia were more common in patients where RBV was added to the DAAs and improved with dose reduction.

This observation is near to **Werner CR et al (17)** that reported that the most frequent adverse events are headache, fatigue, and anemia no serious adverse events reported. More studies are needed to determine the benefits of direct-acting antiviral therapy in the long term.

5. Conclusion and Recommendations

In conclusion, DAAs was associated with high rates of SVR reaching to 100%, direct-acting antiviral treatment was not associated with a

significant decrease in the development of hepatic decompensation or hepatocellular carcinoma in the first year of follow-up compared to literature reports for untreated compensated cirrhotic patients.

We recommend: Future prospective studies on larger population should be performed reaching a more accurate results. Regular follow up for chronic hepatitis C cirrhotic patients for early detection of HCC every 6 months by abdominal ultrasound and AFP, even after achievement of SVR.

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