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Effect of sofosbuvir plus daclatasvir on virological response and liver function tests as a line of treatment for HCV related cirrhosis (a prospective cohort study)

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Abstract

Background: Patients with chronic HCV infection are the most in need for antiviral treatment. However, patients with cirrhosis exhibit difficulty with direct antiviral agents (DAA) treatment. We intended to evaluate the virological response of DAA in HCV-related cirrhosis treatment as well as its effect on liver function tests and other laboratory tests. Our study was a prospective cohort study of 240 patients with HCV-related liver cirrhosis. Those patients were consecutively selected from Gastroenterology and Hepatology out-patient clinic at Aswan University Hospital. They were subjected to the DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg).

Results: The study showed a rapid decrease in HCV viral load; HCV RNA was undetectable in 65% of patients on 4th week of treatment and in 88.3% of patients on 8th week of treatment. It was undetectable in 100% of patients on 12th week of treatment and remained unchanged until therapy was completed (24 weeks). The SVR (sustained virological response) was 96.3%. Other laboratory tests demonstrated that serum level of alanine aminotransferase (ALT) decreased rapidly to normal limits on 4th week of treatment and remained within normal range until 12th week post-treatment. Significant improvements in serum albumin, total bilirubin, INR, and alpha-fetoprotein (AFP) levels were observed during and after treatment. Child-Pugh score showed a significant improvement post-treatment. We also observed a significant improvement in platelet count during and after treatment.

Conclusion: The DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg) for treatment of HCV-related liver cirrhosis can achieve satisfactory virological response (SVR more than 96%). It can lead to improvement of serum ALT, serum albumin, total bilirubin, INR, AFP, and Child-Pugh score and also increase in platelet count after treatment.

Keywords: Sofosbuvir, Daclatasvir, SVR, ALT, Albumin, Total bilirubin, INR, AFP, Platelet

Background

Liver cirrhosis may be caused by chronic HCV infection which can lead to advanced liver disease and hepatocellular carcinoma [1]. The Egyptian Health Issues Survey (EHIS, 2015) estimates that the prevalence rate of HCV in Egypt is 10% [2]. Chronic hepatitis C was treated with interferon alpha (IFNa) and ribavirin (RBV). This combination can lead to serious side effects and less tolerability [3].

Interferon-based antiviral therapy for chronic hepatitis C patients may lead to improved liver function, decreased incidence of HCC, and decreased hepatic-related mortality. However, it is not known how much liver functions may improve with direct antiviral therapy in advanced liver cirrhosis. One may also question whether there is a "no-return point" where HCV treatment is no longer useful in these cases [4].

Successful antiviral treatment of decompensated hepatitis B with HBV polymerase inhibitors has been shown

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to be associated with improvement of liver functions; it may even lead to removal of the patients from the transplant waiting list. However, it remains to be seen whether suppression of viral replication would lead to similar improvements in HCV-related liver cirrhosis [5].

Our study aims to investigate the efficacy of DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg) in 240 patients with HCV-related liver cirrhosis in a prospective cohort study, and also to estimate the effect of this regimen on liver function tests and platelet count.

Methods

Study design

Our study was a prospective cohort study of 240 patients with HCV-related liver cirrhosis. Those patients were consecutively selected from Gastroenterology and Hepatology out-patient clinic at Aswan University Hospital from May 2018 to April 2019. They were subjected to the DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg).

The eligible patients were as follows:

- Adult patients over 18 years of age.
- Patients with HCV-related cirrhosis. The diagnosis of cirrhosis was made on the basis of transient elastography (fibroscan) stage F4 > 14.5 kPa.
- Patients who were scheduled to receive (DAA) regimen.

Patients with the following criteria were excluded:

- Positive HBs Ag
- Current hepatocellular carcinoma (HCC)
- Creatinine clearance < 30 mL/min

Data collection

In the present study, all eligible patients were subjected to as follows:

- Full history taken (age, gender, occupation, previous history of anti-HCV therapy, etc.).
- Physical examination.
- Abdominal ultrasonography.
- Fibroscan.
- Complete blood picture.
- Liver function tests.
- Kidney function tests.
- Detection of serum AFP levels: AFP was detected by using the Cobas601 electrochemiluminescence immunoassay analyzer.
- HCV RNA (viral load) testing: The viral load was done with Roche COBAS AmpliPrep/COBAS TaqMan, Version 2 (Roche, Pleasanton, CA, USA) according to manufactures instructions with a lower limit of quantification and detection of 15 IU/mL, before the start of treatment (baseline viral load).

Treatment and follow-up

The treatment consisted of sofosbuvir 400 mg once daily plus daclatasvir 60 mg once daily for 24 weeks. Patients were seen on 4th, 8th, 12th, and 24th weeks of treatment and on 12th week after treatment. Patients were subjected to serial follow-up of HCV RNA (viral load), serum ALT, serum albumin, total bilirubin, INR, alpha-fetoprotein levels, and platelet count for each patient and each visit. Child-Pugh score was assessed and calculated for each patient and each visit.

Ethical statement

We confirm that this study is consistent with international ethical standards and the applicable local regulatory guidelines. The study has no physical, psychological, social, legal, economic, or other expected risks to the study participants. Participants in the target institutions were informed about the objectives of the study, methodology, risk, and benefits. A written informed consent was obtained from each eligible patient prior to study's enrolment. The study was approved and consent to participate by Local Ethics Committee, Faculty of Medicine, Aswan University.

Statistical analysis

An Excel spreadsheet was established for data entry. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. The analyses were carried with the SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). The normality of data was assessed using Shapiro-Wilk Test. Numerical data was described as mean ± SD if normally distributed or median and interquartile range [IQR] if not normally distributed. Frequency tables with percentages were used for categorical variables. Paired *t*-test was used to compare parametric quantitative variables. While Wilcoxon matched pair test was used to compare non-parametric quantitative variables, a p value of < 0.05 is considered statistically significant.

Results

Our study was a prospective cohort study of 240 patients with HCV-related liver cirrhosis. Those patients were consecutively selected from Gastroenterology and Hepatology out-patient clinic at Aswan University Hospital from May 2018 to April 2019. They were subjected to the DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg).

Baseline characteristics of our patients are shown in Table 1. The mean age of the study group was 52.9 ± 8.8 years, and the majority were males (59.6%). All

Table 1 Baseline characteristic data of the studied patients

Variables	Studied patients (***N*** = 240)
Age	
Mean ± SD	52.9 ± 8.8 years
Gender	
Male	143 (59.6%)
Female	97 (40.4%)
Previous HCV treatment	
Treatment naïve	240 (100%)
Treatment experienced	0 (0.0%)
Viral load, IU/L	
Median (IQR)	5455685 (496040–18102824)
Fibroscan value, kPa	
Mean ± SD	25.8 ± 4.5
Serum ALT, IU/L	
Median (IQR)	62.5 (40.0–98.5)
Serum albumin, g/dL	
Mean ± SD	3.54 ± 0.46
Total bilirubin, mg/dL	
Mean ± SD	1.42 ± 0.60
INR	
Mean ± SD	1.19 ± 0.22
Child-Pugh score	
Mean ± SD	7.3 ± 1.5
Serum creatinine, mg/dL	
Mean ± SD	1.1 ± 0.3
AFP, ng/mL	
Median (IQR)	21.0 (18.0–30.0)
Platelet count, × 10^9 per liter	
Mean ± SD	131.5 ± 37.1
Treatment regimen	
Sofosbuvir + daclatasvir	240 (100.0%)
Other regimens	0 (0.0%)
Serious adverse effects	0 (0.0%)
Discontinuation of treatment	0 (0.0%)

Data are presented as mean ± SD, median (IQR), or number (%)
SD standard deviation, *IQR* interquartile range, *HCV* hepatitis C virus, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *INR* international normalization ratio

patients were treated naively; the mean Child-Pugh score was 7.3, and the mean fibroscan value was 25.8 kPa. Baseline serum ALT, serum albumin, total bilirubin, INR, alpha fetoprotein, serum creatinine, platelet count, and viral HCV load are shown in Table 1.

Treatment characteristics

All patients were treated with sofosbuvir 400 mg once daily plus daclatasvir 60 mg once daily for 24 weeks. There were no serious adverse effects during treatment requiring discontinuation (Table 1).

Virological response

During treatment, there was a rapid decrease in HCV viral load; HCV RNA became undetectable in 65% of patients on 4th week of treatment and in 88.3% of patients on 8th week of treatment. It was undetectable in 100% of patients on 12th week of treatment and remained unchanged until therapy was completed (24 weeks). Follow-up of patients reported SVR (96.3%) after 12 weeks of treatment (Table 2). Patients who did not achieve SVR showed mild viraemia on 12th week post-treatment visit with no change in the clinical and other laboratory data .They were subjected to another DAA line of treatment.

Biochemical and hematological responses during and post-treatment

Serum alanine aminotransferase (ALT) decreased rapidly within normal values on 4th week of treatment and remained within normal range until follow-up (12 weeks post-treatment) (P value < 0.001) (Fig. 1). Serum albumin, total bilirubin, and INR showed significant improvement during and after treatment (P < 0.001) (Figs. 2, 3, and 4, respectively). Serum alpha-fetoprotein (AFP) levels showed a significant decline during and post-treatment (P value =

Table 2 Virological response in the studied patients

Viral load	Studied patients (***N*** = 240)
Viral load on 4th week	
< 15 IU/L	156 (65.0%)
> 15 IU/L	84 (35.0%)
Viral load on 8th week	
< 15 IU/L	212 (88.3%)
> 15 IU/L	28 (11.7%)
Viral load on 12th week	
< 15 IU/L	240 (100.0%)
> 15 IU/L	0 (0.0%)
Viral load on 24th week	
< 15 IU/L	240 (100.0%)
> 15 IU/L	0 (0.0%)
Viral load on 12th week post-treatment	
< 15 IU/L	231 (96.3%)
> 15 IU/L	9 (3.7%)
SVR	
Yes	231 (96.3%)
No	9 (3.7%)

Data are presented as number (%)
SVR sustained virological response

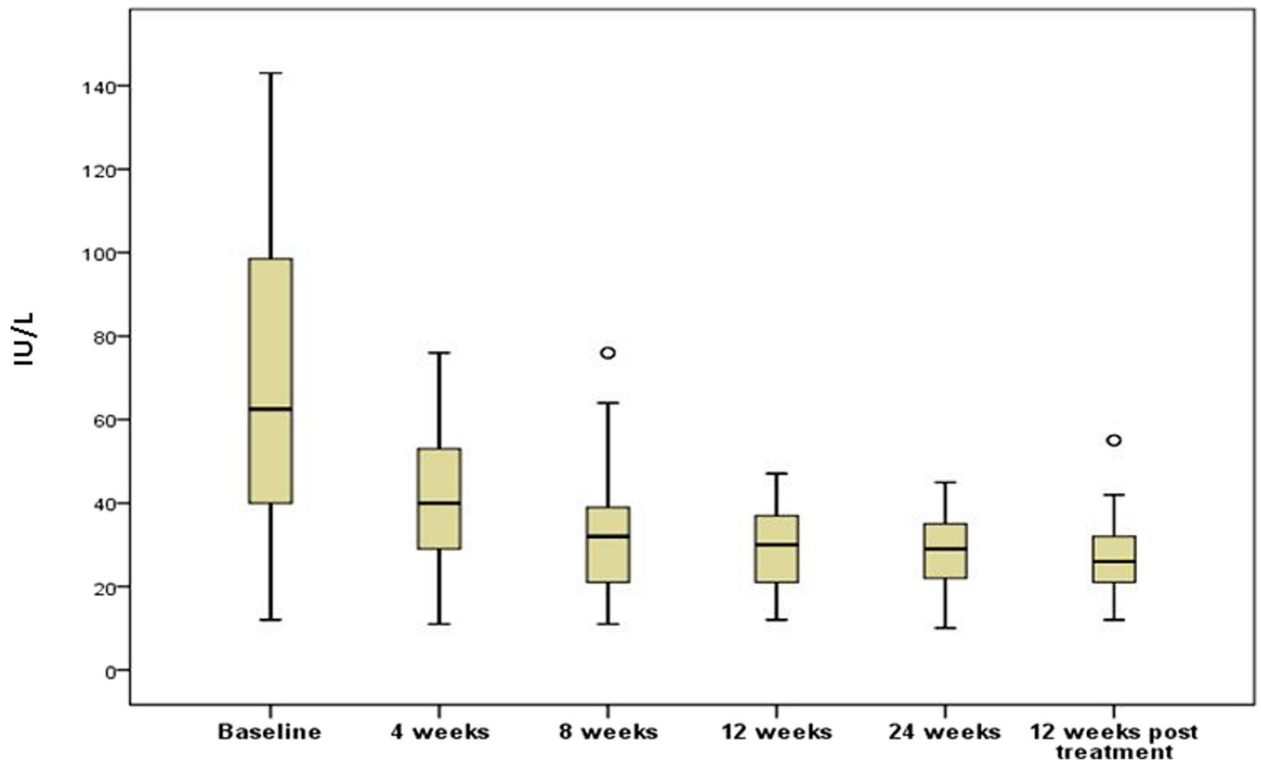

Fig. 1 Change in serum ALT during and post-treatment of the studied patients. *P* value < 0.001; *ALT*, alanine aminotransferase

0.02) (Fig. 5). Child-Pugh score showed a significant improvement on 12th week post-treatment (*P* value < 0.001) (Fig. 6). Also, we observed a significant increase in platelet count in studied patients during and post-treatment (*P* value < 0.001) (Fig. 7).

Discussion

Hepatitis C virus (HCV) is a worldwide health problem, because infection often leads to chronic hepatitis, eventually progressing to liver cirrhosis and hepatocellular carcinoma. Improved insight into HCV replication cycle and the role of non-structural HCV proteins has recently enabled the identification of drugs directly acting on specific HCV target structures. Combinations of two or more of these drugs from different classes achieve high (> 90%) HCV clearance rates and are well tolerated [6].

In our study, all patients received the regimen (sofosbuvir 400 mg once daily plus daclatasvir 60 mg once daily) for 24 weeks. More than 96% of patients achieved sustained virological response (SVR) after treatment. Regarding the primary outcome of the present study, we found that serum level of ALT had returned to the normal range in concordance with the rapid viral clearance. This course of treatment indicates that hepatic inflammation due to HCV replication might induce substantial stress on the liver. Hence, eradication of HCV infection could reverse the hepatic function abnormalities, even in patients with advanced cirrhosis. Surprisingly, serum AFP levels decreased significantly during and after treatment. Previously, an elevated AFP level was associated with an increased risk of HCC [7]. Post-interferon treatment, elevated ALT, and AFP levels were associated with a risk of hepatocarcinogenesis in patients with HCV-related liver cirrhosis [8]. It remains unclear whether the further development of HCC will be inhibited by HCV eradication with DAA therapy. It is important to monitor patients for HCC development after treatment [9]. Our study follow-up lasted for 12 weeks after treatment, and none of our patients developed HCC. Therefore, further studies with long-term follow-up are recommended to give more impressions about the occurrence of HCC after treatment.

In agreement with these findings, Yek and colleagues conducted a retrospective observational study involving all patients receiving DAA-based HCV therapy. The authors reported an SVR of 95% of patients who had been followed up [10].

Similarly, Del Rio-Valencia and colleagues performed an observational study to evaluate the efficacy of DAA's

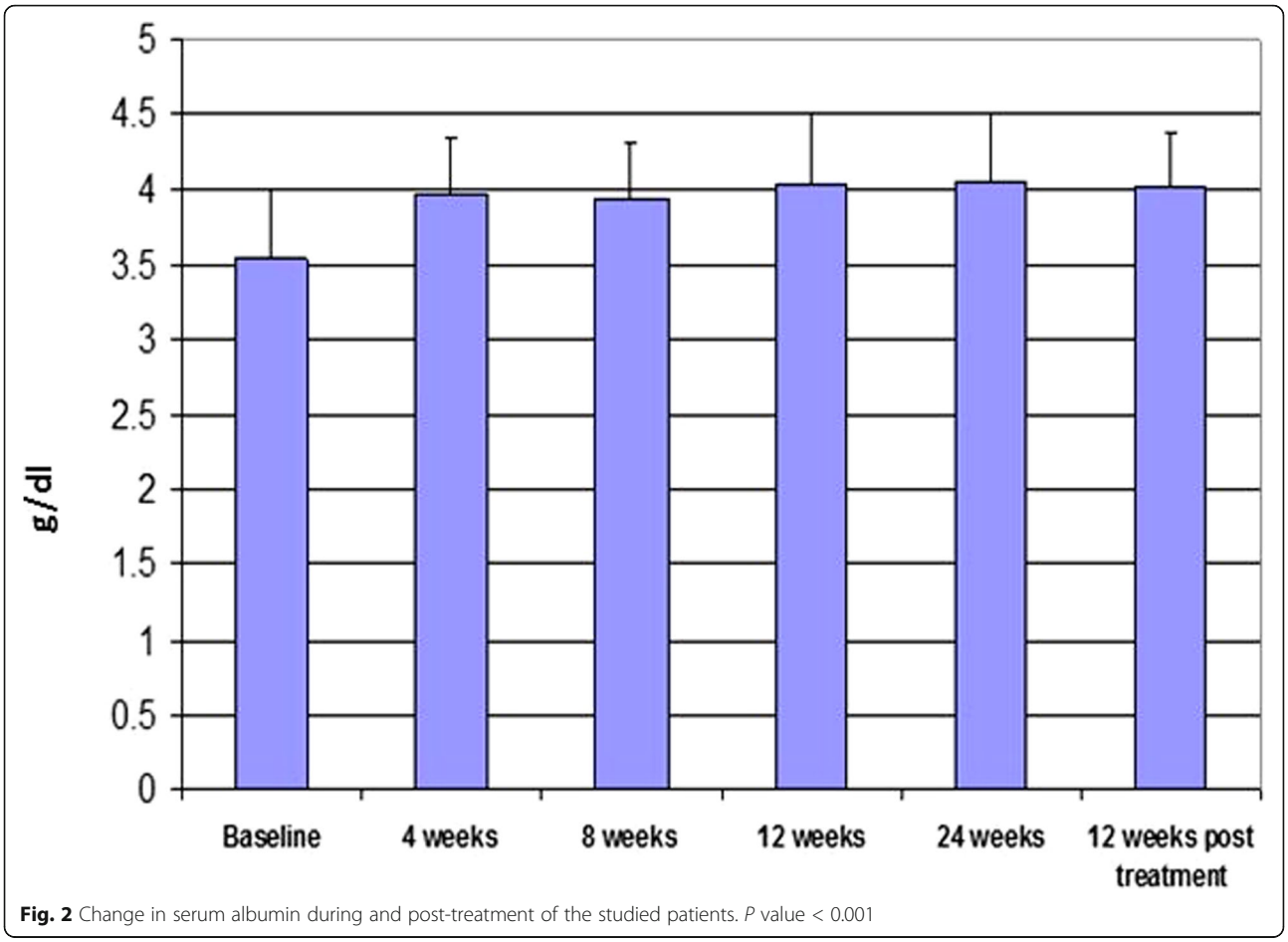

Fig. 2 Change in serum albumin during and post-treatment of the studied patients. *P* value < 0.001

regimens for patients with chronic HCV genotype 1–4 infections. Different DAA's regimens achieved SVR more than 95% [11]. Ahmed and colleagues conducted a systematic review of six randomized trials (n = 1427 patients) to investigate the safety and efficacy of velpatasvir plus sofosbuvir in treatment of chronic HCV infection. The authors reported that the regimen achieved 99% SVR in patients with chronic genotype 4 infection [12]. Similarly, daclatasvir containing regimen achieved 95% SVR in patients with genotype 4 infection [13].

In return, laboratory data in our study as serum albumin, total bilirubin, INR, and Child-Pugh score were significantly improved after treatment. Our study has shown that liver cirrhosis is not a "point of no return." HCV eradication with DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg) does not result in an improvement of liver function tests only but can also lead to a significant improvement in platelet count post-treatment. The adverse effects of this regimen (sofosbuvir 400 mg plus daclatasvir 60 mg) were generally minimal and tolerable; there was no premature treatment discontinuation.

In agreement to these findings, Sharma et al. [14] studied the efficacy and tolerability of direct antiviral agents by assessing liver function parameters (ALT, AST, and albumin) in HCV patients awaiting renal transplantation. The results showed that serum AST/ALT levels decreased significantly (P < 0.0001) after DAA therapy.

In concordance with our findings, Morii et al. [15] intended to estimate whether patients with HCV-related cirrhosis and clinically significant portal hypertension could demonstrate reasonable virological and safety outcomes for DAA therapy. A total of 113 patients were included in this study; 26 with clinically significant portal hypertension and 87 without clinically significant portal hypertension. SVR rates were equally good in patients with clinically significant portal hypertension (96%) and in those without (93%). Proper improvement in hepatic function has been detected in patients who have achieved SVR. The main limitations of this study were single-center experience and short-term follow-up.

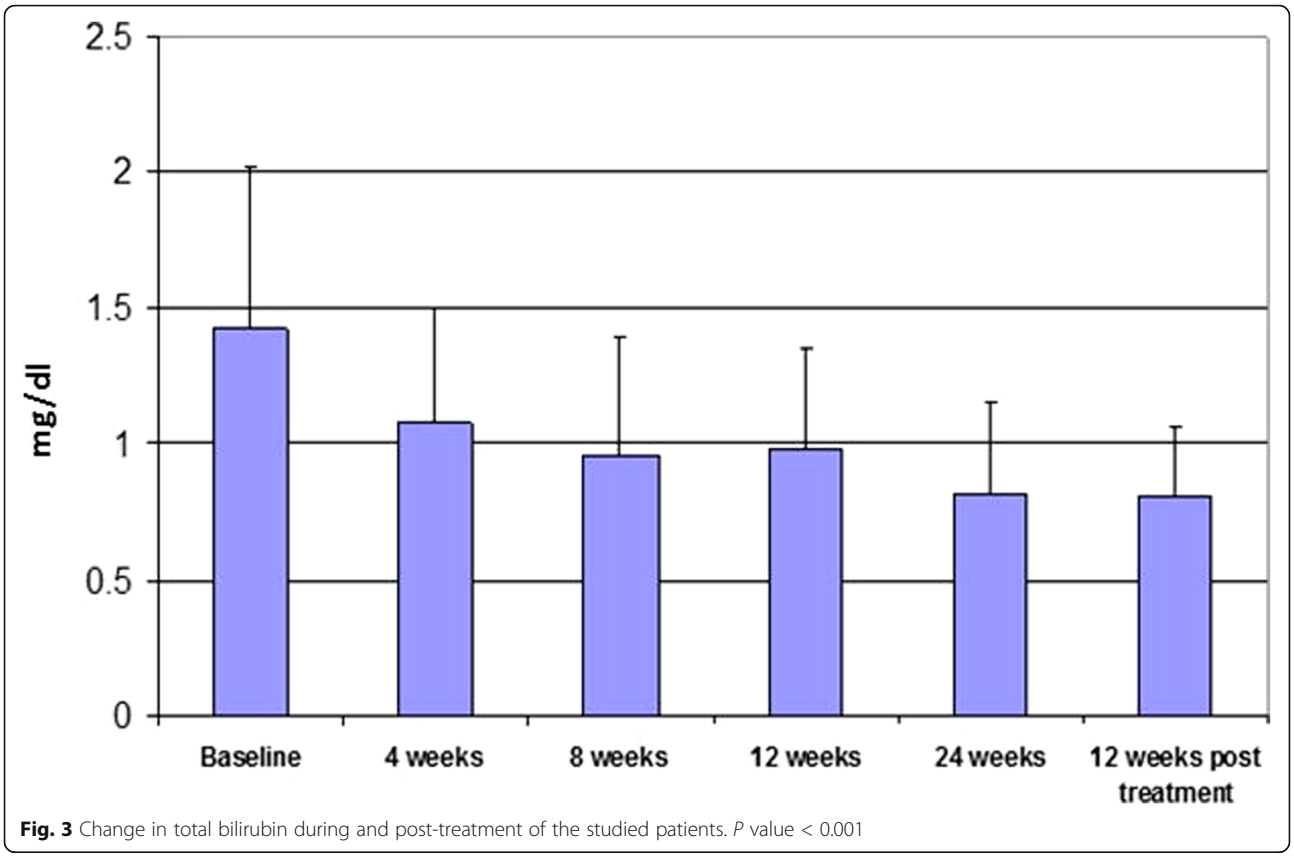

Fig. 3 Change in total bilirubin during and post-treatment of the studied patients. *P* value < 0.001

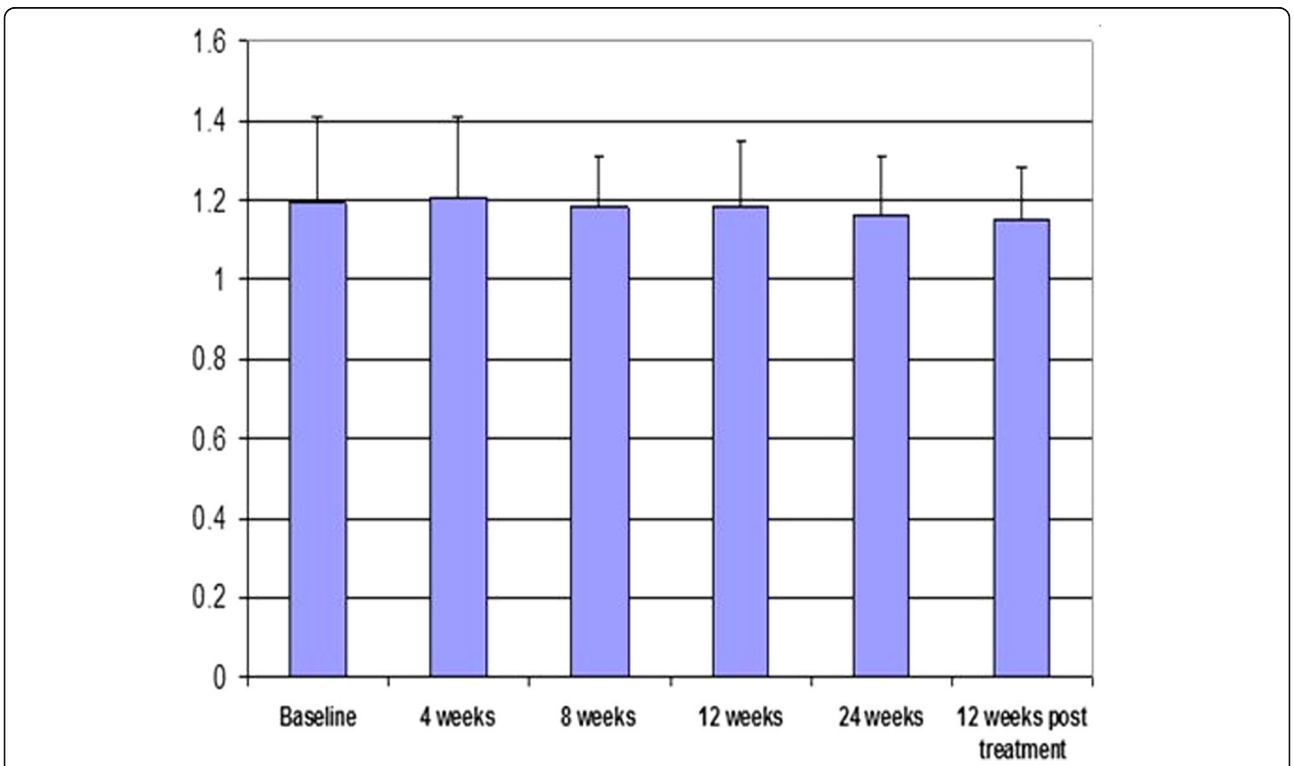

Fig. 4 Change in INR during and post-treatment of the studied patients. *P* value < 0.001; INR, international normalization ratio

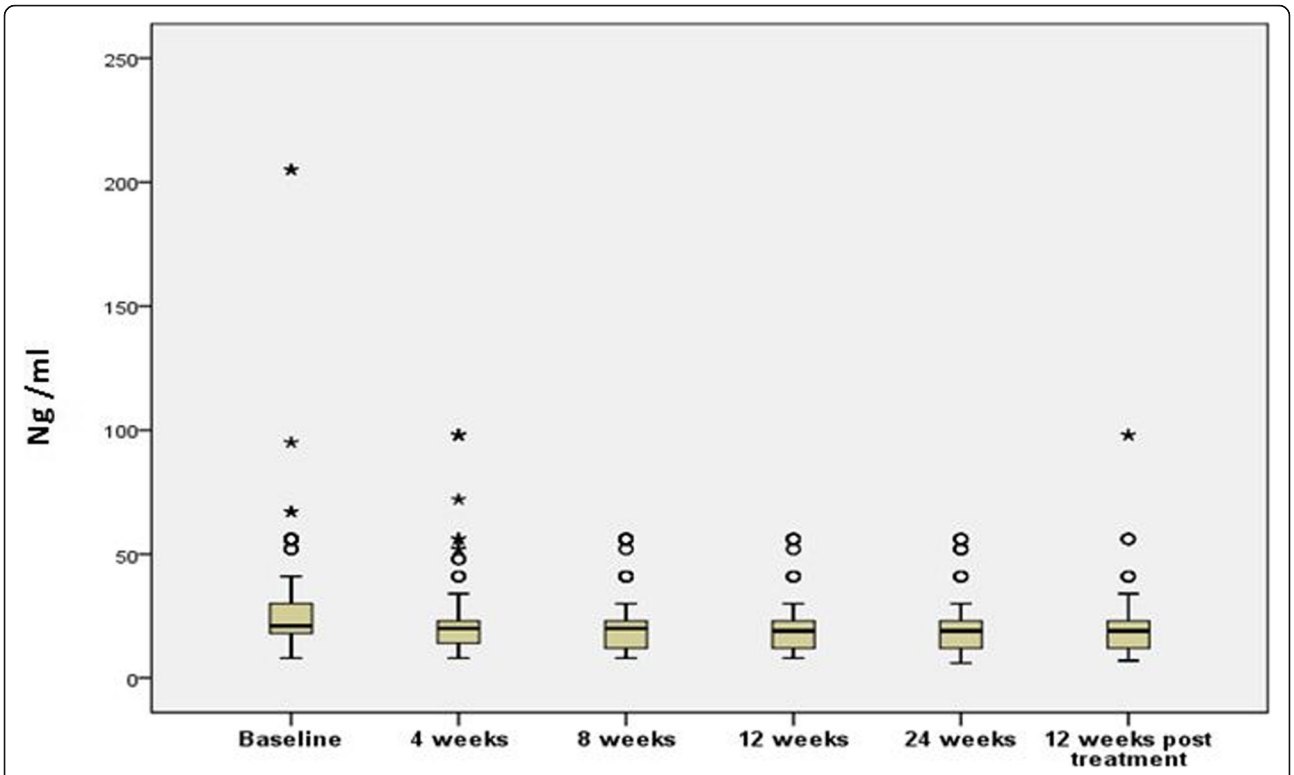

Fig. 5 Change in AFP levels during and post-treatment of the studied patients. *P* value = 0.02; AFP, alpha-fetoprotein

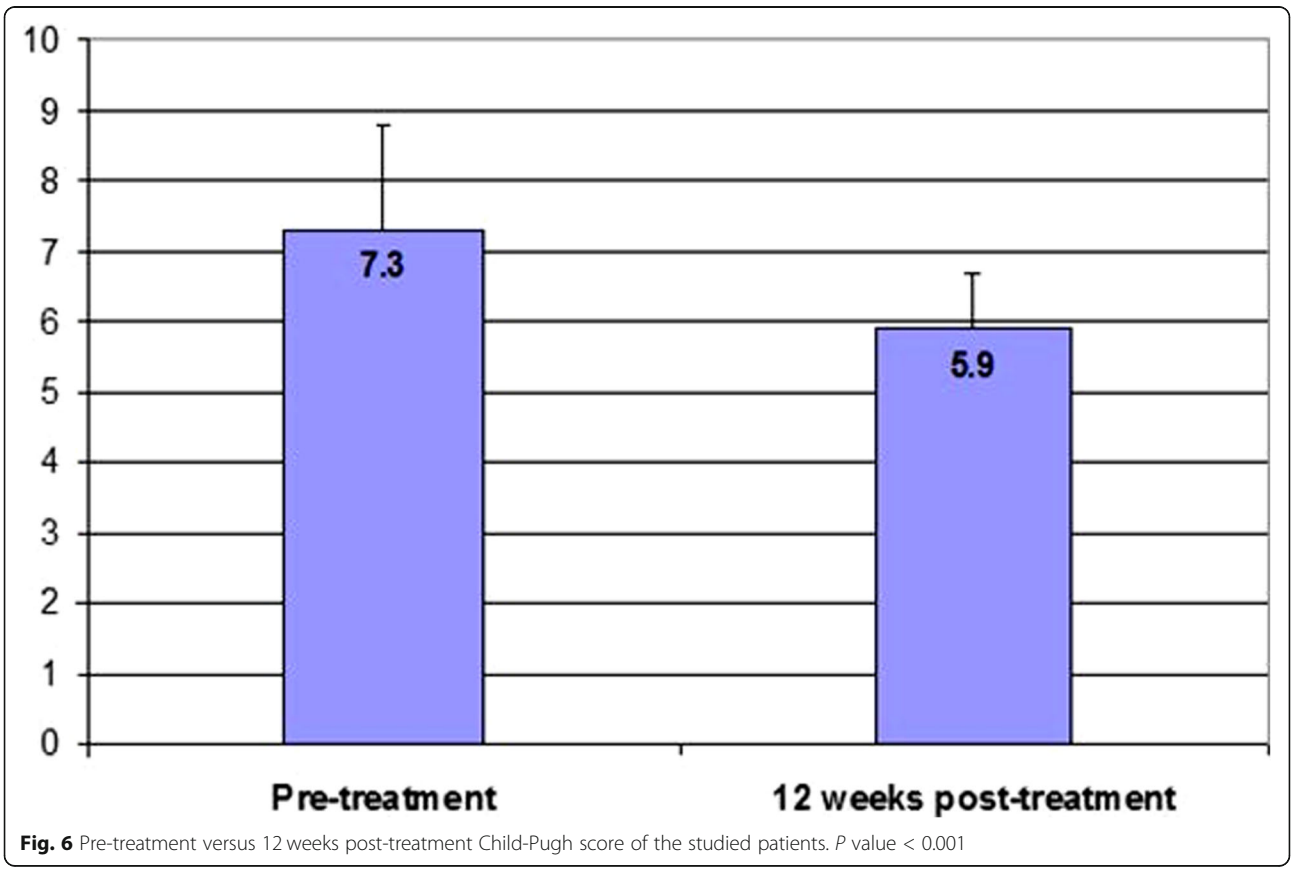

Fig. 6 Pre-treatment versus 12 weeks post-treatment Child-Pugh score of the studied patients. *P* value < 0.001

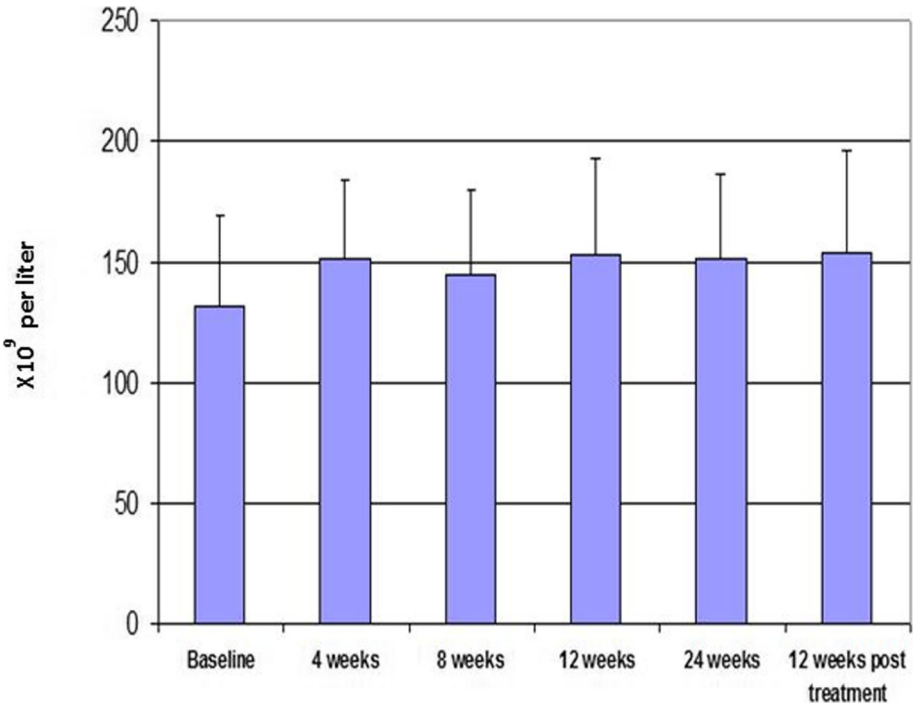

Fig. 7 Change in platelet count during and post-treatment of the studied patients. *P* value < 0.001

Conclusion

In conclusion, the DAA regimen (sofosbuvir 400 mg plus daclatasvir 60 mg) for treatment of HCV-related liver cirrhosis can achieve proper virological response (SVR more than 96%). It can lead to improvement in serum ALT, serum albumin, total bilirubin, INR, AFP levels, Child-Pugh score, and platelet count after treatment.

Abbreviations

AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; DAA: Direct antiviral agents; EHIS: Egyptian Health Issues Survey; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; IFNa: Interferon alpha; INR: International normalization ratio; RBV: Ribavirin; SVR: Sustained virological response

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Not applicable

Consent of publication

Not applicable

Authors' contributions

OM, AA, and WA collected, critically interpreted the study data, and contributed in the manuscript writing. Laboratory investigations were done by EF. OM and AA contributed in the manuscript writing. WA was a major contributor to the manuscript writing and revising. All authors have read and approved the final manuscript.

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Availability of data and materials

Data materials are available under reasonable request.

Ethics approval and consent to participate

The study was approved and consent to participate by Local Ethics Committee, Faculty of Medicine, Aswan University; reference number is not available. Informed written consent was obtained from each participant before enrolment in the study.

Competing interests

The authors declare that they have no competing interests.

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